SEROTONIN AND THE CENTRAL NERVOUS SYSTEM

An Autoradiographic Study

by

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To

Ann, Bryan and Catherine.

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SUMMARY

The use of behavioural models and electrophysiology are two commonly used approaches for studying the effects of the substance serotonin and serotonin-like drugs on the central nervous system.

The behavioural tests were developed following the discovery that pharmacological manipulations resulted in an increase in serotonin concentration in the central nervous system and led to the production of a definable behavioural syndrome. However, this is a gross measure of central serotoninergic interactions in the brain since it does not provide any information on the precise location of the cerebral regions involved.

The measurement of electrical activity has proved a powerful tool for directly measuring the functional activity of neurones and their responses to the micro-iontophoretic application of serotonin or serotonin-mimetic drugs. This technique is limited, in a practical sense, by the number of cells which can be measured in any one area of the brain and as an inevitable consequence of the use of anaesthesia in these preparations.

In recent years, a more direct measurement of regional cerebral function in the conscious rat has been developed. As glucose is the sole energy substrate for the brain under non-pathological conditions, its measurement is a direct index of cerebral function. The method in question uses ^{14}C - 2 deoxyglucose to measure local cerebral glucose utilisation by quantitative autoradiography. It provides, due to the unique properties of 2 deoxyglucose, a measure of the integrated response of the central nervous system

to pharmacological manipulation.

The results of this thesis are presented in four parts. In the first, (Chapter III), serotonin, when administered into the carotid artery of halothane anaesthetised rats was found to have no effect on glucose utilisation unless the animal was first treated with the monoamine oxidase inhibitor, clorgyline. When these substances were combined, a number of regions were found to have decreased rates of glucose use, particularly in the cortex. The problem associated with this model will be discussed, particularly in relation to the depressive actions of halothane anaesthesia.

The second part (Chapters IV and V) of this thesis deals with the actions of two structurally-differing sets of putative serotonin agonists on the local cerebral glucose utilisation, behaviour and cardiovasculature of conscious rats. Lysergic acid diethylamide and 5 methoxy-N,N-dimethyltryptamine both contain indoleamine portions to their structures; as does serotonin itself. Quipazine and chloropiperazinylpyrazine contain piperazine moeities which make them structurally similar to tricyclic antidepressants.

In the majority of brain areas studied, these two sets of putative serotonin agonists produced a depression in glucose use; and therefore function. However, in a select number of structures in the anterior thalamus and in some extrapyramidal areas, the piperazine-containing compounds were capable of producing significant increases in glucose use. A pattern quite different from that produced by the

indoleamine containing substances.

The third section (Chapter VI) deals with the use of substances which have been suggested as serotonin antagonists in the central nervous system. These compounds, metergoline, methysergide and cyproheptadine, have all been shown to be potent antagonists at serotonin receptors in the periphery. In the present experiments they were found to produce decreases in local cerebral glucose utilisation at relatively high doses. These results have implications with regard to the "classical" concept of receptor antagonists.

In the final section of results, (Chapters VII and VIII) data are provided on the actions of the four putative serotonin agonists following the pretreatment of metergoline and methysergide. The consequence of this combination of treatment was that some but not all agonist effects were inhibited. On the contrary, in certain cerebral areas the functional response to the serotonin agonist was either unaffected or potentiated by the pretreatment of metergoline or methysergide. Thus, the combination of "agonist" and "antagonist" produced a pattern of response which was very different from that produced by either set of compounds alone.

In the subsequent discussion a synthesis of this information is attempted in the light of previous in vivo and in vitro information.

PREFACE AND DECLARATION.

The biogenic amine serotonin (5 hydroxytryptamine) is a strong candidate as a central neurotransmitter and may well be involved in a number of diverse physiological mechanisms such as sleep, behaviour, mood and the control of hormonal secretion from the pituitary.

This thesis deals with the anatomical location of functional changes, as measured by local cerebral glucose utilisation, in brain regions sensitive to pharmacological manipulation by serotonin - mimetic drugs.

The data was obtained from my own original experiments. This material has not been presented as a thesis in any form.

I. INTRODUCTION.

Serotonin has been implicated in a diverse number of physiological functions in the central nervous system such as overt behaviour, (Aprison et al, 1975; Gibbons and Glusman, 1979; Marks et al, 1978; Meyerson et al, 1978 inter alia) anorexia (Blundell, 1977 for review; Clineschmidt et al, 1978; Garattini and Samanin, 1978; Samanin et al, 1980), analgesia (Messing and Lytle, 1977; Yaksh, 1979; York and Maynert, 1978), sleep (Koella et al, 1968; Jouvet, 1969; Jouvet 1972) and the regulation of the hypothalamic/pituitary axis. (Fuller et al, 1976; Krulich, 1979; Meltzer et al, 1978). A role for serotonin in the etiology of mental depression has also been suggested. (Asberg et al, 1973; Murphy et al, 1978; Van Praag and Korf, 1974). Given this diverse functional involvement it is of vital importance to obtain data on the effects of perturbation of the central serotonin system on cerebral function in order that the modulatory role of this substance can be better understood. I shall first consider the information which is available on serotonin in the central nervous system.

1.1 Historical Perspective:

Lesions of the median forebrain bundle produced a depletion of 5HT in the forebrain which paralleled the degeneration of the neurones. (Heller et al, 1962; Heller and Moore, 1965). This indirect evidence was further supported by the direct visualisation of the fluorescent products of serotonin produced by the formaldehyde-condensation histochemical

method of Falk et al (1962). This allowed the mapping of neuronal cell-bodies (Dahlstrom and Fuxe, 1965), terminals (Aghajanian et al, 1973; Fuxe, 1965) and pathways (Anden et al, 1966). The cell-bodies were found to be mainly located within the brainstem raphe nuclei. Nine nuclei were identified and these were designated B1 - B9 (Fig. 1). These perikarya send projections to the spinal cord, brainstem and to much of the forebrain (Fig. 1). The central nervous system also contains all the biochemical apparatus necessary for the synthesis, storage and inactivation of 5HT. (see below and legend to figure 2).

The destruction of the serotonergic cell-bodies leads to a degeneration of histochemically identifiable 5HT terminals in the forebrain. (Aghajanian, 1969; Kuhar et al, 1972) There is also an anatomically selective reduction in 5HT content. (Heller and Moore, 1965; Kostowski et al, 1968; Jacobs et al, 1974; Palkovits, 1977) as well as a selective decrease in forebrain tryptophan hydroxylase activity (Kuhar et al, 1971; Palkovits, 1977). Midbrain raphe lesioning also affected the uptake of serotonin into synaptosomes which were subsequently formed from the forebrain. (Kuhar et al, 1972) Stimulation of the midbrain raphe nuclei produces increased synthesis and turnover of 5HT in the forebrain (Kostowski et al, 1969; Sheard and Aghajanian, 1968; Shields and Eccleston, 1972) Furthermore, a variety of sensory stimuli increase the release of endogenously produced 5HT and the activity of the raphe nuclei. (Aghajamian et al, 1978; Jacobs et al, 1980; Le Moal et al, 1979; Trulson et al, 1979; Reisine et al, 1982.)

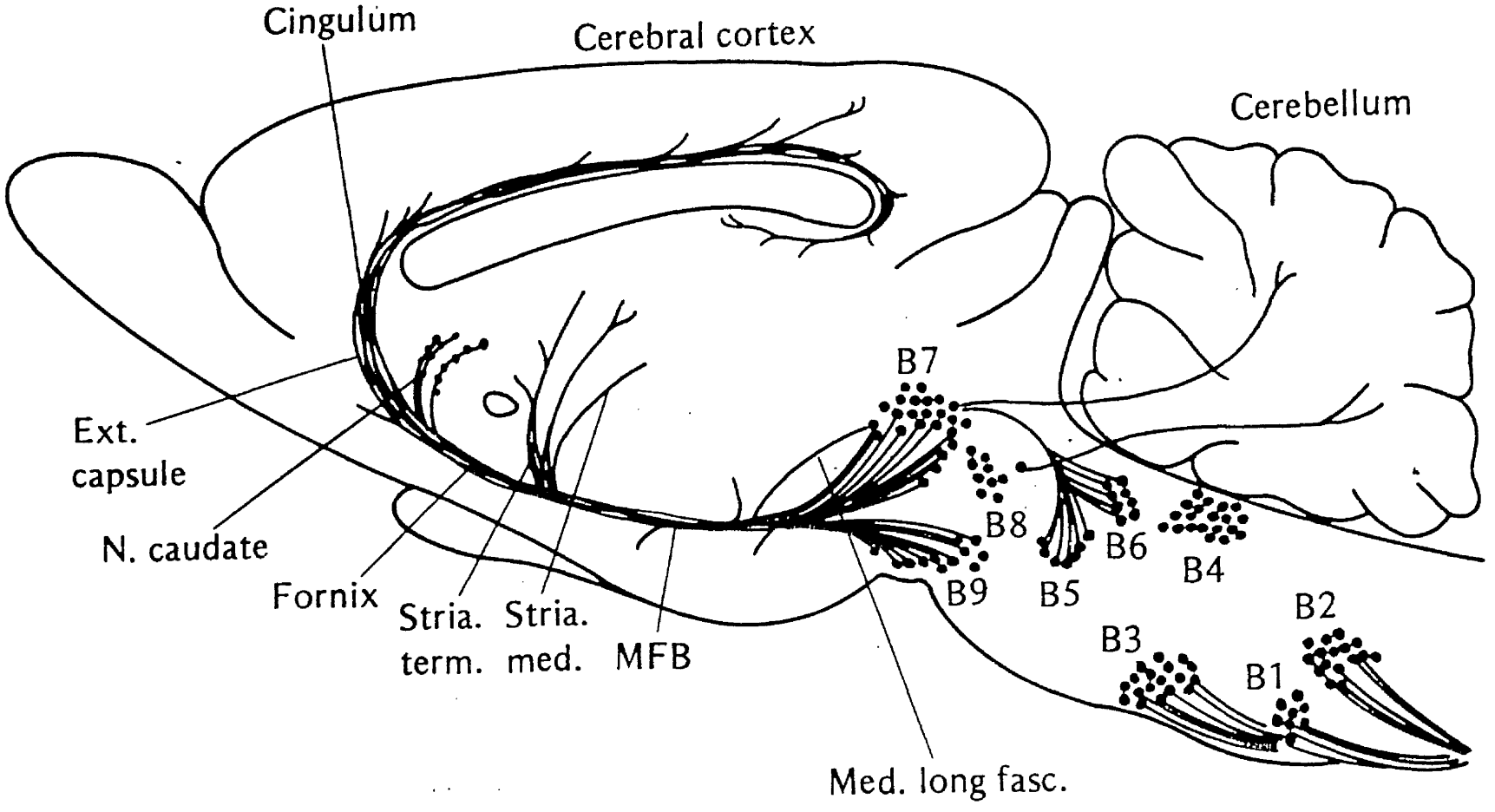


Figure 1. Schematic diagram illustrating the distribution of the main serotoninergic pathways in rat central nervous system. (modified after G. Breese. Handbook of psychopharmacology, Vol. 1, 1975). Note that the dorsal raphe nucleus (B7) and the median raphe nucleus (B.8) send fibers almost exclusively to the forebrain.

This brief resume is enough to suggest that serotonin is a neurotransmitter in the central nervous system of the rat. The biochemistry, anatomy and electrophysiology of the serotonergic system in the rat forebrain will now be studied in more detail.

I. 2 Serotonin Metabolism in the C.N.S.

The substrate for serotonin synthesis, the naturally occurring amino acid L-tryptophan, enters the brain via a transport mechanism for neutral amino acids. (Fernstrom and Wurtman, 1972). In vitro studies have shown that a similar mechanism regulates the entry of the L-tryptophan into the serotonergic neurone. (Grahame-Smith and Parfitt, 1970; Parfitt and Grahame-Smith, 1974.) Once inside the cell it becomes the substrate for the enzyme tryptophan hydroxylase which produces 5-hydroxytryptophan as a product. This is the rate-limiting step for 5HT synthesis in the brain (Green and Grahame-Smith, 1975). The Km for tryptophan (in the presense of biopterin H_4:BH_4) is almost equal to the C.N.S. tissue level of tryptophan. Under these conditions increasing the L-tryptophan levels may result in an inhibition of tryptophan hydroxylase activity. (Azmitia and McEwan, 1974; Freidman et al, 1972; Knapp and Mandel, 1973.) (Fig. 2) Once synthesised 5HTP is almost immediately decarboxylated to yield serotonin. The enzyme responsible, 5 - hydroxytryptophan decarboxylase, is similar to the enzyme which decarboxylates dihydroxyphenylalanine. The serotonin formed may control its own synthesis since increased levels

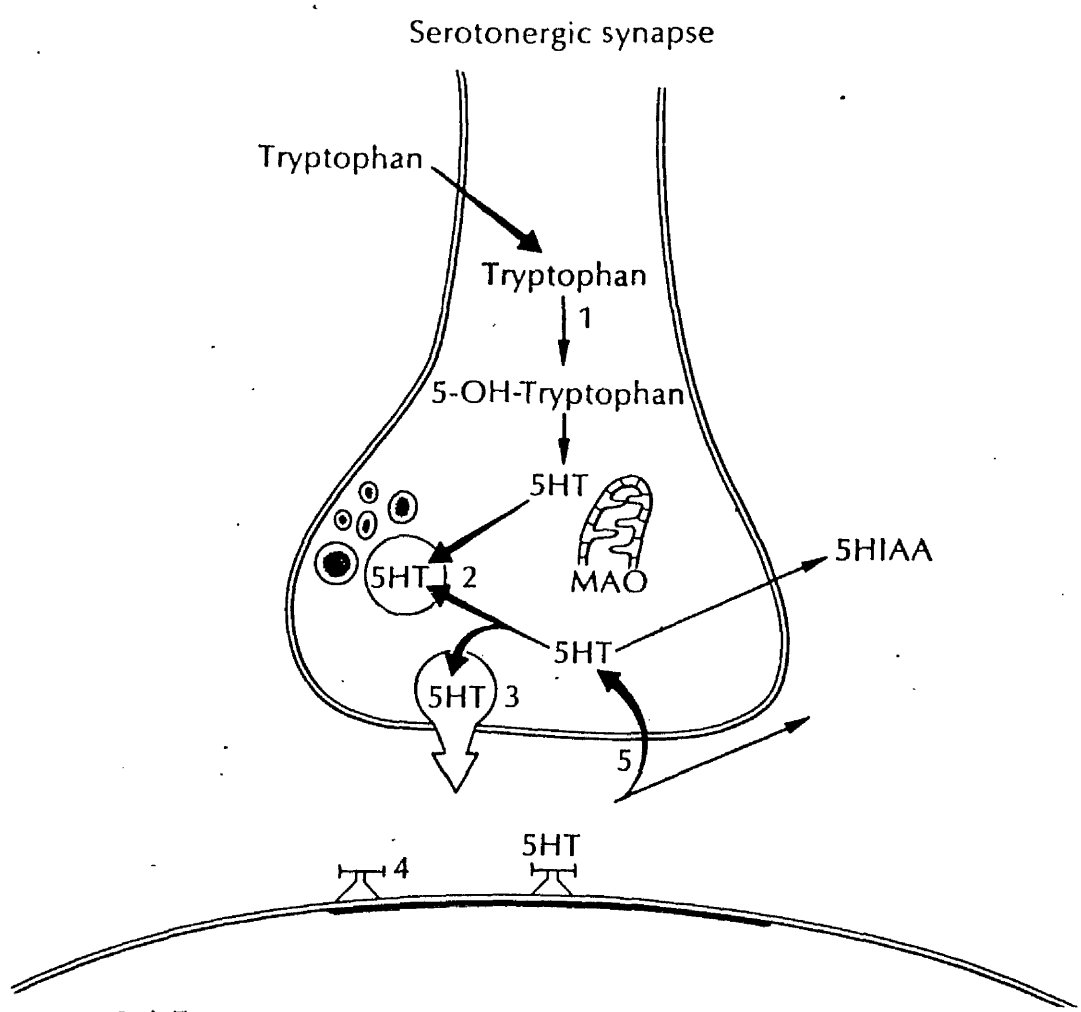


Figure 2 1.The enzyme tryptophan hydroxylase - the rate-limiting enzyme of 5HT synthesis. 2. 5HT after synthesis is stored in vesicles. 3. The propagation of an action potential to the synapse leads to the release of 5HT. 4. Post-synaptic 5HT receptor. 5. Uptake back into the synapse by high-affinity uptake system. 5HT is taken up by vesicles or is inactivated by monoamine oxidase. (MAO) (Modified from Cooper et al, 1978).

of the neurotransmitter reduce the activity of tryptophan hydroxylase. (Hamon et al, 1973; Carlsson and Lindquist, 1973, and Hamon and Glowinski, 1974 for review.)

The major route of catabolism for serotonin is deamination by the enzyme monoamine oxidase. Different forms of this enzyme have been demonstrated in vivo and in vitro. (Sandler and Youdim, 1972) Using clorgyline Johnston (1968) distinguished between "Type A" and "Type B" monoamine oxidase enzymes. Type A deaminates serotonin as well as noradrenaline and dopamine. (Sandler and Youdim 1974; Houslay and Tipton, 1974). This enzyme deaminates serotonin to form 5 hydroxyindoleacetaldehyde which can be further catabolised to 5 hydroxyindoleacetic acid or 5 hydroxytryptophal by aldehyde dehydrogenase and alcohol dehydrogenase respectively. (See Sandler and Youdim, 1972 for review.)

The rate of turnover of serotonin is an important biochemical method of assessing the activity of serotonin systems. However, such changes have to be treated with caution since large doses of tryptophan, which clearly increase brain 5HT turnover, produced no behavioural effects. (Grahame-Smith, 1971). Following monoamine oxidase inhibition (Grahame-Smith, 1974) a vivid behavioural syndrome was observed. Thus, the brain has all the necessary mechanisms to enable it to rapidly synthesise and catabolise serotonin. How is serotonin distributed in the brain?

I. 3 Anatomy of Serotonin Systems in the Forebrain of the Rat

The bulk of the information given in this thesis concerns the

actions of putative 5HT agonists and antagonists on the function of the cerebellum, hindbrain and forebrain. These are the only areas which will be covered by the present discussion, although the spinal cord does receive a heavy innervation by serotonergic processes arising in medullary nuclei. (Dahlstrom and Fuxe, 1965; Zivin et al, 1975).

I. 3.1. Serotonin-Containing Cell-Bodies: The majority of serotonergic fibers innervating the forebrain arise from cell-bodies within the dorsal and median raphe nuclei (Azmitia and Segal, 1978; Chan-Palay, 1977; Steinbusch, 1981; Takeuchi et al, 1982.) and an area just outside the median raphe nucleus and lying laterally to it. These clusters of cells correspond with the cell groups described by Dahlstrom and Fuxe, 1964 and as B7, B8 and B9 respectively. (Fig. 1).
As well as these locations, there is evidence of serotonin-containing cell-bodies in the periventricular and paraventricular nuclei of the hypothalamus, the suprachiasmatic nucleus and the medial habenular nucleus (Chan-Palay, 1977.) However, it has been suggested that the latter results are a technical artifact due to the uptake of ^{3}H-serotonin by dopaminergic processes in these areas. (Steinbusch, 1981)
I. 3.2. Cortical Areas: Previous investigators have found that the raphe nuclei project to all areas of the cortex (Azmitia and Segal, 1978) and that these areas can be shown to have a diffuse system of serotonergic nerve-endings. (Chan-Palay, 1977; Steinbusch, 1981). It is interesting to note that there is evidence of differential, although

overlapping fields of cortical innervation arising from the dorsal and median raphe nuclei (Azmitia and Segal, 1978). The dorsal raphe nucleus seems to project mainly to the temporal, parietal and pyriform cortices. The median raphe nucleus projects mainly to frontal, cingulate and entorhinal cortices.

I. 3.3 Diencephalic Areas: One means of differentiating the thalamic nuclei is by means of their projections. (Donaldson et al, 1975). Under this criterion the 'specific' thalamic nuclei are those which project to layer IV of the cortex. These nuclei make up the majority of the thalamic mass in the rat. (Donaldson, 1975; Jasper, 1961).

The second group are the non-specific thalamic nuclei which, although fewer in number, have diverse connections with cortex, other thalamic and subthalamic areas, and other sub-cortical areas (Herkenham, 1978; Schiebel and Schiebel, 1967). The pertinance of this nomenclature is that the serotonergic fibers arising from the midbrain raphe nuclei innervate most heavily the 'non-specific' thalamic nuclei such as the nucleus reuniens (Azmitia and Segal, 1978; Steinbusch, 1981) with the possible exception of the lateral thalamic nucleus (Chan-Palay, 1977; Steinbusch, 1981). Epithalamic areas such as the medial and lateral habenula receive substantial inputs from the dorsal and median raphe nuclei (Azmitia and Segal, 1978; Chan-Palay, 1977; Steinbusch, 1981). Most of the hypothalamic nuclei receive serotonergic fibers from raphe nuclei; in particular the suprachiasmatic nucleus, the arcuate nucleus, the

periventricular nucleus and paraventricular nucleus. (Chan-Palay, 1977; Saavedra et al, 1974B, Van de Kar and Lorens, 1979).

I. 3.4 Limbic Areas: The term 'limbic' is functional rather than anatomical. It forms an integrated system which is involved in a great number of autonomic and viceral functions and in the regulation of behaviour. (MacLean, 1954). For the purposes of this thesis I shall concentrate on the serotonergic inputs into the limbic cortex (pyriform, entorhinal and cingulate cortices) and its sub-cortical regions; the hippocampal formation, septal nuclei, amygdaloid nuclei, ventral tegmental area and the nucleus accumbens.

The limbic cortical areas all receive a serotonergic input arising in the midbrain raphe nuclei. (Azmitia and Segal, 1978; Beckstead, 1978; Kohler et al, 1980: Segal, 1977). The hippocampal formation is innervated mainly by the raphe nucleus but it also receives inputs from the dorsal raphe nucleus (Azmitia, 1981; Azmitia and Segal, 1978; Moore and Halarrs, 1975). One of the serotonergic pathways from the raphe nuclei innervates the dentate gyrus via the perforant pathway which runs from the entorhinal cortex to the molecular layer of dentate gyrus. (Azmitia and Segal, 1978; Hjort-Simonsen and Jeuve, 1972; Srebro et al, 1982). Another major pathway travels via the cingulate cortex. (Azmitia and Segal, 1978: Moore and Halaris, 1975). Fibers from this pathway innervate the septal nuclei and nucleus accumbens in passage. The amygdaloid nuclei receive innervation from serotonergic fibers particularly the medial nucleus and anterior amygdaloid area. (Azmitia and Segal 1978 Steinbusch, 1981).

I. 3.5 Extrapyramidal Areas: As with the limbic system, the term extrapyramidal cannot be wholly defined anatomically. However, it has become synonymous with the caudate nucleus, globus pallidus, substantia nigra and subthalamic nucleus. (Nauta and Domesick, 1979). All of these areas receive innervation from the midbrain raphe nuclei, particularly the dorsal raphe nucleus. (Azmitia, 1978; Bunney and Aghajamian, 1978; Miller et al, 1975; Steinbusch, 1981; Ternaux et al, 1977). An interesting finding based on both anatomical and biochemical evidence is that the distribution of the serotonergic innervation of the caudate nucleus is uneven. The ventromedial and caudal areas of this structure are much more heavily innervated than the dorsolateral or central portions. (Euvrard et al, 1977; Guyanet et al, 1977; Ternaux et al, 1977; Vizi et al, 1981). As will become evident from the results and discussion sections of this thesis, interesting comparisons can be made between the anatomical innervation of the forebrain by serotonergic neurons and the changes in local cerebral function following the pharmacological manipulation of the central serotonin mechanisms. However, how does the serotonin present in the neuronal endings interact with the cellular processes in close proximity to it, to produce a physiological response?

I. 4 Central Serotonin Receptors

Numerous attempts have been made to define the 5HT receptor populations in the rat brain, using ^{3}H-5HT (Bennet and Snyder, 1976; Fillion et al, 1978; Nelson et al, 1980 a.b.) ^{3}H-L.S.D. (Bennet and Snyder, 1976; Fillion et al, 1978;

Love and Freedman, 1978), ^{3}H-Spiroperidal (only in the cerebral cortex and hippocampus) (Creese and Snyder, 1978; Leysen et al, 1978) and ^{3}H-metergoline (Hamon et al, 1981). Known agonists and antagonists of serotonin are potent displacers of these tritiated compounds. (Bennet and Snyder, 1976; Creese and Snyder, 1978; Fillion et al, 1978; Lovell and Freedman, 1975; Nelson et al 1978; Nelson et al, 1980; Nelson et al, 1981; Peroutka and Snyder, 1979). The postsynaptic location of these binding sites was confirmed when selective lesioning of the serotonergic neurons failed to modify the kinetic parameters of the tritiated ligands (Bennet and Snyder, 1976; Fillion et al, 1978, Hamon et al, 1981).

There is little stimulation by 5HT of the synthesis of cyclic adenosine monophosphate (cAMP) from ATP in crude membrane preparations from the brain of adult rats but the activity of adenylate cyclase doubles in cell-free extracts from new-born rats (Enjalbert et al, 1978; Von Hungen et al, 1975). In young animals then, there is good evidence that this 5 HT - sensitive adenylate cyclase is coupled to specific post-synaptic serotonin receptors. (Bourgoin et al, 1977 a.b. Enjalbert et al, 1978 a.b. Nelson et al, 1980 a.b. Von Hungen et al, 1975).

Are there any differences to be found between binding sites bound by the ligands?

It was found that ^{3}H-spiroperidal bound strongly to specific sites in the frontal cortex and hippocampus. At these sites the binding of ^{3}H-spiroperidal was inhibited more by serotonin-active drugs than dopamine agonists and

antagonists. (Creese and Snyder, 1978; Lysen et al, 1978; Palacios et al, 1981; Pedigo et al, 1981; Seeman et al, 1980). It was also found that known serotonin agonists such as 5-HT, 5 Methoxy -N,N-dimethyltryptamine and quipazine were much more potent at displacing ^{3}H-5HT than ^{3}H-spiroperidol (in frontal cortex and hippocampus). However, serotonin antagonists such as methiothepin, metergoline, cyproheptadine, methysergide and mianserin inhibited ^{3}H-spiroperidol binding better than ^{3}H-5HT binding. (Nelson et al, 1979; Nelson et al, 1980 a.). These findings have been confirmed by using ^{3}H-metergoline to bind to the 'antagonist' site. (Hamon et al, 1981). It cannot be concluded however, that ^{3}H-5HT and ^{3}H-spiroperidol bind to two different 5HT receptors. The binding site may well exist in multiple interconverting forms. If this were the case then the regional distribution of ^{3}H-5HT and ^{3}H-spiroperidol sites should be the same. In the hippocampus, there is a close relationship between the number of specific binding sites for ^{3}H-5HT, ^{3}H-spiroperidol and ^{3}H-metergoline. (Creese and Snyder, 1978; Hamon et al, 1981; Nelson et al, 1978). The subcellular distribution of ^{3}H-5HT and ^{3}H-spiroperidol were also very closely linked in adult rats. (Hamon et al, 1980). Thus, this evidence is suggestive of a single receptor existing in different conformational attitudes.

However, there are differences in the pharmacological profiles. Metergoline blocks ^{3}H-5HT binding to a much greater extent than ^{3}H-spiroperidol (Nelson et al, 1978). Futhermore, quipazine is much less potent than 5HT at displacing ^{3}H-5HT,

but much more potent than 5HT at inhibiting ^{3}H-spiroperidol binding. (Hamon et al, 1980; Quik et al, 1978). Thus, the question is not totally resolved and further experiments will be required before the problem, of whether or not ^{3}H-5HT and ^{3}H-spiroperidol bind to the same or different sets of 5HT receptors, can be adequately resolved.

What similarities, if any, are there between ^{3}H-5HT and ^{3}H-spiroperidol binding sites, and the 5HT- sensitive adenylate cyclase found in young rats? Several serotonin agonists (5 methoxy-N,N-dimethyltryptamine, L.S.D., bufotenine) stimulate 5HT-sensitive adenylate cyclase. (Von Hungen et al, 1975). The 5HT-sensitive adenylate cyclase is located on post-synaptic membranes since midbrain raphe lesioning did not alter the enzymatic response. (Bourgoin et al, 1977).

The binding of 3H-5HT increased by more than 250% between the 1st week and the 3rd month after birth in the hippocampus and the striatum but the activity of the 5HT-sensitive adenylate cyclase did not change significantly. (Hamon et al, 1980; Nelson et al, 1980b). Furthermore, serotonin agonists with a piperazine group (quipazine, 1 (m-trifluoromethylphenyl)-piperazine and 6 chloro 2-[1-piperazinyl] pyrazine were potent displacers of ^{3}H-5HT but neither stimulated nor inhibited 5HT sensitive adenylate cyclase. (Fuller et al, 1978; Nelson et al, 1980a). Therefor it is difficult to conclude that the ^{3}H-5HT binding site is associated with the 5HT-sensitive adenylate cyclase.

In a similar fashion, quipazine which fails to stimulate

the 5HT- sensitive adenylate cyclase was a potent inhibitor of ^{3}H-spiroperidol binding (Hamon et al, 1980). Metergoline is almost equally as potent as spiroperidol in blocking 5HT-sensitive adenylate cyclase stimulation by 5HT, but is 100 times weaker than this compound in displacing bound ^{3}H-spiroperidol (Hamon et al, 1980). Thus, it would seem unlikely from this evidence that ^{3}H-5HT or ^{3}H-spiroperidol are identical to the 5HT receptor site which is coupled to adenylate cyclase in membranes of tissues from young rats.

However, the nucleotide, guanosine triphosphate (G.T.P.) reduces the specific binding of ^{3}H-5HT to cell membranes, in adult and 1 week-old rats. (Hamon et al, 1980; Mallat and Hamon, 1982). Conversely, G.T.P. does not alter ^{3}H-spiroperidol binding in the caudate nucleus, cerebral cortex and hippocampus. (Hamon et al, 1980). Furthermore, the ability of 5HT to displace ^{3}H-spiroperidol was markedly reduced by the presence of G.T.P. (Hamon et al, 1980). This data suggests that 5HT can act as an agonist at some receptors binding 3H-spiroperidol. The presence of G.T.P. also reduced the potency of 5 methoxy-N,N-dimethyltryptamine displacement of ^{3}H-spiroperidol, but had no effect on the actions of quipazine i.e. the agonists that displace less ^{3}H-spiroperidol are those which stimulate adenylate cyclase (5HT and 5 methoxy-N,N-dimethyltryptamine). (Hamon et al, 1980). However GTP potentiated the effects of 5HT on adenylate cyclase. This apparently opposite action of G.T.P. on 5HT binding and 5HT-sensitive adenylate cyclase activity might however, be explained by the recent findings of Mallat

and Hamon, 1982a.) They found that Kainic acid lesioning (a compound which destroys cell-bodies but not fibers of passage) led to a marked reduction in the effects of G.T.P. on the suriving ^{3}H-5HT binding. This suggests that the population of receptors binding ^{3}H-5HT is heterogeneous and that some of the ^{3}H-5HT binding sites may be coupled with adenylate cyclase. They also found that the pattern of ^{3}H-G.T.P. binding corresponded to the G.T.P. subunits regulating adenylate cyclase activity including those binding ^{3}H-5HT. (Mallat and Hamon, 1982b.) In conclusion, there is reasonable evidence of multiple serotonin receptors in the central nervous system. Whether these are different receptor populations or interconverting forms of the same set of serotonin receptors is unclear. In young rats, 5HT is capable of stimulating adenylate cyclase activity. There are differences in the way serotonin agonists which have piperazine and indoleamine moeties bind to ^{3}H-5HT and ^{3}H-spiroperidol binding sites (in the presence of G.T.P.) and to 5HT receptors coupled with adenylate cyclase.

The major problem however with this data is that much of it stems from in vitro work. Thus, there is no means of ascertaining the physiological role of these receptors.

I. 5 The Neurophysiology of the Serotonin-Containing Neurons

We have now seen that serotonin in the central nervous system is contained within neuronal processes which innervate anatomically discrete areas of the rat brain. There are also specific receptors for serotonin but what

physiological effect does the interaction of neuronally released serotonin have following combination with serotonin receptors?

In a study on the anaesthetised rat Aghajanian, 1972, showed that the firing rate of raphe neurons was between 0.5 and 2.5 spikes/sec. A similar range of neuronal firing is found in the conscious cat, 0.5 - 5 spikes/sec. (McGinty and Harper, 1976). This is very slow when compared to cells which form part of the reticular formation. These fire at a rate of 100 - 300 spikes/sec. (Szerb, 1967).

Serotonergic axons can be identified using the intracerebroventricular administration of ^{3}H-5HT (Aghajanian and Bloom, 1967; Aghajanian et al, 1966). The axons labelled by ^{3}H-5HT were found to be fine and unmyelinated in type. Using antidromic stimulation of the ventral tegmentum, it was found that their conduction velocity was of the order of 0.5 - 1.5 m/sec. which is a relatively slow conduction velocity (Aghajanian and Wang, 1977).

Iontophoretically applied 5HT had an inhibitory effect on cell-firing rate on most cells tested. (Bloom et al, 1972). When 5HT itself or the 5HT mimetic substances, lysergic acid diethylamide (L.S.D.) and 5 methoxy-N,N-dimethyltryptamine (5MeO) are injected iontophoretically into the dorsal raphe nucleus they cause an inhibition of firing rate. (Aghajanian et al, 1972; Bramwell and Gonye, 1976; de Montagny and Aghajanian, 1977). This would suggest the presence of a 5HT receptor which is an autoreceptor (i.e. a receptor mediating the response of a neuron to its own neurotransmitter).

In the forebrain, the effects of microiontophoretically

administered 5HT have been tested on the firing rate of cells in a number of anatomically diverse areas; the amygdala (Wang and Aghajanian, 1977), the ventrolateral geniculate (Haigler and Aghajanian, 1974), the hippocampus (Segal, 1975; Segal, 1976) the cerebral cortex (Sastry and Phillis, 1977) the corpus striatum (Olpe and Koella, 1977) substantia nigra (Dray et al, 1976) and cerebellum (Strahlendorf et al, 1979).

In the hindbrain, iontopheretic 5HT causes an increase in firing rate in the brain stem reticular formation (Aghajanian et al, 1974; Aghajanian and Wang, 1978; Bloom et al, 1973; Bradley and Wolstencroft, 1965) and in the motoneurones of the facial nerve (McCall and Aghajanian, 1979; Van der Maelen and Aghajanian, 1980). In these latter cases the effects of 5HT were blocked by peripheral serotonin antagonists (e.g. methysergide). However, this is not always the case with the inhibitory responses of cells to 5HT administration. (Aghajanian and Wang, 1978; Haigler and Aghajanian, 1974; Wang and Aghajanian, 1977).

These observations suggest that there are at least two types of physiological receptor for 5HT in the central nervous system. The first mediates a depression in cell-firing rate and is not always blocked effectively by classical 5HT antagonists. The second appears to mediate a 5HT-induced excitation in cell-firing and is antagonised by methysergide and cyproheptadine. This latter in effect may not be the result of a direct interaction of 5HT with its receptor but may be a facilitation of excitatory inputs (McCall and Aghajanian, 1979).

This electrophysiological data suggests that the main effect of 5HT in a diverse number of cerebral areas is to produce an inhibition of cell-firing. It is capable, however, of producing an excitatory response. This latter is most clearly antagonised by methysergide and cyproheptadine, the former less consistently.

There are, however, problems in interpreting the data obtained from these experiments particularly with respect to other in vivo approaches (e.g. behavioural studies.) Firstly, the micriontopheretic technique only allows a small number of cells to be tested. Secondly, it gives no indication of what the integrated functional response of the brain would be when a drug is administered by a peripheral route. Thirdly, it is a normal prerequisite of this experimental approach for the animal to be anaesthetised. This, as we shall see, may be of particular importance when studying cerebral function (See Grome and McCulloch, 1981 a.b.; Grome and McCulloch, 1983, and this thesis.)

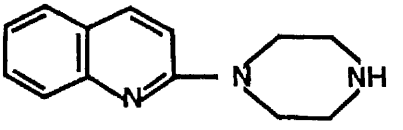
I. 6. The Value of the 2-Deoxyglucose Method

Since its introduction (Sokoloff et al, 1977), the ^{14}C 2 deoxyglucose quantitative autoradiographic method has become widely used to measure the effects of physiological, pharmacological and pathological manipulations on cerebral function as measured by local cerebral glucose utilisation. (For examples see Discussion and Synthesis section of this thesis).

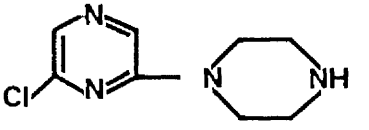
Its main advantages over other available technology are that it can be used in both conscious and anaesthetised animals; that it allows both the precise anatomical

localisation of changes in cerebral function and by comparing these effects, the integrated functional response of a group of anatomically connected structures. For these reasons it provides new information which could not be obtained in any other way at the present time. For the work about to be presented, the fully quantitative 2 deoxyglucose method, as devised by Sokoloff and his colleagues, 1977, was used throughout and so, in the following sections of this thesis, data will be provided on the actions of 5HT itself, putative 5HT-mimetic drugs (L.S.D., 5 methoxy-N,N-dimethyltryptamine, quipazine and chloropiperazinylpyrazine) and putative 5HT antagonists (methysergide, metergoline and cyproheptadine) on local cerebral glucose utilisation, a direct measurement of cerebral function. (Fig. 3)

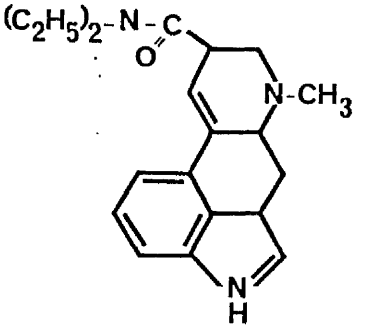
Figure 3 Structures of drugs used in this study.



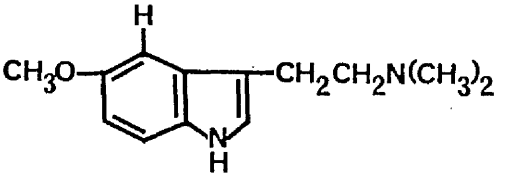
Quipazine



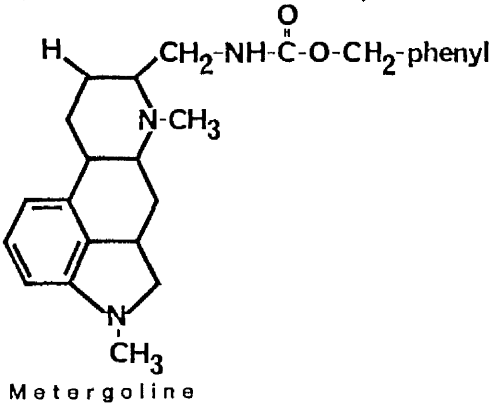
Chloropiperazinylpyrazine



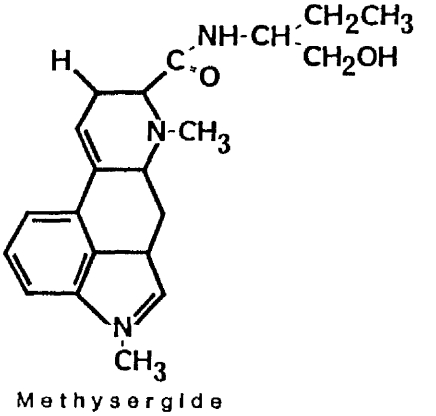
Lyergic Acid Diethylamide



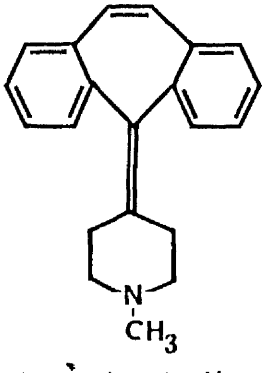
5 methoxy-N,N-dimethyltryptamine



Metergoline



Methysergide



Cyproheptadine

II. MATERIALS AND METHODS

2. 1. Background to the ^{14}C-2 deoxyglucose method.

There are major problems when faced with the task of measuring the functional activity of the central nervous system. The subunits which integrate to form the functional networks of the brain are anatomically discrete and subserve physiologically diverse roles. Furthermore, the central nervous system is constantly reacting to the input it receives. Therefore, any method purporting to define brain activity should ideally be able to make dynamic measurements of both local and integrated function. In a similar manner to heart and skeletal muscle, it has been found that there is a close relationship between the activity of the brain tissue and the quantity of energy substrates which it consumes. (De Weer, 1975; Greengard and Ritchie, 1971; Ritchie, 1967).

Since under non-pathological conditions the central nervous system meets all its energy demands by the oxidative catabolism of glucose, (see Sokoloff, 1960), it might be supposed that the measurement of the rate of glucose or oxygen use would be an effective way of calculating functional activity. The direct measurement of these parameters is unfortunately fraught with difficulty. The level of oxygen content and its turnover can be measured by oxygen electrodes (Greengard and Ritchie, 1971; Ritchie, 1967). However this technique has similar

problems to that of the electrophysiological measurement of cell-firing rate. (see previous section) The measurement of turnover of isotopes of oxygen is also difficult due to their short half-lifes, and they are rapidly cleared from the cerebral tissue.

This latter problem also applies to the use of ^{14}C-glucose to measure cerebral functional activity. Sacks, 1957 showed that significant concentrations of CO_2 were lost within two minutes of commencing the experiment. This leads to an underestimate of glucose utilisation. (Hawkins et al, 1974)

These problems have been largely overcome by the use of ^{14}C-2 deoxyglucose; an analogue of glucose.

2. 2 2 Deoxyglucose

The molecule 2-deoxyglucose differs from glucose only in as much as the hydroxyl group on the second carbon has been replaced by hydrogen. This single change produces a number of interesting metabolic features. Firstly, it is transported between the blood and brain by the same hexose transport mechanism as glucose. (Bidder, 1968; Horton et al, 1973). Secondly, 2 deoxyglucose and glucose are substrates for the enzyme hexokinase which phosphorylates them to 2 deoxyglucose- 6-phosphate and glucose-6-phosphate respectively (Sols and Crane, 1954). Thirdly, and most important of all, 2 deoxyglucose 6 phosphate, unlike glucose 6 phosphate is not a substrate for phosphohexose-isomerase. Nor does 2 deoxyglucose 6-phosphate seem to be a substrate for any other metabolic pathway. (Sols and

Crane, 1954; Bachelard et al, 1971; Horton et al, 1973). Deoxyglucose 6 phosphate can be broken down to deoxyglucose by glucose-6-phosphatase. However, the concentration of this enzyme is reported to be very low in mammalian brain. (Ruggi et al, 1960; Prasannan and Subrahmayan, 1968). Although this poses a theoretical problem, in practice it can be minimised. Thus, the 2 deoxyglucose-6-phosphate formed is trapped intracellularly and the concentration of this substance increases at a rate which is directly related to the phosphorylation of glucose which in turn is controlled directly by the rate of glucose utilisation.

2. 3 Theoretical Model

The model is based on the unique biochemical 'personality' of 2 deoxyglucose as described in the previous section. The theoretical model is diagrammatically presented in fig. 4. It can be seen that ^{14}C 2 deoxyglucose and glucose enter the brain from the plasma via a common carrier in the blood-brain barrier. Once in the brain, these two compounds enter a common precursor pool in which they compete for either the carrier, to be transported back to plasma, or the enzyme to be phosphorylated to their respective hexose 6 phosphates. The hexokinase reaction is far from equilibrium and since ^{14}C deoxyglucose 6 phosphate is unable to take part in any known metabolic process, it is trapped within the cell.

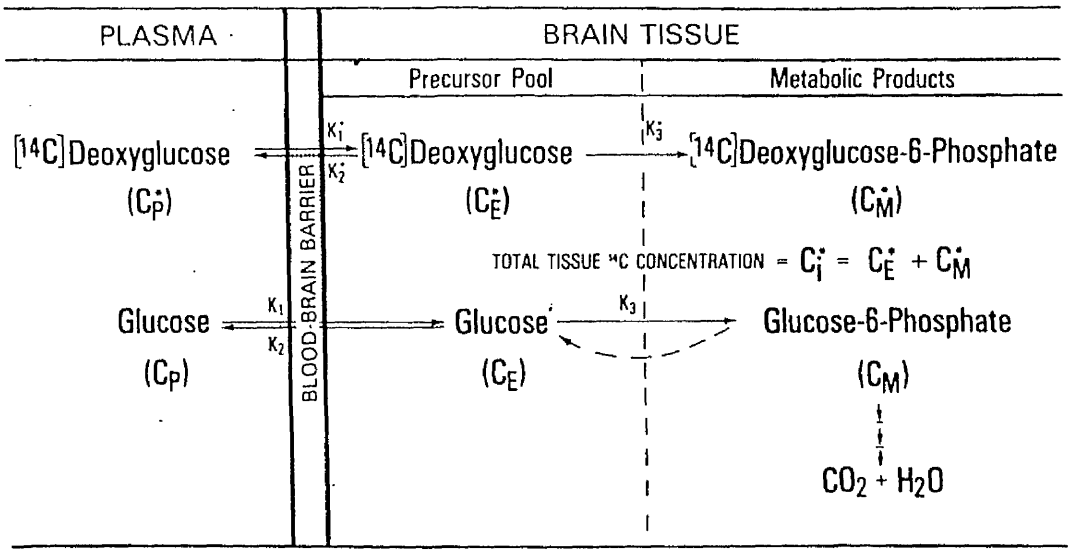


Figure 4 Representation of the theoretical model for the 2 deoxyglucose (2DG) technique.

Where: C_i^* - total ^{14}C concentration in tissue.

C_E^* and C_E - precursor pool concentrations of 2DG and glucose.

C_M^* - concentration of 2DG-6-P in tissue.

K_1^*, K_2^* and K_3^* - rate constants for 2DG transport from plasma to brain, brain to plasma and its use by hexokinase respectively.

K_1, K_2 and K_3 - respective rate constants for glucose (for further explanation see Sokoloff, 1977.)

Glucose-6-phosphate does not accumulate, and is eventually metabolised to carbon dioxide and water.

2. 4 Assumptions and Conditions of the Model

1. ^{14}C deoxyglucose and ^{14}C deoxyglucose 6 phosphate are present in tracer amounts.
2. Free ^{14}C deoxyglucose and glucose are in a single compartment.
3. Carbohydrate metabolism in the brain is in steady state.
4. The capillary concentrations of ^{14}C deoxyglucose and glucose are approximately equal to their arterial plasma concentrations.

2. 5. Explanation of Operational Equation

The operational equation is illustrated in fig. 5. The equation may look complex but in effect it is simply a mathematical statement of the requirements of the method. In other words, in order to quantify the amount of glucose consumed by an area of cerebral tissue, we measure the amount of labelled products formed during the experimental period. The quantity of labelled product still in the form of ^{14}C deoxyglucose is subtracted from this and the remainder is divided by a lumped constant (which is a value expressing the differences in kinetics and distribution of deoxyglucose and glucose) multiplied by the integral of the plasma history for ^{14}C deoxyglucose and glucose during the experimental period which is corrected for the lag time of equilibration.

$$\text{Rate of Reaction} = \frac{\text{Labeled Product Formed in Interval of Time, 0 to T}}{\left[\text{Isotope Effect Correction Factor}\right]\left[\text{Integrated Specific Activity of Precursor}\right]}$$

Operational Equation of [^{14}C]Deoxyglucose Method:

$$R_i = \frac{\overbrace{\underbrace{C_i^*(T)}_{\text{Total } ^{14}C \text{ in Tissue at Time, T}} - \underbrace{k_1^* e^{-(k_2^*+k_3^*)T}\int_0^T C_p^* e^{(k_2^*+k_3^*)t}\,dt}_{^{14}C \text{ in Precursor Remaining in Tissue at Time, T}}}^{\text{Labeled Product Formed in Interval of Time, 0 to T}}}{\underbrace{\left[\frac{\lambda \cdot V_m^* \cdot K_m}{\Phi \cdot V_m \cdot K_m^*}\right]}_{\text{Isotope Effect Correction Factor}}\underbrace{\left[\int_0^T \left(\frac{C_p^*}{C_p}\right)dt - e^{-(k_2^*+k_3^*)T}\int_0^T \left(\frac{C_p^*}{C_p}\right)e^{(k_2^*+k_3^*)t}\,dt\right]}_{\text{Integrated Plasma Specific Activity}\;\;\text{Correction for Lag in Tissue Equilibration with Plasma}}}$$

Integrated Precursor Specific Activity in Tissue

Figure 5 Operational equation of the ^{14}C - 2DG method.

Where: C_i^* - total ^{14}C concentration in tissue.

T - time at termination of experiment.

Cp^* and Cp - plasma 2DG and glucose concentrations.

K_1^*, K_2^*, K_3^* - rate constants for 2DG transport from plasma to brain, brain to plasma and its use by hexokinase respectively.

K_1, K_2, K_3 - respective rate constants for glucose.

λ - the ratio of the distribution space of 2DG in the tissue to that of glucose.

Φ - fraction of glucose that, once phosphorylated continues down glycolytic pathway.

K_m^* and V_m^* - Michaelis-Menton Kinetic constants for 2DG.

K_m and V_m - Kinetic constants for glucose.

These last four sets of constants make up the 'lumped' constant. (Modified from Sokoloff et al, 1977).

2. 6. Values of Rate Constants and the Lumped Constant.

The rate constants and lumped constants relating to the operational equation of the method (Fig 5) were obtained from Sokoloff et al, 1977.

For the albino rat, they are as follows:-

K 1* - 0.189 (min^{-1}).

K 2* - 0.245 (min^{-1}).

K 3* - 0.052 (min^{-1}).

'Lumped Constant' - 0.481.

Full details pertaining to the use of these constants, with particular reference to the errors involved have been previously published. (Sokoloff et al, 1977; Sokoloff, 1979; Sokoloff, 1982).

2. 7. Animal Preparation

Male Sprague-Dawley rats (300g-450g), which were allowed free access to food and water until the day of the experiment, were used throughout these studies.

Two preparations were used: -

2. 7. 1 Anaesthetised rats for the study of the intracarotid administration of drugs.

For these studies, rats were initially anaesthetised with 5% halothane in a mixture of nitrous oxide and oxygen (70%:30%). The rat had a cannulainserted into the trachea and was mechanically ventilated with a positive pressure, pump (Starling). The halothane concentration was then reduced to 0.5% and, under this anaesthetic regime, polyethylene catheters were placed into the femoral artery and vein of each hindlimb. The skin on the right side of the neck was retracted in order to expose the

carotid artery. A cannula was placed retrogradely into the external carotid artery such that the tip lay at the bifurcation of the internal and external carotid arteries. Temperature was maintained by a heating bed which was regulated by a rectal thermometer to keep the core temperature in the range 36.8°C to 37.2°C. The rats were then left for a period of not less than 45 minutes to allow the animal to stabilise.

2.7.2. Conscious rats for the study of the intravenous administration of drugs.

Anaesthesia was induced as above. Under light halothane anaesthesia (1% halothane in 70%: 30% oxygen), lasting less than 30 minutes, polyethylene catheters were introduced into the femoral artery and vein of each hindlimb. The incision sites were then liberally covered with a cream containing a local anaesthetic (Anethaine) and closed with sutures. These areas were protected by pads impregnated with the same anaesthetic cream, and an elasticated bandage, before the application of a loose-fitting plaster cast around the lower abdomen to restrain the animal. Anaesthesia was discontinued. The rats were allowed to recover for at least two hours before further manipulations were performed. During this time, core body temperature was measured by a rectal thermometer and maintained using heat lamps. Prior to commencing the experimental procedure, appropriate responses were elicited to slight auditory and sensory stimuli.

All rats, whether anaesthetised or conscious, had

measurements made of blood pressure and heart rate, (Gould) the partial pressures of oxygen and carbon dioxide and the pH of arterial blood (Corning) and the plasma glucose concentration (Beckman).

2.8. The measurement of local cerebral glucose utilisation. The measurement was initiated by the delivery of a bolus intravenous injection of U-^{14}C - 2 deoxyglucose (50 uCi dissolved in 0.7 ml of saline.) During the subsequent 45 minutes, 14 timed samples of arterial blood (approximately 70 ul in volume) were obtained according to a pre-determined time schedule. These samples were immediately centrifuged. Twenty microlitres of plasma was withdrawn for the determination of ^{14}C concentrations, and a further 10 ul was used to measure the glucose concentration by means of a semi-automated glucose oxidase assay (Beckman U.S.A.) Forty-five minutes after the administration of the isotope, the rat was killed by decapitation. Following this, the brain was carefully removed in under 2.5 minutes and frozen in isopentane, cooled by a dry ice/acetone jacket to -45^{o}C. The frozen brain was embedded in Tissue-Tek II (R.A. Lamb, London, U.K.) and coronal sections (20 microns thick) prepared in a cryostat maintained at -22^{o}C. The entire length of the brain from the medulla oblongata to the prefrontal cortex was sampled, three sections being taken for every 260 microns of brain. The sections were mounted on coverslips and rapidly dried on a hotplate. These coverslips were fixed to a pre-cut piece of cardboard which enabled them to maintain

maintain good contact when they were laid, along with pre-calibrated plastic ^{14}C standards (44 - 1475 nCi/g, against x-ray film (Kodak SB-5) in a light-tight x-ray cassette. After seven days the x-ray plates were developed by normal photographic procedures. Sections immediate adjacent to those used for auto-radiography were fixed in formalin and stained with cresyl violet for the identification of anatomical regions and nuclei in the autoradiographs with reference, of necessary, to the atlases of Konig and Klippel (1967) and Zeman and Innes (1963). Using a computerised densitometer system (Gamma Scientific, U.S.A.), the mean of 12 optical density measurements per brain region was calculated. This figure, when compared to the optical densities produced by the ^{14}C standards, (100u) gave the value of the tissue ^{14}C concentrations. By using the operational equation devised by Sokoloff et al, 1977, the concentration of ^{14}C in each brain region, the history of ^{14}C and glucose levels in the arterial plasma during the experimental period and the appropriate rate constants for the rat, the rate of glucose utilisation in each brain region was calculated.

2. 9 Experimental Protocols for Drug Administration

2. 9.1 The effects of serotonin following clorgyline on local cerebral glucose utilisation.

The experiment commenced when 50 µg/kg/min of clorgyline at a rate of 100 µl/min, or the same volume of saline, was infused into the carotid catheter. After 15 minutes this

was replaced by either an infusion of serotonin at a concentration of 50 ng/kg/min and a rate of 100 ul/min, or the same volume of saline, and was continued for the duration of the measurement of local cerebral glucose utilisation, in these anaesthetised rats.

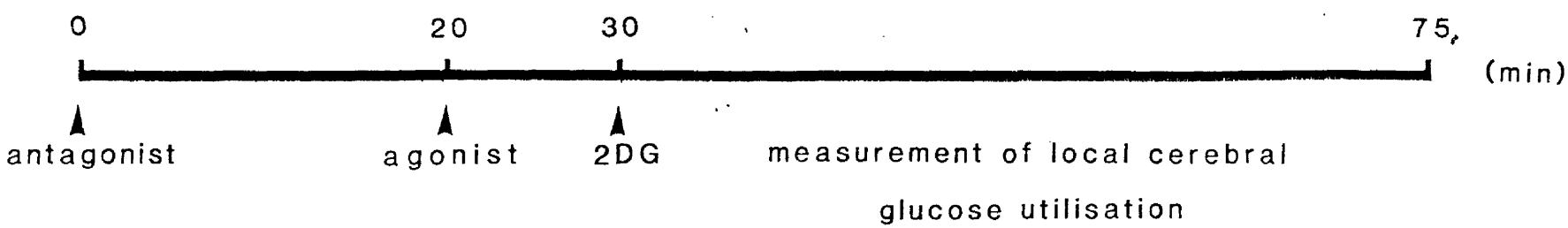
2.9.2. The effects of putative serotonin agonists on local cerebral glucose utilisation.

Quipazine maleate (2-(1-piperazinyl) quinoline maleate: courtesy of Miles Laboratories) was administered in doses of 1, 3 or 10 mg/kg, intravenously. Conscious rats were intravenously injected with lysergic acid diethylamide (L.S.D.: courtesy of Sandoz Laboratories) in doses of 5, 15, 50 or 150 ug/kg. 5-Methoxy N,N dimethyltryptamine (5MeO Sigma) was administered in doses of 0.2, 0.75 or 2 mg/kg, intravenously. 6-Chloro-2 1-piperazinyl - pyrazine (C.P.P. courtesy of Merck, Sharpe and Dohme) was administered intravenously in doses of 0.8, 2.5 or 8 mg/kg. The drugs were all administered as a bolus in 1ml/kg of saline 10 minutes before the infusion of ^{14}C 2 - deoxy-glucose. (fig. 6) to the conscious rat preparation.

2.9.3 The effects of putative serotonin antagonists on local cerebral glucose utilisation.

Methysergide bimaleate (Courtesy of Sandoz) was given in doses of 5 and 15 mg/kg intravenously. Metergoline (Farmitalia) was given intravenously in doses of 0.3 and 3 mg/kg. cyproheptadine (Merck, Sharpe and Dohme) was administered in doses of 0.1 and 1.0 mg/kg intravenously. All these drugs were administered in 1 m /kg of physiological saline, 30 minutes before the administration of ^{14}C-2-deoxyglucose. (fig. 6)

Figure 6 Experimental Protocol



2.9.4. The measurement of cardiovascular parameters.

The measurements of heart rate and mean arterial pressure quoted in this thesis were made at the end of the two hour recovery period, immediately prior to drug administration (controls), and immediately before the bolus administration of ^{14}C - 2 deoxyglucose.

2.10. Statistical Analysis

Data are presented as mean $\pm$ standard error of the mean, unless otherwise specified. Statistical differences in measured variables were analysed using the t-test by paired comparison when comparing regions bilaterally in the same animals, and by analysis of variance with the Scheffe test for multiple group analysis. The numbers of rats in each group are given under the appropriate headings in each table.

III. THE ACTIONS OF SEROTONIN ON LOCAL CEREBRAL GLUCOSE UTILISATION FOLLOWING MONOAMINE OXIDASE INHIBITION.

3.1. General Results.

The administration of serotonin into the internal carotid artery, (50 ng/kg/min) had no significant effect on local cerebral glucose utilisation as compared to saline controls. Similarly, clorgyline, the monoamine oxidase A inhibitor, (Johnston, 1968) produced only minimal effects on glucose use by itself. (Table 1)

Following a combination of serotonin and clorgyline, the majority of structures measured showed little change in the rate of glucose use. Only six out of the 34 brain areas measured, displayed significant changes following clorgyline and serotonin, with decreases in glucose utilisation of between 16% and 33%. All but one of these regions were cortical, the exception being the caudate nucleus. All of these areas would normally be supplied by blood from the internal carotid artery. However, not all such areas showed changes in the rate at which they used glucose, e.g. the hippocampus and cingulate cortex (Table 1). None of the brain regions perfused by blood from the vertebro-basilar arteries showed significant changes in local cerebral glucose utilisation. None of these manipulations affected the blood pressure or heart rate of these animals. (Table 2)

3.2. Comments on Results

The results show that the intracarotid administration of

serotonin is incapable, by itself, of affecting local cerebral glucose utilisation. This is obviously due not only to the presence of a physical blood-brain barrier, but is also due to the presence, in the endothelia of cerebral vessels, of the major catabolic enzyme for serotonin, monoamine oxidase. (Hardebo and Owman, 1980). When this enzyme is inhibited by the specific monoamine oxidase A inhibitor, clorgyline (Johnston, 1968) given into the carotid at a cose of 50 ng/kg/min, serotonin is able to cause a number of discrete decreases in local cerebral glucose utilisation. However, there are a number of disadvantages with the protocol. Firstly, the effects of serotonin following clorgyline could be seen only within areas of the brain supplied by blood from the carotid artery. This did not allow investigation of such important serotoninergic areas such as the raphe nuclei. Secondly, the effects were small and did not occur in all of the areas making up carotid territory. Thirdly, and perhaps of most importance, the rats are anaesthetised. As can be seen from Table 3, halothane anaesthesia, administered as described previously for this preparation, significantly decreased glucose utilisation in a diverse range of anatomically defined areas of the rat forebrain as compared to conscious controls. From this data it is clear that serotonin is producing its effects against a background of depressed cerebral function.

It was necessary to find a new animal model. One of the major advantages of the ^{14}C-2 deoxyglucose quantitative

autoradiographic technique is that it can be used with fully conscious rats. Pharmacological manipulation of the central serotonin system was therefore continued using the intravenous administration of putative serotonin agonists and antagonists to conscious rats.

TABLE 1 LOCAL CEREBRAL GLUCOSE UTILIZATION (μmols/100g/min)

Structures		Saline	Clorgyline	Serotonin	Clorgyline & Serotonin
Cortical Areas:					
Visual	Ipsi.	78 ± 3	80 ± 3	79 ± 3	65 ± 1 * ø
	Contra.	74 ± 4	78 ± 4	81 ± 3	83 ± 3
Auditory	Ipsi.	67 ± 3	68 ± 3	72 ± 1	52 ± 1 * ø
	Contra.	68 ± 2	66 ± 2	74 ± 1	74 ± 3
Parietal	Ipsi.	67 ± 2	68 ± 5	66 ± 2	46 ± 2 * ø
	Contra.	69 ± 4	67 ± 1	68 ± 2	67 ± 2
Sensory-Motor	Ipsi.	54 ± 2	59 ± 3	54 ± 2	47 ± 3 * ø
	Contra.	54 ± 1	55 ± 2	54 ± 2	59 ± 2
Frontal	Ipsi.	53 ± 4	47 ± 4	53 ± 2	40 ± 3 * ø
	Contra.	49 ± 2	48 ± 2	56 ± 4	60 ± 3 *
Posterior Cingulate	Ipsi.	73 ± 5	79 ± 3	82 ± 7	77 ± 6
	Contra.	75 ± 5	79 ± 3	82 ± 7	78 ± 6
Anterior Cingulate	Ipsi.	92 ± 6	80 ± 2	84 ± 6	77 ± 6
	Contra.	88 ± 5	80 ± 3	87 ± 6	78 ± 6
Diencephalic Areas:					
Thalamus (Lateral)	Ipsi.	54 ± 5	55 ± 2	53 ± 2	55 ± 5
	Contra.	55 ± 3	54 ± 2	52 ± 4	56 ± 4
Thalamus (Mediodorsal)	Ipsi.	76 ± 5	75 ± 1	74 ± 6	68 ± 4
	Contra.	77 ± 7	76 ± 2	72 ± 6	70 ± 4
Habenula	Ipsi.	60 ± 1	59 ± 2	64 ± 5	59 ± 4
	Contra.	59 ± 2	62 ± 3	63 ± 4	60 ± 4

TABLE 1 (CONTD.)

		Saline	Clorgyline	Serotonin	Clorgyline & Serotonin
Medial Genculate	Ipsi.	75 ± 4	78 ± 3	71 ± 4	77 ± 3
	Contra.	76 ± 4	77 ± 2	71 ± 6	77 ± 2
Lateral Geniculate	Ipsi.	85 ± 3	83 ± 2	83 ± 6	83 ± 4
	Contra.	82 ± 7	83 ± 2	89 ± 5	88 ± 4
Hypo - thalamus	Ipsi.	39 ± 1	40 ± 2	40 ± 3	41 ± 3
	Contra.	38 ± 3	37 ± 2	39 ± 4	41 ± 4
Mesencephalic Areas					
Red Nucleus	Ipsi.	48 ± 2	47 ± 4	46 ± 3	48 ± 4
	Contra.	49 ± 4	47 ± 3	50 ± 5	49 ± 5
Substantia Nigra	Ipsi.	65 ± 4	64 ± 2	62 ± 6	61 ± 5
	Contra.	62 ± 4	61 ± 4	62 ± 6	58 ± 3
Laterial Lemniscus	Ipsi.	71 ± 5	74 ± 6	71 ± 2	74 ± 2
	Contra.	73 ± 6	73 ± 6	71 ± 4	73 ± 4
Superior Colliculus	Ipsi.	60 ± 1	61 ± 3	61 ± 6	59 ± 2
	Contra.	61 ± 2	59 ± 1	62 ± 6	62 ± 2
Telencephalic Areas					
Hippo- campus	Ipsi.	74 ± 3	71 ± 3	77 ± 6	74 ± 4
	Contra.	74 ± 4	67 ± 5	76 ± 7	73 ± 4
Dentate Gyrus	Ipsi.	61 ± 2	56 ± 3	58 ± 3	56 ± 5
	Contra.	59 ± 2	57 ± 2	57 ± 2	55 ± 4
Septal Nucleus	Ipsi.	48 ± 2	48 ± 3	51 ± 3	48 ± 3
	Contra.	47 ± 2	48 ± 3	50 ± 3	50 ± 1

TABLE 1 (CONTD.)

		Saline	Clorgyline	Serotonin	Clorgyline & Serotonin
Caudate Nucleus	Ipsi.	75 ± 3	69 ± 3	69 ± 5	63 ± 2 * ø
	Contra.	70 ± 2	69 ± 1	72 ± 3	75 ± 2
Nucleus Accumbens	Ipsi.	66 ± 3	64 ± 4	61 ± 4	67 ± 3
	Contra.	66 ± 2	61 ± 5	62 ± 5	65 ± 5
Globus Pallidus	Ipsi.	40 ± 2	43 ± 4	40 ± 3	37 ± 4
	Contra.	41 ± 2	43 ± 3	42 ± 4	40 ± 4
Hindbrain Areas					
Vestibular Nucleus	Ipsi.	69 ± 3	68 ± 4	66 ± 5	64 ± 4
	Contra.	70 ± 2	69 ± 4	67 ± 5	66 ± 6
Cochlear Nucleus	Ipsi.	103 ± 7	97 ± 6	109 ±10	90 ± 7
	Contra.	115 ± 8	100 ± 8	97 ± 9	97 ±10
Superior Olive	Ipsi.	73 ± 8	77 ± 3	76 ± 2	72 ± 5
	Contra.	75 ± 6	74 ± 3	71 ± 4	74 ± 3
Inferior Olive	Ipsi.	46 ± 3	45 ± 2	47 ± 4	45 ± 2
	Contra.	48 ± 4	44 ± 3	43 ± 4	45 ± 3
Median Raphe	Mid.	60 ± 4	55 ± 3	63 ± 4	57 ± 3
Dorsal Raphe	Mid.	70 ± 2	67 ± 2	68 ± 2	62 ± 3
Cerebellum Hemispheres	Ipsi.	33 ± 3	36 ± 1	38 ± 4	36 ± 2
	Contra.	32 ± 3	35 ± 3	37 ± 3	34 ± 2
Cerebellum Vermis	Mid.	38 ± 5	41 ± 3	39 ± 3	41 ± 3
		40 ± 4	44 ± 5	30 ± 4	40 ± 2

TABLE 1 (CONTD.)

		Saline	Clorgyline	Serotonin	Clorgyline & Serotonin
Fiber Tracts					
Internal Capsule	Ipsi.	25 ± 2	26 ± 2	26 ± 2	26 ± 2
	Contra.	24 ± 2	25 ± 1	28 ± 2	25 ± 2
Corpus Callosum	Ipsi.	30 ± 2	29 ± 1	28 ± 2	28 ± 2
	Contra.	29 ± 2	31 ± 1	28 ± 2	28 ± 3
Genu of the Corpus. Callosum	Mid.	26 ± 1	25 ± 2	24 ± 2	25 ± 2
	n	5	4	4	6

Ipsi = ipsilateral to infusion. Contra. = contralateral to infusion.

Mid = midline structure.

* significant with respect to the contralateral side ($p<0.05$)

ø significant with respect to the saline control rats ($p<0.05$)

TABLE 2

CARDIOVASCULAR AND RESPIRATORY STATUS

	Saline	Serotonin	Clorgyline	Serotonin + Clorgyline
pCO_2 (mmHg)	40 ± 2	40 ± 1	39 ± 1	39 ± 1
pO_2 (mmhg)	116 ± 5	119 ± 7	117 ± 7	120 ± 6.
pH	7.43 ± 0.02	7.42 ± 0.01	7.43 ± 0.02	7.44 ± 0.02
Mean Arterial Blood Pressure	115 ± 7	112 ± 4	113 ± 3	119 ± 6
n	5	4	4	6

TABLE 7

LOCAL CEREBRAL GLUCOSE UTILISATION

Structures	Conscious Group	Halothane Anaesthetised Group	
Visual Cortex	102 ± 2	73 ± 3	***
Auditory Cortex	139 ± 5	80 ± 2	***
Parietal Cortex	95 ± 2	57 ± 2	***
Sensory-Motor Cortex	92 ± 4	56 ± 2	***
Entorphinal Cortex	71 ± 2	36 ± 4	***
Pyriform Cortex	104 ± 1	81 ± 6	**
Frontal Cortex	93 ± 6	49 ± 3	***
Anterior Cingulate Cortex	94 ± 2	90 ± 5	
Posterior Cingulate Cortex	93 ± 4	68 ± 4	**
Prefrontal Cortex	119 ± 3	63 ± 3	***
Thalamus (Mediodorsal)	91 ± 4	72 ± 1	**
Thalamus (Ventrolateral)	80 ± 4	59 ± 4	**
Thalamus (Anterior-ventral)	104 ± 4	101 ± 8	
Thalamus (Anterior-medial)	108 ± 4	86 ± 2	**
Thalamus (Lateral)	92 ± 2	85 ± 6	
Subthalamic Nucleus	77 ± 4	59 ± 5	*
Habenula (Lateral)	98 ± 4	58 ± 1	***
Habenula (Medial)	70 ± 2	63 ± 5	
Geniculate (Medial)	115 ± 3	73 ± 1	***
Geniculate (Lateral)	83 ± 4	66 ± 2	*
Hypothalamus	53 ± 2	38 ± 3	**
Hippocampus	82 ± 3	79 ± 2	
Dentate Gyrus	65 ± 2	64 ± 2	
Septal N. (Lateral)	62 ± 3	48 ± 3	*
Septal N. (Medial)	57 ± 3	36 ± 2	***
Amygdala	48 ± 2	33 ± 1	**
Anterior Amygdaloid Area	71 ± 3	41 ± 3	***
Nucleus Accumbens	73 ± 4	66 ± 4	
Ventral Tegmental Area	60 ± 3	38 ± 4	**
Pons	59 ± 3	46 ± 2	*
Median Raphe	93 ± 5	62 ± 6	**
Caudate Nucleus	88 ± 4	73 ± 5	
Globus Pallidus	52 ± 2	44 ± 6	
Substantia Nigra (pars compacta)	81 ± 2	70 ± 5	
Substantia Nigra (pars reticulata)	60 ± 2	39 ± 4	**
Red Nucleus	77 ± 4	57 ± 3	*
Inferior Olive	70 ± 2	46 ± 3	***
Vestibular Nucleus	102 ± 2	67 ± 4	***
Cerebellar Nuclei	90 ± 6	60 ± 4	**
Cerebellar Hemisphere	49 ± 3	34 ± 3	*
Cerebellum Vermis	66 ± 4	38 ± 5	**
Dorsal Raphe	84 ± 2	57 ± 7	**
Superior Colliculus (superficial layer)	83 ± 3	69 ± 5	*
Superior Colliculus (deep layer)	81 ± 3	61 ± 4	**

Structures	Conscious Group	Halothane Anaesthetised Group
Cochlear Nucleus	136 ± 7	86 ± 5 **
Inferior Colliculus	177 ± 4	69 ± 9 ***
Superior Olive	143 ±10	73 ± 8 **
Lateral Lemniscus	110 ± 3	44 ± 6 ***
Cerebellar White	33 ± 4	22 ± 1
Corpus Callosum	33 ± 4	29 ± 2
Genu of the Corpus Callosum	28 ± 2	22 ± 1 *
Internal Capsule	34 ± 2	22 ± 1 **
n	6	5

Data are given as mean ± standard error of the mean.

* : $p<0.05$ ** : $p<0.01$ *** : $p<0.001$

Statistical analysis by t-test by unpaired comparison.

IV. THE EFFECTS OF INDOLEAMINE-CONTAINING SEROTONIN AGONISTS ON LOCAL CEREBRAL GLUCOSE UTILISATION.

4. 1. Behavioural effects

In these experiments behaviour was observed but not quantified. Despite the fact that the hindlimbs were not allowed free movement, the upper body was able to respond to drug treatment as previously described. (Gessner and Page, 1962; Grahame-Smith, 1971). Saline control animals showed little obvious sustained behaviour other than licking and general cleaning. With low doses of both lysergic acid diethylamide (L.S.D.) and 5-methoxy N,N-dimethyltryptamine (5MeO) there was a short, but vivid increase in the general activity of the rat, particularly sniffing. Increasing the dose produced a more sustained and complex behavioural pattern. This included side-to-side head movements and forepaw padding which, with time, gave way to forepaw rigidity and splayed toes.

4. 2. Cardiovascular effects

L.S.D. affected blood pressure only at the highest dose (150 ug/kg), producing a 7 $\pm$ 3% increase (mean $\pm$ SEM; $p < 0.05$). The heart rate was significantly reduced by L.S.D. at doses of 15, 50 and 150 ug/kg; with a maximal change of 16 $\pm$ 4% ($p < 0.05$) ocurring at 50 ug/kg. (table 4) 5MeO produced similar changes in blood pressure and heart rate at doses of 750 and 2,000 ug/kg, blood pressure being increased by 23 $\pm$ 3% ($p < 0.05$) at a dose of 2,000 ug/kg and heart rate being reduced by 11 $\pm$ 4% ($p < 0.05$) by the

same dose (Table 6).

4.3. Local Cerebral Glucose Utilisation.

4.3.1. Cortical Areas

As can be seen from the results (Tables 5 and 7), LSD and 5MeO produce parallel decreases in glucose utilisation in cortical areas. The most sensitive areas appear to be 'limbic cortex' (Robertson and Katz, 1981). In particular, pyriform cortex, posterior cingulate cortex and prefrontal cortex are markedly affected, even at low doses of these compounds. (see Fig. 7) By comparison, the glucose use of cortical areas subserving sensory function, such as parietal and sensory-motor cortex, are significantly affected only at the highest dose levels of LSD and 5MeO. (Tables 5 and 7)

4.3.2. Diencerhalic Areas

Both of these putative serotonin agonists produced significant decreases in the lateral nucleus of the thalamus and the medial and ventral portions of the anterior thalamus, (Fig. 8) while having lesser effects on the glucose use of the mediodorsal and ventrolateral nuclei, which were affected only at the highest doses. In the hypothalamus, the medial nuclei and periventricular nucleus show little change in the rate of glucose usage. However, LSD produces highly significant decreases in glucose phosphorylation in the median forebrain bundle; 5MeO also induces decreased rates of glucose use, but to a lesser extent. The habenular complex of the

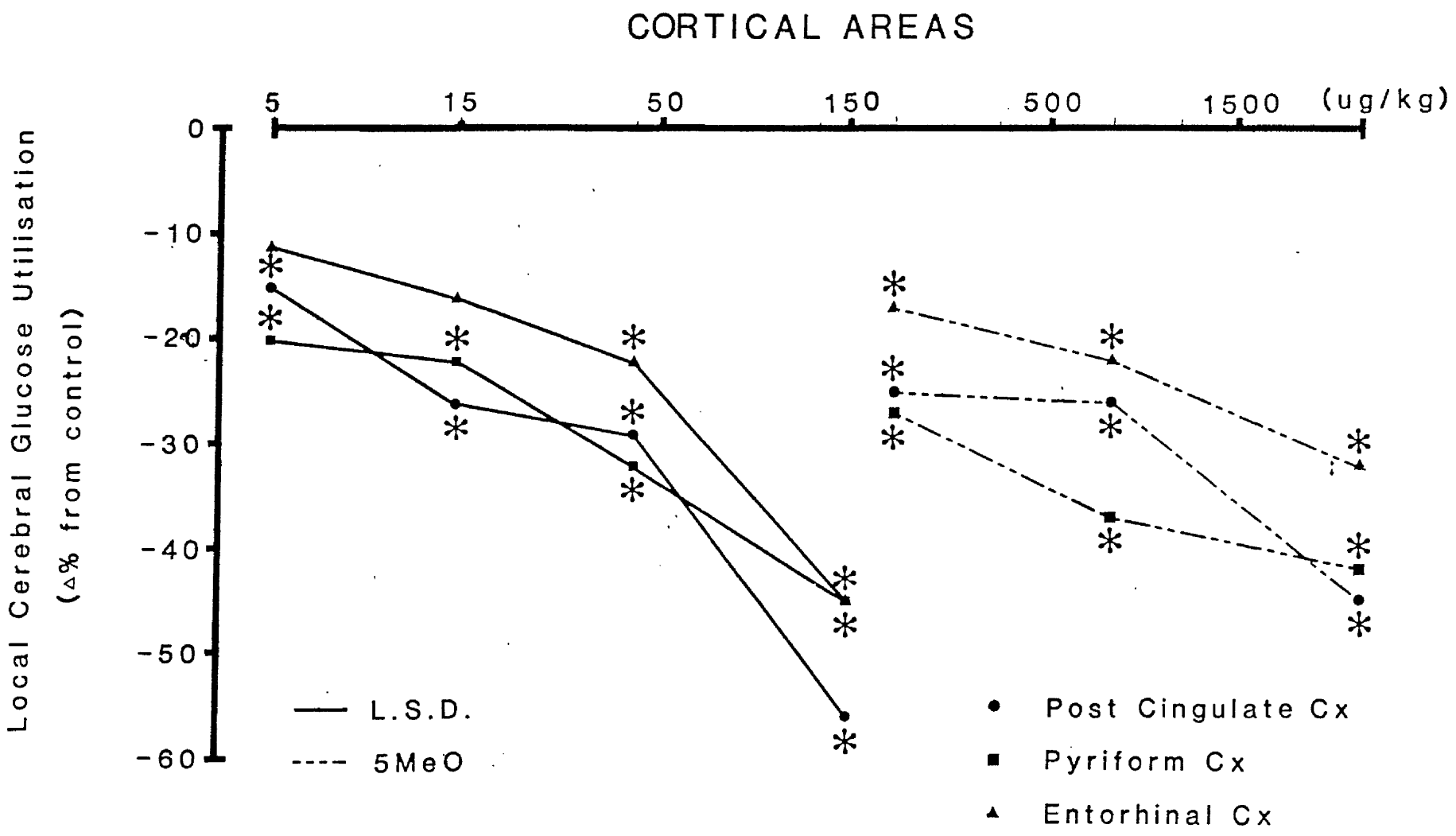


Figure 7. Log dose-response curves to lysergic acid diethylamide (LSD) and 5 methoxy-N,N-dimethyltryptamine (5MeO)-dortical areas. Results are given as percent difference from saline-treated controls. LSD is given in doses of 5, 15, 50 and 150 ug/kg. and 5MeO in doses of 200, 750 and 2,000 ug/kg. Note the difference in potency between LSD and 5MeO. * $p < 0.05$. Significance by ANOVA and Scheffe with respect to saline controls.

epithalamus had a decreased rate of glucose use following LSD and 5MeO administration, but again this effect was only significant at the highest dose. (Tables 5 and 7)

4.3.3. Limbic Areas

The nucleus accumbens, anterior amygdaloid area and dentate gyrus have significantly decreased rates of glucose use even following low doses of L.S.D. (15 ug/kg) suggesting a greater sensitivity of these areas to this drug. 5MeO, however, had no significant effect on the glucose utilisation of limbic structures at the lowest dose (200 ug/kg), but all the structures were markedly decreased at the next highest dose (750 ug/kg). (Tables 5 and 7)

4.3.4. Extrapyramidal Areas

Both LSD and 5MeO decrease glucose utilisation in the major extrapyramidal regions of the rat brain. (Fig.9) In the four areas of the caudate nucleus measured, parallel changes occurred. With each drug the caudal portion of the caudate nucleus was most affected, while the decrease in glucose phosphorylation in the body of the caudate nucleus was less marked. (Tables 5 and 7) The effects of these two compounds on the substantia nigra was to produce parallel decreases in the rate of glucose use in the pars compacta and pars reticulata of this structure. LSD produces a rather uniform decrease in glucose use in the globus pallidus with all four doses used. This is in contrast to 5MeO which causes a precipitate fall in glucose phosphorylation in this structure between doses of 200 and 750 ug/kg.

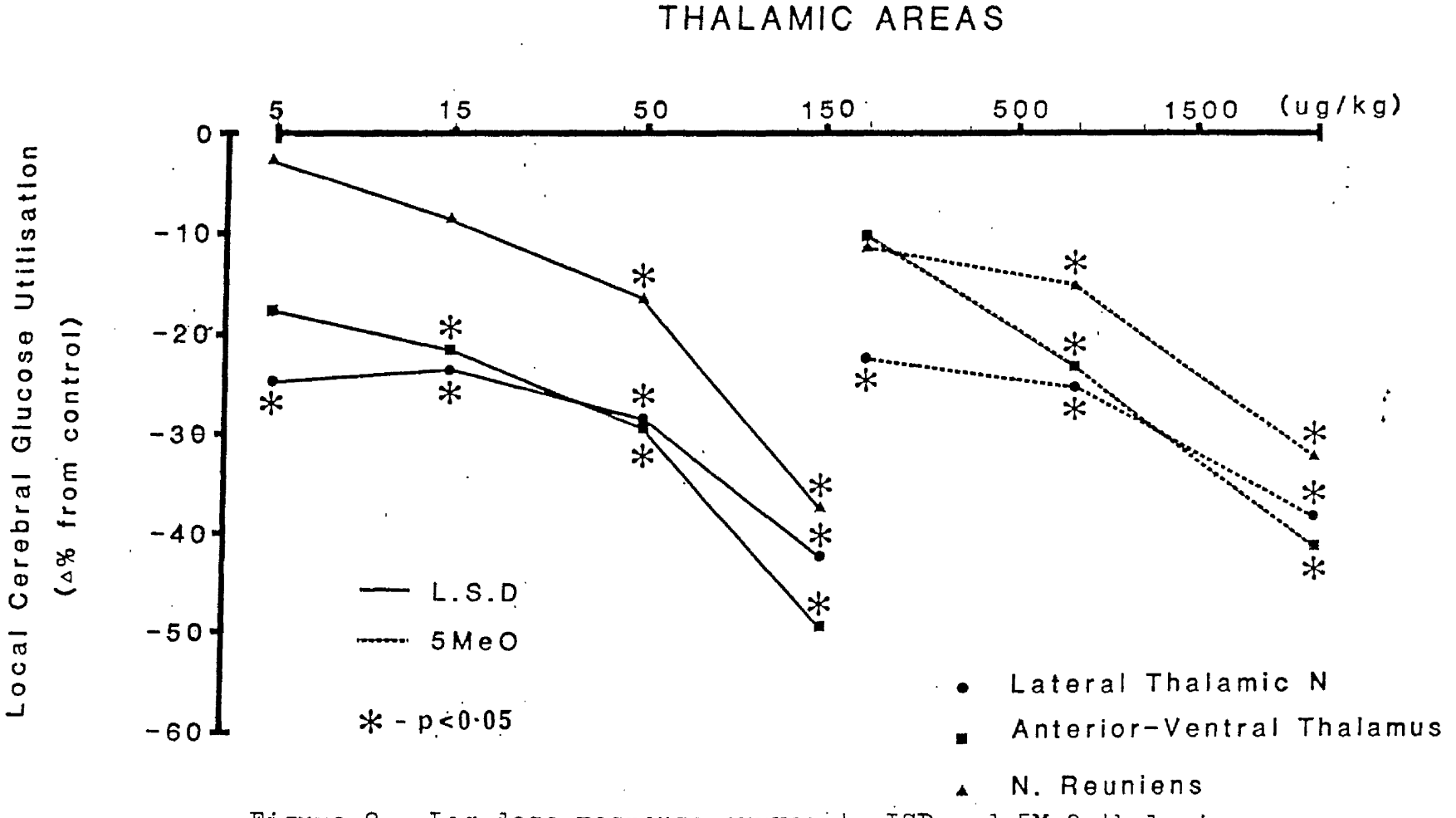


Figure 8. Log dose-response curves to LSD and 5MeO-thalamic areas. Results are given as percent difference from saline treated controls. LSD is given in doses of 5, 15, 50 and 150 ug/kg and 5MeO in doses of 200, 750 and 2,000 ug/kg. * $p < 0.05$. Significance by ANOVA and Scheffe with respect to saline controls.

4.3.5. Primary Visual and Primary Auditory Areas

There are differences in the way in which these putative serotonin agonists act on primary visual and auditory related cerebral regions. With both these drugs, the areas making up the visual pathway show significant decreases in glucose phosphorylation, particularly in the lateral geniculate body and the superior colliculus. The primary auditory structures, although they show a significant decrease in the rate of glucose use with the highest dose of LSD (150 ug/kg), display no significant changes in glucose utilisation following 5MeO.

4.3.6. Hindbrain Areas and Myelinated Fiber Tracts

LSD and 5MeO affect glucose utilisation in the cerebellar areas to a lesser extent than in forebrain areas. This pattern is maintained in other hindbrain areas (Tables 5 and 7 and previous section). The dorsal and median raphe nuclei are an exception to this in that they display significant decreases in glucose usage following LSD and 5MeO treatment.

The white matter fiber tracts are perhaps the least affected cerebral areas to be measured (Tables 5 and 7).

Comments on Results:

The hyperactivity syndrome induced by Lysergic acid diethylamide (L.S.D.) and 5 Methoxy -N,N -dimethyltryptamine (5MeO) was qualitatively similar to that observed by previous investigators (Gessner and Page, 1962; Grahame-Smith, 1971a). This syndrome was in turn similar to that produced by

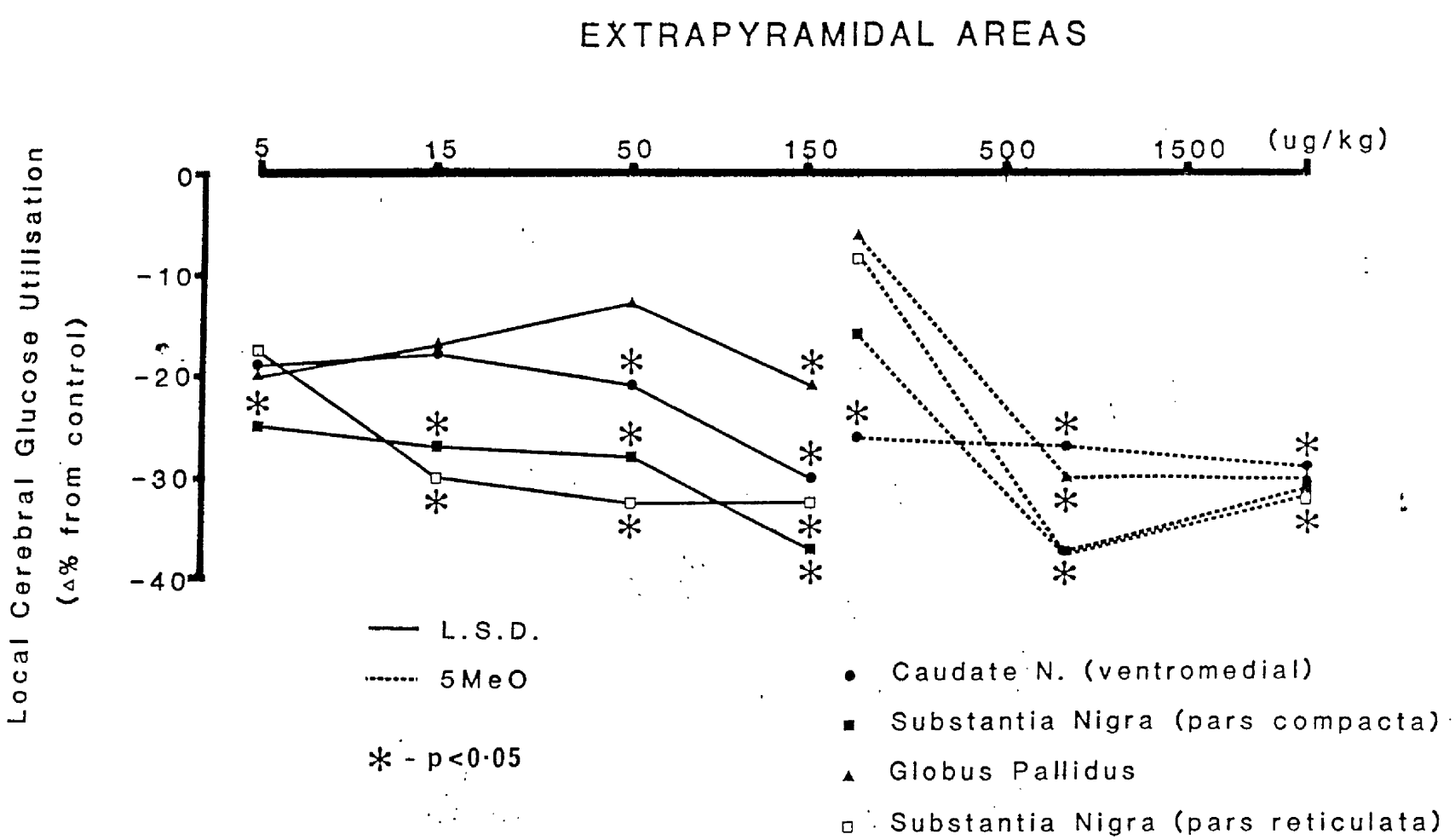


Figure 9. Log dose-response curves to LSD and 5MeO-extrapyramidal areas. Results are given as percent difference from saline treated controls. LSD is given in doses of 5, 15, 50 and 150 ug/kg and 5MeO in doses of 200, 750 and 2,000 ug/kg. * $p < 0.05$. Significance by ANOVA and Scheffe with respect to saline controls.

L-tryptophan administered after monoamine oxidase inhibition (Grahame-Smith, 1971b). Neither L.S.D. nor 5MeO may be considered to be acting exclusively on 5HT receptors. It should be noted that the central dopaminergic system has been implicated in the actions of LSD and 5MeO. (Green and Grahame-Smith, 1974; Pieri et al, 1974.) LSD also binds to dopamine receptors (Whittaker, 1979). This does not necessarily imply a direct cerebral action via dopamine receptors since dopamine agonists may inhibit 5-hydroxtryptophan-induced behaviour but do not induce it. (Volkman et al, 1978; Weiner et al, 1979). Thus, it may be stated with some confidence that the behavioural pattern produced by these indoleamine-containing compounds involves the central serotonin system. (See Sloviter, 1978, for review).

The peripheral effects of 5HT and putative serotonin agonists on blood pressure are highly complex. LSD and 5MeO do produce marked cardiovascular effects but mainly at the highest dose levels used. It seems likely that the pressor effect and bradycardia observed may well be derived from a combination of both the peripheral and central actions of these compounds (See Goodman and Gilman, 1979; Kuhn et al, 1980 for reviews).

Local cerebral glucose utilisation was measured in sixty anatomically discrete areas of the brain. None of the areas measured showed increases in glucose utilisation. The majority of brain regions reacted to the administration of LSD and 5MeO with dose-dependent decreases in glucose use. (Tables 5 and 7) In fact, very few areas did <u>not</u> show a

decrease in function at the highest doses of these drugs. Where a significant response was obtained, L.S.D. produced changes in the rate of glucose use at much lower doses than 5MeO. Overall, 15ug/kg i.v. of L.S.D. produced a similar decrease in glucose use as 750ug/kg of 5MeO; a difference in potency of about 50 times.

The majority of electrophysiological data suggests that the stimulation of raphe nuclei produces an inhibition in the cell-firing rate of post-synaptic (non-serotonergic) cells. (Bloom et al, 1972; Dray et al, 1978; Olpe and Koella, 1977; Segal, 1975; Wang and Aghajanian, 1977). Furthermore, the iontophoretic ejection of 5HT mimics this effect. (Bloom et al, 1972; Haigler and Aghajanian, 1974; Wang and Aghajanian, 1977).

Much attention has been paid by electrophysiologists to the actions of L.S.D., 5MeO and other 5HT-like compounds on the firing rate of the 5HT-containing cells in the hindbrain raphe nuclei. (Aghajanian and V n der Maelen, 1982; Haigler 1981, for review and Roganski and Aghajanian, 1981). These investigators have found that L.S.D. and 5MeO decrease the spontaneous firing activity of raphe neurons. For this reason it has been suggested that much of their central effect is due to a preferential action of L.S.D. and 5MeO on 5HT receptors situated on the serotoninergic cell-bodies. (Aghajanian et al, 1972; de Montagny and Aghajanian, 1977). In view of this data, it might seem that there is a good correlation with the present findings using deoxyglucose. The electrophysiological data, although produced by a method in many ways very different from the ^{14}C-2 deoxyglucose technique, is at least comparable measure of functional

activity. Therefore, it can be concluded that there is at least a qualitative compatability. This view is strengthened by the evidence that there is a close correlation between the level of deoxyglucose phosphorylation and the activity of $Na^+ - K^+$- ATPase in nervous tissue (Mata et al, 1980) and that in consequence changes in glucose utilisation reflect changes in nervous activity.

One problem arises, however, from the work of Haigler and Aghajanian, 1974, who found that the intravenous administration of L.S.D. at a dose of 20 ug/kg, produced an acceleration of the firing rate of cells which reacted with a decrease in activity to 5HT administration. It is difficult, given the lack of increased glucose use in this study following similar doses of L.S.D., to reconcile these qualitatively opposing data at the present state of knowledge.

In summary, L.S.D. and 5MeO produced significant decreases in local cerebral glucose utilisation. Particularly sensitive areas were:-

Cortex	- posterior cingulate cortex.
	- pyriform cortex.
	- prefrontal cortex.
Thalamus	- medial and ventral anterior nuclei.
	- lateral nucleus.
Limbic System	- n. accumbens.
	- anterior amygdaloid area
	- dentate gyrus.
Extrapyramidal System	- caudate nucleus
	- substantia nigra
Visual System	- lateral geniculate body
	- superior colliculus
Hindbrain areas	- raphe nuclei

TABLE 4

CARDIOVASCULAR DATA

L.S.D. (ug/kg)	Heart Rate (bts/min)		Blood Pressure (mmHg)	
	Control	Peak	Control	Peak
Saline	419 ± 7	419 ± 8	134 ± 3	132 ± 2
5	404 ± 7	408 ± 2	117 ± 5	119 ± 4
15	424 ± 3	404 ± 3 *	126 ± 4	125 ± 3
50	396 ± 9	341 ±10 *	135 ± 3	132 ± 3
150	386 ± 8	345 ±11 *	125 ± 3	134 ± 3 *
n	6	6	6	6

Data are presented as mean ± standard error of the mean.

* $p<0.05$ Statistical analysis by ANOVA and Scheffe.

TABLE 5

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100/min)

LYSERGIC ACID DIETHYLAMIDE (μg/kg)

Cerebral Structures	Saline	5	15	50	150
Parietal Cortex	94 ± 3	92 ± 4	82 ± 4	82 ± 3	66 ± 5 *
Sensory-Motor Cortex	98 ± 3	94 ± 3	90 ± 5	92 ± 4	64 ± 4 *
Entorhinal Cortex	74 ± 3	66 ± 4	62 ± 4	58 ± 2 *	41 ± 2 *
Pyriform Cortex	97 ± 4	78 ± 2 *	76 ± 3 *	66 ± 3 *	53 ± 2 *
Frontal Cortex	97 ± 3	92 ± 3	92 ± 4	95 ± 4	68 ± 4 *
Anterior Cingulate Cortex	94 ± 4	79 ± 3 *	81 ± 2 *	81 ± 3 *	57 ± 4 *
Posterior Cingulate Cortex	99 ± 3	84 ± 3 *	73 ± 4 *	70 ± 3 *	44 ± 3 *
Prefrontal Cortex	123 ± 4	94 ± 2 *	99 ± 6 *	93 ± 3 *	63 ± 4 *

TABLE 5 CONTD.

LYSERGIC ACID DIETHYLAMIDE (µg/kg)

Diencephalic Structures	Saline	5	15	50	150
Habenula (lateral)	107 ± 3	100 ± 4	91 ± 6	83 ± 4 *	75 ± 4 *
Habenula (medial)	72 ± 4	71 ± 3	56 ± 3 *	62 ± 3 *	57 ± 3 *
Thalamus - (mediodorsal nucleus)	94 ± 2	89 ± 4	82 ± 4	83 ± 3	66 ± 3 *
Thalamus-(ventrolateral nucleus)	84 ± 2	74 ± 4	68 ± 3 *	70 ± 4	58 ± 1 *
Thalamus (Anterior-ventral)	115 ± 3	96 ± 3 *	91 ± 4 *	83 ± 3 *	59 ± 3 *
Thalamus (Anterior-medial)	113 ± 3	93 ± 1 *	94 ± 4 *	77 ± 5 *	61 ± 4 *
Thalamus (lateral nucleus)	102 ± 2	78 ± 3 *	79 ± 7 *	74 ± 5 *	59 ± 3 *
Nucleus Reuniens	99 ± 4	101 ± 2	91 ± 4	83 ± 2 *	62 ± 4 *
Subthalamic Nucleus	79 ± 2	75 ± 3	69 ± 4	73 ± 3	55 ± 4 *
Zona Incerta	77 ± 3	72 ± 3	60 ± 5	68 ± 3	53 ± 4 *
Hypothalamus (medial)	51 ± 3	48 ± 2	45 ± 3	48 ± 2	47 ± 3
Median Forebrain Bundle	66 ± 2	50 ± 3 *	56 ± 3 *	52 ± 1 *	50 ± 3 *
Periventricular Nucleus	49 ± 3	54 ± 2	49 ± 3	51 ± 3	51 ± 4

TABLE 5 CONTD.

LYSERGIC ACID DIETHYLAMIDE (μg/kg)

Limbic Structures	Saline	5	15	50	150
Hippocampus (molecular layer)	86 ± 3	73 ± 4	70 ± 4*	66 ± 1*	59 ± 3*
Dentate Gyrus	75 ± 3	61 ± 4*	54 ± 3*	49 ± 1*	51 ± 3*
Septal Nucleus (lateral)	56 ± 3	54 ± 3	50 ± 3	49 ± 3	52 ± 3
Septal Nucleus (medial)	46 ± 3	38 ± 1	39 ± 1	36 ± 2*	39 ± 2
Nucleus Accumbens	80 ± 2	61 ± 1*	62 ± 3*	60 ± 3*	53 ± 4*
Amygdala (medial nucleus)	47 ± 3	40 ± 3	39 ± 3	41 ± 3	39 ± 2
Anterior Amygdaloid Area	84 ± 2	66 ± 2*	62 ± 4*	65 ± 2*	55 ± 3*
Ventral Tegmental Area	69 ± 3	54 ± 3*	52 ± 3*	50 ± 1*	45 ± 3*

TABLE 5 CONTD.

LYSERGIC ACID DIETHYLAMIDE (μg/kg)

Extrapyramidal Structures	Saline	5	15	50	150
Caudate Nucleus -					
- dorsolateral	94 ± 3	81 ± 2	78 ± 4	76 ± 4	61 ± 5*
- body	83 ± 2	71 ± 1*	70 ± 3	69 ± 4	58 ± 3*
- ventromedial	84 ± 3	68 ± 2	69 ± 4	66 ± 3	59 ± 5*
- caudal	82 ± 2	68 ± 1*	63 ± 3*	67 ± 2*	53 ± 2*
Globus Pallidus	54 ± 3	43 ± 1*	45 ± 3	47 ± 3	47 ± 3
Substantia Nigra (pars compacta)	81 ± 3	61 ± 3*	59 ± 3*	58 ± 2*	51 ± 3*
Substantia Nigra (pars reticulata)	60 ± 2	49 ± 4	42 ± 4*	41 ± 2*	41 ± 2*
Red Nucleus	76 ± 4	73 ± 4	64 ± 4	63 ± 3	54 ± 4*
Inferior Olive	75 ± 4	59 ± 3	64 ± 5	71 ± 3	63 ± 4
Vestibular Nucleus	109 ± 5	89 ± 6	92 ± 5	93 ± 5	78 ± 4*

TABLE 5 CONTD.

LYSERGIC ACID DIETHYLAMIDE (μg/kg)

Hindbrain	Saline	5	15	50	150
Cerebellum Hemisphere	51 ± 3	48 ± 3	47 ± 3	45 ± 2	52 ± 2
Cerebellum Nuclei	89 ± 4	76 ± 3	79 ± 5	78 ± 4	71 ± 3*
Cerebellum Vermis	96 ± 4	79 ± 4	77 ± 5	78 ± 4	78 ± 5
Cerebellum White Matter	35 ± 2	32 ± 4	31 ± 3	30 ± 2	30 ± 3
Pons (reticular formation)	61 ± 1	55 ± 5	50 ± 3*	51 ± 2*	41 ± 4*
Dorsal Raphe Nucleus	95 ± 3	73 ± 4*	75 ± 5*	67 ± 3*	62 ± 4*
Median Raphe Nucleus	96 ± 3	81 ± 4	72 ± 4*	67 ± 3*	67 ± 3*
Myelinated Fiber Tracts					
Corpus Callosum	34 ± 2	36 ± 3	31 ± 3	29 ± 2	34 ± 3
Genu of Corpus Callosum	27 ± 2	24 ± 2	27 ± 2	26 ± 1	30 ± 1
Internal Capsule	33 ± 1	32 ± 3	34 ± 1	33 ± 2	31 ± 3

TABLE 5 CONTD

LYSERGIC ACID DIETHYLAMIDE (ug/kg)

Primary Auditory	Saline	5	15	50	150
Auditory Cortex	139 ± 3	136 ± 4	123 ± 5	123 ± 5	92 ± 4*
Medical Geniculate	115 ± 3	106 ± 5	96 ± 5	99 ± 4	86 ± 3*
Inferior Colliculus	168 ± 5	162 ± 4	160 ± 5	167 ± 6	110 ± 4
Lateral Lemniscus	112 ± 3	99 ± 3	96 ± 7	99 ± 5	71 ± 4*
Superior Olive	141 ± 4	144 ± 7	136 ± 6	133 ± 5	76 ± 3*
Cochlear Nucleus	140 ± 3	134 ± 4	129 ± 6	133 ± 6	75 ± 5*
Primary Visual					
Visual Cortex	99 ± 3	94 ± 5	88 ± 4	81 ± 3*	65 ± 3*
Lateral Geniculate - dorsal	83 ± 1	78 ± 3	69 ± 3*	71 ± 3*	57 ± 3*
- ventral	88 ± 2	66 ± 3*	57 ± 3*	65 ± 3*	52 ± 4*
Superior Colliculus - superficial	84 ± 2	71 ± 2*	70 ± 4*	73 ± 2*	61 ± 3*
- deep	80 ± 3	68 ± 3*	66 ± 3*	65 ± 1*	59 ± 3*
n	6	6	6	6	6

Data are given as mean ± standard error of the mean in μmols/100g/min. *: $p < 0.05$. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

TABLE 6

CARDIOVASCULAR DATA

5MeO (ug/kg)	Heart Rate (Beats/min)		Blood Pressure (mmHg)	
	Control	Peak	Control	Peak
Saline	420 ± 8	419 ± 8	134 ± 2	132 ± 2
200	415 ±10	417 ±12	125 ± 5	126 ± 4
750	408 ±10	362 ±14*	126 ± 3	139 ± 3*
2000	388 ± 9	347 ± 8*	129 ± 5	146 ±10*
n	6	6	6	6

Data are presented as mean ± standard error of the mean.
* : $p<0.05$ Statistical analysis by ANOVA and Scheffe.

TABLE 7

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

5 Methoxy - N, N - dimethyltryptamine (μg/kg)

Cerebral Cortex Structures	Saline	200	750	2000
Parietal Cortex	94 ± 3	76 ± 3*	74 ± 3*	74 ± 5*
Sensory - Motor Cortex	98 ± 4	86 ± 5	83 ± 1*	97 ± 4
Enthorhinal Cortex	74 ± 4	62 ± 3	58 ± 1*	50 ± 3*
Pyriform Cortex	97 ± 4	70 ± 2*	61 ± 3*	56 ± 4*
Frontal Cortex	97 ± 4	94 ± 4	80 ± 2*	85 ± 4·
Anterior Cingulate Cortex	94 ± 3	77 ± 3*	74 ± 2*	69 ± 3*
Posterior Cingulate Cortex	99 ± 4	74 ± 1*	73 ± 2*	54 ± 3*
Prefrontal Cortex	124 ± 7	85 ± 4*	90 ± 3*	85 ± 2*

TABLE 7 CONTD.

5 METHOXY - N,N -DIMETHYLTRYPTAMINE (µg/kg)

Diencephalic Structures	Saline	200	750	2000
Habenula (Lateral)	107 ± 3	93 ± 4	88 ± 3*	60 ± 4*
Habenula (Medial)	72 ± 4	63 ± 2	59 ± 3*	46 ± 3*
Thalamus - Mediodorsal N.	94 ± 1	87 ± 2	76 ± 4*	69 ± 5*
Thalamus - Ventrolateral N.	84 ± 2	74 ± 2	59 ± 3*	59 ± 4*
Thalamus - Anteriorventral	115 ± 4	104 ± 3*	88 ± 1*	68 ± 4*
Thalamus - Anteriomedial	114 ± 4	103 ± 3*	82 ± 3*	66 ± 4*
Thalamus - Lateral N.	102 ± 2	80 ± 3*	77 ± 2*	63 ± 3*
Nucleus Reuniens	99 ± 4	88 ± 5	84 ± 2	67 ± 2*
Subthalamic Nucleus	79 ± 2	72 ± 4	64 ± 3*	70 ± 3
Zona Incerta	77 ± 3	70 ± 4	89 ± 3*	70 ± 1
Hypothalamus (Medial)	52 ± 3	48 ± 2	39 ± 1*	36 ± 2*
Median Forebrain Bundle	66 ± 2	70 ± 4	46 ± 3*	45 ± 1*
Periventricular N.	50 ± 4	62 ± 2	45 ± 2	47 ± 5

TABLE 7 CONTD.

5 METHOXY - N,N -DIMETHYLTRYPTAMINE (μg/kg)

Limbic Structures	Saline	200	750	2000
Hippocampus (molecular layer)	86 ± 3	74 ± 3	64 ± 3*	62 ± 4*
Dentate Gyrus	75 ± 5	66 ± 4	53 ± 1*	44 ± 2*
Septal N. (lateral)	56 ± 3	53 ± 5	44 ± 3*	44 ± 2*
Septal N. (medial)	46 ± 3	43 ± 2	35 ± 2*	33 ± 2*
Nucleus Accumbens	80 ± 2	72 ± 5	55 ± 3*	61 ± 3*
Amygdala (medial N)	47 ± 3	40 ± 3	35 ± 1*	32 ± 2*
Anterior Amygdaloid Area	84 ± 3	76 ± 3	57 ± 1*	55 ± 3*
Ventral Tegmental Area	69 ± 4	58 ± 3	44 ± 4*	44 ± 3*

TABLE 7 CONTD.

5 METHOXY - N,N -DIMETHYLTRYPTAMINE (μg/kg)

Extrapyramidal Structures	Saline	200	750	2000
Caudate Nucleus (dorsolateral)	94 ± 4	75 ± 1*	68 ± 4*	69 ± 4*
(body)	83 ± 2	81 ± 1	62 ± 2*	63 ± 4*
(ventromedial)	84 ± 4	67 ± 2*	61 ± 2*	68 ± 3*
(caudal)	82 ± 2	72 ± 2*	56 ± 2*	65 ± 5*
Globus Pallidus	54 ± 3	57 ± 2	38 ± 2*	38 ± 3*
Substantia Nigra (pars compacta)	81 ± 3	68 ± 4*	51 ± 2*	65 ± 5*
(pars reticulata)	60 ± 2	55 ± 2	38 ± 2*	41 ± 2*
Red Nucleus	76 ± 3	70 ± 2	56 ± 2*	61 ± 4
Inferior Olive	75 ± 4	64 ± 2*	50 ± 3*	61 ± 5
Vestibular Nucleus	109 ± 4	88 ± 5*	86 ± 1*	80 ± 4*

TABLE 7 CONTD.

5 METHOXY - N,N - DIMETHYLTRYPTAMINE (µg/kg)

Hindbrain Structures	Saline	200	750	2000
Cerebellum Hemisphere	51 ± 4	47 ± 4	37 ± 2	38 ± 3
Cerebell Nuclei	89 ± 4	75 ± 2	75 ± 2	73 ± 4
Cerebellum Vermis	96 ± 5	83 ± 6	76 ± 3*	68 ± 4*
Cerebellum White Matter	35 ± 2	38 ± 3	36 ± 1	36 ± 1
Pons (reticular formation)	61 ± 1	53 ± 3	46 ± 2*	48 ± 2*
Dorsal Raphe Nucleus	95 ± 3	77 ± 4*	64 ± 3*	69 ± 4*
Median Raphe Nucleus	96 ± 5	76 ± 3*	70 ± 2*	67 ± 5*
Myelinated Fiber Tracts				
Corpus Callosum	34 ± 2	42 ± 2	32 ± 3	33 ± 1
Genu of the Corpus Callosum	27 ± 2	30 ± 3	31 ± 2	32 ± 1
Internal Capsule	33 ± 1	36 ± 4	35 ± 2	35 ± 2

TABLE 7 CONTD.

5 METHOXY - N,N - DIMETHYLTRYPTAMINE (µg/kg)

			Saline	200	750	2000
Primary Auditory						
Auditory Cortex			139 ± 4	122 ± 6	130 ± 5	133 ± 3
Medial Geniculate			115 ± 4	89 ± 5*	91 ± 2*	95 ± 5*
Inferior Colliculus			168 ± 6	150 ± 6	165 ± 5	167 ± 3
Lateral Lemniscus			112 ± 3	89 ± 4*	91 ± 4*	94 ± 5*
Superior Olive			151 ± 4	107 ± 7	117 ± 6*	125 ± 8
Cochlear Nucleus			141 ± 3	107 ± 7	117 ±10	111 ± 7
Primary Visual						
Visual Cortex			99 ± 4	83 ± 6	87 ± 1	79 ± 2*
Lateral Geniculate	-	dorsal	92 ± 4	77 ± 3*	66 ± 2*	70 ± 1*
	-	ventral	86 ± 4	67 ± 3*	55 ± 2*	54 ± 1*
Superior Colliculus	-	superficial layer	84 ± 2	76 ± 3	72 ± 2*	69 ± 3*
	-	deep layer	80 ± 3	75 ± 4	63 ± 2*	59 ± 3*
n			6	6	6	6

Data are given as mean ± standard error of the mean in umols/100g/min. *p: <0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

V. THE EFFECTS OF PIPERAZINE-CONTAINING SEROTONIN AGONISTS ON LOCAL CEREBRAL GLUCOSE UTILISATION

5.1. Behavioural Effects

Saline control animals, two hours after the discontinuation of anaesthesia, displayed normal grooming behaviour. Quipazine and chloropiperazinylpyrazine (C.P.P.) produced an obvious increase in activity. Despite the qualitative nature of these observations it was clear that the lowest doses of these two compounds produced only an increase in sniffing and movement. At the highest doses, the rats displayed a pronounced behavioural pattern of response including head-weaving and padding of the forepaws. These effects normally lasted for thirty minutes, i.e. until the twentieth minute of the measurement of glucose utilisation.

5.2. Cardiovascular Effects

Quipazine and C.P.P. both produced vivid effects on heart rate and mean arterial blood pressure. Quipazine produced significant decreases in heart rate (12% - 34%) and concommitant increases in mean arterial blood pressure (18% - 41%). In a similar fashion, C.P.P. reduced heart rate significantly at all doses used, by between 11% and 20% and increased mean arterial pressure by between 21% and 36% (Tables 8 and 10).

5.3. Local Cerebral Glucose Utilisation

5.3.1. Cortical Areas

Both quipazine and chloropiperazinylpyrazine (C.P.P.) produce dose-dependant decreases in glucose utilisation. (Tables 9 and 11) The highest doses of C.P.P. and quipazine

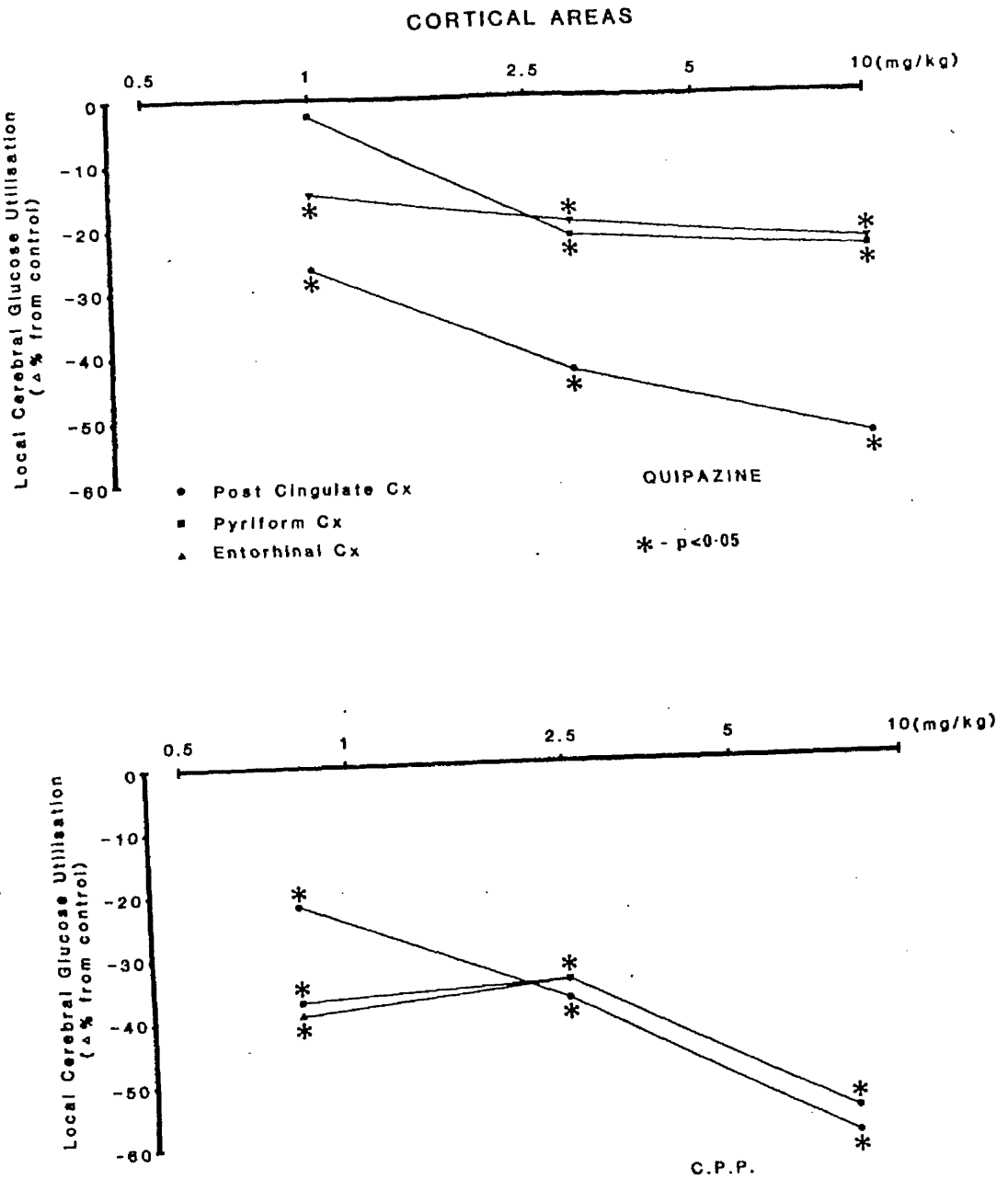


Figure 10. Log dose-response curves to quipazine and chloropiperazinylpyrazine (C.P.P.)-cortical areas. Results are given as percent change from control values. Quipazine was administered in doses of 1, 3 and 10mg/kg and C.P.P. in doses of 0.8, 2.5 and 8.0 mg/kg. *p: < 0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

(8 mg/kg and 10 mg/kg respectively) produces significant decreases in glucose use in all the cortical areas measured; with the exception of a muted response of the frontal cortex to quipazine administration. Especially cingulate and entorhinal cortices, which have significantly decreased levels of glucose use at 0.8 mg/kg of C.P.P. and 1 mg/kg quipazine are sensitive to C.P.P. and quipazine administration. (Fig. 10)

5.3.2. Diencephalic Areas

There is a distinct dichotomy in the actions of C.P.P. and quipazine on glucose utilisation in diencephalic areas. Quipazine produced increases in glucose use in the Zona Incerta by 116 $\pm$ 7% at 10 mg/kg ($p < 0.05$), nucleus reuniens by 68 $\pm$ 3% at 10 mg/kg ($p < 0.05$) and the periventricular nucleus of the hypothalamus by 27 $\pm$ 2% at 10 mg/kg ($p < 0.05$). Similarly, C.P.P. also produces increases in these areas and additionally in the lateral habenular nucleus. (25 $\pm$ 4% at 2.5 mg/kg : $p < 0.05$). (Fig. 15)

Quipazine and C.P.P. also produced marked decreases in glucose utilisation in the lateral, anterior ventral and anterior medial nuclei of the thalamus. C.P.P. also produced a marked decrease in the glucose metabolism of the median forebrain bundle whilst quipazine was relatively inaffective in this structure. (Fig.11, Tables 9 and 11)

5.3.3. Limbic Areas

Quipazine produced no change in the pattern of glucose use in subcortical limbic areas 1 mg/kg. Even at 10 mg/kg only the dentate gyrus molecular layer of the hippocampus and the septal nucleus show significant decreases in glucose

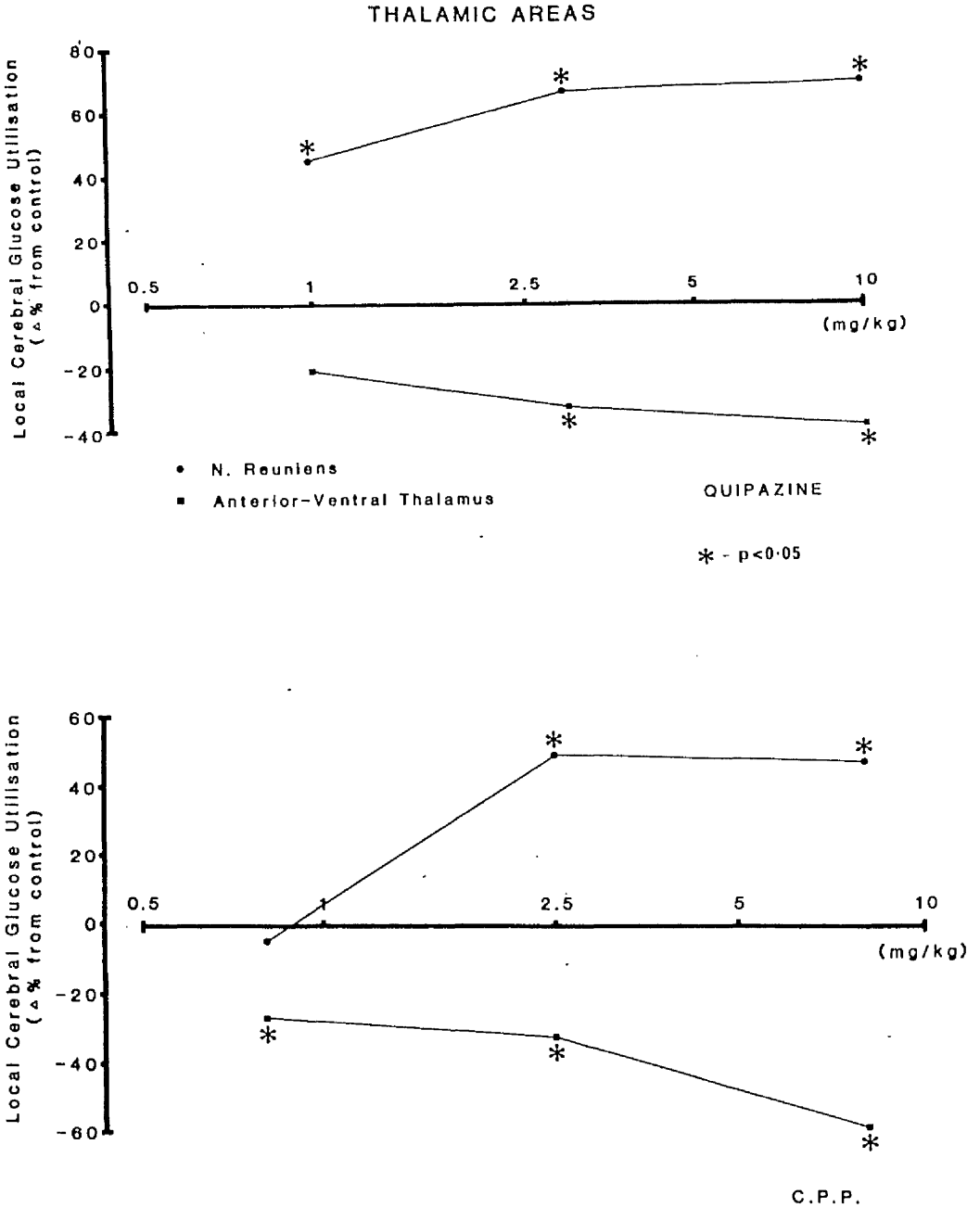


Figure 11. Log dose-response curves to quipazine and C.P.P. thalamic areas. Results are given as percent change from saline control values. Quipazine was administered in doses of 1, 3 and 10mg/kg and C.P.P. in doses of 0.8, 2.5 and 8.0 mg/kg. *p: < 0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

use following quipazine. The dentate gyrus, nucleus accumbens, anterior amygdaloid area and ventral tegmental area all show sensitivity to C.P.P. treatment across the dose range used.

The hippocampus (molecular layer), medial amygdaloid nucleus and the septal nucleus are comparatively resistant to C.P.P. pretreatment. (Fig.12; Tables 9 and 11)

5.3.4. Extrapyramidal Structures

Following C.P.P. and quipazine administration there is an interesting dose-dependant effect on the glucose use of the caudate nucleus and substantia nigra. In the caudate nucleus, although the body and dorsomedial portion of this structure remain relatively unchanged at all doses of quipazine or C.P.P., glucose utilisation in the caudal portion of the caudate nucleus is reduced significantly in a dose-dependant manner. The ventromedial portion has a decreased glucose use at a dose of 3 mg/kg of quipazine but has increased glucose catabolism at 10 mg/kg of quipazine. The effect of C.P.P. is to produce a similar pattern in that at 2.5 mg/kg the glucose utilisation in the ventromedial caudate nucleus is decreased and at 8 mg/kg it is above control levels, but not significantly so. (Fig. 13 and 14)

Similarly, the substantia nigra (pars compacta) displays dose-dependant reductions in glucose utilisation following C.P.P. and quipazine. The pars reticulata of this structure has a significantly reduced level of glucose utilisation following 3 mg/kg quipazine. However, 10 mg/kg of quipazine, increases the rate of glucose use in this area.

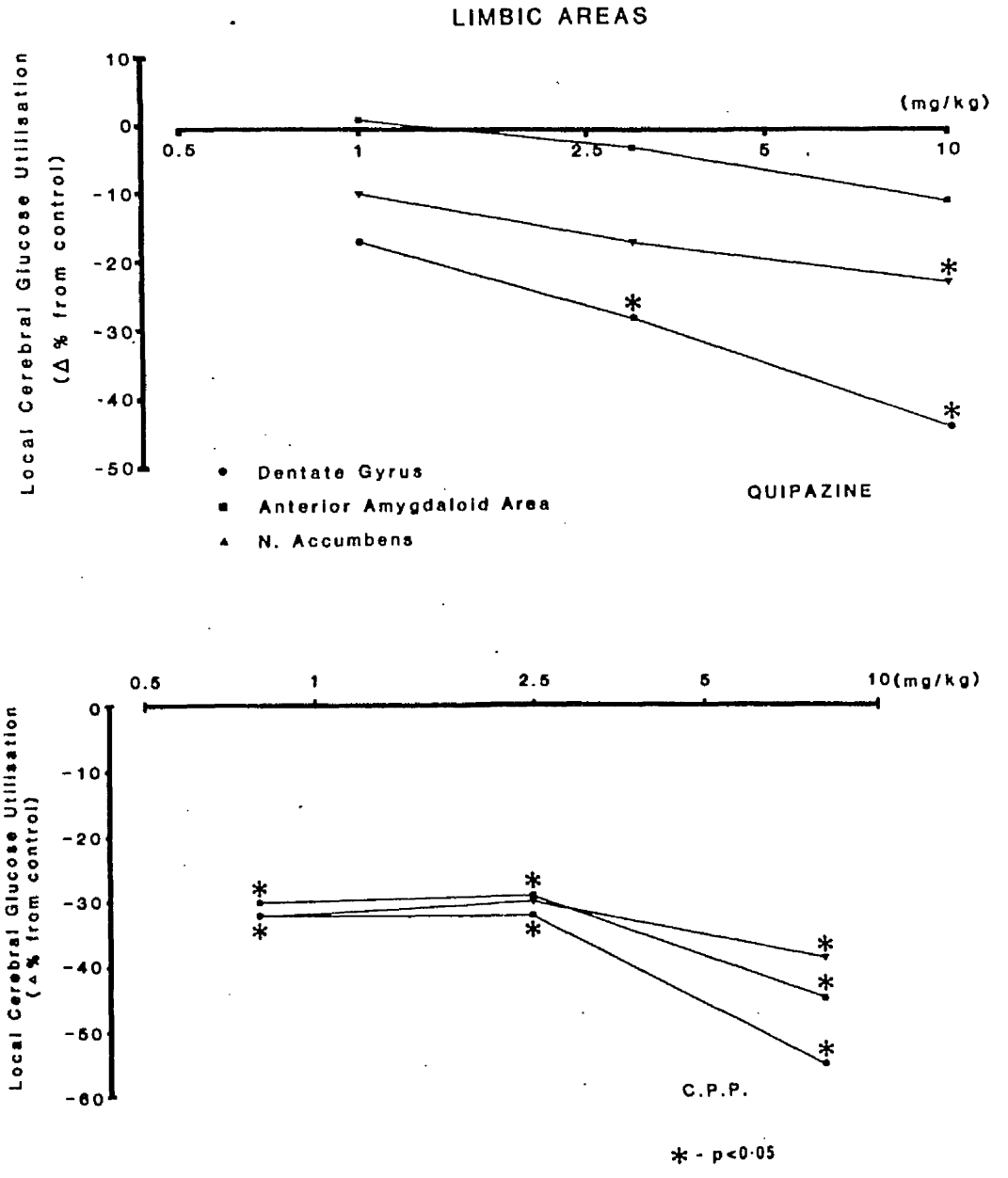


Figure 12. Log dose-response curves to quipazine and C.P.P. -limbic areas. Results are given as percent change from saline control values. Quipazine was administered in doses of 1, 3 and 10mg/kg and C.P.P. in doses of 0.8, 2.5 and 8.0 mg/kg. *p:$<$0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

At a dose of 10 mg/kg, quipazine also produced a marked increase in the globus pallidus. C.P.P. produced significant decreases in the glucose use of the substantia nigra (pars reticulata) at low doses but at the highest dose of 8mg/kg, the rate of glucose use had returned to near control levels. The red nucleus, inferior olive and vestibular N, have small, non-significant changes in glucose use following quipazine and are significantly decreased only at the highest dose of C.P.P. (Fig. 13. Tables 9 and 11).

5.3.5. Primary Auditory and Visual Areas

Quipazine significantly decreased glucose catabolism in the auditory system, only at the highest dose (10mg/kg), by between 17% and 29%. Following C.P.P. treatment there were marked decreases in glucose utilisation in the auditory areas; particularly in medial geniculate body. Both C.P.P. and quipazine produced pronounced changes in the visual system. It is noteworthy that the rank order of effect with either drug was visual cortex lateral geniculate body superior colliculus. (Tables 9 and 11)

5.3.7. Comments on Results

The qualitative observations made on the behavioural syndrome produced by quipazine and chloropiperzinylpyrazine (C.P.P.) were similar in appearance to previously published data. (Green et al, 1976; Clineschmidt et al, 1977). In no way could they be considered different from the effects of L.S.D. and 5 methoxy-N,N-dimethyltryptamine. (See Chapter IV)

There is limited data available on the effects of these compounds on blood-pressure and heart rate. Quipazine and C.P.P. both

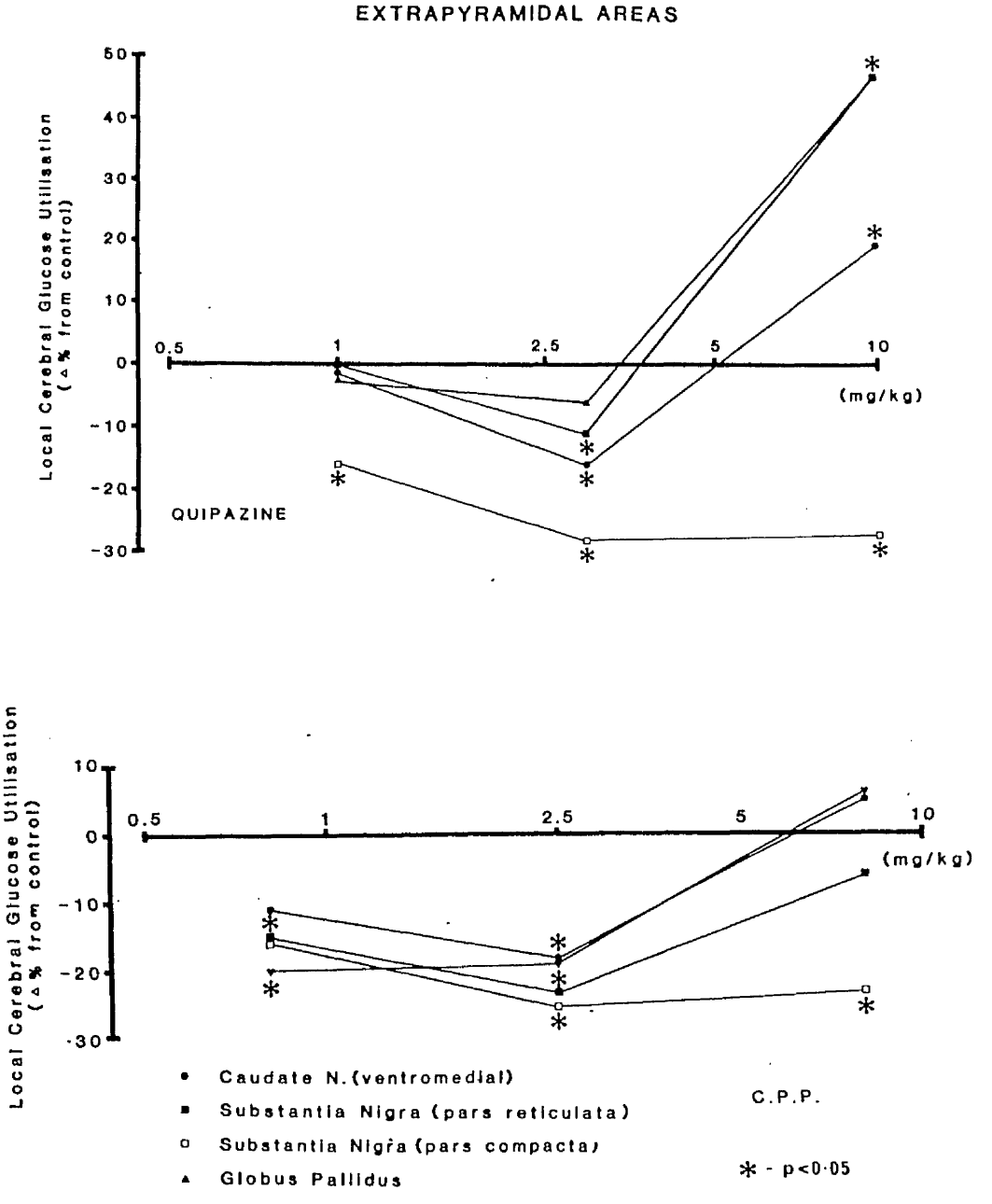


Figure 13. Log dose-response curves to quipazine and C.P.P. -extrapyramidal areas. Results are given as percent change from saline control values. Quipazine was administered in doses of 1, 3 and 10 mg/kg and C.P.P. in doses of 0.8, 2.5 and 8.0mg/kg. *p:$<$0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

produced a profound effect on the cardiovascular parameters measured over their entire dose range. These effects were qualitatively similar to those obtained with the highest doses of LSD and 5 methoxy - N,N - dimethyltryptamine. (See previous section of this thesis). Blatt et al, 1979 reported that C.P.P. diminished cardiac susceptability to ventricular fibrillation. This was thought to be due to a decrease in the flow of arrythmogenic sympathetic nerve traffic to the heart.

The majority of the sixty structures measured responded to quipazine and C.P.P. treatment with decreases in glucose utilisation. In a small number of areas these piperazine-containing putative serotonin agonists were capable of producing dose-dependant increases in glucose use. There is little electrophysiological evidence to support either of these effects on cerebral function by quipazine and C.P.P. Briggs, 1975, reported that the iontophorectic application of quipazine onto brain stem neurons in the rat had little direct effect but prolonged the actions of serotonin. This evidence supports the view that both quipazine and C.P.P. act in an indirect manner by blocking the uptake of serotonin at the synapse (Hamon et al, 1976: Clineschmidt et al, 1978a.b. and also by an increase in the release of serotonin from the nerve endings (Clineschmidt, 1979; Hamon et al, 1976.) However, there is good evidence that both quipazine and C.P.P. inhibit the binding of ^{3}H-5HT to cell membranes (Clineschmidt, 1979; Fuller et al, 1978; Nelson et al, 1978). Of particular importance in this respect is the

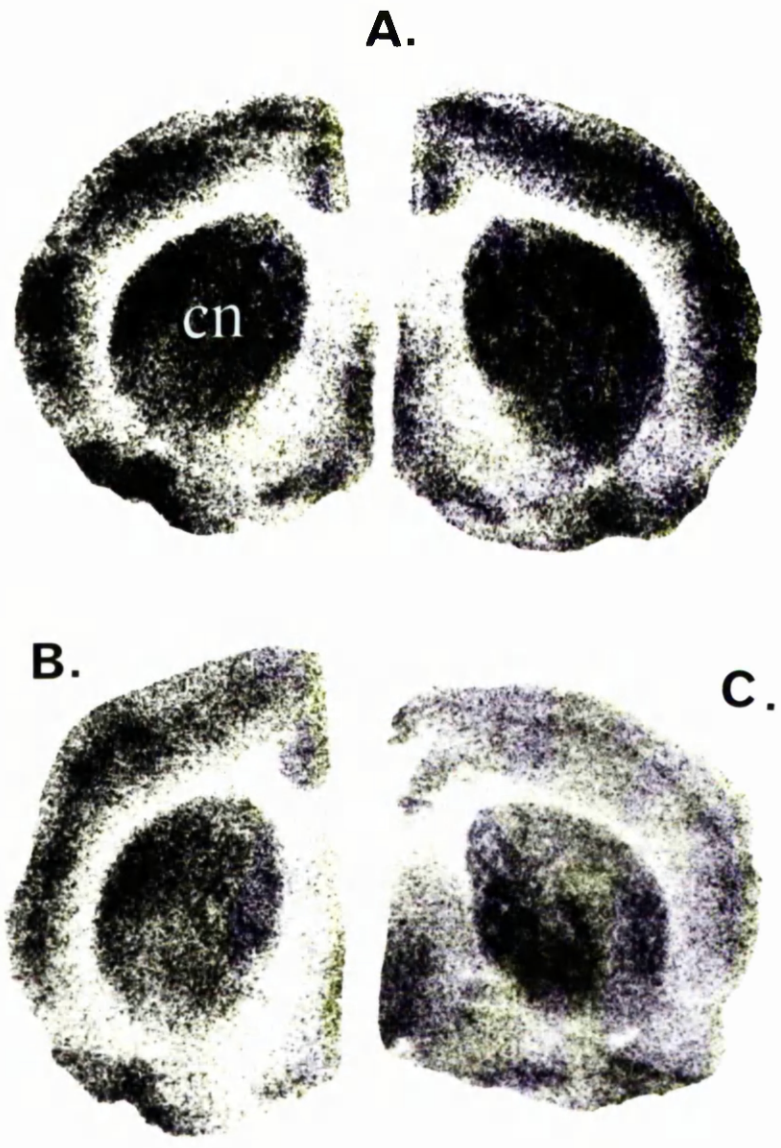

A.
cn
B.
C.

Figure 14 **Autoradiographs** at the level of the caudate nucleus illustrating the effects on this structure of quipazine treatment. The optical density is directly related to local cerebral glucose utilisation. A: In the saline control the caudate nucleus is seen, in the coronal plane, as a dark relatively homogeneous oval structure. B: This hemisection was obtained from a rat treated with 3mg/kg of quipazine. The ventromedial portion of the caudate nucleus has a lower optical density than the saline control, A. C: This coronal hemisection was obtained from a rat treated with 10mg/kg of quipazine. The ventromedial portion of the caudate nucleus has now a much higher optical density than either A or B. key:- c.n. - ventromedial caudate nucleus.

fact that quipazine still displaces ^{3}H-5HT following the intracerebroventricular injection of 5, 7 - dihydroxy-tryptamine given in a dose sufficient to destroy the serotonin neuronal processes. (Nelson et al, 1978). Therefore, it is likely that quipazine and C.P.P. have both direct and indirect effects on central serotonin systems.

Whatever the means by which quipazine and C.P.P. have their effect, the similarity of the effects of these two compounds on local cerebral function are apparent. Quipazine and C.P.P. produce similar parallel decreases in glucose use in cerebral cortex and in sub-cortical limbic areas; results which resemble those obtained with LSD and 5MeO. (previous section of this thesis) What is different with the responses to quipazine and C.P.P. administration is the patterns of functional activity obtained in the extrapyramidal and diencephalic groups of structures.

The decreases in glucose use in the substantia nigra and the ventromedial caudate nucleus obtained with 3 mg/kg of quipazine and 2.5 mg/kg of C.P.P. compare favourably with the electrophysiological findings which show that stimulation of the raphe nuclei or iontophorectic administration of 5HT produces an overall decrease in the firing rate of these structures. (Dray et al, 1976; Dray et al, 1978, Miller et al, 1975; Olpe and Koella, 1977). The increases in glucose utilisation obtained by quipazine administration at 10 mg/kg are not so easily explained. Although there is evidence that electrical

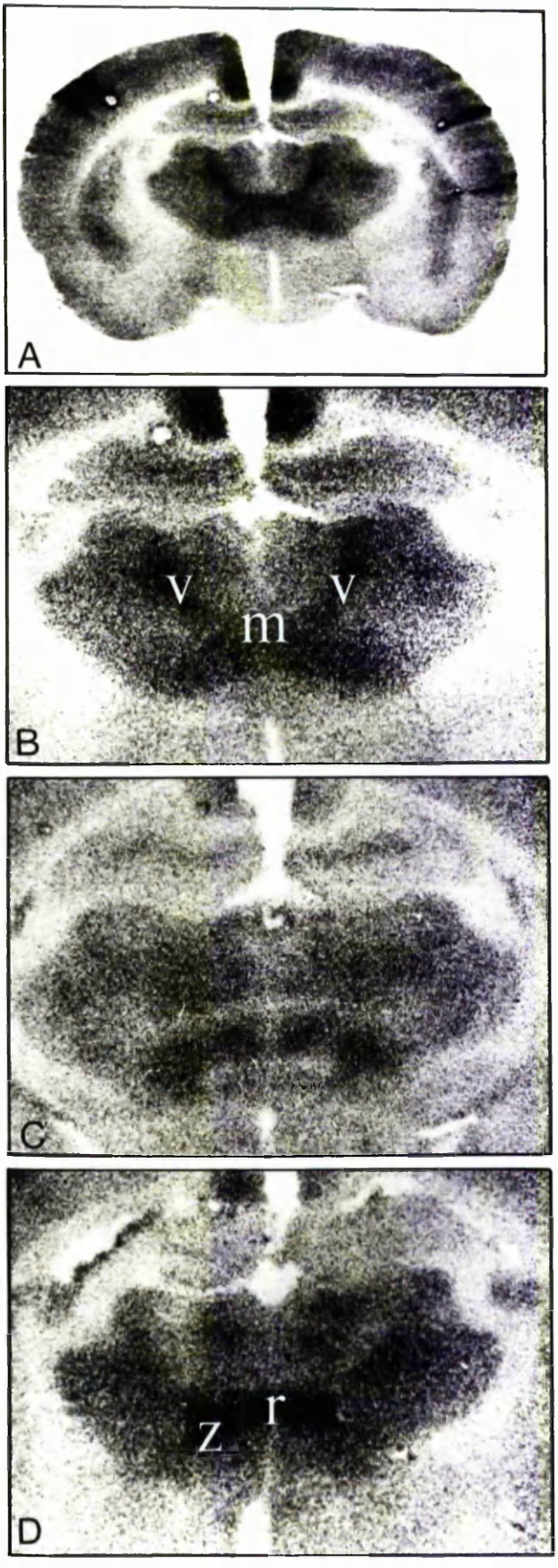

A
v
v
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Figure 15. Autoradiographic impressions at the level of the anterior thalamic complex. The optical density is directly related to local cerebral glucose utilisations. A: Whole section from saline control rat. B : An enlargement of the thalamic area depicted in A. The anterior ventral and anterior medial nuclei form a U-shaped area which is darker than the surrounding thalamus. C. The anterior thalamus at the same level as B. Following 50 ug/kg of L.S.D. Note the homogeneous nature of the pattern of optical density as compared to B. D: The anterior thalamus at the same level as B following quipazine (3mg/kg) administration. A different pattern of response has ensued. The anterior medial and anterior ventral nuclei have clearly decreased glucose use as compared to surrounding thalamic areas. The very dark area corresponds mainly to the n. reuniens but also includes elements of the zona incerta. Thus, saline, L.S.D. and quipazine treated rats have different patterns of response in the anterior thalamus. Key:- V-anterior ventral thalamic nucleus. M - anterior medial thalamic nucleus. r - nucleus reuniens. z - zona incerta.

stimulation of the dorsal raphe nucleus can lead to excitatory postsynaptic potentials, these were invariably followed by an inhibitory post-synaptic potential. (Van der Maelen et al, 1979). It should also be noted that although the ventromedial caudate nucleus, the globus pallidus and the substantia nigra (pars reticulata) show increases in glucose use at 10 mg/kg quipazine, the substantia nigra (pars compacta) still has a significantly decreased level of glucose use. Although there is no way of establishing the mechanism of this effect several factors may play a part. There are multiple inputs by serotonin fibers from the raphe nuclei into the caudate nucleus, substantia nigra and globus pallidus. (Azmitia and Segal, 1978; Dray et al, 1978; Miller et al, 1975). The effects of quipazine and C.P.P. may be subtly different in a dose-dependant manner on these synapses. Another possibility is that the change in effect is due to the fact that only at the highest doses used are quipazine and C.P.P. capable of producing a decrease in the functional activity of the sensory-motor cortex. Since this is the highest integrating centre for motor control (Nauta and Domesick, 1979) it might be hypothesised that a direct inhibition of this area by these compounds might release sub-cortical motor control areas from its inhibitory influence. (Scatton et al, 1982). This would mean that these particular serotonin agonists produce a change, not simply in the individual areas making up the extrapyramidal and motor areas, but in the integration of this system as a whole.

A third possibility is of course, that at high doses quipazine and C.P.P. interact with receptors other than 5HT receptors; in particular dopaminergic binding sites (Clineschmidt, 1979; Grabowska et al, 1974). However, the interpretation of this data is difficult given the afferent (Azmitia and Segal, 1978: Dray et al, 1978) and efferent (Stern et al, 1979; Sakai et al, 1977) connections of the dopaminergic-containing cell bodies of the substantia nigra and the serotonergic cell bodies of the raphe nuclei. Furthermore, C.P.P. and quipazine in vitro fail to displace ^{3}H - N,N - proplynorapomorphine from its specific binding sites in the rat (Luscombe et al, 1982). The possibility that C.P.P. and quipazine are producing these effects via receptors other than 5HT receptors, cannot however, be wholly discounted.

The actions of quipazine and C.P.P. on diencephalic structures was to produce a dichotomy in the pattern of response (Tables 9 and 11). What mechanisms might underly such an effect? It can be seen that those areas which show a decrease in glucose utilisation or are unaffected by quipazine and C.P.P. treatment fall into the category known as specific thalamic nuclei. (Donaldson et al, 1975) so called because they relay information from sub-cortical structures such as the cerebellum, basal ganglia and sensory systems to specific areas of cortex. These areas according to Azmitia and Segal, 1978 and Steinbusch, 1981 have only

sparse serotonergic innervation, yet functional activity of the lateral thalamic and the anterior thalamic nuclei are markedly affected by C.P.P. and quipazine administration. This may be explained not only by direct actions of the putative serotonin agonists but also by the effects of these drugs or input areas to these structures, e.g. basal ganglia, cortex, etc. (Zeman and Innes, 1963). The areas of thalamus showing increases in glucose utilisation , the zona incerta and nucleus reuniens are termed non-specific thalamic nuclei. They project to a number of areas in the cortex and thalamus (Schiebel and Schiebel, 1967) the hippocampus (Herkenham, 1978) striatum (Powell and Cowan, 1956) and the globus pallidus (Nauta and Mehler, 1966). These areas are also capable of producing a strong recruiting response in both thalamus and cortex and have a marked effect on electroencephalographic arousal. (Moruzzi and Magown, 1949; Jasper, 1949). Of importance to this study is that these areas also receive the highest concentration of serotonergic input to thalamic areas. (Azmitia and Segal, 1978; Steinbusch, 1981).

This does not, of itself, explain the increases in glucose use in the nucleus reuniens and zona incerta but it is further evidence that those effects produced by C.P.P. and quipazine seem to coincide with known serotonergic pathways.

To summarise, these two putative serotonin agonists which bear a close structural resemblance to one another, produce similar patterns of response in the cerebrum. It can be seen too that the spectrum of changes in functional activity produced by C.P.P. and quipazine are

different from those elicited by L.S.D. and 5 methoxy-N,N - dimethyltryptamine. This will be discussed further. (See Discussion and Synthesis)

In summary, quipazine and C.P.P. produced both decreases and increases in local cerebral glucose utilisation. Areas which were sensitive to the administration of low doses of these drugs were as follows:-

Cortex	-	posterior cingulate cortex.
	-	entorhinal cortex.
Thalamus	-	anterior ventral and anterior medial nuclei.
	-	lateral nuclei
	-	nucleus reuniens
Limbic System	-	dentate gyrus
Extrapyramidal System	-	caudate nucleus
	-	substantia nigra.

TABLE 8

CARDIOVASCULAR DATA

Quipazine (mg/kg)	Heart Rate (beats/min)		Blood Pressure (mmHg)	
	Control	Peak	Control	Peak
Saline	411 ± 8	422 ± 8	128 ± 1	130 ± 2
1	414 ± 7	364 ±10*	137 ± 4	161 ± 3*
3	418 ± 6	313 ±11*	134 ± 1	172 ± 3*
10	422 ± 9	279 ±12*	133 ± 2	188 ± 3*
n	6	6	6	6

Data are presented as mean ± standard error of the mean.

* : $p<0.05$. Statistical analysis by ANOVA and Scheffe.

TABLE 9

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

QUIPAZINE (mg/kg i.v.)

Cerebral Structures	Saline	1	3	10
Parietal Cortex	96 ± 2	79 ± 4	84 ± 5	74 ± 6*
Sensory Motor Cortex	97 ± 4	98 ± 4	90 ± 5	81 ± 4*
Entorhinal Cortex	72 ± 5	61 ± 5*	58 ± 4*	56 ± 2*
Pyriform Cortex	100 ± 4	98 ± 4	79 ± 4*	77 ± 4*
Frontal Cortex	92 ± 3	94 ± 5	78 ± 4*	81 ± 5
Anterior Cingulate Cortex	94 ± 3	83 ± 3	78 ± 4	67 ± 4*
Posterior Cingulate Cortex	95 ± 4	70 ± 3*	55 ± 3*	46 ± 4*
Prefrontal Cortex	128 ± 5	102 ± 6	80 ± 6*	71 ± 4*

TABLE 9 CONTD.

	QUIPAZINE (mg/kg i.v.)			
Diencephalic Structures	Saline	1	3	10
Mediodorsal Thalamus	92 ± 2	102 ± 4	93 ± 4	88 ± 6
Ventrolateral Thalamus	85 ± 3	96 ± 4	82 ± 5	72 ± 6
Anterior-Ventral Thalamus	108 ± 5	94 ± 4	72 ± 3*	70 ± 4*
Anterior-Medial Thalamus	114 ± 6	90 ± 6	77 ± 4*	71 ± 5*
Lateral Thalamus	102 ± 2	91 ± 4	74 ± 2*	73 ± 4*
Subthalamic Nucleus	79 ± 3	91 ± 7	79 ± 5	80 ± 6
Zona Incerta	77 ± 4	88 ± 3	87 ± 2	166 ± 7*
Nucleus Reuniens	94 ± 4	136 ± 9*	156 ± 6*	158 ± 8*
Habenula (Lateral)	108 ± 4	122 ± 9	104 ± 8	102 ± 4
Habenula (Medial)	73 ± 5	79 ± 8	69 ± 3	64 ± 2
Medial Geniculate	120 ± 2	116 ± 6	103 ± 4*	94 ± 5*
Lateral Geniculate	93 ± 6	96 ± 6	74 ± 6*	67 ± 3*
Hypothalamus	55 ± 3	61 ± 5	57 ± 4	55 ± 2
Medial Forebrain Bundle	60 ± 3	68 ± 8	64 ± 3	66 ± 4
Periventricular N.	51 ± 2	48 ± 2	62 ± 2*	63 ± 2*

TABLE 9 CONTD.

QUIPAZINE (mg/kg i.v.)

Limbic Structures	Saline	1	3	10
Hippocampus (Molecular Layer)	89 ± 2	83 ± 4	94 ± 2	67 ± 3*
Dentate Gyrus	82 ± 2	68 ± 5	59 ± 3*	50 ± 4*
Septal Nucleus (Lateral)	66 ± 5	64 ± 3	61 ± 4	44 ± 2*
Septal Nucleus (Medial)	52 ± 5	54 ± 3	42 ± 2*	44 ± 2*
Nucleus Accumbens	82 ± 2	74 ± 5	68 ± 4	63 ± 3
Amygdala (Medial)	49 ± 3	51 ± 5	47 ± 2	43 ± 3
Anterior Amygdaloid Area	83 ± 3	84 ± 4	81 ± 3	74 ± 3
Ventral Tegmental Area	63 ± 4	67 ± 2	56 ± 4	62 ± 4
Pontine Reticular Formation	61 ± 1	52 ± 2	56 ± 4	51 ± 5

TABLE 9 CONTD.

QUIPAZINE (mg/kg i.v.)

Extrapyramidal Structures	Saline	1	3	10
Caudate Nucleus (Dorsolateral)	99 ± 4	93 ± 3	94 ± 5	102 ± 4
Caudate Nucleus (Central)	84 ± 2	87 ± 4	78 ± 6	86 ± 6
Caudate Nucleus (Ventromedial)	86 ± 4	85 ± 3	72 ± 3*	102 ± 3*
Globus Pallidus	54 ± 1	53 ± 5	51 ± 2	78 ± 6*
Substantia Nigra (Pars Compacta)	83 ± 2	70 ± 4*	60 ± 4*	61 ± 4*
Substantia Nigra (Pars Reticulata)	62 ± 1	62 ± 3	55 ± 2*	89 ± 6*
Red Nucleus	78 ± 2	76 ± 4	69 ± 5	74 ± 6
Inferior Olive	73 ± 5	80 ± 3	66 ± 3	67 ± 6
Vestibular Nucleus	101 ± 5	120 ± 8	114 ± 6	104 ± 6

TABLE 9 CONTD.

	QUIPAZINE (mg/kg i.v.)			
Primary Auditory	Saline	1	3	10
Auditory Cortex	144 ± 9	131 ± 4	136 ± 6	109 ± 5*
Medial Geniculate	120 ± 2	116 ± 6	103 ± 6*	94 ± 5*
Inferior Colliculus	171 ± 7	166 ± 6	172 ± 6	142 ± 6*
Lateral Lemniscus	112 ± 4	109 ± 6	99 ± 6	84 ± 1*
Superior Olive	152 ± 9	159 ± 9	135 ± 7	108 ± 8*
Cochlear Nucleus	137 ± 2	130 ± 8	117 ± 6	109 ± 9
Primary Visual				
Visual Cortex	104 ± 4	94 ± 6	84 ± 3*	63 ± 3*
Lateral Geniculate	93 ± 6	96 ± 6	74 ± 6*	67 ± 3*
Superior Colliculus Superficial	83 ± 2	90 ± 4	64 ± 4*	60 ± 4*
Superior Colliculus Deep	82 ± 2	83 ± 5	79 ± 7	73 ± 3*

TABLE 9 CONTD.

	QUIPAZINE (mg/kg i.v.)			
Hindbrain Structures	Saline	1	3	10
Cerebellum Hemisphere	51 ± 4	60 ± 2	52 ± 3	48 ± 4
Cerebellum Nuclei	93 ± 4	91 ± 5	87 ± 7	85 ± 6
Cerebellum Vermis	93 ± 6	89 ± 7	108 ± 9	79 ± 8
Cerebellum White Matter	35 ± 1	38 ± 3	36 ± 2	35 ± 4
Dorsal Raphe Nucleus	95 ± 2	98 ± 3	94 ± 3	78 ± 5*
Median Raphe Nucleus	92 ± 2	96 ± 3	87 ± 4	83 ± 6
Myelinated Fiber Tracts				
Corpus Callosum	34 ± 2	37 ± 2	36 ± 2	29 ± 3
Genu of the Corpus Callosum	28 ± 2	31 ± 1	29 ± 1	24 ± 2
Internal Capsule	35 ± 2	34 ± 3	30 ± 3	24 ± 2*
n	6	6	6	6

Data are given as mean ± standard error of the mean in µmols/100g/min. *:$p < 0.05$. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

TABLE 10

CARDIOVASCULAR DATA

C.P.P. (mg/kg)	Heart Rate (beats/min)		Mean Arterial Blood Pressure (mmHg)	
	Control	At Study	Control	At Study
Saline	404 ± 6	408 ± 8	125 ± 3	127 ± 3
0.8	430 ±14	344 ±18*	121 ± 3	146 ± 2*
2.5	392 ±12	349 ±12*	128 ± 3	165 ± 4*
8.0	387 ± 4	321 ± 5*	122 ± 2	166 ± 2*
n	6	6	6	6

Data arepresented as mean ± standard error of the mean.
* $p<0.05$. Statistical analysis by ANOVA and Scheffe.

TABLE 11

	6 - Chloro - 2 - [1 - Piperazinyl] Pyrazine (mg/kg i.v.)			
Cerebral Structures	Saline	0.8	2.5	8
Parietal Cortex	94 ± 3	90 ± 2	76 ± 3*	55 ± 2*
Sensory Motor Cortex	95 ± 4	88 ± 3	94 ± 2	68 ± 2*
Entorhinal Cortex	76 ± 4	46 ± 2*	50 ± 2*	34 ± 2*
Pyriform Cortex	97 ± 4	61 ± 3*	64 ± 2*	44 ± 2*
Frontal Cortex	94 ± 3	81 ± 2	82 ± 5	57 ± 2*
Anterior Cingulate Cortex	94 ± 4	78 ± 2*	68 ± 3*	55 ± 2*
Posterior Cingulate Cortex	99 ± 5	77 ± 3*	62 ± 2*	41 ± 2*
Prefrontal Cortex	126 ± 5	75 ± 2*	79 ± 3*	61 ± 2*

TABLE 11 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

6 - Chloro - 2 - [1- Piperazinyl] Pyrazine (mg/kg)

Diencephalic Structures	Saline	0.8	2.5	8.0
Habenula (lateral)	104 ± 3	103 ± 6	133 ± 3*	120 ± 4*
Habenula (medial)	69 ± 4	71 ± 3	73 ± 3	55 ± 3*
Thalamus - mediodorsal N.	90 ± 2	85 ± 4	88 ± 4	68 ± 2*
Thalamus - ventromedial N.	82 ± 3	72 ± 4	75 ± 2	57 ± 2*
Thalamus - anterioventral N.	110 ± 5	80 ± 3*	75 ± 3*	46 ± 2*
Thalamus - anteriomedial N.	109 ± 4	65 ± 2*	72 ± 3*	53 ± 3*
Thalamus - lateral N.	100 ± 2	78 ± 4*	73 ± 3*	49 ± 2*
Nucleus Reuniens	92 ± 6	87 ± 3	137 ± 3*	135 ± 5*
Subthalamic Nucleus	79 ± 3	75 ± 5	77 ± 2	51 ± 2*
Zona Incerta	72 ± 3	71 ± 6	84 ± 2	93 ± 2*
Hypothalamus (medial)	51 ± 3	53 ± 3	55 ± 2	49 ± 2
Median Forebrain Bundle	66 ± 3	46 ± 2*	50 ± 2*	40 ± 2*
Periventricular N.	50 ± 3	42 ± 3	77 ± 2*	74 ± 3*

TABLE 11 CONTD.

6 - Chloro -2- [1- Piperzinyl] Pyrazine (mg/kg)

Limbic Structures	Saline	0.8	2.5	8.0
Hippocampus (molecular layer)	81 ± 3	78 ± 2	82 ± 3	55 ± 2*
Dentate Gyrus	78 ± 5	57 ± 2*	57 ± 2*	39 ± 2*
Septal N. (Lateral)	54 ± 3	52 ± 2	56 ± 4	45 ± 2
Septal N. (Medial)	42 ± 3	35 ± 2	43 ± 3	38 ± 2
Nucleus Accumbens	76 ± 2	55 ± 3*	57 ± 4*	50 ± 2*
Amygdala (medial Nucleus)	47 ± 3	43 ± 2	48 ± 2	38 ± 2
Anteriolar Amygdaloid Area	84 ± 2	63 ± 2*	64 ± 2*	50 ± 2*
Ventral Tegmental Area	69 ± 3	52 ± 2*	57 ± 2	38 ± 2*

TABLE 11 CONTD.

6 - Chloro -2-[1- Piperazinyl] Pyrazine (mg/kg)

Extrapyramidal Structures	Saline	0.8	2.5	8.0
Caudate Nucleus (dorsolateral)	84 ± 3	88 ± 2	89 ± 2	82 ± 3
(body)	83 ± 2	89 ± 2	87 ± 2	78 ± 2
(ventromedial)	84 ± 3	75 ± 3	69 ± 2*	88 ± 2
(caudal)	82 ± 2	75 ± 2	63 ± 1*	59 ± 2*
Globus Pallidus	54 ± 2	43 ± 2*	44 ± 3	57 ± 3
Substantia Nigra (pars compacta)	81 ± 3	68 ± 4*	57 ± 2*	61 ± 3*
(pars reticulata)	62 ± 2	53 ± 2	48 ± 2*	58 ± 2
Red Nucleus	76 ± 4	83 ± 2	69 ± 2	60 ± 2*
Inferior Olive	75 ± 4	70 ± 2	67 ± 3	53 ± 1*
Vestibular Nuoleus	102 ± 7	96 ± 5	100 ± 2	83 ± 4*

TABLE 11 CONTD.

	6-Chloro -2- [1-Piperazinyl] Pyrazine (mg/kg)			
Primary Auditory	Saline	0.8	2.5	8.0
Auditory Cortex	131 ± 3	133 ± 4	114 ± 6*	86 ± 3*
Medial Geniculate	115 ± 3	92 ± 2	75 ± 5*	51 ± 2*
Inferior Colliculus	168 ± 6	151 ± 7	150 ± 3	107 ± 3*
Lateral Lemnicus	112 ± 3	76 ± 3	81 ± 5*	67 ± 2*
Superior Olive	151 ± 7	105 ± 6	109 ± 6*	74 ± 3*
Cochlear Nucleus	141 ± 3	106 ± 6	103 ± 3*	72 ± 4*
Primary Visual				
Visual Cortex	99 ± 3	77 ± 3*	68 ± 2*	60 ± 2*
Lateral Geniculate-dorsal	96 ± 4	77 ± 3*	78 ± 2*	55 ± 2*
-ventral	89 ± 5	66 ± 2*	64 ± 3*	59 ± 2*
Superior Colliculus - superficial layer	83 ± 2	70 ± 3*	74 ± 2	59 ± 3*
Superior Colliculus - deep layer	80 ± 3	68 ± 4	75 ± 2	60 ± 3*

TABLE 11 CONTD.

6 - Chloro - 2 [1 Piperazinyl] Pyrazine (mg/kg)

Hindbrain Structures	Saline	0.8	2.5	8.0
Cerebellum Hemisphere	53 ± 3	45 ± 2	39 ± 2*	36 ± 2*
Cerebellum Nuclei	89 ± 4	83 ± 3	70 ± 4*	70 ± 3*
Cerebellum Vermis	96 ± 5	71 ± 3*	82 ± 3	72 ± 3*
Cerebellum White Matter	32 ± 2	41 ± 1	39 ± 2	38 ± 2
Pons (reticular formation)	64 ± 3	62 ± 2*	57 ± 1*	47 ± 1*
Dorsal Raphe Nucleus	95 ± 3	70 ± 3*	74 ± 2*	57 ± 2*
Median Raphe Nucleus	92 ± 4	69 ± 2*	71 ± 2*	62 ± 2*
Myelinated Fiber Tracts				
Corpus Callosum	34 ± 2	36 ± 2	36 ± 4	33 ± 2
Genu of the Corpus Callosum	29 ± 2	28 ± 2	31 ± 4	32 ± 2
Internal Capsule	33 ± 2	31 ± 3	31 ± 3	28 ± 2
n	6	6	6	6

Data are given as mean ± standard error of the mean in umols/100g/min. *: $p < 0.05$. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

VI. THE ACTIONS OF PUTATIVE SEROTONIN ANTAGONISTS ON LOCAL CEREBRAL GLUCOSE UTILISATION.

6.1. Behavioural Effects

Careful observation of the rats, before and after the administration of putative serotonin antagonists methysergide and metergoline, failed to detect any overt changes in behaviour. Cyproheptadine at the highest dose used, 1 mg/kg, did produce a short-lasting effect which might be described as a Straub tail effect. The behaviour of all rats was apparently 'normal' by the time of study.

6.2. Cardiovascular Effects

Methysergide (5 and 15 mg/kg) and metergoline (0.3 and 3 mg/kg) did not produce any significant changes in heart rate or blood pressure other than minor fluctuation during the injection time. (Tables 14 and 16) Cyproheptadine produced a definite decrease in mean arterial blood pressure of 6 $\pm$ 2% ($p < 0.05$: $n = 6$) which lasted for 2 - 3 minutes after the cessation of the intravenous administration. (Table 12) The blood pressure and heart rate of all rats was not significantly different from saline control animals or pre-administration values at the time of study.

6.3. Local Cerebral Glucose Utilisation

Methysergide at a dose of 5 mg/kg and metergoline at a dose of 0.3 mg/kg did not produce any significant effects on local cerebral glucose utilisation in the sixty areas

measured. Cyproheptadine produced almost identical responses at 0.1 mg/kg and 1.0 mg/kg. Therefore, for ease of presentation the data will be presented only in terms of methysergide (15mg/kg), metergoline (3 mg/kg) and cyproheptadine (1 mg/kg). All other relevant data are available in Tables 13, 15 and 17.

6.3.1. Cortical Areas

The rank order of percentage decreases in cortical glucose use was similar to that seen with serotonin agonists (see **chapters IV and V.)** The pyriform, prefrontal and cingulate cortices were particularly susceptible to treatment by methysergide, (15 mg/kg) and metergoline (3 mg/kg). All these structures had significantly decreased rates of glucose use. Lesser decreases were seen in the sensory-motor cortex. Interestingly, from the data given in tables 15 and 17, the entorhinal cortex was much less affected by these putative serotonin antagonists than by LSD, 5MeO, Quipazine and C.P.P. Cyproheptadine reduced the level of glucose use in all cortical areas measured at a dose of 1 mg/kg. (Tables 13, 15, 17 and Fig. 16)

6.3.2. Diencephalic Areas

Methysergide (15 mg/kg i.v.) produces significant decreases in the rate of glucose use in the medial and ventral anterior thalamus, lateral thalamic nucleus and median forebrain bundle of 18-25%. Comparatively smaller non-significant decreases occur in the epithalamus (habenula, subthalamic nucleus) and elsewhere in thalamus and hypothalamus.

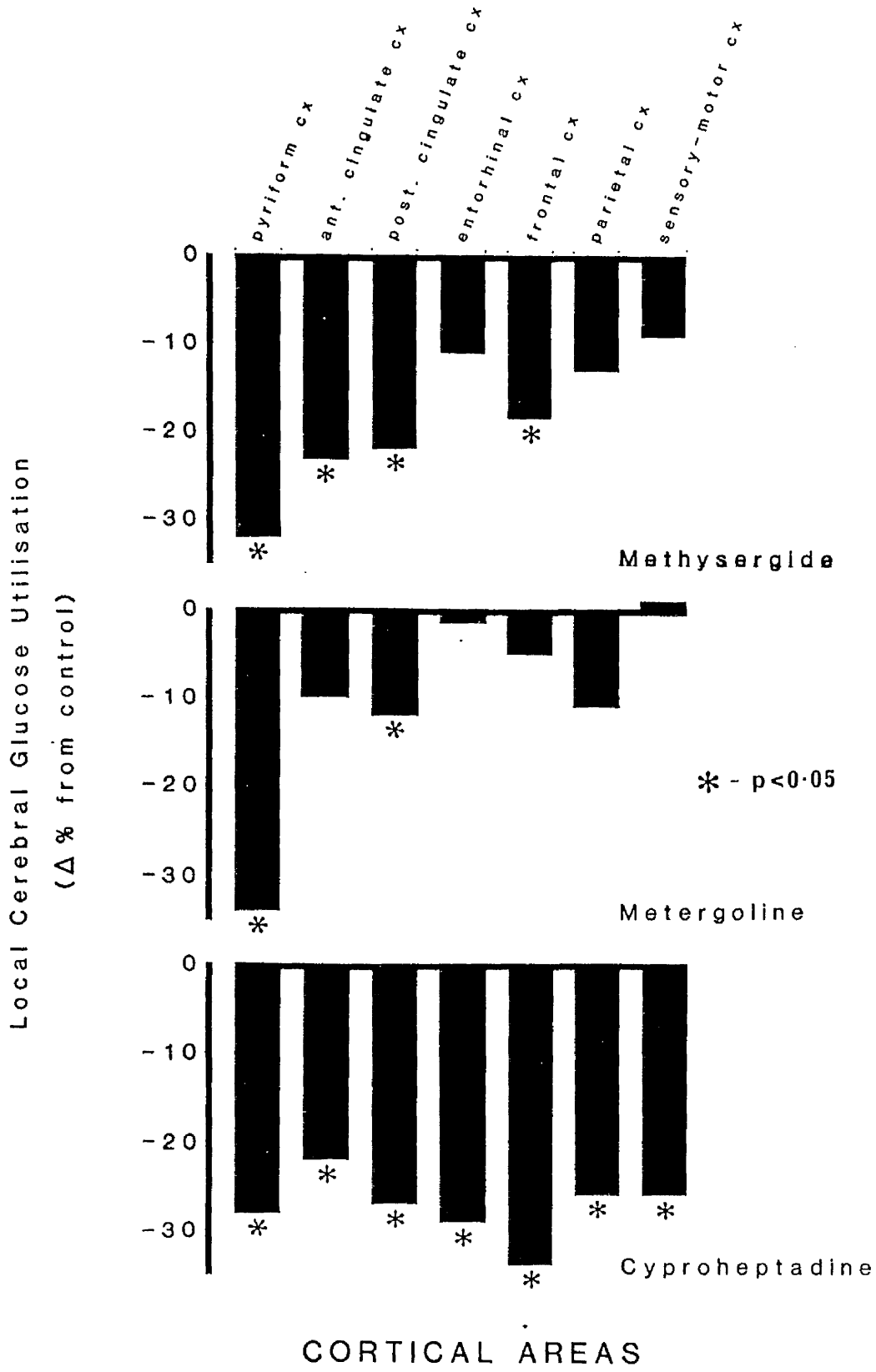

Figure 16. The pattern of response produced by methysergide (15mg/kg), metergoline (3mg/kg) and cyproheptadine (1mg/kg) in cortical areas. Results are given as percent difference from control. *p:$<$0.05. Statistical analysis by ANOVA and and Scheffe.

Metergoline (3 mg/kg) causes decreased glucose utilisation in the ventrolateral thalamic nucleus, medial hypothalamic nuclei, of between -17% and -19% ($p < 0.05$). All the other structures have non-significant changes in glucose use of between -3% and -10%.

Cyproheptadine reduces glucose use significantly in all the thalamic areas measured by between -16% and -29%, ($p < 0.05$). The erithalamic and hypothalamic regions display changes of +3% to -6%. (Tables 13, 15, 17 and Fig. 17)

6.3.3. Limbic Areas

Following treatment by methysergide (15 mg/kg) there are significant decreases in glucose utilisation of between -17% and -32% ($p < 0.05$) in the ventral tegmental areas the dentate gyrus, the anterior amygdaloid area, nucleus accumbens and hippocampus (molecular layer). It also produced small decreases in glucose use in the medial and lateral septal nucleus and the medial nucleus of the amygdala of -4% to -7%.

At this dose of metergoline (3 mg/kg) only the anterior amygdaloid area, the ventral tegmental area and the dentate gyrus were significantly different from saline control values by -19% to -20%. ($p < 0.05$) There is no clear demarcation since the areas which do not show significant changes still have their rates of glucose use decreased by between -13% and 17%.

Cyproheptadine (1 mg/kg) administration led to decreased glucose metabolism in the ventral tegmental area, dentate gyrus, anterior amygdaloid area and molecular layer of the hippocampus which had values 22% to 29% ($p < 0.05$) below

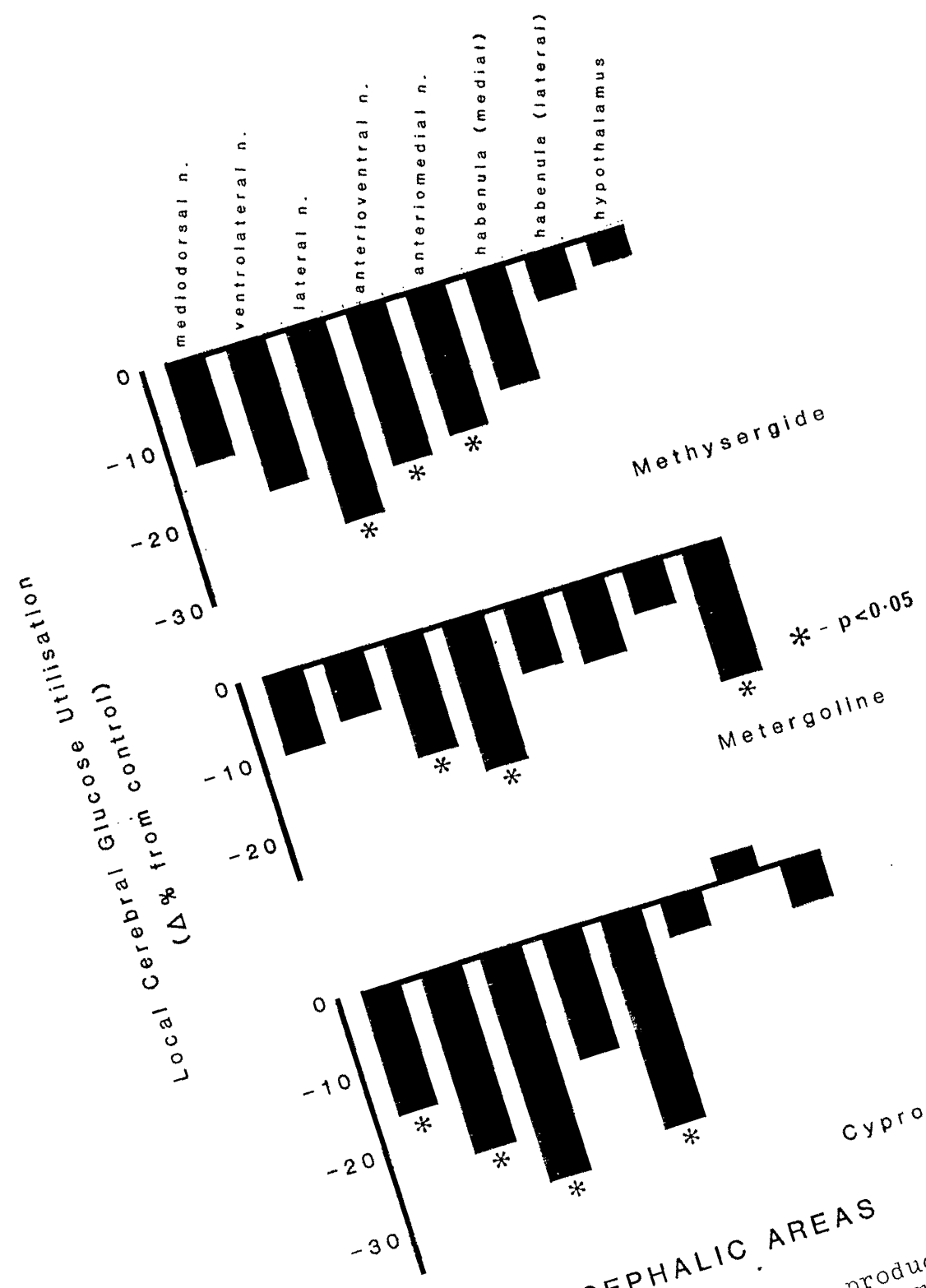

Figure 17. The pattern of response produced by methysergide (15mg/kg), metergoline (3mg/kg) and cyproheptadine (1mg/kg) in diencephalic areas. Results are given as percent differenc from control. *p: <0.05. Statistical analysis by ANOVA and Scheffe.

the level of saline controls. The nucleus accumbens, the medial nucleus of the amygdala and the medial and lateral septal nucleus were minimally affected by cyproheptadine by between +2% and -9%. (Tables 13, 15, 17)

6.3.4. Extrapyramidal Areas

The most affected areas following methysergide (15 mg/kg) treatment were the substantia nigra (pars compacta and pars reticulata) and the caudate nucleus (body, ventromedial and caudal portions.) These structures showed significant decreases of between 17% and 33% ($p < 0.05$). The other extrapyramidal areas showed decreased rates of glucose use of between 12% and 17%.

With metergoline (3 mg/kg) treatment significant decreases in glucose use were found in the substantia nigra, pars reticulata but not the pars compacta of this structure; also the globus pallidus, the caudal and ventromedial portions of the caudate nucleus but not in the body or the dorsolateral parts of the caudate nucleus.

The substantia nigra (pars compacta and pars reticulata), the caudal caudate nucleus, red nucleus, inferior olive and vestibular nucleus all have decreased rates of glucose utilisation following cyproheptadine (1 mg/kg) treatment which are -18% to -30% ($p < 0.05$) below saline control values. Non-significant changes of between -13% and -16% are found in the dorsolateral, body and ventrolateral portion of the caudate nucleus and the globus pallidus. (Tables 13,15 and 17).

6.3.5. Primary Visual and Primary Auditory Systems

There is an obvious difference in the way in which methysergide (15 mg/kg) effects the levels of glucose

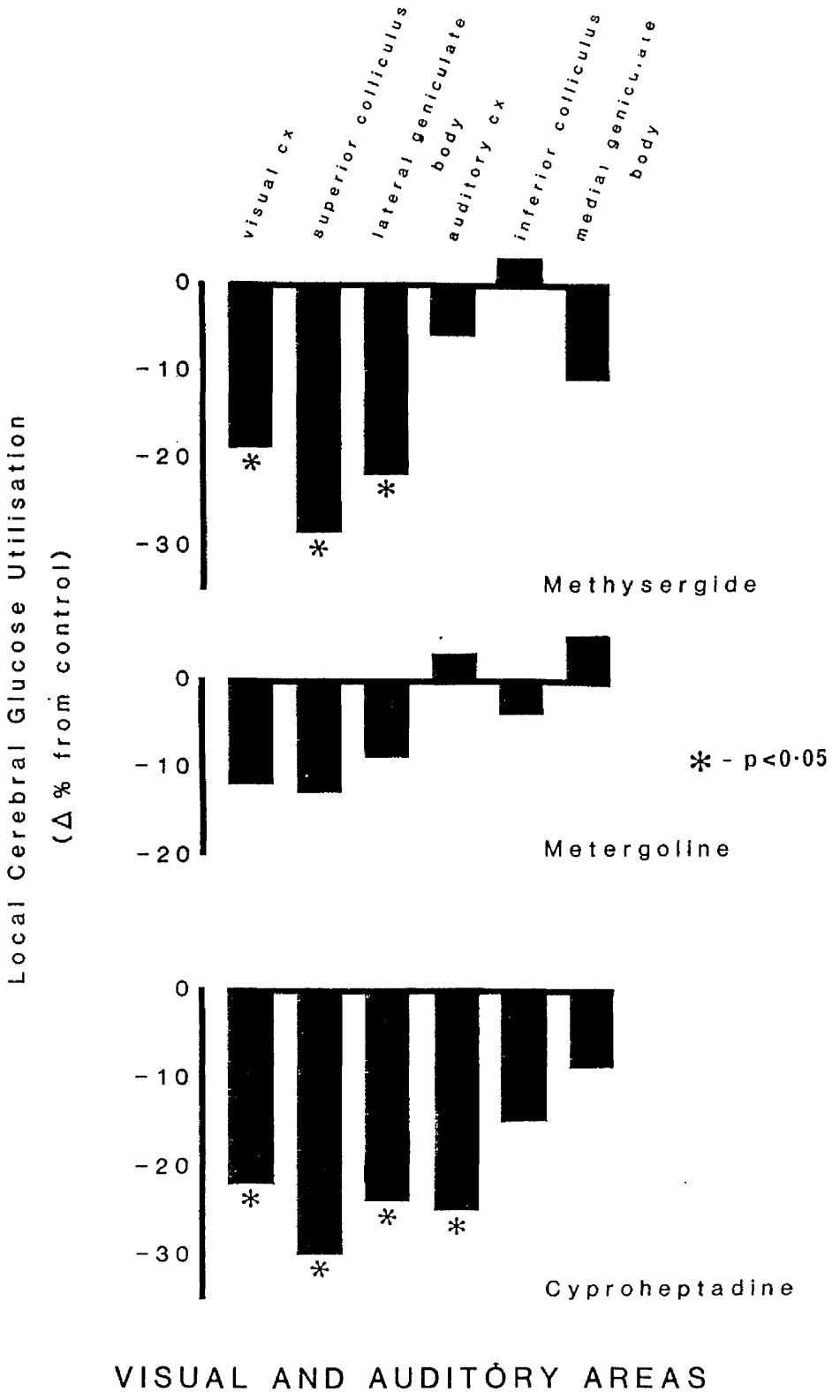

Figure 18. The pattern of response produced by methysergide (15mg/kg), metergoline (3mg/kg) and cyproheptadine (1mg/kg) in primary visual and primary auditory areas. Data are presented as percent difference from saline controls. *p: <0.05. Statistical analysis by ANOVA and Scheffe.

utilisation in visual and auditory systems. All the visual areas have significantly decreased rates of glucose use following treatment with decreases ranging between -19% and -28% ($p < 0.05$). The auditory systems are not significantly changed with effects on glucose use of between +4% and -11%. Metergoline (3 mg/kg) produced no significant changes in either visual or auditory systems. Cyproheptadine (1 mg/kg) reduced glucose use significantly in all visual areas and also in auditory cortex. (Tables 13,15 and 17 and Fig. 18)

6.3.6. Hindbrain Areas and Myelinated Fiber Tracts

Methysergide (15 mg/kg) and cyproheptadine (1 mg/kg) produce significant decreases in the raphe nuclei. Cyproheptadine also produces significant decreases in the rate of glucose use in the cerebellar nuclei. Metergoline (3 mg/kg) produces no significant changes in any of the structures measured in this category. There were no significant changes in glucose use in any of the fiber tracts areas produced by any of these putative serotonin antagonists. (Tables 13,15 and 17)

6.3.7. Comments on Results

The lack of behavioural effects displayed by the putative serotonin antagonists is in line with the finding of a recent comprehensive study of their effects on rat behaviour. (Green et al, 1981).

In a similar fashion, the lack of effect of methysergide, metergoline and cyproheptadine on blood pressure and heart rate is in keeping with the previously published data.

These putative serotonin antagonists have been shown to have little or no action on blood pressure and heart rate in normotensive rats. However, they block the blood pressure increase produced by the intracerebroventricular administration of 5HT. (Lambert et al, 1975; Lambert et al, 1978; Smith and Struyker-Boudier, 1976; Wolf et al, 1981).

The major action of these compounds was to produce a decrease in the level of cerebral function. However, it is apparent that while the pattern of response to methysergide (15mg/kg) and metergoline (3mg/kg) was similar, the actions of cyproheptadine produced quite a different pattern of response. This was seen, particularly in the cortical structures where cyproheptadine (1mg/kg) produced significant decreases in glucose use in all of the cortical areas measured. (Tables 13, 15 and 17. Fig. 15)

These results are of particular interest in two respects. The first is that these putative serotonin antagonists affect local cerebral glucose utilisation in a manner similar to putative serotonin agonists. The second, that there are greater similarities between the responses to methysergide and metergoline than there are between these compounds and cyproheptadine.

The depressive effects on local cerebral function are in keeping with the electrophysiological data of Haigler and Aghajanian, 1974 who found that methysergide, metergoline and cyproheptadine inhibit the firing rate of cells in the brain when given alone and enhanced the inhibitory actions of

5HT. A similar inhibitory action is seen in studies on cat spinal cord. (Gilbey et al, 1981; Proudfit and Anderson, 1973). Does this mean that these compounds which are potent antagonists of 5HT actions in a number of peripheral systems (Brownlee and Johnston, 1963; Day and Vane, 1963; Gaddum and Picarelli, 1957; Muller-Schweinitzer, 1980; Porquet et al, 1982; Roch E Silva et al, 1953; Sakai et al, 1979; Goodman and Gilman, 1970 for review) are agonists in the central nervous systems?

The situation is much more complex. Firstly, metergoline blocked the effects of 5HT in the cortex (Sastry and Phillis, 1977), methysergide and cyproheptadine block some, but not all, of the inhibitory responses to 5HT in the hippocampus (Segal 1975; Segal 1976) and these drugs block the 5HT-induced facilitation of the firing rate of facial motoneurones (McCall and Aghajanian, 1979; Van Der Maelen and Aghajanian, 1980). Thus, there is evidence of antagonism of at least some central serotonergic actions by these compounds. (This will be discussed more fully in the next section).

Secondly, there is in vitro evidence that putative serotonin agonists and antagonists bind to different serotonin binding sites or different forms of the same receptor. (Bennet and Snyder, 1976; Enjalbert et al, 1978; Nelson et al, 1978; Nelson et al, 1979). Thus, although LSD, 5MeO, C.P.P. and quipazine on one hand, and methysergide, cyproheptadine and metergoline on the other, produce decreases in glucose utilisation in the rat brain, they may be acting by different mechanisms. (As will be

seen in the next section of this thesis, metergoline (3mg/kg) and methysergide (15mg/kg) interact in an interesting manner with putative serotonin agonists.)

As mentioned above, the pattern of response produced by cyproheptadine was different from that following methysergide and metergoline treatment. Since this compound is nearly as potent on histamine receptors as on serotonin receptors (Stone et al, 1961) this may be due to the action of this drug on systems other than serotonergic ones. For this reason, and due to the fact that this compound has been shown to poorly block the actions of serotonin agonists (Green et al, 1981) it was used no further in these experiments.

In summary, methysergide (15mg/kg), metergoline (3mg/kg) and cyproheptadine (1mg/kg) produced decreases in local cerebral glucose utilisation. Areas sensitive to their administration were:-

Cortex	-	pyriform cortex
	-	posterior cingulate cortex
Thalamus	-	lateral nuclei
	-	anterior ventral and anterior medial nuclei
Limbic System	-	dentate gyrus
	-	anterior amygdaloid area
Extrapyramidal System	-	caudate nucleus
	-	substantia nigra.

TABLE 12

CARDIOVASCULAR DATA

Cyproheptadine (mg/kg)	Heart Rate (beats/min)		Mean Arterial Blood Pressure (mmHg)	
	Control	At Study	Control	At Study
Saline	426 ± 6	423 ± 8	132 ± 3	131 ± 3
0.1	419 ± 7	419 ± 8	128 ± 4	124 ± 3
1.0	411 ± 8	414 ± 6	128 ± 4	121 ± 4
n	6	6	6	6

Data are given as mean ± standard error of the mean
Statistical analysis by ANOVA and Scheffe.

TABLE 13

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

CYPROHEPTADINE (mg/kg)

Cerebral Structures	Saline	0.1	1.0
Parietal Cortex	94 ± 3	77 ± 4*	68 ± 4*
Sensory Motor Cortex	98 ± 4	77 ± 4*	76 ± 2*
Entorhinal Cortex	74 ± 4	57 ± 3	54 ± 2*
Pyriform Cortex	97 ± 4	74 ± 4*	69 ± 4*
Frontal Cortex	97 ± 4	77 ± 3*	64 ± 3*
Anterior Cingulate Cortex	94 ± 3	77 ± 4*	70 ± 3*
Posterior Cingulate Cortex	99 ± 4	81 ± 4	73 ± 3*
Prefrontal Cortex	124 ± 7	93 ± 4*	73 ± 2*

TABLE 13 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g./min)

	Cyproheptadine (mg/kg)		
Diencephalic Structure	Saline	0.1	1.0
Mediodorsal Thalamus	94 ± 1	79 ± 3*	79 ± 4*
Ventrolateral Thalamus	84 ± 2	65 ± 2*	65 ± 5*
Anterior-Ventral Thalamus	115 ± 3	94 ± 4*	92 ± 3*
Anterior-Medial Thalamus	113 ± 5	90 ± 4*	83 ± 2*
Lateral Thalamus	102 ± 2	73 ± 3*	72 ± 5*
Subthalamic Nucleus	79 ± 2	71 ± 3	75 ± 4
Zona Incerta	77 ± 3	73 ± 4	74 ± 3
Nucleus Reuniens	99 ± 6	81 ± 3*	74 ± 2*
Habenula (Lateral)	107 ± 3	99 ± 5	111 ± 4
Habenula (Medial)	72 ± 4	63 ± 2	68 ± 4
Hypothalamus	52 ± 3	46 ± 2	49 ± 4
Medial Forebrain Bundle	66 ± 2	68 ± 2	69 ± 4
Periventricular N.	50 ± 3	54 ± 3	51 ± 4

TABLE 13 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umol/100g/min)

	Cyproheptadine (mg/kg)		
Limbic Structures	Saline	0.1	1.0
Hippocampus (Molecular layer)	86 ± 3	67 ± 3*	60 ± 5*
Dentate Gyrus	75 ± 4	54 ± 3*	48 ± 2*
Septal Nucleus (Lateral)	56 ± 3	57 ± 4	58 ± 4
Septal Nucleus (Medial)	46 ± 3	46 ± 3	39 ± 2
Nucleus Accumbens	80 ± 2	73 ± 4	60 ± 3*
Amygdala (Medial)	47 ± 3	49 ± 3	41 ± 3
Anterior Amygdaloid Area	84 ± 2	65 ± 4*	57 ± 3*
Ventral Tegmental Area	69 ± 4	49 ± 3*	52 ± 4

TABLE 13 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (u mols/100g/min)

	Cyproheptadine (mg/kg)		
Extrapyramidal Structures	Saline	0.1	1.0
Caudate Nucleus (Dorsolateral)	94 ± 4	79 ± 3*	80 ± 3*
Caudate Nucleus (Central)	83 ± 2	72 ± 4	70 ± 2*
Caudate Nucleus (Ventromedial)	84 ± 4	71 ± 3	63 ± 4*
Caudate Nucleus (Caudal)	82 ± 2	67 ± 1*	66 ± 3*.
Globus Pallidus	54 ± 3	47 ± 2	42 ± 2*
Substantia Nigra (Pars Compacta)	81 ± 3	57 ± 3*	54 ± 3*
Substantia Nigra (Pars Reticulata)	60 ± 2	43 ± 2*	41 ± 1*
Red Nucleus	76 ± 3	57 ± 4*	59 ± 4*
Inferior Olive	75 ± 4	55 ± 4*	57 ± 4*
Vestibular Nucleus	109 ± 6	77 ± 3*	83 ± 4*

TABLE 13 contd.

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

		Cyproheptadine (mg/kg)		
Primary Auditory		Saline	0.1	1.0
Auditory Cortex		139 ± 4	106 ± 5*	105 ± 4*
Medial Geniculate		115 ± 4	93 ± 3	98 ± 4
Inferior Colliculus		168 ± 6	150 ± 4	153 ± 4
Lateral Lemniscus		112 ± 3	86 ± 4*	99 ± 4
Superior Olive		151 ± 4	124 ± 7	107 ± 2*
Cochlear Nucleus		141 ± 3	110 ± 5*	119 ± 8*
Primary Visual				
Visual Cortex		99 ± 4	71 ± 3*	77 ± 4*
Lateral Geniculate	Dors l	96 ± 4	82 ± 3*	70 ± 4*
	Ventr l	89 ± 3	79 ± 3*	63 ± 4*
Superior Colliculus	Superficial	84 ± 1	68 ± 1*	63 ± 4*
Superior Colliculus	Deep	80 ± 3	59 ± 2*	61 ± 4*

TABLE 13 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

	Cyproheptadine (mg/kg)		
Hindbrain Structures	Saline		
Cerebellum Hemisphere	51 ± 4	38 ± 2*	43 ± 1*
Cerebellum Nuclei	89 ± 3	67 ± 3*	71 ± 3*
Cerebellum Vermis	96 ± 5	69 ± 4*	73 ± 4
Cerebellum White Matter	35 ± 2	30 ± 2	32 ± 2
Dorsal Raphe Nucleus	95 ± 3	67 ± 3*	67 ± 4*.
Median Raphe Nucleus	96 ± 3	70 ± 3*	75 ± 4*
Pontine Reticular Formation	61 ± 1	50 ± 2*	50 ± 2*
Myleinated Fiber Tracts			
Corpus Callosum	34 ± 2	32 ± 2	31 ± 3
Genu of the Corpus Callosum	27 ± 2	27 ± 1	27 ± 2
Internal Capsule	33 ± 1	29 ± 2	27 ± 3
N	6	6	6

Data are given as mean ± standard error of the mean in umols/100g/min. *p: <0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

TABLE 14

CARDIOVASCULAR DATA

	Heart Rate (beats/min)		Mean Arterial Blood Pressure (mmHg)	
Methysergide	Control	At Study	Control	At Study
Saline	422 ± 6	418 ± 7	127 ± 3	130 ± 4
0.3	418 ± 5	423 ± 5	125 ± 4	127 ± 2
3.0	418 ± 7	418 ± 6	126 ± 3	130 ± 3
n	6	6	6	6

Data is given as mean ± standard error of the mean.

Statistical analysis by ANOVA and Scheffe.

TABLE 15

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

Methysergide (mg/kg)

Cerebral Structures	Saline	5	15
Parietal Cortex	94 ± 3	90 ± 5	82 ± 2
Sensory Motor Cortex	98 ± 5	96 ± 3	89 ± 6
Entorhinal Cortex	74 ± 4	65 ± 4	66 ± 3
Pyriform Cortex	97 ± 4	89 ± 3	96 ± 1
Frontal Cortex	97 ± 4	98 ± 4	80 ± 2*
Anterior Cingulate Cortex	94 ± 3	88 ± 3	72 ± 2*
Posterior Cingulate Cortex	99 ± 4	85 ± 3	77 ± 3*
Prefrontal Cortex	124 ± 7	116 ± 4	81 ± 2*

TABLE 15 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

Methysergide (mg/kg)

Diencephalic Structures	Saline	5	15
Mediodorsal Thalamus	94 ± 1	94 ± 3	82 ± 3
Ventrolateral Thalamus	84 ± 2	83 ± 4	69 ± 4
Anterior-Ventral Thalamus	115 ± 6	107 ± 3	92 ± 6*
Anterior-Medial Thalamus	113 ± 5	106 ± 3	93 ± 2*
Lateral Thalamus	102 ± 2	96 ± 3	77 ± 4*
Subthalamic Nucleus	79 ± 2	81 ± 4	69 ± 3
Zona Incerta	77 ± 3	75 ± 2	72 ± 4
Nucleus Reuniens	99 ± 6	91 ± 2	83 ± 4
Habenula (Lateral)	107 ± 3	100 ± 4	101 ± 3
Habenula (Medial)	72 ± 4	68 ± 3	61 ± 5
Hypothalamus	52 ± 3	51 ± 3	50 ± 6
Medial Forebrain Bundle	66 ± 2	70 ± 2	72 ± 4
Periventricular Nucleus	50 ± 3	51 ± 3	51 ± 3

TABLE 15 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umol/100g/min)

Methysergide (mg/kg)

Limbic Structures	Saline	5	15
Hippocampus (Molecular Layer)	86 ± 3	84 ± 1	71 ± 3*
Dentate Gyrus	75 ± 4	67 ± 3	57 ± 3*
Septal Nucleus (Lateral)	56 ± 3	59 ± 3	54 ± 5
Septal Nucleus (Medial)	46 ± 3	42 ± 2	43 ± 2
Nucleus Accumbens	80 ± 2	79 ± 2	66 ± 2
Amygdala (Medial)	47 ± 3	50 ± 2	45 ± 2
Anterior Amygdaloid Area	84 ± 2	81 ± 3	68 ± 2*
Ventral Tegmental Area	69 ± 4	66 ± 4	47 ± 2*

TABLE 15 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

Extrapyramidal Structure	Methysergide (mg/kg) Saline	5	15
Caudate Nucleus (Dorsolateral)	94 ± 4	86 ± 2	80 ± 1
Caudate Nucleus (Central)	83 ± 2	79 ± 3	68 ± 2*
Caudate Nucleus (Ventromedial)	84 ± 4	82 ± 3	66 ± 3*
Caudate Nucleus (Caudal)	82 ± 2	82 ± 3	63 ± 3*
Globus Pallidus	54 ± 3	51 ± 2	46 ± 3
Substantia Nigra (Pars Compacta)	81 ± 3	76 ± 3	65 ± 4*
Substantia Nigra (Pars Reticulata)	60 ± 2	61 ± 2	40 ± 2*
Red Nucleus	76 ± 4	70 ± 2	66 ± 2
Inferior Olive	75 ± 4	80 ± 3	62 ± 5
Vestibular Nucleus	109 ± 7	96 ± 4	96 ± 3

TABLE 15 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

		Methysergide (mg/kg)		
Primary Auditory		Saline	5	15
Auditory Cortex		139 ± 4	136 ± 3	130 ± 4
Medial Geniculate		115 ± 4	110 ± 2	102 ± 3
Inferior Colliculus		168 ± 7	181 ± 5	173 ± 4
Lateral Lemniscus		112 ± 3	104 ± 2	103 ± 4
Superior Olive		151 ± 4	156 ± 3	157 ± 4
Cochlear Nucleus		141 ± 4	136 ± 3	130 ± 4
Primary Visual				
Visual Cortex		99 ± 3	92 ± 3	80 ± 3*
Lateral Geniculate	dorsal	96 ± 4	94 ± 2	77 ± 2*
	ventral	89 ± 5	87 ± 1	69 ± 2*
Superior Colliculus S		84 ± 1	80 ± 4	62 ± 4*
Superior Colliculus D		80 ± 3	81 ± 3	58 ± 4*

TABLE 15 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

Methysergide (mg/kg)

Hindbrain Structures	Saline	5	15
Cerebellum Hemisphere	51 ± 4	46 ± 4	43 ± 3
Cerebellum Nuclei	89 ± 4	89 ± 2	80 ± 3
Cerebellum Vermis	96 ± 5	103 ± 6	75 ± 4
Cerebellum White Matter	35 ± 2	34 ± 2	36 ± 3
Dorsal Raphe Nucleus	95 ± 3	89 ± 3	68 ± 5*
Median Raphe Nucleus	96 ± 5	88 ± 2	69 ± 5*
Pontine Reticular Formation	61 ± 2	55 ± 2	51 ± 4
Myelinated Fiber Tracts			
Corpus Callosum	34 ± 2	34 ± 3	32 ± 2
Genu of the Corpus Callosum	27 ± 2	30 ± 2	25 ± 4
Internal Capsule	33 ± 1	34 ± 2	28 ± 2
n	6	6	6

Data are given as mean ± standard error of the mean in umols/100g/min. *p:<0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

TABLE 16

CARDIOVASCULAR DATA

	Heart Rate (beats/min)		Mean Arterial Blood Pressure (mmHg)	
Metergoline	Control	At Study	Control	At Study
Saline	409 ± 4	411 ± 8	125 ± 4	130 ± 3
0.1	412 ± 5	422 ± 7	122 ± 3	126 ± 4
1.0	415 ± 8	418 ± 5	128 ± 3	123 ± 3
n	6	6	6	6

Data are given as mean ± standard error of the mean.
Statistical analysis by ANOVA and Scheffe.

TABLE 17

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

Cerebral Structures	Metergoline (mg/kg) Saline	1	3
Parietal Cortex	92 ± 3	91 ± 3	84 ± 3
Sensory Motor Cortex	96 ± 2	96 ± 3	91 ± 3
Entorhinal Cortex	76 ± 3	72 ± 3	73 ± 3
Pyriform Cortex	96 ± 3	92 ± 3	64 ± 3*
Frontal Cortex	94 ± 3	96 ± 2	92 ± 3
Anterior Cingulate Cortex	93 ± 2	97 ± 3	85 ± 2
Posterior Cingulate Cortex	98 ± 3	94 ± 3	86 ± 3*
Prefrontal Cortex	120 ± 4	110 ± 7	94 ± 3*

TABLE 17 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

Metergoline (mg/kg)

Diencephalic Structures	Saline	1	3
Mediodorsal Thalamus	89 ± 3	81 ± 3	85 ± 4
Ventrolateral Thalamus	86 ± 2	78 ± 2	68 ± 3*
Anterior-Ventral Thalamus	118 ± 4	118 ± 3	106 ± 5
Anterior-Medial Thalamus	110 ± 3	113 ± 4	97 ± 5
Lateral Thalamus	102 ± 1	104 ± 3	87 ± 4*
Subthalamic Nucleus	79 ± 2	80 ± 3	76 ± 4
Zona Incerta	79 ± 4	76 ± 2	75 ± 2
Nucleus Reuniens	97 ± 4	94 ± 3	94 ± 3
Habenula (Lateral)	101 ± 3	104 ± 5	101 ± 4
Habenula (Medial)	68 ± 4	65 ± 3	61 ± 3
Hypothalamus	52 ± 2	54 ± 2	47 ± 2
Medial Forebrain Bundle	60 ± 2	60 ± 1	56 ± 3
Periventricular Nucleus	51 ± 2	52 ± 2	55 ± 3

TABLE 17 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umol/100g/min)

	Metergoline (mg/kg)		
Limbic Structures	Saline	1	3
Hippocampus (Molecular Layer)	84 ± 3	81 ± 3	75 ± 3
Dentate Gyrus	77 ± 3	75 ± 3	61 ± 3*
Septal Nucleus (Lateral)	51 ± 3	48 ± 3	49 ± 2
Septal Nucleus (Medial)	42 ± 3	40 ± 2	38 ± 2
Nucleus Accumbens	76 ± 3	75 ± 2	70 ± 3
Amygdala (Medial)	45 ± 3	45 ± 2	40 ± 1
Anterior Amygdaloid Area	86 ± 2	78 ± 3	66 ± 3*
Ventral Tegmental Area	71 ± 3	68 ± 4	56 ± 3*

TABLE 17 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

Metergoline (mg/kg)

Extrapyramidal Structures	Saline	1	3
Caudate Nucleus (Dorsolateral)	92 ± 3	86 ± 4	88 ± 3
Caudate Nucleus (Central)	88 ± 3	85 ± 3	74 ± 5
Caudate Nucleus (Ventromedial)	86 ± 2	82 ± 3	71 ± 3*
Caudate Nucleus (Caudal)	86 ± 3	82 ± ?	71 ± 3*
Globus Pallidus	55 ± 2	51 ± 3	46 ± 2
Substantia Nigra (Pars Compacta)	76 ± 3	74 ± 2	73 ± 3
Substantia Nigra (Pars Reticulata)	58 ± 2	56 ± 3	46 ± 1*
Red Nucleus	77 ± 2	71 ± 3	67 ± 4
Inferior Olive	80 ± 3	71 ± 4	69 ± 4
Vestibular Nucleus	106 ± 4	98 ± 3	92 ± 3

TABLE 17 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

Metergoline (mg/kg)

		Saline	1	3
Primary Auditory				
Auditory Cortex		136 ± 3	133 ± 3	143 ± 5
Medial Geniculate		111 ± 2	117 ± 2	110 ± 4
Inferior Colliculus		177 ± 7	181 ± 2	176 ± 7
Lateral Lemniscus		110 ± 3	104 ± 4	102 ± 3
Superior Olive		150 ± 3	149 ± 4	157 ± 3
Cochlear Nucleus		144 ± 4	142 ± 3	143 ± 8
Primary Visual				
Visual Cortex		94 ± 3	86 ± 3	87 ± 3
Lateral Geniculate	dorsal	96 ± 4	88 ± 3	77 ± 2*
	ventral	91 ± 3	86 ± 4	69 ± 2*
Superior Colliculus	superficial	86 ± 3	81 ± 1	79 ± 2
Superior Colliculus	deep	83 ± 3	82 ± 2	73 ± 2

TABLE 17 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (umols/100g/min)

Metergoline (mg/kg)

Hindbrain Structures	Saline	1	3
Cerebellum Hemisphere	52 ± 3	53 ± 3	47 ± 2
Cerebellum Nuclei	87 ± 2	85 ± 2	84 ± 3
Cerebellum Vermis	89 ± 3	90 ± 1	82 ± 6
Cerebellum White Matter	33 ± 2	31 ± 2	34 ± 1
Dorsal Raphe Nucleus	91 ± 3	93 ± 2	83 ± 2
Median Raphe Nucleus	94 ± 3	95 ± 3	88 ± 2
Pontine Reticular Formation	58 ± 2	56 ± 2	57 ± 1
Myelinated Fiber Tracts			
Corpus Callosum	34 ± 1	32 ± 1	34 ± 2
Genu of the Corpus Callosum	29 ± 2	29 ± 2	27 ± 2
Internal Capsule	31 ± 1	30 ± 3	32 ± 3
n	6	6	6

Data are given as mean ± standard error of the mean in umols/100g/min. *p: <0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

VII. THE EFFECTS OF METHYSERGIDE ON THE ACTION OF PUTATIVE SEROTONIN AGONISTS

7.1. Behavioural Effects

From qualitative observations only, this dose of methysergide (15mg/kg) was capable of blocking or attenuating behavioural effects produced by L.S.D. (15ug/kg) 5MeO (750ug/kg), quipazine (3mg/kg) and C.P.P. (2.5mg/kg). There was some hyperactivity and increased sniffing following agonist administration but this was not as marked as could be observed following the agonist alone. These effects were also of short duration.

7.2. Cardiovascular Effects

As has been described previously the putative agonists reduce heart rate from saline control values; L.S.D. at a dose of 15 ug/kg does not do this significantly. However, the overall effect was the reduction in heart rate of between 6% and 25% (Fig. 19, Tables 18,20,22,24). LSD administration produced little effect on mean arterial blood pressure. Quipazine (3mg/kg), 5MeO (750 ug/kg) and C.P.P. (2.5mg/kg) increased mean arterial blood pressure by between 13% and 35%. ($p<0.05$). (Fig. 20)

7.3. Local Cerebral Glucose Utilisation

7.3.1. Cortical Areas

In the cortical structures measured, methysergide (15mg/kg) did not block any of the responses to LSD (15 ug/kg). There was, however, a significant increase in the effects of LSD on glucose utilisation in the pyriform cortex from $-20 \pm 5\%$ ($p<0.05$) with LSD alone to $-54 \pm 6\%$ ($p<0.05$) following LSD and methysergide administration. In the

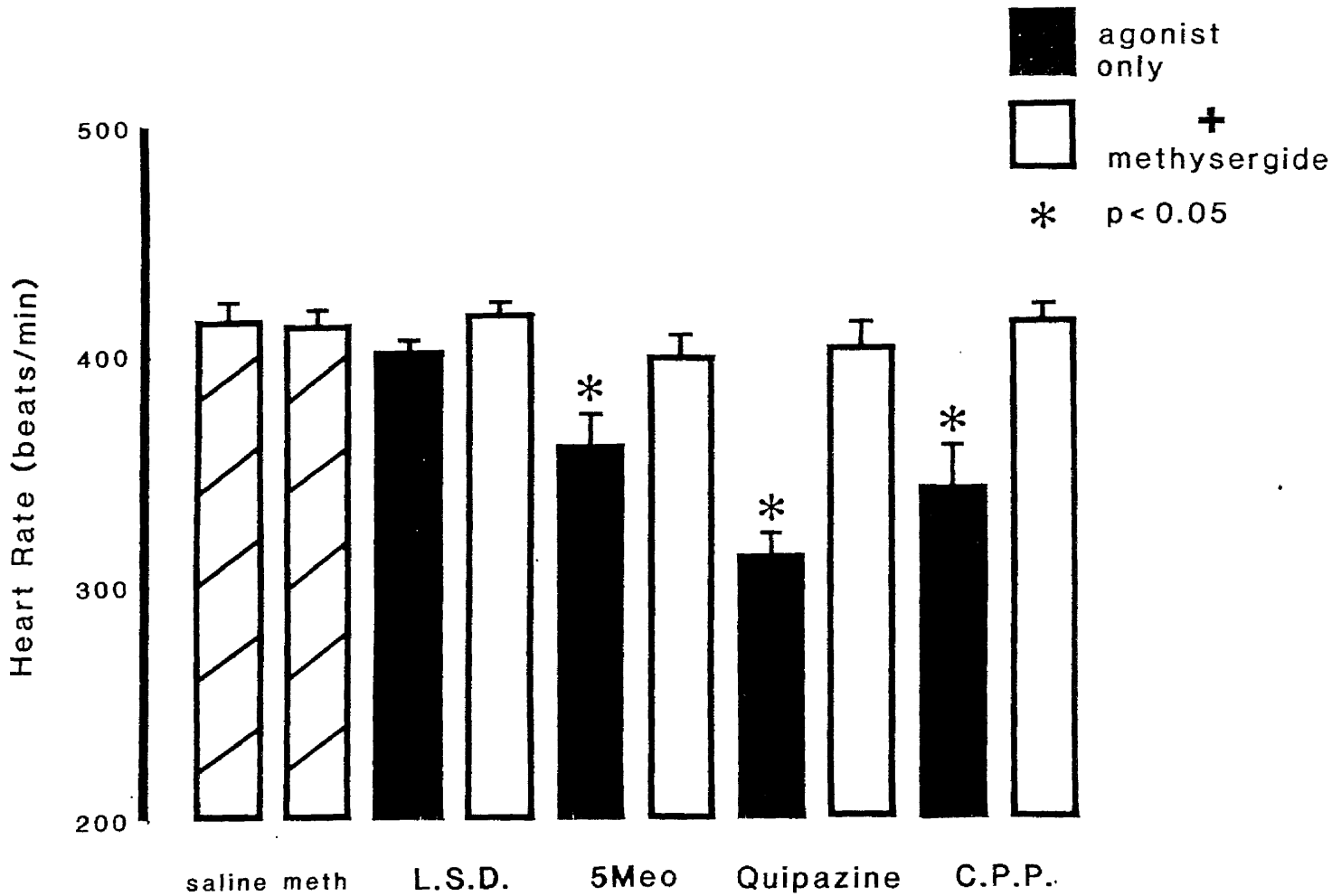

Figure 19. The effects of methysergide pretreatment on the heart rate responses to the administration of putative serotonin agonists. Key:- meth = methysergide (15mg/kg); L.S.D. (15ug/kg); 5MeO (750ug/kg); quipazine (3mg/kg); C.P.P. (2.5mg/kg). * p:<0.05. Statistical analysis by ANOVA and Scheffe with respect to the saline controls.

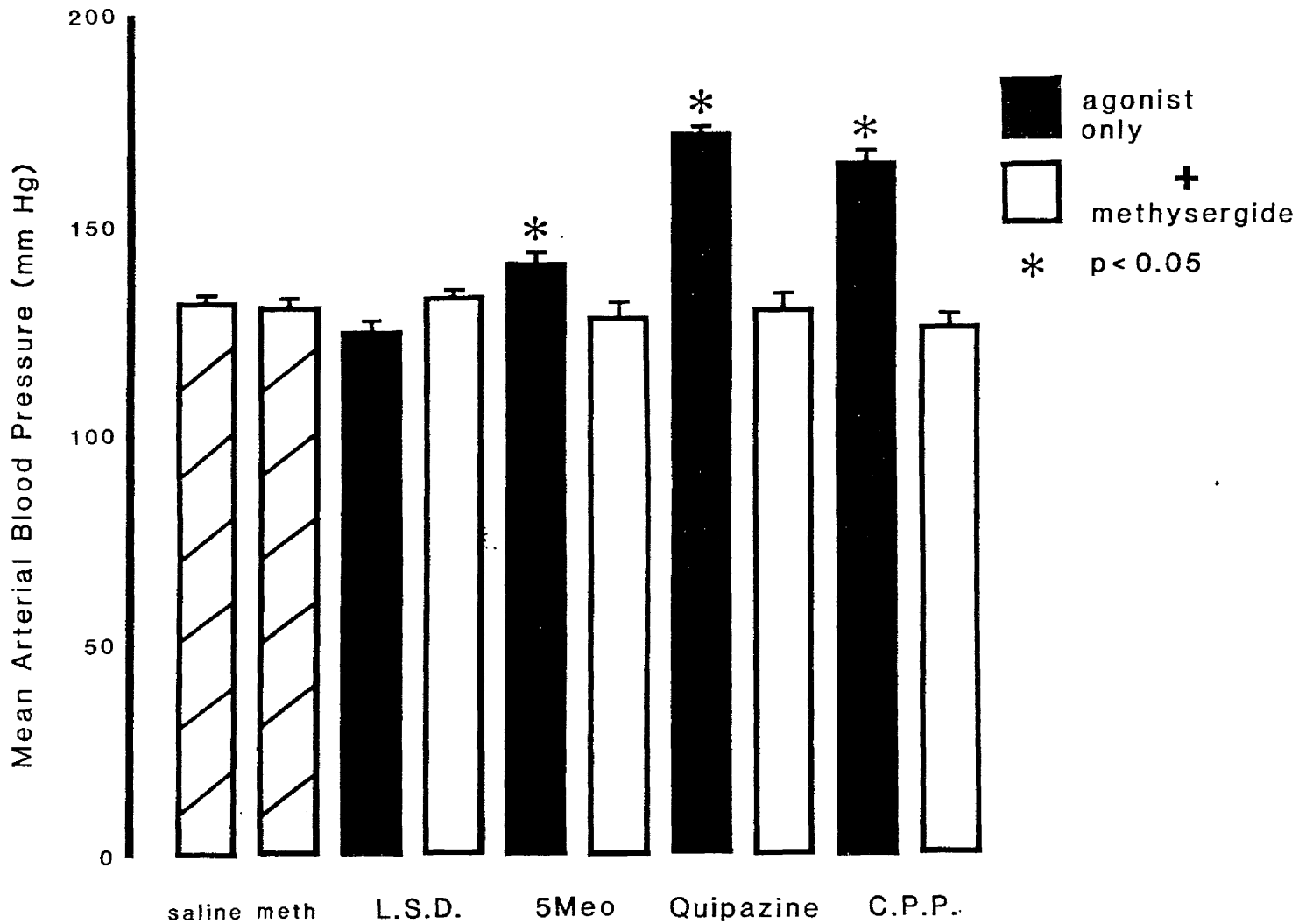

Figure 20. The effects of methysergide pretreatment on the blood pressure response to the administration of putative serotonin agonists. Key:- meth = methysergide (15mg/kg) L.S.D. (15ug/kg); 5MeO (750 ug/kg); quipazine (3mg/kg); C.P.P. (2.5mg/kg). *p:<0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

other cortical structures there was a tendency for methysergide pretreatment to increase the LSD - induced changes in glucose utilisation.

Methysergide blocked or attenuated decreases in the rate of glucose use elicited by 5MeO (750 ug/kg) in the parietal cortex, pyriform cortex, frontal cortex, anterior and posterior cingulate cortices. For example, in the anterior cingulate cortex, 5MeO alone decreased glucose use by -26 ± 4% ($p < 0.05$). In combination with methysergide there was a 9 ± 4% increase in glucose utilisation. (Fig. 21) In the other cortical structures the pre-administration of methysergide had no effect on the 5MeO-induced response of glucose utilisation.

Quipazine (3mg/kg) produced significant decreases in glucose utilisation in 6 our of 9 cortical areas measured. Of these, the pre-administration of methysergide blocked or diminished the response to quipazine in all but one area, the entorhinal cortex.

The actions of C.P.P. (2.5mg/kg) on cortical glucose utilisation were wholly or partially blocked by methysergide only in the anterior and posterior cingulate cortices. The other cortical structures respond in a similar manner to C.P.P. whether alone or in combination with methysergide. (Tables 19,21,23,25: Fig. 21)

7.3.2. Diencephalic Areas

Methysergide blocked or attenuated the LSD - induced decreases in glucose utilisation in the ventral and medial portions of the anterior thalamic nucleus, the lateral thalamic nucleus, the lateral and medial habenula and the zona incerta. (Table 19)

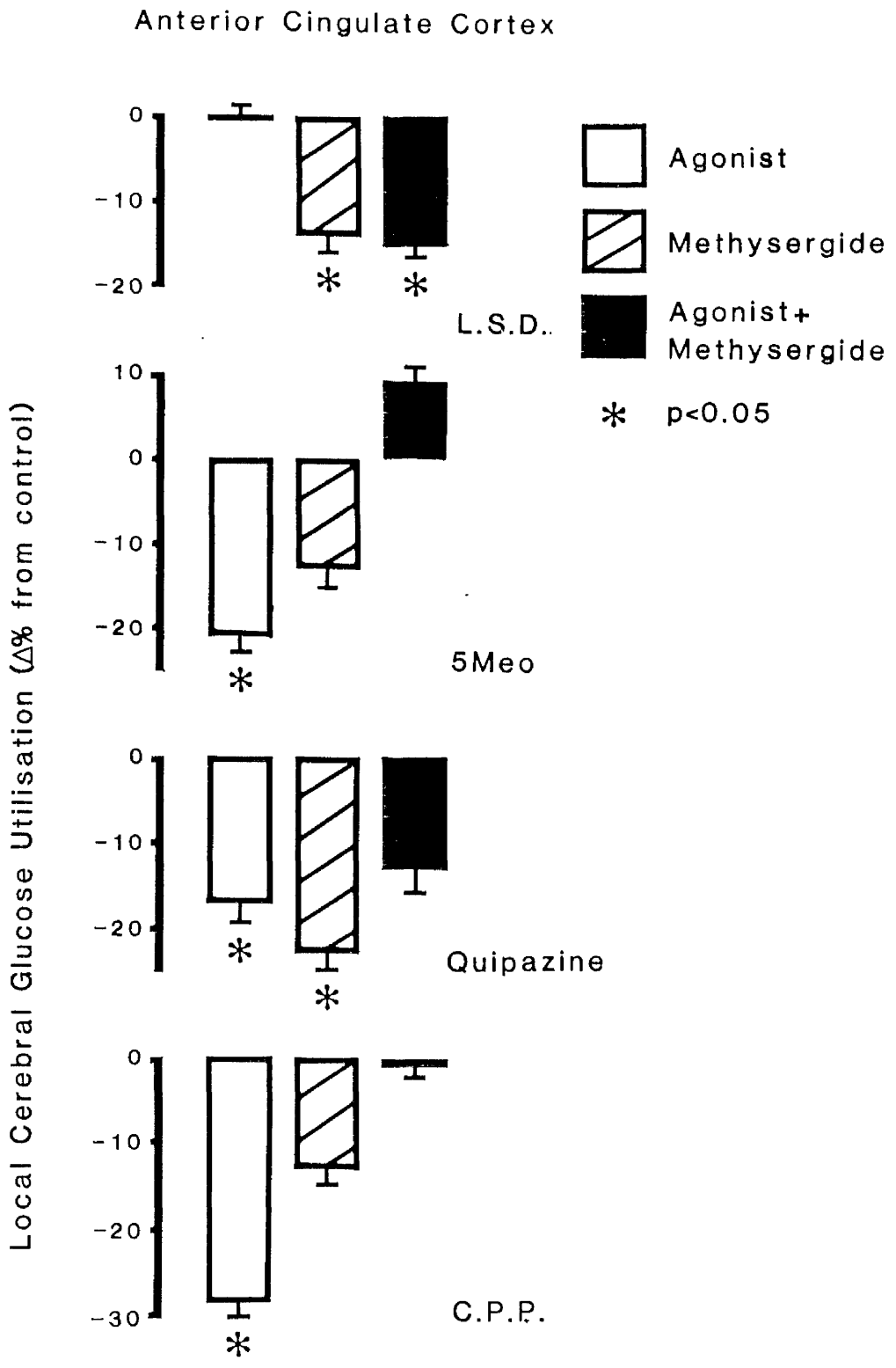

Figure 21. The effect of methysergide (15mg/kg) pretreatment on the response of glucose utilisation in the anterior cingulate cortex to the administration of putative serotonin agonists: L.S.D. (15ug/kg); 5MeO (750ug/kg); quipazine (3mg/k, and C.P.P. (2.5 mg/kg). *p: <0.05 with respect to saline controls. Statistical analysis by ANOVA and Scheffe.

In the diencephalic areas which responded significantly to 5MeO alone, the pretreatment of methysergide blocked or reduced the effect of this drug on glucose use. These changes were particularly noticeable in anterior ventral thalamus where 5MeO alone elicited a 23 ± 7% ($p < 0.05$) decrease in glucose use but in combination with methysergide the response was only -5 ± 6%. (Table 21; Fig. 22)

The anterior ventral and anterior medial portions of the thalamus have significantly decreased levels of glucose use following quipazine treatment. These areas showed no significant changes in glucose utilisation following methysergide pretreatment unlike the lateral thalamic nucleus where methysergide had no effect on the response to quipazine. The nucleus reuniens and periventricular nucleus of the hypothalamus where quipazine produced increases in glucose use also failed to respond significantly to this drug following methysergide administration. (Table 23)

Methysergide blocked or diminished the effects of C.P.P. on the rates of glucose use in all the areas which respond significantly to this drug alone. The one exception to this being the ventrolateral nucleus of the thalamus where the response to C.P.P. administration was approximately the same whether given alone or in combination with methysergide. C.P.P. alone increased glucose use in the medial habenula by 3 ± 4%. Following methysergide administration C.P.P. reduces the rate of glucose use in the medial habenula by 18 ± 4% ($p < 0.05$).

7.3.3. Limbic Areas

Methysergide/

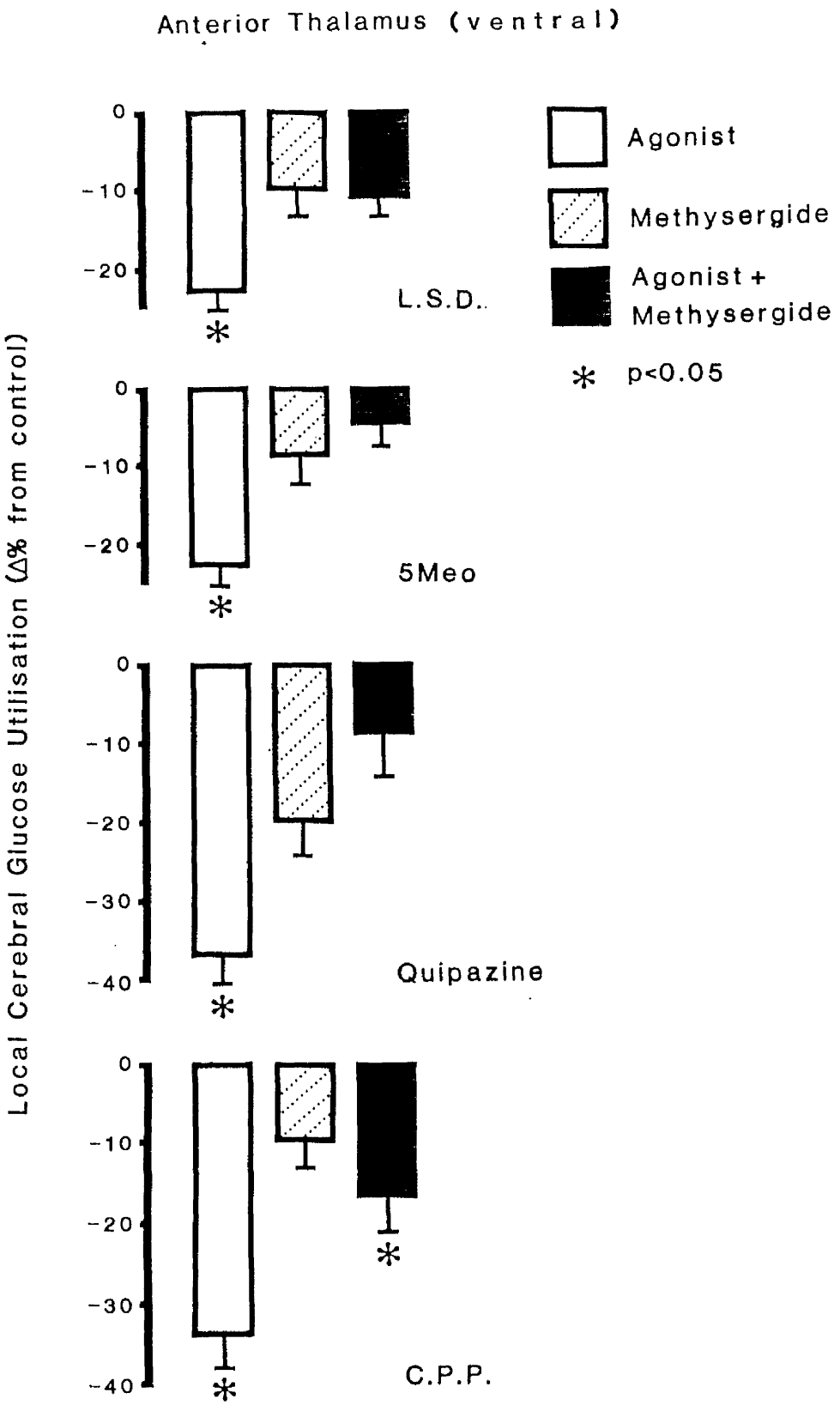

Figure 22. The effect of methysergide (15mg/kg) pretreatment on the response of glucose utilisation in the anterior ventral thalamus to the administration of putative serotonin agonists: L.S.D. (15ug/kg); 5MeO (750ug/kg) quipazine (3mg/kg) and C.P.P. (2.5 mg/kg). * $p:<0.05$. with respect to saline controls. Statistical analysis by ANOVA and Scheffe.

Methysergide (15mg/kg) affected the limbic responses to LSD (15 ug/kg), in the nucleus accumbens, dentate gyrus and the ventral tegmental area; where the effects of LSD on glucose utilisation are reduced by methysergide pre-administration.

5MeO (750 ug/kg) on the other hand, significantly reduced glucose utilisation in all the limbic areas. These effects are all blocked by methysergide, with the exception of the ventral tegmental area.

Quipazine only produces significant changes in glucose utilisation in one limbic area, the dentate gyrus at this dose (3mg/kg) where a decrease in glucose utilisation was unaffected by methysergide administration. (Fig. 23)

Significant reductions in glucose use were found in the dentate gyrus, medial septal nucleus, nucleus accumbens, anterior amygdaloid area and ventral tegmental area following C.P.P. (2.5 mg/kg) administration. Of these, the responses of the medial septal nucleus and nucleus accumbens, were blocked and those of the dentate gyrus, anterior amygdaloid area and ventral tegmental area were unaffected by methysergide pretreatment. (Fig. 23)

Furthermore, the hippocampus (molecular layer) which shows a $-9 \pm 3\%$ decrease in glucose use following C.P.P. alone, now demonstrates a $-19 \pm 3\%$ ($p < 0.05$) decrease in the rate of glucose utilisation following C.P.P. and methysergide.

7.3.4. Extrapyramidal Areas

LSD (15 ug/kg) produced significant decreases in glucose use in the four portions of caudate nucleus measured and the substantia nigra, pars compacta and pars reticulata. However, whilst methysergide (15mg/kg) blocked completely

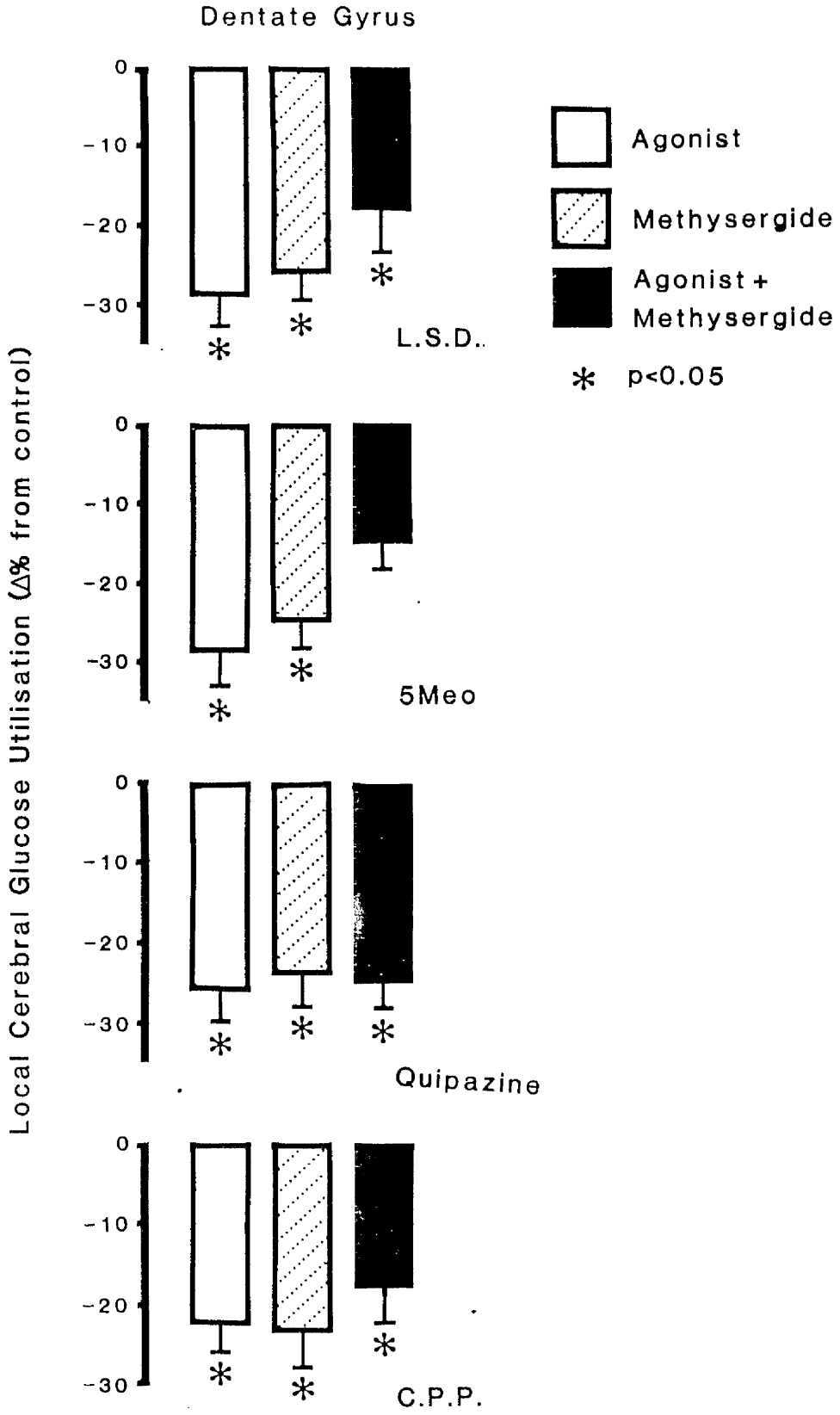

Figure 23. The effect of methysergide (15mg/kg) pretreatment on the response of glucose utilisation in the dentate gyrus to the administration of putative serotonin agonists: LSD (15ug/kg); 5MeO (750ug/kg); quipazine (3mg/kg) and C.P.P. (2.5mg/kg). * p:<0.05. with respect to saline controls. Statistical analysis by ANOVA and Scheffe.

the actions of LSD on the dorsolateral, central, ventromedial and caudal parts of the caudate nucleus, it failed to affect significantly, the responses of the substantia nigra to LSD treatment.

5MeO (750 ug/kg) induced large significant decreases in glucose use in all the extrapyramidal structures measured. With the exception of the vestibular nucleus which is unaffected, all these responses are blocked or reduced by methysergide pretreatment.

Quipazine (3mg/kg) significantly decreased the rate of glucose use in only two areas of the caudate nucleus, ventromedial and caudal, and the substantia nigra, pars compacta and reticulata. None of these responses were markedly affected by methysergide treatment.

C.P.P. (2.5mg/kg) produced a very similar pattern of response in the caudate nucleus and substantia nigra as quipazine. Methysergide did not seriously affect any of these actions of C.P.P. However the inferior olive had a decreased rate of glucose utilisation of -11 $\pm$ 3% following C.P.P. alone and a decrease of -25 $\pm$ 3% ($p<0.05$) following C.P.P. and methysergide. (Tables 19,21,23, 25; Fig. 24)

7.3.5. Primary Visual and Primary Auditory Areas

LSD (15 ug/kg) affected only one area of auditory function significantly; the nucleus of the lateral lemniscus. Methysergide had no effect on the response of this structure to LSD. However, it increased to significant levels the responses of auditory cortex and superior olivary nucleus. In contrast, LSD reduced glucose utilisation in all of the

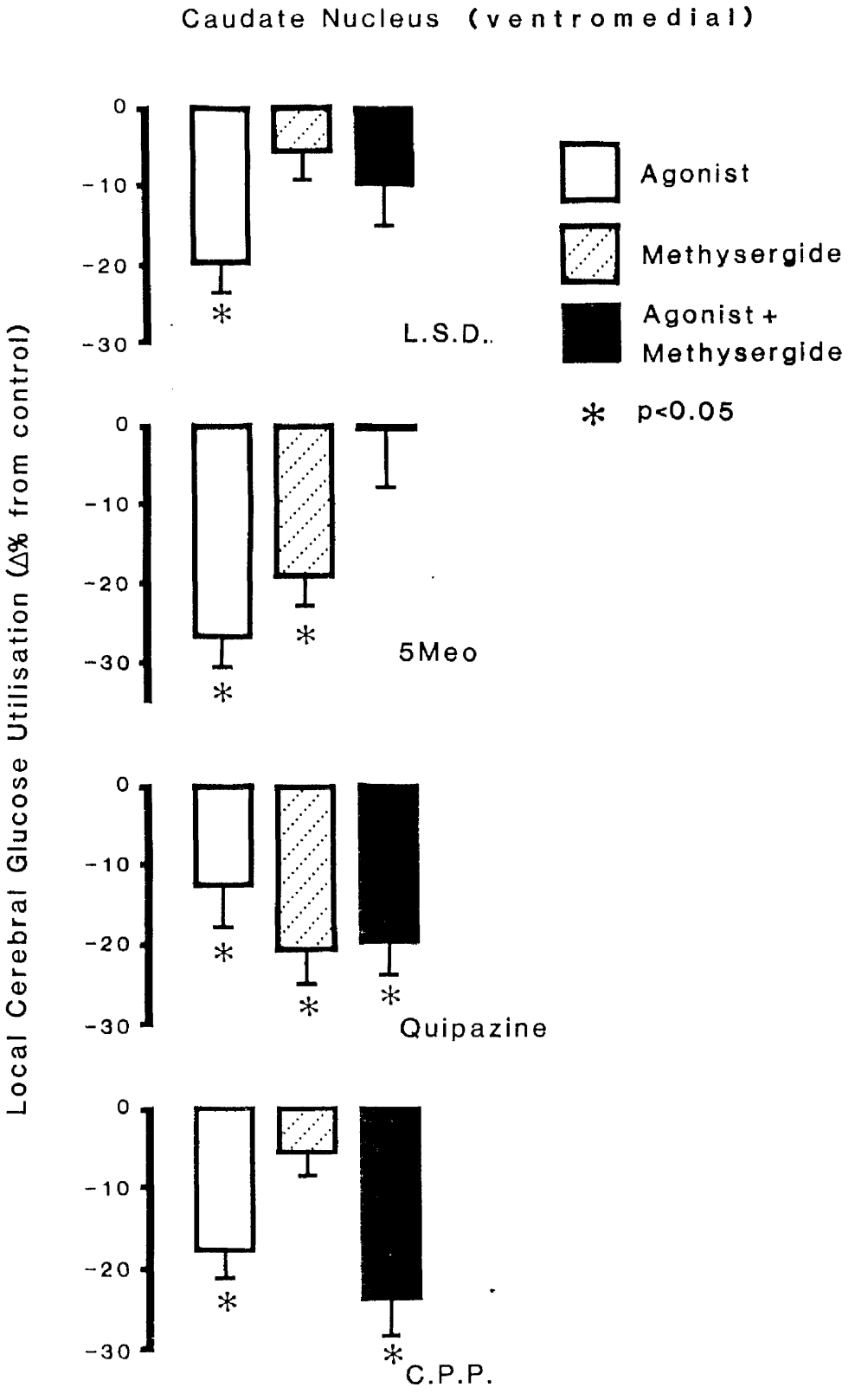

Figure 24. The effect of methysergide (15mg/kg) pretreatment on the response of glucose utilisation in the caudate nucleus (ventro medial) to the administration of putative serotonin agonists: L.S.D. (15ug/kg); 5MeO (750 ug/kg); quipazine (3mg/kg) and C.P.P. (2.5mg/kg). *p: <0.05. with respect to saline controls. Statistical analysis by ANOVA and Scheffe.

primary visual areas measured. Methysergide blocked all of these effects.

5MeO decreased the rate of glucose use significantly in the medial geniculate body and lateral lemniscus. These responses are blocked, and unaffected, respectively by methysergide administration. In primary visual areas 5MeO reduced glucose utilisation in the superior colliculus and lateral geniculate body but not visual cortex. Methysergide blocked completely the actions of 5MeO on the superior colliculus and the dorsal portion of the lateral geniculate body but had no effect on the 5MeO induced response of the ventral part of the lateral geniculate body.

Quipazine had only minimal effects on the glucose catabolism of the primary auditory areas at this dose. Quipazine did, however, reduce glucose use in visual-related cortex, lateral geniculate body and the superior colliculus (superficial layer). This latter effect was not blocked by methysergide but the actions of quipazine on the rate of glucose use in the visual cortex and lateral geniculate body were reduced to nonsignificance.

C.P.P.(2.5 mg/kg), unlike the other agonists used, reduced glucose use in all of the primary auditory areas with the exception of the inferior colliculus. Methysergide had no effect on any of these responses. Of the C.P.P. - induced effects on the visual system, only the response of visual cortex was blocked by.methysergide.

7.3.6. Hindbrain Areas

LSD produced significant changes in the level of glucose

use only in the dorsal and median raphe nuclei. These responses were unaffected by methysergide administration.

5MeO produced significant decreases in the cerebellar hemisphere and vermis, the pontine reticular formation, and the median and dorsal raphe nuclei. Only the effects of 5MeO on the cerebellar hemispheres were blocked by methysergide pre-administration. The rest were unaffected. Quipazine produced no significant changes in glucose use in any of the hindbrain areas. The combination of quipazine and methysergide did, however, produce a decrease in pontive glucose utilisation of $-20 \pm 3\%$ ($p < 0.05$). C.P.P. produced significant decreases in the glucose utilisation of the dorsal and median raphe nuclei which were unaffected by methysergide administration.

7.3.7. Myelinated Fiber Tracts

In these areas LSD, quipazine, C.P.P. and methysergide had no effects given singly or in combination. However, 5MeO significantly reduced the glucose catabolism of cerebellar white matter and the corpus callosum. Both of these affects were severely attenuated by methysergide.

VIII. THE EFFECTS OF METERGOLINE ON THE ACTIONS OF PUTATIVE SEROTONIN AGONISTS

8.1. Behavioural Effects

The behaviour of the rats was carefully observed at all times following the discontinuation of anaesthesia. The behaviour following the administration of putative serotonin agonists and metergoline have previously been described (see chapters IV, V and VI IV of this thesis). The administration of metergoline (3mg/kg) twenty minutes prior to LSD, 5MeO, quipazine or C.P.P. led to a visible diminuation in the behavioural syndrome produced by these substances. Particularly affected were the more ' vivid' aspects of the behavioural responses i.e. the forepaw padding and head swaying. This dose did not however, completely block the hyper-activity and sniffing which occurred.

8.2. Cardiovascular Effects

Metergoline at a dose of 3mg/kg had no significant effect on either heart rate or mean arterial blood pressure. There was a small, non-significant, decrease following LSD (15ug/kg) administration. 5MeO (750 ug/kg) produced a 11 $\pm$ 4% ($p < 0.05$) decrease in heart rate. Quipazine (3mg/kg) and C.P.P. (2.5mg/kg) dramatically decreased the heart rate by 26 $\pm$ 3% and 20 $\pm$ 7% ($p < 0.05$) respectively. Metergoline and LSD had very little effect on mean arterial blood pressure whilst 5MeO, quipazine and C.P.P. produced increases in blood pressure of between 10% and 29%.

Metergoline (3mg/kg), although having no intrinsic effect on heart rate and blood pressure, blocks the actions of the serotonin agonists on heart and blood pressure. (Tables, 26, 28,30,32)

8.3. LOCAL CEREBRAL GLUCOSE UTILISATION

8.3.1. Cortical Areas

Following metergoline administration, LSD (15 ug/kg), which on its own produced significant decreases in glucose utilisation in 5 out of the 8 cortical structures, now produced decreases in all of the areas measured. Furthermore, there was good evidence from the data that the combination of LSD and metergoline potentiated the effects of the agonist alone. For example, in the frontal cortex, LSD and metergoline alone produced a change of $5 \pm 4\%$ and $5 \pm 3\%$ respectively; however in combination they produced a significant decrease in glucose utilisation of $33 \pm 5\%$ ($p < 0.05$).

The interaction of metergoline and 5MeO produced a more varied pattern. 5MeO (750 ug/kg) produced significant decreases in glucose utilisation in 7 out of the 8 cortical areas measured. Metergoline reduced the effect of 5MeO on glucose use in the frontal cortex from $-28 \pm 4\%$ ($p < 0.05$) to $-16 \pm 6\%$. It also potentiated the effects of 5MeO on the entorhinal cortex by increasing its effects on glucose in this structure from $-22 \pm 4\%$ ($p < 0.05$) to $-42 \pm 4\%$ ($p < 0.05$). In the remaining structures metergoline had no effect on the response

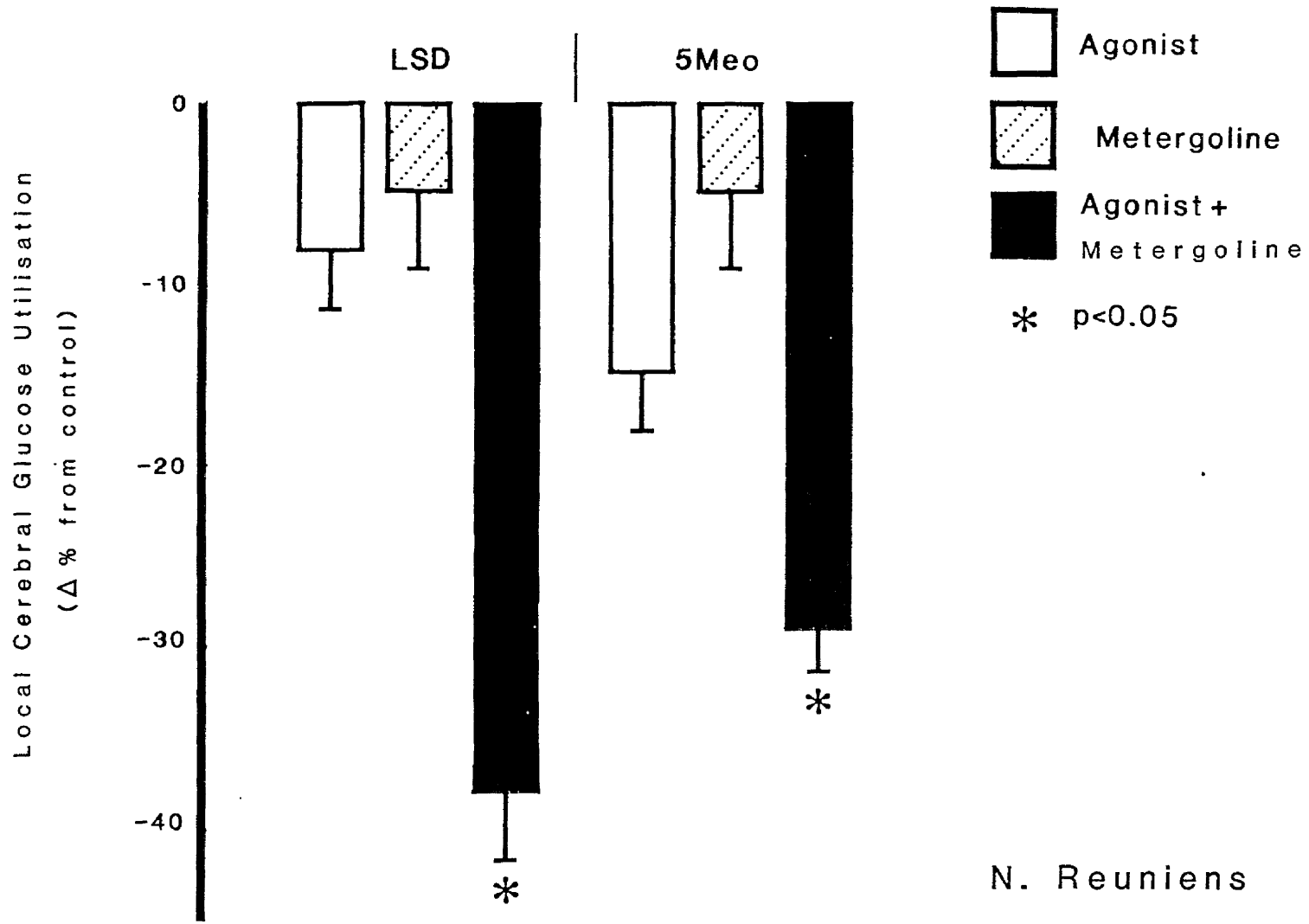

Figure 25. The effect of metergoline (3mg/kg) pretreatment on the response of the n. reuniens to L.S.D. (15ug/kg) and 5MeO (750ug/kg). *p:<0.05. Analysis by ANOVA and Scheffe.

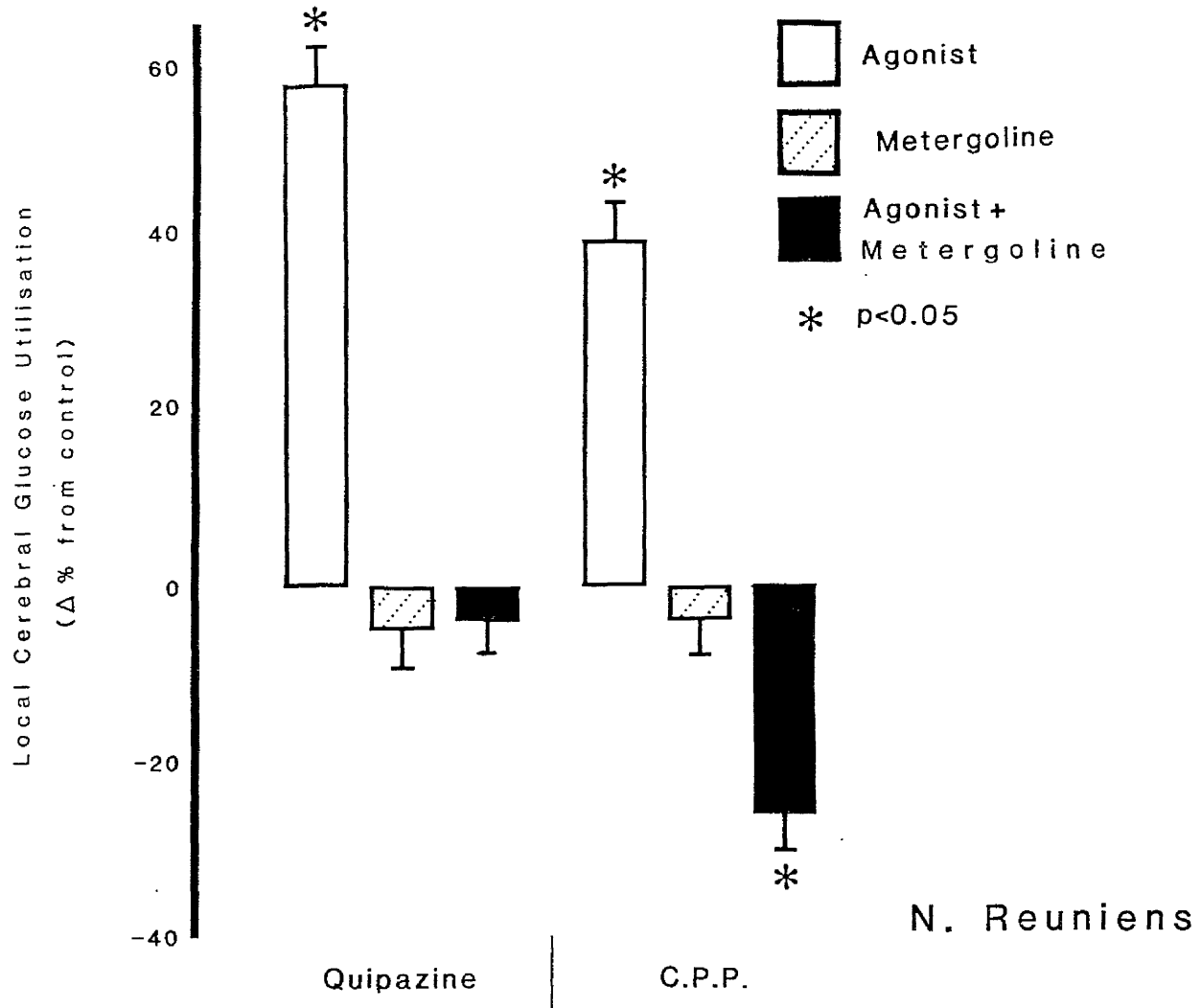

Figure 26. The effects of metergoline (3mg/kg) pretreatment on the response of the n. reuniens to quipazine (3mg/kg) and C.P.P. (2.5 mg/kg). *p: <0.05. Analysis by ANOVA and Scheffe.

response produced by 5MeO.

Of the cortical structures which responded to quipazine (3mg/kg) administration with a significant decrease in glucose utilisation, two, the frontal cortex and the posterior cingulate cortex, showed a blockade and an attenuation of the response, respectively, following metergoline administration. In the other structures, metergoline did not significantly change the glucose utilisation response to quipazine. There were no examples of a potentiation of the quipazine response.

Metergoline reduced the effects of C.P.P. (2.5mg/kg) on the rate of glucose use in the anterior and posterior cingulate cortices. For example, C.P.P. alone produced a 36 $\pm$ 5% ($p < 0.05$) decrease in glucose in the posterior cingulate cortex. Following metergoline pre-treatment it produced a decrease of 19 $\pm$ 5% ($p < 0.05$) in glucose use in this structure. In the other structuresthere was no evidence of potentiation of C.P.P. induced responses (Table 27, 29, 31, 32).

8.3.2. Diencephalic Areas

LSD produced an overall decrease in the level of glucose utilisation in thalamic and hypothalamic structures. Metergoline blocked this effect in only one structure, the medial habenula. In this structure the 22 $\pm$ 8% ($p < 0.05$) decrease in glucose use produced by LSD alone is reduced to a 11 $\pm$ 4% decrease following metergoline. Metergoline administration potentiated the effect of LSD on the nucleus reuniens from a decrease in glucose use of 8 $\pm$ 4% to 38 $\pm$ 6% ($p < 0.05$). (Fig. 25) The pattern

of response was further complicated by the fact that some of the effects of the combination of L.S.D. and metergoline were the sum total of the response to L.S.D. and metergoline alone. For example, in the hypothalamus, decreases in glucose use of 13 ± 7% and 17 ± 5% for L.S.D. and metergoline alone became a 29 ± 7% decrease when L.S.D. and metergoline were given together. There are also thalamic structures such as the ventrolateral thalamic nucleus which did not respond differently to L.S.D. following metergoline administration. Three diencephalic areas had their responses to 5MeO blocked by metergoline administration. These were the mediodorsal thalamus, the subthalamic nucleus and the zona incerta. The pretreatment of the rat with metergoline led to a potentiation of the action of 5MeO in reducing glucose use in the nucleus reuniens from 15 ± 5% to 29 ± 5% (p 0.05) as can be seen in figure 25. In the other structures which responded to 5MeO administration there was little effect on the response produced by 5MeO following metergoline administration.

Interestingly, the areas in which glucose utilisation increased with quipazine (3mg/kg) were blocked by metergoline i.e. the nucleus reuniens and periventricular nucleus of the hypothalamus. (Fig. 26) In addition metergoline blocked the responses to quipazine in the anterior ventral and anterior medial thalamic nuclei. Metergoline did not potentiate the affect of quipazine in these areas.

A very similar pattern occurred when C.P.P. was given to metergoline-treated rats. The increases in glucose use in the lateral habenula and periventricular nucleus of the hypothalamus were blocked by metergoline pre-treatment. The nucleus reuniens was of particular interest. (Fig. 26) C.P.P. (2.5mg/kg) produced a 40 ± 6% ($p<0.05$) increase in glucose utilisation. Following metergoline, C.P.P. induced a 26 ± 5% ($p<0.05$) decrease in glucose use.

The effects of C.P.P. on the rate of glucose use in the anterior ventral and anterior medial thalamus were blocked and reduced respectively by metergoline. There is no evidence of potentiation of C.P.P. responses following metergoline in any of these areas. (Tables 27, 29, 31, 33)

8.3.3. Limbic Areas

The administration of metergoline had virtually no effect on the ability of limbic areas to respond to LSD treatment. None of these areas displayed blockade or potentiation of glucose utilisation effects.

Similarly, the pattern of response produced by 5MeO on glucose use in these regions of the limbic system was very similar whether administered alone or with metergoline.

There was evidence of metergoline potentiating the effect of quipazine on the glucose use of the hippocampus (molecular layer). Quipazine (7mg/kg) decreased glucose use in this area by 8 ± 6% but decreased the rate of glucose utilisation by 34 ± 7% ($p<0.05$) when administered after metergoline. The only structure which was

significantly affected by quipazine alone, the dentate gyrus, responded in a similar manner to a combination of metergoline and quipazine.

Metergoline blocked the actions of C.P.P. on glucose use in the dentate gyrus; reducing the effects from -22 ± 4% ($p < 0.05$) to -16 ± 5%. There is also a marked increase in the response of the hippocampus (molecular layer); -9 ± 5% to -24 ± 4% ($p < 0.05$). (Tables 27, 29, 31, 33)

8.3.4. Extrapyramidal Areas

Three extrapyramidal regions displayed significant decreases in glucose use following LSD administration; the substantia nigra (pars reticulata and pars compacta) and the caudal portion of the caudate nucleus. Metergoline had no effect on these responses. However, in 6 out of the 10 regions measured metergoline pretreatment potentiated the actions of LSD. For example, in the dorsolateral caudate nucleus, metergoline increases the effects of LSD from -17 ± 7% to -34 ± 6% ($p < 0.05$). No area showed a blockade of an LSD induced response by metergoline. (Fig. 27)

Metergoline failed to block any of the responses produced by 5MeO in this group of structures. In only one area, the vestibular nucleus, did this pattern change. In this structure, the response to 5MeO administration was a 21 ± 6% ($p < 0.05$). Following metergoline pretreatment, 5MeO elicited a -46 ± 9% decrease in glucose utilisation.

The overall effect of a combination of metergoline and quipazine was to increase the actions of quipazine on

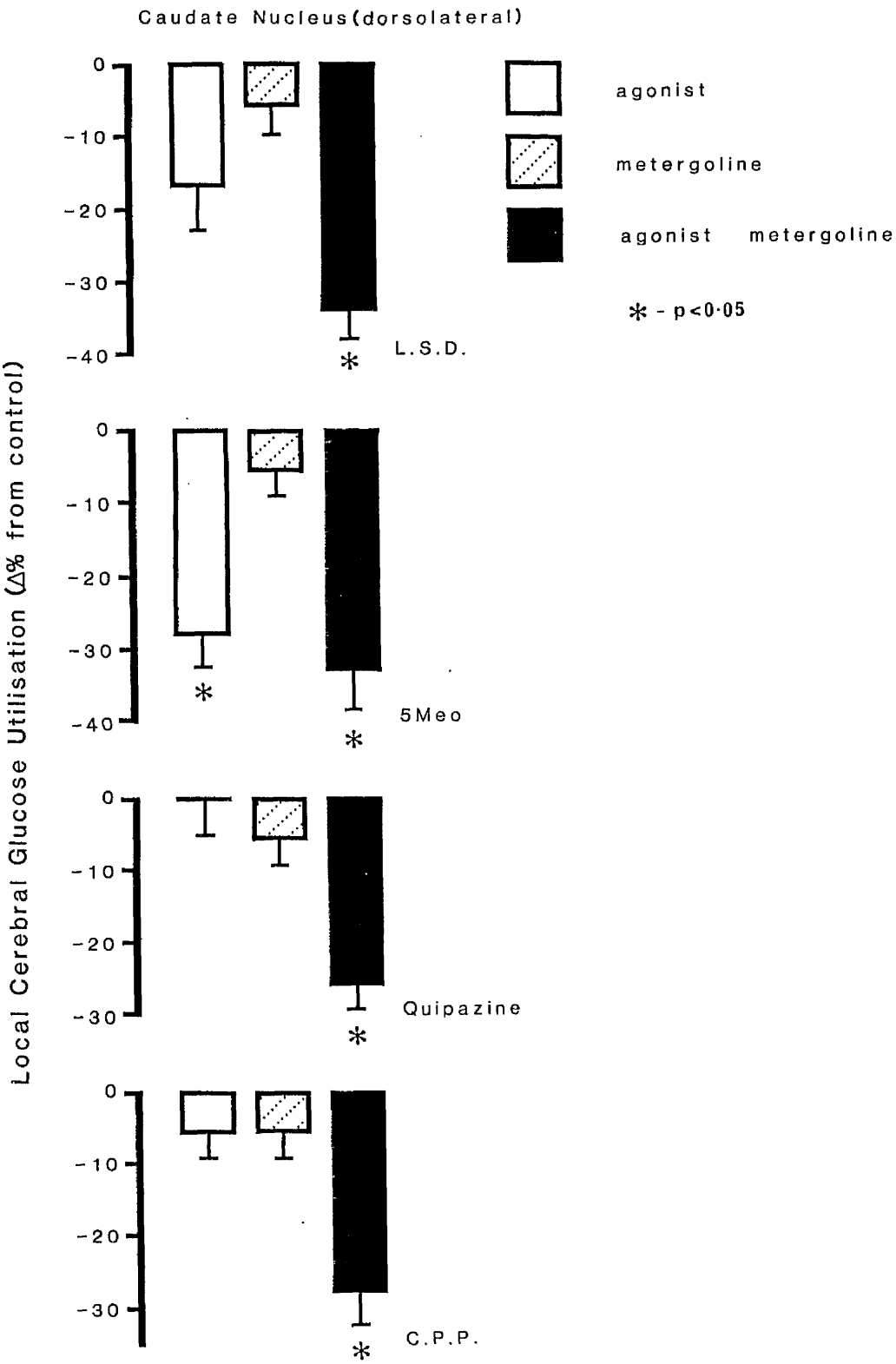

Figure 27. The effect of metergoline (3mg/kg) pretreatment on the response of glucose utilisation in the dentate gyrus to the administration of putative serotonin agonists: LSD (15ug/kg); 5MeO (750ug/kg); quipazine (3mg/kg) and C.P.P. (2.5mg/kg). *p:$<$0.05. Statistical analysis by ANOVA and Scheffe.

glucose use. For example, quipazine did not change the rate of glucose use in the dorsolateral caudate nucleus, but the combination of metergoline and quipazine reduced glucose catabolism by 34 ± 4% ($p < 0.05$).

In the substantia nigra and caudal caudate nucleus there was no affect on the response of these structures to C.P.P. following metergoline administration. However, in the dorsolateral and central portions of the caudate nucleus and in the inferior olivary complex and vestibular nucleus the combination of metergoline pre-treatment and C.P.P. caused a marked potentiation of the effect of the agonist alone. (Tables 27, 29, 31, 33)

8.3.5. Primary Visual and Primary Auditory Areas

LSD (15 ug/kg) produced only one significant change in glucose use in primary auditory areas of the rat brain; in the lateral lemniscus. However, following metergoline pretreatment, which itself has no significant actions on glucose use in these areas, all of the auditory-related structures show large, significant decreases in glucose utilisation. For example, the auditory cortex responds to LSD treatment with a decrease in glucose catabolism of 12 ± 8%. Following metergoline treatment LSD produced a -34 ± 7% decrease in the level of glucose use in this area. The effects of LSD and metergoline on the visual-related areas of the rat brain were somewhat more complex. With the exception of the lateral geniculate body, whose response to LSD is unaffected, the visual areas all show an increase in their response

to LSD following metergoline administration. An almost identical pattern of response occured when 5MeO and metergoline were administered, alone and in combination.

On the other hand, quipazine induced only minor non-significant responses in auditory areas whether alone or in combination with metergoline (with the exception of the superior olivary nucleus). The effect of this drug on structures with a visual function was increased following the administration of metergoline.
C.P.P. (2.5 mg/kg) produced a number of significant decreases in glucose utilisation in primary auditory areas. These responses were largely unaffected or slightly increased by the administration of C.P.P. in the presence of metergoline. The actions of C.P.P. on visual-related structures are, at this dose, only significant in the visual cortex and lateral geniculate body. In the visual cortex the effect of C.P.P. is decreased and there is no effect on the response of the lateral geniculate body by metergoline pretreatment.

8.3.6. Hindbrain Areas

With the exception of the cerebellar hemispheres, there was an increase in the reactivity of glucose use in hindbrain areas to LSD administration following metergoline. The pattern of glucose utilisation in hindbrain areas was slightly different following 5MeO and metergoline treatment. There was no effect on the response to 5MeO in the cerebellar hemispheres, dorsal raphe nucleus and pontine reticular formation but there was an increase in the 5MeO induced decrease in glucose utilisation following metergoline in the cerebellar nuclei, cerebellar vermis and median raphe nucleus.

Quipazine elicits only minor, non-significant changes in hindbrain areas. In the median raphe and the pontine reticular formation, where quipazine decreased glucose non-significantly alone, in the presence of metergoline it induced changes of -21 ± 7% ($p < 0.05$) and -29 ± 4% ($p < 0.05$) respectively.

Metergoline increases the effects of C.P.P. on the rate of glucose use in the hindbrain areas measured, with the exception of the cerebellar hemisphere.

8.3.7 Myelinated Fiber Tracts

There were some significant effects on glucose use produced by the putative serotonin agonists L.S.D. and 5MeO. These effects were blocked by metergoline pre-treatment.

8.3.8 Comments on Results

There were similarities and differences in the patterns of cerebral response produced by methysergide and metergoline pretreatment. If we consider only the significant responses, methysergide (15mg/kg) attenuated 63% of the L.S.D. effects, 80% of the 5MeO effects, 52% of the quipazine effects and 33% of the C.P.P. effects on local cerebral glucose utilisation. In contrast, metergoline (3mg/kg) pre-treatment decreased 4% of the L.S.D. effects, 16% of the 5MeO effects, 22% of the quipazine effects and 23% of the significant responses to C.P.P.

Furthermore, the combination of the antagonist and agonist led, on a number of occasions, to an increase in the action of the agonist, (i.e. a potentiation of the agonist effect or the summation of the actions of both agonist and antagonist.) Again there were differences in the resultant

interactions between the putative serotonin agonists and antagonists. Methysergide potentiated the significant response to L.S.D., quipazine and C.P.P. on 17%, 9% and 18% of occasions respectively. This effect did not occur with the combination of 5MeO and methysergide. Metergoline potentiated the significant actions of L.S.D. 5MeO, quipazine and C.P.P. in 58%, 39%, 53% and 33% respectively of the structures which showed significant changes. The percentage of affected structures whose agonist response was unaffected by the administration of the peripheral antagonists was between 20% and 49% for methysergide, and 25% and 45% for metergoline pre-treatment.

These data raise some interesting points. Firstly, these studies show quite clearly that methysergide and metergoline do not block all the effects of the putative serotonin agonists on local cerebral function. Secondly, in some areas the combination of the putative agonists and antagonists leads to a summation of their individual effects, the potentiation of the action of the agonist, or even, in one structure, the nucleus reuniens (only with C.P.P.) a reversal of the effect of the agonist or antagonist alone. Thirdly, the methysergide-agonist and the metergoline-agonist effects produced differing patterns of cerebral response which are difficult to reconcile with the fact that both of these putative antagonists blocked the behavioural and cardiovascular actions of the putative serotonin agonists in the same groups of rats. Admittedly the cardiovascular effects

produced by the serotonin-mimetic drugs are probably a complex combination of peripheral and central effects. (See previous sections of this thesis for discussion). The hypertensive effect of the intracerebrovascular administration of serotonin has been shown to be blocked by various putative serotonin antagonists. (Antonaccio and Cote, 1976; Kirstic and Djurkovic, 1976; Lambert et al, 1975; Lambert et al, 1978).

There have been numerous studies measuring differing behavioural parameters induced by alteration of central serotonin machanisms. (Balsara et al, 1979; Chadwick et al, 1978; Clineschmidt and Lotti, 1974; Corne et at, 1963; Corne and Pickering, 1967; Costall and Naylor, 1975; Green et al, 1981; James and Starr, 1980; Langlais and Gabay, 1977; Malick et al, 1977; Vetalani et al, 1979; Weiner et al, 1975. inter alia). In all of these studies known peripheral antagonists of 5HT actions have been used and found to block or reduce the serotonin mimetic effects. From the data presented here it would seem that this reduction of the behavioural effect is due not to a simple negation of the actions of the serotonin agonists but perhaps by the production of a different pattern of cerebral function. Electrophysiological data is equivocal. Serotonin antagonists have been shown to block the effects of serotonin and serotonin-mimetic manipulations of the cell-firing rates of cells in a number of areas in

in the brain. (Ennis et al, 1981; McCall and Aghajanian, 1979; Olpe and Kuelle, 1977; Proudfit and Anderson, 1974; Sastry and Phillis, 1977; Segal 1975; Van der Maelen and Aghajanian, 1980, inter alia).

In other studies, putative serotonin antagonists not only had an 'agonistic' action per se but also failed to block the depression in cell-firing rate produced by serotonin itself. (Roakes et al, 1970; Haigler and Aghajanian, 1974 a,b.) although they did block the excitatory responses of serotonin. Furthermore, in the hippocampus, methysergide could block some but not all the inhibitory effects of serotonin. (Segal 1975; Segal, 1976). Thus, the electrophysiological information available seems to run the full gamut of possibilities and in this sense is qualitatively similar to the complex pattern of cerebral response found in this study.

Bennet and Snyder, 1976 proposed that serotonin agonists and antagonists bind to different serotonin receptors or to the same receptor in different conformations. This work has been confirmed and extended by a number of other investigators (Hamon et al, 1980; Hamon et al, 1981; Nelson et al, 1978; Nelson et al, 1979; Nelson et al, 1981). It is of interest in this respect that metergoline is a potent displacer of ^{3}H-5HT (the 'agonist site') as ^{3}H - spiroperidal (the 'antagonist site') although a recent paper by Hamon et al, 1981 has shown that ^{3}H - metergoline was poorly displaced by 5HT, 5 methoxy

N,N-dimethyltryptamine, quipazine or trifluoromethyl-phenylpiperazine.

Biochemical evidence seems to suggest a similar dichotomy. Serotonin agonists all increase 5HT turnover and decrease 5 hydroxyindoleacetic acid levels in the rat brain. (Clineschmidt, 1979; Freedman et al, 1970; Hamon et al, 1976; Jacoby et al, 1976; Miskiewicz et al, 1979; Rosecrams et al, 1967). Putative antagonists of serotonin have been shown to be largely inaffective at producing changes in these parameters (D'amico et al, 1976; Jacoby et al, 1978) except at high doses. (Sofia and Vassar, 1975).

This evidence taken together suggests that the putative serotonin agonists, LSD, 5MeO, quipazine and C.P.P., and the putative antagonists methysergide and metergoline may be acting on differing but overlapping sets of serotonin receptors. The combination of 'agonist' and 'antagonist' produces a complex pattern of functional response in the brain of the conscious rat.

In summary, the administration of methysergide and metergoline before treatment with serotonin agonists produces a complex pattern of response in which the effects of the agonists are attenuated, potentiated or unchanged.

TABLE 18

CARDIOVASCULAR DATA

Drug (mg/kg)	Heart Rate (beats/min)		Mean Arterial Blood Pressure (mmHg)	
	Control	At Study	Control	At Study
Saline	419 ± 7	419 ± 8	134 ± 3	132 ± 2
L.S.D. (0.015)	424 ± 3	400 ± 3	126 ± 4	126 ± 3
Methysergide (15)	419 ± 6	418 ± 6	130 ± 2	133 ± 2
L.S.D. + Methysergide	418 ± 7	418 ± 7	128 ± 3	133 ± 2
n	6	6	6	6

Data are given as mean ± standard error of the mean.
* $p<0.05$. Statistical analysis by ANOVA and Scheffe.

TABLE 19

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Cortical Structures	Drug (mg/kg) Saline	LSD(0.015)	Methysergide(15)	LSD+Methysergide
Parietal Cortex	94 ± 2	82 ± 4	87 ± 3	86 ± 3
Sensory Motor Cortex	99 ± 4	90 ± 3	77 ± 2*	82 ± 4
Entorhinal Cortex	74 ± 2	62 ± 2*	55 ± 1*	43 ± 3*
Pyriform Cortex	95 ± 2	76 ± 3*	92 ± 3	55 ± 4*
Frontal Cortex	94 ± 2	92 ± 4	85 ± ?	82 ± 3
Anterior Cingulate Cortex	94 ± 2	94 ± 3	81 ± 2*	80 ± 3*
Posterior Cingulate Cortex	96 ± 4	73 ± 4*	83 ± 3	72 ± 3*
Prefrontal Cortex	117 ± 4	91 ± 4*	93 ± 6	76 ± 4*

TABLE 19 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

	Drug (mg/kg)			
Diencephalic Structures	Saline	LSD.(0.015)	Methysergide(15)	LSD+Methysergide
Mediodorsal Thalamus	94 ± 1	82 ± 4	94 ± 2	87 ± 4
Ventrolateral Thalamus	84 ± 2	69 ± 3*	79 ± 3	67 ± 3*
Anterior-Ventral Thalamus	114 ± 4	88 ± 4	103 ± 3	104 ± 3
Anterior-Medial Thalamus	113 ± 4	87 ± 3*	102 ± 3	102 ± 3
Lateral Thalamus	102 ± 2	79 ± 4*	73 ± 4*	94 ± 4
Subthalamic Nucleus	79 ± 3	69 ± 4	78 ± 4	75 ± 5
Zona Incerta	77 ± 3	63 ± 3*	78 ± 1	68 ± 4
Nucleus Reuniens	98 ± 4	88 ± 4	89 ± 3	88 ± 4
Habenula (Lateral)	107 ± 2	91 ± 3*	107 ± 4	96 ± 4
Habenula (Medial)	71 ± 3	58 ± 3*	69 ± 3	65 ± 3
Hypothalamus	53 ± 3	46 ± 2	48 ± 3	52 ± 3
Medial Forebrain Bundle	67 ± 2	59 ± 3	52 ± 2*	59 ± 4
Periventricular N.	48 ± 3	46 ± 3	51 ± 2	55 ± 3

TABLE 19 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmol/100g/min)

Limbic Structures	Drug (mg/kg) Saline	LSD.(0.015)	Methysergide(15)	LSD+Methysergide
Hippocampus (Molecular Layer)	86 ± 3	72 ± 3*	86 ± 3	69 ± 3*
Dentate Gyrus	73 ± 3	52 ± 3*	54 ± 3*	60 ± 3*
Septal Nucleus (Lateral)	57 ± 4	51 ± 3	55 ± 1	56 ± 2
Septal Nucleus (Medial)	46 ± 3	42 ± 3	41 ± 1	43 ± 2
Nucleus Accumbens	80 ± 2	61 ± 3*	79 ± 1	71 ± 3
Amygdala (Medial)	47 ± 2	41 ± 2	38 ± 2	43 ± 3
Anterior Amygdaloid Area	83 ± 2	75 ± 3	86 ± 3	76 ± 3
Ventral Tegmental Area	69 ± 4	52 ± 3*	63 ± 2	56 ± 2

TABLE 19 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Extrapyramidal Structures	Saline	LSD(0.015)	Methysergide(15)	LSD+Methysergide
Caudate Nucleus (Dorsolateral)	95 ± 3	78 ± 3*	89 ± 2	82 ± 3
Caudate Nucleus (Central)	83 ± 1	64 ± 4*	74 ± 3	79 ± 3
Caudate Nucleus (Ventromedial)	84 ± 3	67 ± 3*	79 ± 2	76 ± 3
Caudate Nucleus (Caudal)	82 ± 2	61 ± 2*	69 ± 3	76 ± 3
Globus Pallidus	54 ± 3	48 ± 2	54 ± 2	48 ± 3
Substantia Nigra (Pars Compacta)	81 ± 3	59 ± 3*	64 ± 3*	65 ± 4*
Substantia Nigra (Pars Reticulata)	61 ± 2	42 ± 4*	50 ± 3	45 ± 3*
Red Nucleus	76 ± 4	69 ± 3	70 ± 3	76 ± 4
Inferior Olive	75 ± 3	69 ± 3	76 ± 3	76 ± 4
Vestibular Nucleus	109 ± 5	95 ± 4	88 ± 3*	97 ± 4

TABLE 19 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

		Drug (mg/kg)			
Primary Auditory		Saline	LSD(0,015)	Methysergide(15)	LSD+Methysergide
Auditory Cortex		139 ± 2	123 ± 4	131 ± 4	113 ± 3*
Medial Geniculate		114 ± 4	94 ± 4	115 ± 4	93 ± 4
Inferior Colliculus		173 ± 6	163 ± 9	168 ± 7	137 ± 9
Lateral Lemniscus		113 ± 3	86 ± 8*	103 ± 6	86 ± 6*
Superior Olive		150 ± 9	126 ± 8	157 ± 7	102 ± 3*
Cochlear Nucleus		140 ± 7	126 ± 8	130 ± 6	120 ± 6
Primary Visual					
Visual Cortex		99 ± 2	78 ± 3*	88 ± 3	88 ± 5
Lateral Geniculate	D	83 ± 2	69 ± 3*	87 ± 3	77 ± 4
	V	81 ± 2	57 ± 3*	77 ± 2	68 ± 4
Superior Colliculus	S	85 ± 2	70 ± 3*	62 ± 3*	77 ± 4
Superior Colliculus	D	82 ± 2	66 ± 4*	62 ± 3*	75 ± 4

TABLE 19 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

	Drug (mg/kg)			
Hindbrain Structures	Saline	LSD(0.015)	Methysergide(15)	LSD+Methysergide
Cerebellum Hemisphere	51 ± 5	44 ± 3	48 ± 1	50 ± 3
Cerebellum Nuclei	89 ± 3	78 ± 4	74 ± 5	84 ± 3
Cerebellum Vermis	96 ± 6	77 ± 4	75 ± 4	77 ± 3
Cerebellum White Matter	33 ± 1	31 ± 2	34 ± 1	37 ± 2
Dorsal Raphe Nucleus	91 ± 2	75 ± 3*	77 ± 3*	74 ± 2*
Median Raphe Nucleus	93 ± 2	77 ± 3*	81 ± 3	74 ± 4
Pontine Reticular Formation	60 ± 2	54 ± 3	57 ± 2	52 ± 3
Myelinated Fiber Tracts				
Corpus Callosum	33 ± 2	29 ± 1	28 ± 2	34 ± 2
Genu of the Corpus Callosum	27 ± 1	25 ± 1	26 ± 1	29 ± 2
Internal Capsule	32 ± 1	28 ± 1	29 ± 1	32 ± 2
N	6	6	6	6

Data are given as mean ± standard error of the mean in μmols/100g/min. *p:<0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

TABLE 20

CARDIOVASCULAR DATA

Drug (mg/kg)	Heart Rate (beats/min) Control	Heart Rate (beats/min) At Study	Mean Arterial Blood Pressure (mmHg) Control	Mean Arterial Blood Pressure (mmHg) At Study
Saline	420 ± 8	419 ± 8	134 ± 3	132 ± 2
5 MeO (0.75)	408 ±10	362 ± 8*	126 ± 3	143 ± 3*
Methysergide (15)	409 ± 6	408 ± 6	130 ± 2	133 ± 1
5MeO + Methysergide	401 ± 6	398 ± 6	127 ± 5	129 ± 3
n	6	6	6	6

Data are presented as mean ± standard error of the mean.
* $p<0.05$. Statistical analysis by ANOVA and Scheffe.

TABLE 21

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Cerebral Structures	Drug (mg/kg) Saline	MeO (0.75)	Methysergide(15)	MeO+Methysergide
Parietal Cortex	94 ± 2	74 ± 2*	87 ± 6	101 ± 4
Sensory Motor Cortex	99 ± 4	83 ± 1*	77 ± 2*	103 ± 3
Entorhinal Cortex	74 ± 2	58 ± 1*	55 ± 1*	48 ± 1*
Pyriform Cortex	95 ± 2	61 ± 3*	92 ± 4*	79 ± 1*
Frontal Cortex	94 ± 2	70 ± 2*	84 ± 2	99 ± 4
Anterior Cingulate Cortex	94 ± 2	74 ± 2*	82 ± 2	102 ± 2
Posterior Cingulate Cortex	96 ± 4	73 ± 2*	83 ± 4	86 ± 4
Prefrontal Cortex	117 ± 4	90 ± 3*	93 ± 7*	93 ± 5*

TABLE 21 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Diencephalic Structures	Drug (mg/kg) Saline	MeO(0.75)	Methysergide(15)	MeO+Methysergide
Mediodorsal Thalamus	94 ± 1	74 ± 3*	99 ± 5	94 ± 3
Ventrolateral Thalamus	84 ± 2	59 ± 3*	78 ± 3	78 ± 1
Anterior-Ventral Thalamus	114 ± 4	88 ± 2*	105 ± 3	109 ± 9
Anterior-Medial Thalamus	113 ± 4	82 ± 3*	100 ± 4	103 ± 6
Lateral Thalamus	102 ± 2	77 ± 2*	73 ± 4*	86 ± 3*
Subthalamic Nucleus	79 ± 3	64 ± 2*	78 ± 4	77 ± 4
Zona Incerta	77 ± 3	59 ± 3*	78 ± 1	74 ± 1
Nucleus Reuniens	98 ± 4	84 ± 1	88 ± 4	84 ± 4
Habenula (Lateral)	107 ± 2	88 ± 3*	104 ±10	106 ± 5
Habenula (Medial)	71 ± 3	59 ± 3*	67 ± 4	75 ± 3
Hypothalamus	53 ± 3	39 ± 1*	51 ± 3	52 ± 3
Medial Forebrain Bundle	67 ± 2	46 ± 3*	55 ± 2*	55 ± 2*
Periventricular Nucleus	48 ± 3	45 ± 3	51 ± 2	54 ± 2

TABLE 21 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmol/100g/min)

	Drug (mg/kg)			
Limbic Structures	Saline	MeO(0.75)	Methysergide(15)	MeO+Methysergide
Hippocampus (Molecular Layer)	86 ± 3	64 ± 3*	89 ± 6	76 ± 4
Dentate Gyrus	73 ± 3	53 ± 1*	56 ± 3*	64 ± 2
Septal Nucleus (Lateral)	57 ± 4	44 ± 3	55 ± 1	61 ± 3
Septal Nucleus (Medial)	46 ± 3	35 ± 2	41 ± 1	47 ± 2
Nucleus Accumbens	80 ± 2	55 ± 3*	77 ± 3	70 ± 3*
Amygdala (Medial)	47 ± 2	35 ± 1*	38 ± 2	44 ± 2
Anterior Amygdaloid Area	83 ± 2	57 ± 2*	82 ± 5	80 ± 4
Ventral Tegmental Area	69 ± 4	44 ± 4*	53 ± 2*	52 ± 3*

TABLE 21 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Extrapyramical Structures	Drug (mg/kg) Saline	MeO(0.75)	Methysergide(15)	MeO+Methysergide
Caudate Nucleus (Dorsolateral)	95 ± 3	68 ± 4*	88 ± 3	87 ± 4
Caudate Nucleus (Central)	83 ± 1	62 ± 2*	72 ± 2*	86 ± 3
Caudate Nucleus (Ventromedial)	84 ± 3	61 ± 2*	67 ± 4*	83 ± 3
Caudate Nucleus (Caudal)	82 ± 2	56 ± 2*	64 ± 6*	67 ± 3*
Globus Pallidus	54 ± 3	38 ± 2*	54 ± 1	52 ± 2
Substantia Nigra(Pars Compacta)	81 ± 3	51 ± 2*	64 ± 3*	66 ± 1*
Substantia Nigra(Pars Reticulata)	61 ± 2	38 ± 2*	45 ± 5*	47 ± 2*
Red Nucleus	76 ± 4	56 ± 2*	70 ± 6	72 ± 3
Inferior Olive	75 ± 3	50 ± 3*	68 ± 4	65 ± 2
Vestibular Nucleus	109 ± 5	86 ± 1*	88 ± 4*	87 ± 2*

TABLE 21 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

		Drug (mg/kg)			
Primary Auditory		Saline	MeO(0.75)	Methysergide(15)	Meo+Methysergide
Auditory Cortex		139 ± 2	130 ± 6	131 ± 8	139 ± 4
Medial Geniculate		114 ± 4	91 ± 2*	115 ± 9	107 ± 3
Inferior Colliculus		173 ± 6	165 ± 5	173 ±12	156 ± 4
Lateral Lemniscus		113 ± 3	91 ± 5*	103 ± 7	87 ± 5
Superior Olive		150 ± 9	117 ± 10	157 ±14	117 ± 8
Cochlear Nucleus		140 ± 7	117 ±10	130 ±12	114 ± 7
Primary Visual					
Visual Cortex		99 ± 2	87 ± 1	88 ± 4	90 ± 2
Lateral Geniculate	D	83 ± 2	66 ± 2*	88 ± 3	82 ± 3
	V	81 ± 2	55 ± 2*	87 ± 4	68 ± 2*
Superior Colliculus	S	85 ± 2	72 ± 2*	62 ± 4*	83 ± 2
Superior Colliculus	D	82 ± 2	63 ± 1*	58 ± 4*	73 ± 4

TABLE 21 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Hindbrain Structures	Saline	MeO(0.75)	Methysergide(15)	MeO+Methysergide
Cerebellum Hemisphere	51 ± 5	37 ± 2*	47 ± 2	48 ± 3
Cerebellum Nuclei	89 ± 3	75 ± 2	74 ± 5	78 ± 3
Cerebellum Vermis	96 ± 6	76 ± 3*	73 ± 5*	73 ± 3*
Cerebellum White Matter	33 ± 1	26 ± 1*	25 ± 2*	34 ± 2
Dorsal Raphe Nucleus	91 ± 2	64 ± 3*	77 ± 3*	72 ± 3*
Median Raphe Nucleus	93 ± 2	70 ± 2*	81 ± 3	66 ± 3*
Pontine Reticular Formation	61 ± 2	46 ± 2*	49 ± 2*	47 ± 3*
Myelinated Fiber Tracts				
Corpus Callosum	33 ± 2	23 ± 1*	28 ± 3	33 ± 3
Genu of the Corpus Callosum	27 ± 1	21 ± 1	26 ± 1	31 ± 2
Internal Capsule	32 ± 1	25 ± 2*	29 ± 1	34 ± 1
n	6	6	6	6

Data are given as mean ± standard error of the mean in umols/100g/min. *p: <0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

TABLE 22

CARDIOVASCULAR DATA

Drug (mg/kg)	Heart Rate (beats / Min)		Mean Arterial Blood Pressure (mmHg)	
	Control	At Study	Control	At Study
Saline	420 ± 8	419 ± 8	134 ± 3	132 ± 2
Quipazine (3)	418 ± 5	314 ±10 *	134 ± 2	172 ± 3*
Methysergide (15)	409 ± 6	408 ± 6	130 ± 2	133 ± 1
Quipazine + Methysergide	403 ± 8	404 ±10	129 ± 4	130 ± 4
n	6	6	6	6

Data are presented as mean ± standard error of the mean.
*: $p<0.05$. Statistical analysis by ANOVA and Scheffe.

TABLE 23

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Cerebral Structures	Saline	Quipazine (3)	Methysergide(15)	Quipazine+Methysergid
Parietal Cortex	93 ± 4	84 ± 4	82 ± 2	87 ± 5
Sensory Motor Cortex	97 ± 4	90 ± 4	89 ± 6	78 ± 1*
Entorhinal Cortex	73 ± 4	55 ± 4*	66 ± 3	55 ± 1*
Pyriform Cortex	94 ± 4	79 ± 3*	96 ± 1	92 ± 3
Frontal Cortex	95 ± 3	78 ± 4*	80 ± 2*	84 ± 1
Anterior Cingulate Cortex	95 ± 3	78 ± 3*	72 ± 2*	82 ± 2
Posterior Cingulate Cortex	97 ± 4	55 ± 3*	77 ± 3*	83 ± 4*
Prefrontal Cortex	119 ± 5	80 ± 5*	81 ± 2*	93 ± 7

TABLE 23 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Diencephalic Structures	Drug (mg/kg) Saline	Quipazine (3)	Methysergide(15)	Quipazine+Methysergid
Mediodorsal Thalamus	96 ± 1	93 ± 4	82 ± 2	98 ± 4
Ventrolateral Thalamus	85 ± 2	82 ± 4	69 ± 4	78 ± 3
Anterior-Ventral Thalamus	117 ± 3	72 ± 3*	92 ± 4*	105 ± 3
Anterior-Medial Thalamus	115 ± 4	77 ± 4*	93 ± 2*	100 ± 4
Lateral Thalamus	103 ± 3	70 ± 3*	77 ± 4*	73 ± 4*
Subthalamic Nucleus	79 ± 2	80 ± 5	69 ± 3	78 ± 4
Zona Incerta	79 ± 2	85 ± 2	72 ± 4	78 ± 1
Nucleus Reuniens	94 ± 3	155 ± 6*	83 ± 4	88 ± 4
Habenula (Lateral)	105 ± 4	104 ± 6	101 ± 3	104 ± 6
Habenula (Medial)	69 ± 3	69 ± 3	61 ± 5	67 ± 4
Hypothalamus	52 ± 3	55 ± 4	50 ± 4	51 ± 3
Medial Forebrain Bundle	66 ± 2	61 ± 3	50 ± 4*	55 ± 2
Periventricular Nucleus	50 ± 3	62 ± 2*	51 ± 3	49 ± 3

TABLE 23 CONTD.

	LOCAL CEREBRAL GLUCOSE UTILISATION (μmol/100g/min) Drug (mg/kg)			
Limbic Structures	Saline	Quipazine(3)	Methysergide(15)	Quipazine+Methysergide
Hippocampus (Molecular Layer)	88 ± 3	94 ± 1	71 ± 3*	89 ± 5
Dentate Gyrus	76 ± 3	55 ± 3*	57 ± 3*	56 ± 4*
Septal Nucleus (Lateral)	56 ± 3	61 ± 3	54 ± 5	55 ± 1
Septal Nucleus (Medial)	46 ± 3	42 ± 2	43 ± 2	41 ± 1
Nucleus Accumbens	81 ± 2	69 ± 4	66 ± 2*	77 ± 2
Amygdala (Medial)	47 ± 3	47 ± 2	45 ± 2	38 ± 2
Anterior Amygdaloid Area	84 ± 2	81 ± 3	68 ± 2*	82 ± 4
Ventral Tegmental Area	69 ± 4	56 ± 4	47 ± 2*	53 ± 2*

TABLE 23 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Extrapyramidal Structures	Saline	Quipazine(3)	Methysergide(15)	Quipazine+Methysergide
Caudate Nucleus (Dorsolateral)	90 ± 4	94 ± 6	80 ± 1	88 ± 3
Caudate Nucleus (Central)	83 ± 2	77 ± 4	68 ± 2*	72 ± 2
Caudate Nucleus (Ventromedial)	86 ± 3	73 ± 3*	66 ± 3*	67 ± 4*
Caudate Nucleus (Caudal)	84 ± 3	66 ± 1*	63 ± 3*	64 ± 5*
Globus Pallidus	54 ± 3	51 ± 2	46 ± 3	54 ± 1
Substantia Nigra (Pars Compacta)	79 ± 2	60 ± 4*	65 ± 4*	66 ± 4*
Substantia Nigra (Pars Reticulata)	63 ± 2	39 ± 1*	40 ± 2*	45 ± 4*
Red Nucleus	75 ± 3	66 ± 3	66 ± 2	70 ± 5
Inferior Olive	73 ± 2	66 ± 3	62 ± 5	68 ± 4
Vestibular Nucleus	106 ± 2	114 ± 6	96 ± 3*	98 ± 3

TABLE 23 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

		Drug (mg/kg)			
Primary Auditory		Saline	Quipazine(3)	Methysergide(15)	Quipazine+Methysergide
Auditory Cortex		140 ± 4	137 ± 8	130 ± 5	131 ± 8
Medial Geniculate		112 ± 3	103 ± 4	102 ± 3	115 ± 6
Inferior Colliculus		170 ± 3	173 ± 4	173 ± 6	176 ± 4
Lateral Lemniscus		110 ± 3	100 ± 5	103 ± 4	104 ± 4
Superior Olive		156 ± 4	135 ± 5	157 ± 6	157 ± 3
Cochlear Nucleus		139 ± 5	117 ± 5	130 ± 6	130 ± 3
Primary Visual					
Visual Cortex		97 ± 3	84 ± 3*	80 ± 3*	88 ± 4
Lateral Geniculate	D	98 ± 6	74 ± 4*	77 ± 2*	88 ± 3
	V	88 ± 4	70 ± 2*	69 ± 2*	87 ± 3
Superior Colliculus	S	82 ± 1	64 ± 4*	62 ± 4*	62 ± 3*
Superior Colliculus	D	78 ± 2	79 ± 6	58 ± 4*	60 ± 2*

TABLE 23 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Hindbrain Structures	Saline	Quipazine(3)	Methysergide(15)	Quipazine+Methysergide
Cerebellum Hemisphere	49 ± 3	52 ± 3	43 ± 3	47 ± 2
Cerebellum Nuclei	86 ± 3	86 ± 7	80 ± 3	72 ± 4
Cerebellum Vermis	92 ± 5	104 ± 8	75 ± 4	73 ± 5
Cerebellum White Matter	34 ± 2	36 ± 2	36 ± 3	35 ± 2
Dorsal Raphe Nucleus	93 ± 3	96 ± 3	68 ± 5*	77 ± 3
Median Raphe Nucleus	93 ± 4	88 ± 4	69 ± 5*	81 ± 2
Pontine Reticular Formation	61 ± 3	56 ± 4	51 ± 4	49 ± 2*
Myelinated Fiber Tracts				
Corpus Callosum	33 ± 2	36 ± 2	32 ± 2	28 ± 2
Genu of the Corpus Callosum	29 ± 2	30 ± 1	25 ± 4	26 ± 1
Internal Capsule	33 ± 2	28 ± 2	28 ± 2	29 ± 1
n	6	6	6	6

Data are given as mean ± standard error of the mean in umols/100g/min. *p: < 0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

TABLE 24

CARDIOVASCULAR DATA

Drug (mg/kg)	Heart Rate (beats/min)		Mean Arterial Blood Pressure (mmHg)	
	Control	At Study	Control	At Study
Saline	404 ± 6	408 ± 8	125 ± 3	127 ± 3
C.P.P. (2.5)	430 ±14	340 ±12*	124 ± 3	168 ± 3*
Methysergide (15)	420 ± 6	428 ± 6	133 ± 2	132 ± 3
C.P.P. + Methysergide	411 ± 8	416 ± 6	120 ± 4	126 ± 3
n	6	6	6	6

Data are given as mean ± standard error of the mean.
* : $p<0.05$. Statistical analysis by ANOVA and Scheffe.

TABLE 25

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Cerebral Structures	Drug (mg/kg) Saline	C.P.P. (2.5)	Methysergide (15)	C.P.P.+ Methysergide
Parietal Cortex	92 ± 3	76 ± 2*	87 ± 5	75 ± 2*
Sensory Motor Cortex	96 ± 2	94 ± 2	77 ± 2*	83 ± 4
Entorhinal Cortex	76 ± 3	50 ± 3*	55 ± 1*	60 ± 3*
Pyriform Cortex	96 ± 3	64 ± 1*	92 ± 3	60 ± 3*
Frontal Cortex	94 ± 3	94 ± 4	84 ± 2	85 ± 3
Anterior Cingulate Cortex	93 ± 2	68 ± 3*	82 ± 2	93 ± 3
Posterior Cingulate Cortex	98 ± 3	61 ± 2*	83 ± 4	78 ± 3*
Prefrontal Cortex	120 ± 4	79 ± 4*	93 ± 6	79 ± 3*

TABLE 25 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Diencephalic Structures	Drug (mg/kg) Saline	C.P.P. (2.5)	Methysergide (15)	C.P.P.+ Methysergide
Mediodorsal Thalamus	89 ± 3	88 ± 4	94 ± 2	87 ± 2
Ventrolateral Thalamus	86 ± 2	75 ± 1*	79 ± 3	69 ± 2*
Anterior-Ventral Thalamus	116 ± 4	75 ± 3*	103 ± 3	95 ± 3*
Anterior-Medial Thalamus	110 ± 3	73 ± 3*	102 ± 3	87 ± 3*
Lateral Thalamus	102 ± 2	73 ± 3*	73 ± 4*	87 ± 3*
Subthalamic Nucleus	79 ± 2	77 ± 1	78 ± 3	73 ± 4
Zona Incerta	79 ± 4	74 ± 3	78 ± 1	69 ± 4
Nucleus Reuniens	97 ± 4	137 ± 3*	89 ± 4	79 ± 3
Habenula (Lateral)	101 ± 3	133 ± 3*	104 ± 6	95 ± 4
Habenula (Medial)	68 ± 4	73 ± 3	69 ± 3	58 ± 2*
Hypothalamus	52 ± 2	55 ± 2	48 ± 3	42 ± 3
Medial Forebrain Bundle	66 ± 2	50 ± 1*	52 ± 2	56 ± 2
Periventricular N.	51 ± 2	77 ± 6*	51 ± 3	51 ± 1

TABLE 25 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Limbic Structures	Saline	C.P.P.(2.5)	Methysergide(15)	C.P.P.+ Methysergide
Hippocampus (Molecular Layer)	84 ± 3	78 ± 1	86 ± 4	70 ± 1*
Dentate Gyrus	77 ± 3	57 ± 2*	56 ± 4*	60 ± 2
Septal Nucleus (Lateral)	51 ± 3	52 ± 1	55 ± 1	55 ± 2
Septal Nucleus	42 ± 3	35 ± 2*	41 ± 1	39 ± 3
Nucleus Accumbens	76 ± 3	55 ± 3*	79 ± 2	70 ± 4
Amygdala (Medial)	45 ± 3	43 ± 2	38 ± 3	41 ± 2
Anterior Amygdaloid Area	86 ± 2	63 ± 1*	86 ± 3	66 ± 3*
Ventral Tegmental Area	71 ± 3	52 ± 2*	63 ± 3	50 ± 3*

TABLE 25 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Extrapyramidal Structures	Saline	C.P.P.(2.5)	Methysergide(15)	C.P.P.+ Methysergide
Caudate Nucleus (Dorsolateral)	92 ± 3	89 ± 2	89 ± 2	80 ± 2*
Caudate Nucleus (Central)	88 ± 3	87 ± 1	75 ± 2*	64 ± 2*
Caudate Nucleus (Ventromedial)	86 ± 2	69 ± 3*	79 ± 2	64 ± 1*
Caudate Nucleus (Caudal)	86 ± 3	63 ± 1*	69 ± 3*	70 ± 1*
Globus Pallidus	55 ± 2	44 ± 3	54 ± 1	47 ± 2
Substantia Nigra (Pars Compacta)	76 ± 3	57 ± 2*	64 ± 3*	62 ± 2*
Substantia Nigra(Pars Reticulata)	58 ± 2	48 ± 2*	50 ± 3	45 ± 2*
Red Nucleus	77 ± 2	69 ± 2	72 ± 3	65 ± 3
Inferior Olive	80 ± 3	67 ± 3	70 ± 3	56 ± 2*
Vestibular Nucleus	106 ± 4	100 ± 2	88 ± 3	85 ± 5

TABLE 25 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

		Drug (mg/kg)			
Primary Auditory		Saline	C.P.P.(2.5)	Methysergide (15)	C.P.P.+ Methysergide
Auditory Cortex		136 ± 3	114 ± 5*	131 ± 4	105 ± 3*
Medial Geniculate		111 ± 2	92 ± 2*	115 ± 3	84 ± 3*
Inferior Colliculus		177 ± 7	150 ± 3	168 ± 7	167 ± 8
Lateral Lemniscus		110 ± 3	81 ± 5*	103 ± 6	73 ± 4*
Superior Olive		150 ± 3	109 ± 6	157 ± 9	100 ± 7*
Cochlear Nucleus		144 ± 4	103 ± 3	130 ± 9	107 ± 6
Primary Visual					
Visual Cortex		94 ± 3	68 ± 1*	88 ± 3	92 ± 3
Lateral Geniculate	D	96 ± 4	78 ± 2*	87 ± 4	74 ± 4
	V	91 ± 3	64 ± 4*	77 ± 2	61 ± 3*
Superior Colliculus	S	86 ± 3	75 ± 2	62 ± 4*	75 ± 2
Superior Colliculus	D	83 ± 3	75 ± 2	62 ± 2*	70 ± 2*

TABLE 25 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

	Drug (mg/kg)			
Hindbrain Structures	Saline	C.P.P.(2.5)	Methysergide(15)	C.P.P.+ Methysergide
Cerebellum Hemisphere	52 ± 3	39 ± 3*	47 ± 2	43 ± 2
Cerebellum Nuclei	87 ± 2	83 ± 2	74 ± 4	74 ± 5
Cerebellum Vermis	89 ± 3	81 ± 3	75 ± 3	67 ± 4*
Cerebellum White Matter	33 ± 2	39 ± 4	34 ± 1	36 ± 2
Dorsal Raphe Nucleus	91 ± 3	74 ± 4*	77 ± 3*	69 ± 2*
Median Raphe Nucleus	94 ± 3	74 ± 2*	81 ± 3*	69 ± 2*
Pontine Reticular Formation	58 ± 2	62 ± 1	57 ± 2	54 ± 3
Myelinated Fiber Tracts				
Corpus Callosum	34 ± 1	29 ± 3	28 ± 2	34 ± 2
Genu of the Corpus Callosum	29 ± 2	34 ± 4	26 ± 1	31 ± 2
Internal Capsule	31 ± 2	34 ± 2	29 ± 1	34 ± 2
n	6	6	6	6

Data are given as mean ± standard error of the mean in umols/100g/min. *p: < 0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

TABLE 26

CARDIOVASCULAR DATA

Drug (mg/kg)	Heart Rate (beats/min)		Mean Arterial Blood Pressure (mmHg)	
	Control	At Study	Control	At Study
Saline	426 ± 6	429 ± 5	125 ± 4	127 ± 2
L.S.D. (0.015)	424 ± 3	404 ± 5	126 ± 4	125 ± 3
Metergoline (3)	416 ±12	413 ±11	126 ± 3	123 ± 2
L.S.D. + Metergoline	419 ± 8	414 ± 6	125 ± 4	125 ± 3
n	6	6	6	6

Data are given as mean ± standard error of the mean.
* $p<0.05$. Statistical analysis by ANOVA and Scheffe.

TABLE 27

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Cerebral Structures	Saline	L.S.D.(0.015)	Metergoline(3)	L.S.D.+ Metergoline
Parietal Cortex	94 ± 3	82 ± 4	84 ± 3	73 ± 2*
Sensory Motor Cortex	98 ± 5	90 ± 4	90 ± 4	65 ± 1*
Entorhinal Cortex	74 ± 4	62 ± 2*	73 ± 3	47 ± 2*
Pyriform Cortex	97 ± 4	76 ± 3*	64 ± 3*	52 ± 3*
Frontal Cortex	97 ± 4	92 ± 4	92 ± 3	65 ± 1*
Anterior Cingulate Cortex	94 ± 3	81 ± 2*	85 ± 2	58 ± 2*
Posterior Cingulate Cortex	99 ± 4	73 ± 3*	87 ± 3	73 ± 3*
Prefrontal Cortex	124 ± 7	99 ± 6	94 ± 5	71 ± 3*

TABLE 27 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Diencephalic Structures	Saline	L.S.D.(0.015)	Metergoline(3)	L.S.D.+ Metergoline
Mediodorsal Thalamus	94 ± 1	82 ± 4	85 ± 4	77 ± 4*
Ventrolateral Thalamus	84 ± 2	68 ± 3*	68 ± 3*	64 ± 5*
Anterior-Ventral Thalamus	115 ± 6	91 ± 2*	106 ± 5	79 ± 3*
Anterior-Medial Thalamus	113 ± 5	94 ± 2*	97 ± 3*	81 ± 6
Lateral Thalamus	102 ± 2	79 ± 5*	87 ± 4*	66 ± 5*
Subthalamic Nucleus	79 ± 2	69 ± 4	76 ± 4	64 ± 2*
Zona Incerta	77 ± 3	60 ± 5*	75 ± 2	59 ± 2*
Nucleus Reuniens	99 ± 6	91 ± 4	94 ± 3	61 ± 4*
Habenula (Lateral)	107 ± 3	91 ± 4	101 ± 4	85 ± 5
Habenula (Medial)	72 ± 4	56 ± 3*	61 ± 3	64 ± 1
Hypothalamus	52 ± 3	45 ± 3	43 ± 2	37 ± 3*
Medial Forebrain Bundle	66 ± 2	56 ± 5	56 ± 3	59 ± 2*
Periventricular Nucleus	50 ± 3	49 ± 3	55 ± 3	47 ± 1

TABLE 27 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Limbic Structures	Saline	L.S.D.(0.015)	Metergoline(3)	L.S.D.+ Metergoline
Hippocampus (Molecular Layer)	86 ± 3	70 ± 4*	75 ± 3	64 ± 1*
Dentate Gyrus	75 ± 4	54 ± 3*	61 ± 3	58 ± 6
Septal Nucleus (Lateral)	56 ± 3	50 ± 4	49 ± 2	46 ± 1
Septal Nucleus (Medial)	46 ± 3	39 ± 1	38 ± 2	39 ± 2
Nucleus Accumbens	80 ± 2	62 ± 5*	70 ± 3	57 ± 3*
Amygdala (Medial)	47 ± 3	39 ± 3	40 ± 1	49 ± 2
Anterior Amygdaloid Area	84 ± 2	76 ± 4	66 ± 3*	54 ± 4*
Ventral Tegmental Area	69 ± 4	52 ± 5*	56 ± 3	52 ± 3*

TABLE 27 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Extrapyramidal Structures	Saline	L.S.D.(0.015)	Metergoline (3)	L.S.D.+ Metergoline
Caudate Nucleus (Dorsolateral)	94 ± 4	78 ± 4*	88 ± 3	62 ± 2*
Caudate Nucleus (Central)	83 ± 2	70 ± 3*	74 ± 5	58 ± 1*
Caudate Nucleus (Ventromedial)	84 ± 4	69 ± 4*	71 ± 3	55 ± 1*
Caudate Nucleus (Caudal)	82 ± 2	63 ± 3*	71 ± 3	58 ± 3*
Globus Pallidus	54 ± 3	45 ± 3	46 ± 2	48 ± 3
Substantia Nigra (Pars Compacta)	81 ± 3	59 ± 5*	73 ± 3	56 ± 1*
Substantia Nigra (Pars Reticulata)	60 ± 2	42 ± 4*	46 ± 1*	48 ± 1*
Red Nucleus	76 ± 4	64 ± 3	73 ± 2	54 ± 3*
Inferior Olive	75 ± 4	64 ± 7	67 ± 4	53 ± 2*
Vestibular Nucleus	109 ± 7	92 ± 8	92 ± 3	65 ± 3*

TABLE 27 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

		Drug (mg/kg)			
Primary Auditory		Saline	L.S.D.(0.015)	Metergoline(3)	L.S.D.+ Metergoline
Auditory Cortex		139 ± 4	123 ± 6	143 ± 7	92 ± 3*
Medial Geniculate		115 ± 4	96 ± 8	110 ± 4	68 ± 3*
Inferior Colliculus		168 ± 7	160 ±13	179 ± 7	109 ± 2*
Lateral Lemniscus		112 ± 3	86 ± 6*	102 ± 3	66 ± 2*
Superior Olive		151 ± 3	126 ± 8	135 ±11	90 ± 3*
Cochlear Nucleus		141 ± 3	129 ± 5	143 ±14	91 ± 3*
Primary Visual					
Visual Cortex		99 ± 3	78 ± 6*	87 ± 4	62 ± 2*
Lateral Geniculate	D	96 ± 4	69 ± 3*	77 ± 2	70 ± 2*
	V	89 ± 5	57 ± 5*	67 ± 1	62 ± 4*
Superior Colliculus	S	84 ± 1	70 ± 5*	79 ± 2	67 ± 4*
Superior Colliculus	D	80 ± 3	66 ± 5*	73 ± 2	57 ± 4*

TABLE 27 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Hindbrain Structures	Saline	L.S.D.(0.015)	Metergoline (3)	L.S.D.+ Metergoline
Cerebellum Hemisphere	51 ± 4	41 ± 5	47 ± 2	50 ± 4
Cerebellum Nuclei	89 ± 4	78 ± 5	84 ± 3	63 ± 3*
Cerebellum Vermis	96 ± 5	73 ± 5	82 ± 4	59 ± 4*
Cerebellum White Matter	35 ± 2	31 ± 3	34 ± 1	29 ± 3
Dorsal Raphe Nucleus	95 ± 3	75 ± 4*	82 ± 1*	59 ± 3*
Median Raphe Nucleus	96 ± 5	72 ± 4*	78 ± 4	54 ± 3*
Pontine Reticular Formation	66 ± 2	50 ± 3*	57 ± 1	41 ± 3
Myelinated Fiber Tracts				
Corpus Callosum	34 ± 2	27 ± 2	34 ± 2	36 ± 4
Genu of the Corpus Callosum	27 ± 2	25 ± 1	27 ± 3	31 ± 3
Internal Capsule	33 ± 1	24 ± 1*	32 ± 3	36 ± 4
n	6	6	6	6

Data are given as mean ± standard error of the mean in umols/100g/min. *p: <0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

TABLE 28

CARDIOVASCULAR DATA

Drug (mg/kg)	Heart Rate (beats/min)		Mean Arterial Blood Pressure (mmHg)	
	Control	At Study	Control	At Study
Saline	426 ± 6	429 ± 5	125 ± 4	127 ± 2
5MeO (0.75)	408 ±10	362 ±14*	128 ± 3	141 ± 3*
Metergoline (3)	416 ±12	413 ±11	126 ± 3	123 ± 2
5MeO + Metergoline	412 ± 8	413 ± 3	127 ± 4	130 ± 4
n	6	6	6	6

Data are given as mean ± standard error of the mean.
* $p<0.05$. Statistical analysis by ANOVA and Scheffe.

TABLE 29

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Cerebral Structures	Saline	MeO (0.75)	Metergoline (3)	MeO + Metergoline
Parietal Cortex	94 ± 2	74 ± 2*	84 ± 4	72 ± 1*
Sensory Motor Cortex	99 ± 4	83 ± 1	90 ± 4	87 ± 2
Entorhinal Cortex	74 ± 2	58 ± 1*	73 ± 3	43 ± 1*
Pyriform Cortex	95 ± 2	61 ± 3*	64 ± 3*	49 ± 2*
Frontal Cortex	94 ± 2	70 ± 2*	92 ± 3	81 ± 4
Anterior Cingulate Cortex	94 ± 2	74 ± 2*	85 ± 2	79 ± 2*
Posterior Cingulate Cortex	96 ± 4	73 ± 2*	87 ± 3	75 ± 4*
Prefrontal Cortex	117 ± 4	90 ± 3*	94 ± 5*	88 ± 1*

TABLE 29 CONTD.

Diencephalic Structures	LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min) Drug (mg/kg) Saline	MeO (0.75)	Metergoline (3)	MeO + Metergoline
Mediodorsal Thalamus	94 ± 1	74 ± 3*	85 ± 4	85 ± 1
Ventrolateral Thalamus	84 ± 2	59 ± 3*	68 ± 3*	58 ± 2*
Anterior-Ventral Thalamus	114 ± 4	88 ± 2*	106 ± 5	83 ± 3*
Anterior-Medial Thalamus	113 ± 4	82 ± 3*	97 ± 3*	78 ± 1*
Lateral Thalamus	102 ± 2	77 ± 3*	87 ± 4*	66 ± 2*
Subthalamic Nucleus	79 ± 3	64 ± 3*	76 ± 4	68 ± 2
Zona Incerta	77 ± 3	59 ± 3*	94 ± 3	62 ± 1*
Nucleus Reuniens	98 ± 4	84 ± 1	101 ± 4	70 ± 1*
Habenula (Lateral)	107 ± 2	88 ± 3*	61 ± 3	85 ± 1*
Habenula (Medial)	71 ± 3	59 ± 3	110 ± 6	59 ± 2
Hypothalamus	53 ± 3	39 ± 1*	43 ± 2	40 ± 1*
Medial Forebrain Bundle	67 ± 2	46 ± 3*	56 ± 3	39 ± 4*
Periventricular Nucleus	48 ± 3	45 ± 3	55 ± 3	46 ± 3

TABLE 29 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Limbic Structures	Saline	MeO (0.75)	Metergoline (3)	MeO + Metergoline
Hippocampus (Molecular Layer)	86 ± 3	64 ± 3*	75 ± 3	60 ± 4*
Dentate Gyrus	73 ± 3	53 ± 1*	61 ± 3	49 ± 1*
Septal Nucleus (Lateral)	57 ± 4	44 ± 3*	49 ± 2	50 ± 3
Septal Nucleus (Medial)	46 ± 3	35 ± 2	38 ± 2	40 ± 3
Nucleus Accumbens	80 ± 2	55 ± 3*	70 ± 3	49 ± 3*
Amygdala (Medial)	47 ± 2	35 ± 1*	40 ± 1	36 ± 3*
Anterior Amygdaloid Area	83 ± 2	57 ± 2*	66 ± 3*	54 ± 2*
Ventral Tegmental Area	69 ± 4	44 ± 4*	56 ± 3	38 ± 1*

TABLE 29 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Extrapyramidal Structures	Saline	Drug (mg/kg) MeO (0.75)	Metergoline (3)	MeO + Metergoline
Caudate Nucleus (Dorsolateral)	95 ± 3	68 ± 4*	88 ± 3	63 ± 1*
Caudate Nucleus (Central)	83 ± 1	62 ± 2*	74 ± 5	64 ± 1*
Caudate Nucleus (Ventromedial)	84 ± 3	61 ± 2*	71 ± 3	56 ± 2*
Caudate Nucleus (Caudal)	82 ± 2	56 ± 2*	71 ± 3	50 ± 3*
Globus Pallidus	54 ± 3	38 ± 2*	46 ± 2	35 ± 2*
Substantia Nigra (Pars Compacta)	81 ± 3	51 ± 2*	73 ± 3	55 ± 2*
Substantia Nigra (Pars Reticulata)	61 ± 2	38 ± 2*	46 ± 1*	41 ± 2*
Red Nucleus	76 ± 4	56 ± 2*	73 ± 2	54 ± 2*
Inferior Olive	75 ± 3	50 ± 3*	67 ± 4	47 ± 2*
Vestibular Nucleus	109 ± 5	86 ± 1*	92 ± 3	59 ± 6*

TABLE 29 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

		Saline	MeO (0.75)	Metergoline (3)	MeO + Metergoline
Primary Auditory					
Auditory Cortex		139 ± 2	130 ± 6	143 ± 7	129 ± 6
Medial Geniculate		114 ± 4	91 ± 2*	110 ± 6	87 ± 6*
Inferior Colliculus		173 ± 6	165 ± 5	176 ± 9	126 ± 4*
Lateral Lemniscus		113 ± 3	91 ± 5*	102 ± 3	58 ± 3*
Superior Olive		150 ± 9	117 ±10	134 ±11	84 ± 3*
Cochlear Nucleus		140 ± 7	117 ±10	143 ±14	93 ± 4*
Primary Visual					
Visual Cortex		99 ± 2	87 ± 1	87 ± 4	70 ± 4*
Lateral Geniculate	D	83 ± 2	66 ± 2*	77 ± 2*	64 ± 2*
	V	81 ± 2	55 ± 2*	67 ± 1	56 ± 2*
Superior Colliculus	S	85 ± 2	72 ± 2*	79 ± 2	68 ± 3*
Superior Colliculus	D	82 ± 2	63 ± 1	73 ± 2	55 ± 3*

TABLE 29 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

	Drug (mg/kg)			
Hindbrain Structures	Saline	MeO (0.75)	Metergoline (3)	MeO + Metergoline
Cerebellum Hemisphere	51 ± 5	37 ± 2*	47 ± 2	36 ± 1*
Cerebellum Nuclei	89 ± 3	75 ± 2	84 ± 3	57 ± 5*
Cerebellum Vermis	96 ± 6	76 ± 3*	82 ± 4	49 ± 4*
Cerebellum White Matter	33 ± 1	26 ± 1*	34 ± 1	28 ± 1*
Dorsal Raphe Nucleus	91 ± 2	64 ± 3*	82 ± 4	61 ± 2*
Median Raphe Nucleus	93 ± 2	70 ± 2*	78 ± 4*	57 ± 1*
Pontine Reticular Formation	61 ± 2	46 ± 2*	57 ± 1*	41 ± 2*
Myelinated Fiber Tracts				
Corpus Callosum	33 ± 2	23 ± 1*	34 ± 2	29 ± 3
Genu of the Corpus Callosum	27 ± 1	21 ± 1	27 ± 3	25 ± 2
Internal Capsule	32 ± 1	25 ± 2*	32 ± 3	36 ± 3
n	6	6	6	6

Data are given as mean ± standard error of the mean in μmols/100g/min. *p: <0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

TABLE 30

CARDIOVASCULAR DATA

Drug (mg/kg)	Heart Rate (beats/min)		Mean Arterial Blood Pressure (mmHg)	
	Control	At Study	Control	At Study
Saline	420 ± 8	419 ± 8	133 ± 3	130 ± 2
Quipazine (3)	418 ± 5	310 ± 8*	136 ± 2	172 ± 2*
Metergoline (3)	406 ±12	403 ±11	126 ± 3	123 ± 2
Quipazine + Metergoline	412 ± 8	410 ± 3	124 ± 3	125 ± 5
n	6	6	6	6

Data are given as mean ± standard error of the mean.

* $p<0.05$. Statistical analysis by ANOVA and Scheffe.

TABLE 31

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Cerebral Structure	Drug (mg/kg) Saline	Quipazine(3)	Metergoline(3)	Quipazine + Metergoline
Parietal Cortex	94 ± 3	79 ± 4	84 ± 3	87 ± 5
Sensory Motor Cortex	96 ± 5	98 ± 6	91 ± 3	91 ± 6
Entorhinal Cortex	74 ± 4	55 ± 4*	73 ± 3*	53 ± 4*
Pyriform Cortex	97 ± 4	79 ± 3*	64 ± 3*	58 ± 2*
Frontal Cortex	97 ± 4	78 ± 5	92 ± 3	88 ± 5
Anterior Cingulate Cortex	94 ± 3	78 ± 4*	85 ± 2	73 ± 2*
Posterior Cingulate Cortex	99 ± 4	55 ± 3*	87 ± 3	80 ± 4
Prefrontal Cortex	126 ± 3	80 ± 3*	94 ± 3*	82 ± 3*

TABLE 31 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Diencephalic Structures	Drug (mg/kg) Saline	Quipazine(3)	Metergoline(3)	Quipazine + Metergoline
Mediodorsal Thalamus	94 ± 1	93 ± 5	85 ± 4	83 ± 4
Ventrolateral Thalamus	84 ± 2	82 ± 5	68 ± 3*	68 ± 3*
Anterior-Ventral Thalamus	115 ± 4	72 ± 3*	106 ± 5	104 ± 7
Anterior-Medial Thalamus	113 ± 5	77 ± 4*	103 ± 2	94 ± 7
Lateral Thalamus	102 ± 1	70 ± 3*	87 ± 4*	77 ± 7*
Subthalamic Nucleus	79 ± 2	80 ± 5	76 ± 4	67 ± 6
Zona Incerta	77 ± 3	85 ± 2	75 ± 2	69 ± 7·
Nucleus Reuniens	99 ± 6	156 ± 6*	94 ± 3	95 ± 4
Habenula (Lateral)	107 ± 3	104 ± 5	101 ± 4	102 ± 8
Habenula (Medial)	72 ± 4	69 ± 4	65 ± 3	58 ± 4*
Hypothalamus	52 ± 3	55 ± 4	43 ± 2*	39 ± 3*
Medial Forebrain Bundle	66 ± 2	61 ± 3	59 ± 3	49 ± 3*
Periventricular Nucleus	50 ± 3	62 ± 2*	55 ± 3	47 ± 2

TABLE 31 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

	Drug (mg/kg)			
Limbic Structures	Saline	Quipazine(3)	Metergoline(3)	Quipazine + Metergoline
Hippocampus (Molecular Layer)	86 ± 3	94 ± 2	75 ± 3	57 ± 3*
Dentate Gyrus	75 ± 4	55 ± 3*	61 ± 3	50 ± 4*
Septal Nucleus (Lateral)	56 ± 3	61 ± 4	49 ± 2	52 ± 3
Septal Nucleus (Medial)	46 ± 3	42 ± 2	38 ± 2	42 ± 3
Nucleus Accumbens	80 ± 2	69 ± 4	70 ± 3	75 ± 5
Amygdala (Medial)	47 ± 3	47 ± 3	40 ± 2	38 ± 2
Anterior Amygdaloid Area	84 ± 2	81 ± 3	66 ± 3*	63 ± 4*
Ventral Tegmental Area	69 ± 4	56 ± 4	55 ± 3*	45 ± 4*

TABLE 31 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Extrapyramidal Structures	Drug (mg/kg) Saline	Quipazine (3)	Metergoline (3)	Quipazine + Metergoline
Caudate Nucleus (Dorsolateral)	94 ± 4	94 ± 6	88 ± 3	76 ± 2*
Caudate Nucleus (Central)	83 ± 2	77 ± 4	74 ± 5	63 ± 1*
Caudate Nucleus (Ventromedial)	84 ± 4	73 ± 3*	71 ± 3*	60 ± 1*
Caudate Nucleus (Caudal)	82 ± 2	66 ± 1*	71 ± 3*	60 ± 2*
Globus Pallidus	54 ± 2	51 ± 2	46 ± 2	43 ± 2*
Substantia Nigra (Pars Compacta)	81 ± 3	60 ± 4*	73 ± 3	61 ± 7*
Substantia Nigra (Pars Reticulata)	60 ± 2	39 ± 1*	46 ± 1*	38 ± 3*
Red Nucleus	76 ± 3	65 ± 3	73 ± 2	58 ± 4*
Inferior Olive	75 ± 3	66 ± 3	67 ± 4	56 ± 6
Vestibular Nucleus	109 ± 6	114 ± 5	98 ± 3	81 ± 6

TABLE 31 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

		Drug (mg/kg)			
Primary Auditory		Saline	Quipazine (3)	Metergoline (3)	Quipazine + Metergoline
Auditory Cortex		139 ± 4	137 ± 8	143 ± 7	125 ± 5
Medial Geniculate		115 ± 4	103 ± 6	110 ± 6	93 ± 6
Inferior Colliculus		168 ± 7	173 ± 6	176 ± 9	167 ± 6
Lateral Lemniscus		112 ± 3	100 ± 5	102 ± 3	98 ± 8
Superior Olive		151 ± 4	135 ± 5	135 ± 5	117 ± 5
Cochlear Nucleus		141 ± 4	117 ± 5	143 ±14	121 ± 7
Primary Visual					
Visual Cortex		99 ± 4	84 ± 3*	87 ± 4	76 ± 3*
Lateral Geniculate	D	96 ± 3	74 ± 4*	77 ± 2*	67 ± 4*
	V	89 ± 5	70 ± 2*	69 ± 2*	64 ± 1*
Superior Colliculus	S	84 ± 1	64 ± 4*	79 ± 2	60 ± 4*
Superior Colliculus	D	80 ± 3	79 ± 6	73 ± 2	58 ± 4*

TABLE 31 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

	Drug (mg/kg)			
Hindbrain Structures	Saline	Quipazine (3)	Metergoline (3)	Quipazine + Metergoline
Cerebellum Hemisphere	51 ± 3	52 ± 2	47 ± 2	43 ± 4
Cerebellum Nuclei	89 ± 3	86 ± 6	84 ± 3	72 ± 4
Cerebellum Vermis	96 ± 5	104 ± 6	82 ± 6	84 ± 7
Cerebellum White Matter	35 ± 2	36 ± 2	34 ± 1	28 ± 1
Dorsal Raphe Nucleus	95 ± 3	96 ± 3	83 ± 4	81 ± 5
Median Raphe Nucleus	96 ± 5	88 ± 4	78 ± 4	68 ± 6*
Pontine Reticular Formation	61 ± 1	56 ± 4	57 ± 1	48 ± 3*
Myelinated Fiber Tracts				
Corpus Callosum	34 ± 1	36 ± 2	34 ± 2	30 ± 1
Genu of the Corpus Callosum	27 ± 2	30 ± 1	27 ± 2	25 ± 1
Internal Capsule	33 ± 1	28 ± 2	32 ± 3	28 ± 1
n	6	6	6	6

Data are given as mean ± standard error of the mean in umols/100g/min. *p: < 0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

TABLE 32

CARDIOVASCULAR DATA

Drug (mg/kg)	Heart Rate (beats/min)		Mean Arterial Blood Pressure (mmHg)	
	Control	At Study	Control	At Study
Saline	404 ± 6	408 ± 8	125 ± 3	127 ± 3
C.P.P. (2.5)	430 ±14	344 ±18*	128 ± 3	165 ± 3*
Metergoline (3)	421 ±10	423 ± 5	130 ± 2	133 ± 2
C.P.P. + Metergoline	413 ± 7	412 ± 7	127 ± 3	125 ± 4
n	6	6	6	6

Data are given as mean ± standard error of the mean.
* $p<0.05$. Statistical analysis by ANOVA and Scheffe.

TABLE 33

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Cerebral Structures	Drug (mg/kg) Saline	C.P.P. (2.5)	Metergoline (3)	C.P.P.+ Metergoline
Parietal Cortex	92 ± 3	76 ± 2*	86 ± 3	74 ± 3*
Sensory Motor Cortex	96 ± 2	94 ± 2	90 ± 2	86 ± 4
Entorhinal Cortex	76 ± 3	50 ± 3*	72 ± 3	48 ± 3*
Pyriform Cortex	96 ± 3	64 ± 1*	69 ± 5*	65 ± 3*
Frontal Cortex	94 ± 3	94 ± 4	92 ± 3*	82 ± 2.
Anterior Cingulate Cortex	93 ± 2	68 ± 3*	85 ± 2	76 ± 4*
Posterior Cingulate Cortex	98 ± 3	61 ± 2*	87 ± 3	78 ± 2*
Prefrontal Cortex	120 ± 4	79 ± 4*	94 ± 5*	78 ± 4*

TABLE 33 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

	Drug (mg/kg)			
Diencephalic Structures	Saline	C.P.P. (2.5)	Metergoline (3)	C.P.P. + Metergoline
Mediodorsal Thalamus	89 ± 3	88 ± 4	85 ± 4	83 ± 3
Ventrolateral Thalamus	86 ± 2	75 ± 1*	68 ± 3*	69 ± 2
Anterior-Ventral Thalamus	116 ± 4	75 ± 3*	106 ± 5	95 ± 5
Anterior-Medial Thalamus	110 ± 3	73 ± 3*	97 ± 3	91 ± 2*
Lateral Thalamus	102 ± 2	73 ± 3*	90 ± 2*	79 ± 3
Subthalamic Nucleus	79 ± 2	77 ± 1	80 ± 3	78 ± 3
Zona Incerta	79 ± 4	74 ± 3	75 ± 3	66 ± 2
Nucleus Reuniens	97 ± 4	137 ± 3*	94 ± 4	73 ± 3*
Habenula (Lateral)	101 ± 3	133 ± 3*	101 ± 4	99 ± 3
Habenula (Medial)	68 ± 3	73 ± 3	61 ± 3	68 ± 3
Hypothalamus	52 ± 2	55 ± 2	43 ± 3	41 ± 2*
Medial Forebrain Bundle	60 ± 2	50 ± 1*	56 ± 4	49 ± 4
Periventricular Nucleus	51 ± 2	77 ± 6*	49 ± 2	43 ± 2

TABLE 33 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Limbic Structures	Saline	C.P.P. (2.5)	Metergoline (3)	C.P.P. + Metergoline
Hippocampus (Molecular Layer)	84 ± 3	78 ± 1	75 ± 3	65 ± 1*
Dentate Gyrus	77 ± 3	57 ± 2*	61 ± 4	61 ± 2
Septal Nucleus (Lateral)	51 ± 3	52 ± 1	49 ± 6	46 ± 2
Septal Nucleus (Medial)	42 ± 3	35 ± 2*	38 ± 2	36 ± 2
Nucleus Accumbens	76 ± 3	55 ± 3*	65 ± 3*	60 ± 2
Amygdala (Medial)	45 ± 3	43 ± 2	40 ± 2	40 ± 3
Anterior Amygdaloid Area	86 ± 2	63 ± 1*	66 ± 4*	63 ± 3*
Ventral Tegmental Area	71 ± 3	52 ± 2*	56 ± 4	55 ± 1*

TABLE 33 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Extrapyramidal Structures	Saline	C.P.P. (2.5)	Metergoline (3)	C.P.P. + Metergoline
Caudate Nucleus (Dorsolateral)	92 ± 2	89 ± 2	88 ± 3	68 ± 3*
Caudate Nucleus (Central)	88 ± 3	87 ± 1	74 ± 4	66 ± 2*
Caudate Nucleus (Ventromedial)	86 ± 2	69 ± 3*	71 ± 4	67 ± 2*
Caudate Nucleus (Caudal)	86 ± 3	63 ± 1*	71 ± 3	62 ± 2*
Globus Pallidus	55 ± 2	44 ± 3	46 ± 3	47 ± 2
Substantia Nigra (Pars Compacta)	76 ± 3	57 ± 2*	73 ± 3	56 ± 1*
Substantia Nigra (Pars Reticulata)	58 ± 2	48 ± 2*	46 ± 2*	42 ± 2*
Red Nucleus	77 ± 2	69 ± 2	73 ± 3	64 ± 4
Inferior Olive	80 ± 3	67 ± 3	67 ± 4	53 ± 2*
Vestibular Nucleus	106 ± 4	100 ± 2	92 ± 3	67 ± 3*

TABLE 33 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

		Drug (mg/kg)			
Primary Auditory		Saline	C.P.P. (2.5)	Metergoline(3)	C.P.P.+ Metergoline
Auditory Cortex		136 ± 3	114 ± 5*	140 ± 4	105 ± 2*
Medial Geniculate		111 ± 2	92 ± 2	110 ± 6	91 ± 2*
Inferior Colliculus		177 ± 7	150 ± 3	176 ± 8	136 ± 7*
Lateral Lemniscus		110 ± 3	81 ± 5*	102 ± 3	73 ± 4*
Superior Olive		150 ± 3	109 ± 6	134 ± 6	97 ± 4*
Cochlear Nucleus		144 ± 4	103 ± 3	142 ± 6	90 ± 6*
Primary Visual					
Visual Cortex		94 ± 3	68 ± 1*	91 ± 2	78 ± 3*
Lateral Geniculate	D	96 ± 4	78 ± 2*	77 ± 2*	72 ± 2*
	V	91 ± 3	64 ± 4*	67 ± 2*	62 ± 1*
Superior Colliculus	S	86 ± 3	75 ± 2	79 ± 3	75 ± 2
Superior Colliculus	D	83 ± 3	75 ± 2	73 ± 3	72 ± 2

TABLE 33 CONTD.

LOCAL CEREBRAL GLUCOSE UTILISATION (μmols/100g/min)

Drug (mg/kg)

Hindbrain Structures	Saline	C.P.P. (2.5)	Metergoline (3)	C.P.P. + Metergoline
Cerebellum Hemisphere	52 ± 3	39 ± 3*	47 ± 2	39 ± 3
Cerebellum Nuclei	87 ± 2	83 ± 2	84 ± 3	67 ± 4*
Cerebellum Vermis	89 ± 3	81 ± 3	82 ± 5	66 ± 2*
Cerebellum White Matter	33 ± 2	39 ± 4	34 ± 2	34 ± 2
Dorsal Raphe Nucleus	91 ± 3	74 ± 4*	82 ± 4	66 ± 2*
Median Raphe Nucleus	94 ± 3	74 ± 2*	78 ± 4*	59 ± 3*
Pontine Reticular Formation	58 ± 2	62 ± 1	57 ± 2	46 ± 2*
Myelinated Fiber Tracts				
Corpus Callosum	34 ± 1	29 ± 3	34 ± 2	34 ± 2
Genu of the Corpus Callosum	29 ± 2	34 ± 4	27 ± 4	27 ± 2
Internal Capsule	31 ± 2	34 ± 2	32 ± 3	33 ± 2
n	6	6	6	6

Data are given as mean ± standard error of the mean in umols/100g/min. *p:<0.05. Statistical analysis by ANOVA and Scheffe with respect to saline controls.

DISCUSSION AND SYNTHESIS

Throughout this text it has been taken for granted that glucose utilisation is equivalent to, or is at least a direct measurement of cerebral function. What evidence is their on which to base this assumption?

The method itself has been used to demonstrate the close relationship between known physiological responses and those of local cerebral glucose utilisation. Perhaps the most convincing example was the patterns of local cerebral glucose utilisation following visual deprivation in the monkey (Kennedy et al, 1975; Kennedy et al, 1976). In these studies the pattern of response, following unilateral visual deprivation, consistently replicated the known physiological and anatomical properties of the ocular dominance columns of Hubel and Wiesel, 1968. This is highly suggestive evidence of a close relationship between function and glucose utilisation.

Since the classic paper of Sokoloff et al, 1977, on the theory and methodology of the 2-deoxyglucose technique, many pharmacological studies have been published. These may be best exemplified by extensive work on the central dopaminergic system (Brown and Wolfson, 1978; McCulloch et al, 1979; McCulloch et al, 1980 a,b.; McCulloch and Kelly, 1981: McCulloch et al, 1982 a,b.), central noradrenergic system (Savaki et al, 1978; Savaki et al, 1982 a,b.), central gabaergic influences (Kelly and McCulloch, 1981; Kelly and McCulloch, 1982; Palacios et al, 1982) and anaesthetics such as barbiturates (Ingvar et al, 1980; Nagai et al, 1980; Sokoloff et al, 1977),

chloralose (Dudley et al, 1982) halothane (Shapiro et al, 1978), Ketamine (Lund et al, 1981) and chloral hydrate (Grome and McCulloch, 1983).

In these papers a general correlation has been found between previously published electrophysiological data and the effects of manipulation on local cerebral glucose utilisation. (see Sokoloff, 1982 for review)

However, they have provided a new perspective on the functional organisation of the brain and they have shown that there is a correlation between energy use and functional activity. What physiological parameter does glucose catabolism most reflect?

The physiological parameter most associated with nervous tissue is the propagation of electrical activity. This process requires the constant maintenance of Na^+/K^+ gradients, which require the breakdown of adenosine triphosphate (ATP). Increased firing of the nerve should entail a concommitant increase in energy use. Since the oxidative metabolism of glucose is the sole provider of energy in the central nervous system under normal conditions (Sokoloff, 1960), there should be a direct correlation between cellular activity and the glucose expended.

In vivo, there was a direct linear relationship between the frequency of the electrical spike activity in the superior cervical ganglion and glucose utilisation. (Yarowsky et al, 1979). Furthermore, Mata et al, 1980, have used preparations of rat posterior pituitary, in vitro, to measure the effects of electrical stimulation on glucose utilisation. Electrical stimulation increased

glucose utilisation; an effect which was blocked by ouabain which inhibits Na^+/K^+ ATPase but not spike activity or vasopressin release. Since Nordmann, 1977 has shown that 42% of the posterior pituatory is made up of axon terminals, which because of their high surface-volume ratios will have larger changes in ionoc concentration gradients for a given amount of spike activity, the changes in glucose utilisation observed by Mata et al, 1980 probably reflect the metabolic activity of axonal terminals. This is in agreement with the previous findings of (Kelly and McCulloch, 1982, Kennedy et al, 1976; Schwartz et al, 1979). Therefore, to summarise, local cerebral glucose utilisation seems to be directly linked via Na^+/K^+ ATPase activity and electrical activity to function.

In the introduction to this thesis, it was stated that "any method purporting to define brain activity should ideally be able to make dynamic measurements of both local and integrated function." It can be seen that the 2-deoxyglucose method does measure both local and integrated functional activity, but what problems are there in relation to its dynamic qualities?

The areas of error associated with this technique are time resolution, the fact that there is glucose - 6 - phosphatase activity in the rat C.N.S., and that there are glycogen stores in the brain which are capable of providing glucose for cellular use quite seperate to that of plasma-borne glucose.

In comparison to electrophysiology, with its ability to

measure near-instantaneous changes in neuronal activity the forty-five minutes required to measure local cerebral glucose utilisation makes the technique at first sight extremely insensitive from the point of view of time resolution. This length of time (45 minutes) is part of the experimental protocol of the 2-deoxyglucose method as defined by Sokoloff et al, 1977 and used in this study. The essence of the problem is that K_1, K_2, and K_3 are all part of exponential terms in the operational equation of the method. (Fig. 5) This means that with increasing time these terms approach zero and so the values of the rate constants do not have to be known exactly. Thus, it is possible to evaluate these constants in a separate series of animals (in this case the albino rat) and to use these numbers with the expectation that this will produce only a small error in the final measurement. This requires, however, that time resolution be sacrificed.

In relation to pharmalological studies this presents a problem since the effects of drugs (particularly at lower doses) may not be sustained throughout the forty-five minute period (e.g. the behavioural changes following the intravenous administration of serotonin agonists). This problem is not perhaps as serious as may at first be thought, due to the fact that since the ^{14}C-2-deoxy-glucose is administered as a bolus intravenous injection, the majority of the integral will be made up of the area under the peak and rapidly falling phase of the curve. Thus, the greatest contribution to ^{14}C tissue concentration

is made in the first ten minutes of the experiment. Thus, drugs producing an action for at least this length of time are capable of eliciting observable responses in the central nervous system. This in no way totally negates the time resolution problem and probably accounts for the requirement of either a continuous input or large initial stimulation (in electrophysological terms) to allow effects to be measured. Time resolution still remains a problem.

As mentioned in the introduction, the 2-deoxyglucose 6 phosphate formed by hexokinase is not a substrate for glucose-6-phosphate isomerase or glucose-6-phosphate dehydrogenase and therefor cannot be metabolised by the glycolytic or pentose phosphate pathway. However, it can be broken down by glucose-6-phosphatase to 2-deoxyglucose and glucose-6-phosphatase is present in the brain. This of course would have disasterous consequences for the method since it breaks the assumption that the 2 deoxyglucose-6-phosphate is trapped intracellularly.

Fortunately, this is not such a problem as it might seem since the activity of glucose-6-phosphate in the brain is low (Horton et al, 1973; Sols and Crane, 1954; Tower, 1958) and the loss of deoxyglucose-6-phosphate by glucose -6- phosphatase activity is not significant during the first forty-five minutes after the bolus injection of ^{14}C-2 deoxyglucose (Sokoloff, 1979). The effect is not negligible but becomes noticeable only after sixty minutes and substantial at ninety minutes.

(Sokoloff, 1982).

Cellular elements in the brain contain depots of glycogen. Since this can provide glucose for energy production it is capable of producing an underestimation in the true rate of glucose utilisation as measured by the 2 deoxyglucose method. However, the concentration of glycogen is low and is incapable of sustaining the energy needs of the brain for more than three minutes (McIlwain and Bachelard, 1971; Siesjo, 1978). Nevertheless, it may be important in cases of sudden increase in glucose requirements (e.g. seizures or decreased glucose supply (e.g. ischaemia). Thus, glycogen stores do not present a major problem to the 2-deoxyglucose method. Therefor, it can be assumed that this technique is able to measure functional changes in the central nervous system within a reasonable degree of experimental accuracy.

As has already been stated the overall effect of the administration of 5-hydroxytryptamine (5HT) lysergic acid diethylamide (LSD), 5 methoxy-N,N-dimethyltryptamine (5MeO), quipazine and chloropiperazinyl pyrazine (C.P.P.) was to produce decreased levels of glucose use in the rat central nervous system. Particularly, when we look at cortical areas, we can see that the effects of LSD, 5MeO, quipazine and C.P.P. on glucose utilisation are qualitatively comparable to those of 5HT itself, when in the presence of a monoamine oxidase inhibitor. Unfortunately, differences in the preparations, route of administration and serotonin's inability to cross the

blood-brain barrier make it difficult to make a more meaningful comparison.

It can be seen that there is a distinct hierarchy of response, judged by percentage change in glucose use, following the lower doses of the putative serotonin agonists. This pattern is almost identical for LSD, 5MeO, C.P.P. and quipazine. In this respect, LSD does seem to be more potent than the other three compounds and is capable of producing significant decreases in glucose utilisation at microgramme dose levels.

These changes in glucose use are in keeping with much of the available electrophysiological data showing that 5HT, LSD and 5MeO produced decreases in the activity of spontaneously firing cells in various areas of the rat brain. (Bloom et al, 1972; de Montagny and Aghajanian, 1977; Dray et al, 1976; Haigler and Aghajanian, 1974; Sastry and Phyllis, Segal, 1975; Olpe and Koella, 1977; Wang and Aghajanian, 1977). Furthermore, these similarities were underlined by the actions of LSD, 5MeO, C.P.P. and quipazine on behaviour and cardiovascular parameters.

The behavioural effects of these compounds have been extensively studied. (Clineschmidt, 1977; Gessner and Page, 1962; Grahame-Smith, 1971a; Green et al, 1976; Jacobs, 1976; Sloviter et al, 1978). This behaviour could not be, at least by crude observation alone, be differentiated from the behavioural syndrome which occurs in rats following treatment with a monoamine oxidase inhibitor and L-tryptophan. (Hess and Doephner, 1961;

Grahame-Smith, 1971). The one part of the syndrome which did not occur was hyperpyrexia. This was due to a decision made before the commencement of these studies to control the core body temperature of the rats at all times and therefore the temperature was kept within the limits of 37.0 $\pm$ 0.5^{o}C (mean $\pm$ S.D.)

Similarly, with the effects of L.S.D., 5MeO, C.P.P. and quipazine on blood pressure and heart rate, it could rightly be claimed that as the drugs were administered intravenously these effects are probably direct actions of these drugs on the cardiovasculature. However, the central administration of 5HT produced hypertension (Antonaccio and Cote, 1976; Krstic and Djurkovic, 1976; Lambert et al, 1975; Lambert et al, 1978). It has also been postulated that 5HT and C.P.P. may produce their cardiovascular effects by a central action which reduces sympathetic output (Antonaccio and Cote, 1976; Blatt et al, 1979). Therefore, some of the cardiovascular effects, produced by these putative serotonin agonists, are probably due to their central actions.

Although the majority of affected brain areas displayed similar changes in glucose use following these compounds, there can be little doubt that there were distinct differences in the patterns of cerebral response produced by the agonists containing an indoleamine moeity (L.S.D. and 5MeO) and those having a piperazine-containing structure.

Two major differences could be seen in the responses produced by these structurally differing serotonin agonists. In the extrapyramidal areas there was a biphasic response

following C.P.P. and quipazine whereas LSD and 5Meo produced dose-dependant decreases in glucose utilisation. In fact, the differences were even more subtle. The 'indoleamine' agonists produced an overall decrease in the four areas of the caudate nucleus measured, the globus pallidus and the substantia nigra. Quipazine and C.P.P. however, had no significant effects on the dorsolateral and central portions of the caudate nucleus, at any dose used and high doses of quipazine produced increases only in the ventromedial caudate nucleus, the globus pallidus and the pars reticulata of the substantia nigra.

As has been previously discussed (Chapters IV and V of this thesis), these effects may be due to a direct action of the drugs on these structures. The effects of LSD and 5MeO, and C.P.P. and quipazine (at low doses) would be in keeping with electrophysiological data describing the mainly inhibitory responses of striatal and nigral neurones to microiontophoretic serotonin administration. (Dray et al, 1976; Miller et al, 1975; Olpe and Keolla, 1977)

Despite the findings of Van der Maelen et al, 1979, of excitatory striatal responses to serotonin administration it is the discrete localisation of the effects of quipazine in the caudate nucleus that is of so much interest. In this respect they correlate very well with the topographical arrangement of serotonergic fibers to the caudate nucleus which are most dense in the ventromedial portion (Ternaux et al, 1977) and the biochemical data which shows that quipazine produces its biggest effect on acetylcholine turnover in this region of the caudate nucleus. (Euvrard

et al, 1977; Guyenet et al, 1977).

As suggested in Chapter V of this thesis, the increases in striatal and nigral glucose use may be due to the fact that only at the highest doses did quipazine and C.P.P. produce decreased glucose utilisation in the sensory-motor cortex, thus, perhaps producing a dis-inhibition of that area of the caudate nucleus. However, LSD and 5MeO both produced significant decreases in sensory-motor cortex without inducing increases in extrapyramidal areas.

In their effects on diencephalic areas too, piperazine and indoleamine-containing compounds had differing effects. Whereas, LSD and 5MeO generally produced dose-dependant decreases in glucose use, C.P.P. and quipazine produced discrete increases in glucose use in the nucleus reuniens of the midline thalamus, the zona incerta, the periventricular nucleus and additionally C.P.P. increased the functional activity of the lateral habenular nucleus.

As stated previously (Chapters IV and V) these structures all receive serotoninergic innervation arising from the raphe nuclei. (Azmitia and Segal, 1979: Steinbusch, 1981). This does not explain why LSD and 5MeO decrease, or leave unaffected, the rate of glucose use in these structures while quipazine and C.P.P. produce the opposite effect.

In this context it should be noted that the peripheral administration of psychoactive drugs will produce changes not only in the areas of the brain where they bind to receptors, but also in areas which are anatomically connected to the primary site of response: in other

words an integrated response will develop .

Thus, there are reciprocal pathways between the nucleus reuniens and the zona incerta (Herkenham, 1978; Ricardo, 1981), the zona incerta sends fibers to the globus pallidus and receives them from the visually-related areas; the ventrolateral geniculate body and superior colliculus (Ricardo, 1981). The nucleus reuniens also sends fibers to the globus pallidus and caudate nucleus (Nauta and Mehler, 1966; Powell and Cowan, 1956) as well as to the hippocampus (Herkenham, 1978) and receives afferent fibers from the nucleus accumbens which also has connections with the globus pallidus (Powell and Leman, 1976; Williams et al, 1977). Furthermore, the ventral tegmental area sends fibers to the ventromedial caudate nucleus, the nucleus accumbens, nucleus reuniens, zona incerta, lateral habenular nucleus and the dorsal and median raphe nucleus (Beckstead et al, 1979).

As can be seen from tables 5, 7, 9 and 11, the anatomical areas mentioned above are all affected by the putative serotonin agonists. That they are anatomically and, we must presume, functionally connected leads to an almost endless series of possibilities as to the initial site of action of these drugs. Thus it might seem reasonable to suggest that these differences are due, not simply to an effect of these drugs on the areas showing increased glucose utilisation, but due to the production of an integrated response in the central nervous system. With the experimental model which I have used in these series of experiments, I cannot define the primary site of action

but can identify areas of the brain which are sensitive to the peripheral administration of these drugs. This being the case, it is still reasonable to assume that the actions of these agonists are due to their interaction with physiological receptor mechanisms. What evidence, if any, is there that there are differences in the way indoleamine - and piperazine-containing serotonin agonists interact with serotonin receptors?

Behavioural data on the effects of these drugs in producing myoclonus in the guinea pig. (Jenner et al 1980; Luscombe et al, 1982), showed that piperazine-containing serotonin agonists rarely produced myoclonic jerking in guinea-pigs, whilst serotonin agonists possessing an indole nucleus induced dose-dependant myoclonus. No behavioural differences could be ascertained in this present series of experiments but it has been shown that the behavioural syndrome in guinea-pigs after central serotoninergic activation is 'simpler' in nature than that produced in the rat. (Chadwick et al, 1978).

There is also some differentiation between these two sets of putative serotonin agonists with regard to their interactions with serotonin receptors. Thus, whilst 5MeO and LSD stimulated 5HT-sensitive adenylate cyclase in young rats (Haron et al, 1976; Von Hungen et al, 1975) quipazine and C.P.P. although potent displacers of ^{3}H-5HT neither stimulated nor inhibited this mechanism (Fuller et al, 1978; Nelson et al, 1980a). Furthermore, the presence of guanosine triphosphate (GTP) reduced the

potency of 5MeO displacement of ^{3}H-spiroperidol but did not affect the actions of quipazine. (Hamon et al, 1980) Since Mallat and Hamon, 1982 a,b. showed that at least some of ^{3}H-5HT binding may be associated with 5HT-sensitive adenylate cyclase, it is very tempting to hypothesise a differential effect of these compounds on different classes of 5HT receptor leading to the production of different but overlapping patterns of physiological response.

One of the major criticisms which might be leveled at the data presented is that the drugs may be acting on receptors other than serotonergic. There is evidence that LSD, 5MeO and quipazine all produce changes which might be interpreted as an affect on dopaminergic systems (Grabowska et al, 1974; Green and Grahame-Smith, 1974; Von Hungen et al, 1974). LSD binds to dopamine receptors. (Whitaker and Seeman 1979)

However, there are several factors which must be taken into account. Firstly, there is the behavioural and biochemical data showing an interaction between drugs acting on the central serotonergic and dopaminergic systems. (Jacobs, 1974; Samanin and Garattini, 1975; Waddington and Crow, 1980; Weiner et al, 1975). Secondly, there are well defined connections between the raphe nuclei and the dopaminergic cell bodies of the substantia nigra (Azmitia and Segal, 1979; Steinbusch, 1981) and these connections are reciprocal (Pasquier et al, 1977; Sakai et al, 1977). Thirdly, whereas the dose-dependant actions of LSD on local cerebral glucose utilisation in the conscious rat are similar to those given in a previous investigation

(Shinohara et al, 1976), the actions of serotonin-mimetic drugs in the present studies are in no way similar to the actions of apomorphine on cerebral function (McCulloch et al, 1982a).

The data given here, suggests that although serotonin agonists and antagonists may bind to dopamine receptors, in vitro, their major action in vivo is probably via serotonin receptors.

Before discussing the actions of methysergide, metergoline and cyproheptadine, it would perhaps be useful to define what we mean by the word 'antagonist'. In pharmacological terms, this is a compound which blocks the action of the agonist by binding to the receptor. The receptor-antagonist complex has no intrinsic physiological action. Methysergide and metergoline had no significant effects on local cerebral glucose utilisation at the lowest doses used (i.e. 5 mg/kg and 0.3 mg/kg respectively) but these doses did not appreciably inhibit the actions of the serotonin agonists on behaviour or the cardiovasculature. The highest doses of these compounds block actions of serotonin agonists on behaviour and the cardiovasculature without having any intrinsic effects. Thus, in terms of behaviour, heart rate and blood pressure, the putative serotonin agonists, methysergide and metergoline fit the definition of a serotonin antagonist.

However, in terms of their actions on local cerebral glucose utilisation, there can be no doubt that they produce changes in their own right. These effects concur

with the electrophysiological data of Haigler and Aghajanian, 1974. Furthermore, methysergide, metergoline and cyproheptadine all decreased glucose utilisation in a manner which was qualitatively similar to the putative serotonin agonists. Closer attention to the data shows that methysergide and metergoline produced a similar pattern of cerebral response which is different from that produced by cyproheptadine. (see Chapter 6 of this thesis).

However, electrophysiological data shows that metergoline and methysergide can block some of the effects of serotonin (Sastry and Phillis, 1977; Segal, 1975; Segal, 1976), particularly the excitatory effects. (McCall and Aghajanian, 1979; Van der Maelen and Aghajanian, 1980) Interestingly enough, it has been suggested, based on in vitro data, that serotonin agonists and antagonists bind to different serotonin binding sites or different forms of the same receptor (Bennet and Snyder, 1976; Enjalbert et al, 1978; Nelson et al, 1978; Nelson et al, 1979).

These data would at least suggest that methysergide and metergoline have the capability of inhibiting the actions of serotonin at some serotonin receptors in the rat central nervous system.

As mentioned above, methysergide and metergoline blocked the behavioural and cardiovascular effects of LSD, 5MeO, C.P.P. and quipazine. The central effects of these

combinations are highly complex.

Methysergide and metergoline block some but not all the actions of the putative serotonin agonists. The most notable inhibition was the total blockade (and in one case reversal) of the increases in local cerebral glucose utilisation produced by the piperazine-containing serotonin agonists. Methysergide at a dose of 15mg/kg seemed to be more potent in this respect (see Chapters 7 and 8 of this thesis). Perhaps the least expected result was the potentiation of some of the actions of the putative serotonin agonists by methysergide and metergoline. In this respect, metergoline (3mg/kg) seemed to be able to produce this action more frequently than methysergide (Chapters 7 and 8 of this thesis).

In a qualitative sense, these data support the previously published electrophysiological information which showed that methysergide and metergoline block excitatory responses to serotonin (McCall and Aghajanian, 1979; Van der Maelen, 1980), some of the inhibitory responses (Sastry and Phillis; Segal, 1976) and enhances or leaves unaffected other serotonin-induced inhibitory responses (Haigler and Aghajanian, 1974). This does not, however, explain why this should occur. One interpretation, is that metergoline and methysergide are partial agonists. In this respect there is evidence that L.S.D. is a partial antagonist. (Anden et al, 1968; Aghajanian and Wang, 1978). Since partial agonism is usually a dose-dependant phenomenon, one might

expect a biphasic dose-response curve. In the dose range used, the dose-response curve to LSD in the majority of cerebral structures is monophasic.

Only the high doses of methysergide and metergoline had any effect, per se, on cerebral function. Furthermore, methysergide blocks or attenuates many of the responses to 5MeO but does not produce any potentiation of 5MeO. Perhaps even higher doses of methysergide and metergoline might produce a 'cleaner' response. Further experiments would be required to elucidate this point.

This would not explain why these compounds are consistantly able to produce marked attenuation of the behavioural syndrome produced by putative serotonin agonists. (Balsara et al, 1979; Chadwick et al, 1978; Clineschmidt and Lotti, 1974; Green et al, 1981 inter alia). One possible explanation is based on the work of Jacobs and Klemfuss, 1975, who found that the complete 'serotonergic behavioural syndrome' (Jacobs, 1976; Sloviter et al, 1978), produced by L-tryptophan and monoamine oxidase inhibition could be elicited following the aspiration of the entire neostriatum. More surprisingly, a transection of the brain posterior to the red nucleus, substantia nigra and midbrain raphe nuclei left the behavioural syndrome intact. These data suggested that the response was mediated by pons, medulla and spinal cord.

This further suggests that either the serotonin agonist action can be blocked due to differences in the serotonin receptors in these areas as opposed to the forebrain or

that the physiological processes which they mediate are simpler than those in the forebrain and therefore can more easily be blocked.

Even if this is the case, in the intact animal the forebrain and particularly neostriatum will reflect in its functional patterns not only the actions of these drugs in the forebrain itself, but also information from within and without the central nervous system. It is, in my opinion, this that we are detecting in the changes in local cerebral glucose utilisation following the administration of both putative serotonin agonists and antagonists - the central integration of all the effects of these drugs.

As was mentioned above, serotonin agonists and antagonists may well show preference for different serotonin receptors in the central nervous system (Bennet and Snyder, 1976; Enjalbert et al, 1978; Nelson et al, 1978; Nelson et al, 1979). If this is the case, then from the data presented here the resultant physiological response is different from that produced by either the agonist or antagonist alone.

The Relevance of These Studies and Future Studies

The serotonin agonists used in this thesis can be classified not only on the basis of their structural properties but also on their effects in the human. Lysergic acid diethylamide is a powerful hallucinogen (Hoffer, 1965, for review), as is 5 methoxy-N,N-dimethyltryptamine, which is a major component of some South American psychoactive snuffs.

(Agurell et al, 1968; Agurell et al, 1969). This latter compound is of particular interest since some investigators have claimed to be able to detect the presence of this compound in the body fluids of schizophrenic patients (Heller et al, 1970; Narasimhachari et al, 1971) which is probably due to 'abnormal methylation' (Banerjee and Snyder, 1973; Mandell and Walker, 1974).

On the other hand quipazine and chloropiperazinylpyrazine have more in common structurally with tricyclic antidepressants. Little information on the actions of chloropiperazinylpyrazine on Man is available. However, quipazine, which has been shown to have many pharmacological actions in common with tricyclic antidepressants in rodents (Rodriguez and Pardo, 1971), produced no psychiatric abnormalities when administered to Man (Parati et al, 1980).

The information given in this thesis, although carried out on rats, reinforces this dichotomy of psychoactive effects in man. In terms of the blockade of these effects by two putative central serotonin antagonists, the problems facing the neuropharmacologist remain. If all the effects of serotonin-mimetic drugs can be blocked by a single compound, the evidence would suggest that this compound still has to be found. In this sense perhaps the most intriguing finding of this work has been that the patterns of cerebral response produced by serotonin agonists, antagonists and the combination of the two were different. This does not fit in with the 'classical' pharmacological view of agonist-

antagonist interactions. More work is required to unravel the problem.

The future continuation of this work could include two approaches. First, selective lesioning of the midbrain raphe nuclei and areas of the brain which have been shown to be 'sensitive' to the peripheral administration of the serotonin agonists. Second, the chronic implantation of cannulae into cerebral structures, shown to be responsive in this present work, for the local administration of serotonin-active compounds.

It is hoped that while this thesis may not have unravelled fully the effects of serotonin agonists and antagonists on cerebral function, it has uncovered some new facets of the actions of these drugs on specific cerebral systems. However, I suspect that it may have created more questions than answers.

APPENDIX I.

The method by which the local cerebral glucose utilisation data is obtained has already been described in the Methods section. However, to completely understand the process by which the data are derived, it is necessary to go into the arithmetical manipulations which are undertaken.

The example given below is real data obtained from a saline control animal (Quip # 8.).

Plasma data: Following the measurement of the plasma ^{14}C concentration by liquid scintillation analysis (Phillips: PW4540) and plasma glucose by semi-automated analysis (Beckman), the information is set out as follows:

Sample	Time	D.P.M.	Plasma glucose (umol/ml)
1	0.05	3	8.5
2	0.26	53458	8.5
3	0.51	86551	8.5
4	0.78	27271	8.5
"	"	"	"
"	"	"	"
"	"	"	"
13	35.14	2485	8.7
14	44.84	1862	8.8

Kill time: 45.12 min.

This data is entered into a computer (Cromenco System Three) and, using a programme devised by Dr. W. Angerson, and given that we use the following rate constants, we can calculate the final deoxyglucose tissue concentration and final plasma integral in grey and white matter:-

	Grey Matter	White Matter
K_1 (min^{-1})	0.189	0.079
K_2 (min^{-1})	0.245	0.133
K_3 (min^{-1})	0.052	0.020
$T_{\frac{1}{2}}$ (min)	2.334	4.530
lumped constant	0.49	

Where K_1, K_2 and K_3 are the rate constants for the transport of ^{14}C deoxyglucose into the brain, from brain back to plasma and the phosphorylation of deoxyglucose by hexokinase, respectively. $T_{\frac{1}{2}}$ is the half-life of ^{14}C deoxyglucose in the percursor pool and is described as $\log_e 2 / (K_2 + K_3)$ (Sokoloff, 1977).

	Grey Matter	White Matter
Final tissue DG concentration (nCi/g)	30	28
Final plasma integral (nCi/umol)	700	680

We can go no further until after the x-ray films have been exposed to the tissue sections for seven days and have been developed.

Densitometry: The first readings are made on the images of the plastic ^{14}C standards. The computer then works out the best fit between the optical density (OD) and the known ^{14}C concentration.

Film No. 1	Standard OD	Standard Concentration (nCi/g)	
		True	Best fit
	0.67	44	46
	0.73	70	67
	1.01	179	179
	1.20	271	271
	1.52	450	451
	1.61	509	507
	2.03	793	793

This is a good fit, so we can proceed. All the optical densities of the structures of interest will be compared to these standards to obtain the ^{14}C tissue concentration.

Thus, using the operational equation of Sokoloff, as described in the Methods section, we can work out, for example, the rate of glucose use by layer IV of the auditory cortex. The optical density is 1.71 which gives a tissue concentration of 572 nCi/g. Thus:-

$$R_i = \frac{\text{Total } ^{14}C \text{ concentration} - ^{14}C \text{ DG remaining in tissue}}{\text{Lumped constant x corrected integrated plasma specific activity.}}$$

$$= \frac{572 - 30}{0.49 \times 700}$$

$$= 1.58 \text{ umols/g/min.}$$

By convention the answer is normally expressed as umol/100g/min. Thus, the rate of glucose use in auditory cortex is 158 umol/100g/min, and in this manner the local cerebral glucose utilisation (LCGU) of the examples below are worked out:

Structure	OD	Concentration (nCi/g)	LCGU (umol/100g/min)
Auditory Cortex	1.71	572	150
Medial geniculate body	1.61	507	121
Substantia nigra (pars compacta)	1.29	319	85
Hippocampus (molecular layer)	1.34	346	.94
Corpus callosum	0.94	120	28

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ADDENDUM

A CONSIDERATION OF THE SEROTONERGIC INTERACTIONS WITH NON-NEURONAL ELEMENTS: POSSIBLE INFLUENCES ON THE MEASUREMENT OF GLUCOSE UTILISATION AS MEASURED BY THE 2-DEOXYGLUCOSE TECHNIQUE.

General Comments: In each of the anatomical areas measured in this study a variety of cellular elements are present. In terms of brain function (as represented by the transfer of electrical information) the neurones could be considered to be the most important. Since, the study of pharmacology in the central nervous system is essentially bound up with acquiring a knowledge of the interactions of drugs with receptors on neurones and thus their ability to facilitate or attenuate the process of information transmission, it is these processes which are of greatest interest.

The method described in this thesis measures glucose utilisation in an area of tissue and so it is a mean of the relative contributions of neuronal and non-neuronal elements. The results presented in this thesis would suggest that in saline control rats the levels of glucose utilisation obtained remains relatively stable i.e. the relative proportions of glucose used by neurones and glia do not vary greatly.

However, the use of this method to assess the potency of serotonin agonists and antagonists raised a number of questions. First, is there evidence of possible differential actions by serotonin mimetic compounds on neurones and glia? Second, what effects would these interactions have on the final measurement of glucose utilisation?

Evidence for Serotonin Receptors on Neurones and Glia

Serotonin receptors in the brain have been studied using a number of radioactive ligands (Bennet and Synder, 1976; Fillion et al., 1978; Nelson et al., 1980). These authors and others have produced a classification of two types of serotonin receptors based on these ligand-binding experiments. The first receptor, termed $5HT_1$, has a high affinity for ^{3}H-5HT, which appears to be dependent on the binding of guanosine triphosphate (G.T.P.) and at least part of this population may be the recognition site for a serotonin - sensitive adenylate cyclase. The second sub-group of receptors, $5HT_2$, have a higher affinity for ^{3}H-spiroperidol than ^{3}H-5HT. These receptors do not appear to require GTP for binding nor do they correspond with recognitions sites for 5HT-sensitive adenylate cyclase (see Fillion, 1983; Nelson, 1983 for reviews). They do, however, appear to correlate with those receptors which are involved in certain behavioural responses which have been associated with changes in the activity of the central serotonin system (Leysen et al., 1981). It has, therefore, been suggested that $5HT_2$ sites mediate the "excitatory" responses to serotonin; such as tryptamine-induced seizures (Leysen et al., 1981) and 5-hydroxy-tryptophan-induced head-twitches in mice (Peroutka et al., 1981). On this basis it has been suggested that the majority of $5HT_2$ receptors are probably post-synaptic and neuronal.

There is good evidence that the $5HT_1$ population is heterogeneous (Fillion et al., 1976; Nelson et al., 1980; Peroutka and Snyder, 1979). Fillion et al., 1979 showed that the high-affinity binding corresponded to postsynaptic neuronal sites. The same group suggested that the low affinity binding sites

correspond to a glial component. At the same time it was observed that two types of adenylate cyclase activity which were sensitive to serotonin were present in homogenates of various brain regions (Fillion et al., 1979). It was further shown in these studies that purified synaptic membranes contained only the high affinity type of adenylate cyclase activity. This was postulated as post-synaptic and neuronal in character (see Fillion, 1983 for review).

Using glial cell membrane preparations and isolated from rat striatum and glial cell lines grown in culture, it was observed that the activation of 5HT sensitive adenylate cyclase corresponded to a low apparent affinity constant (Fillion, 1983). It was, therefore, suggested that the low affinity $5HT_1$ sites are related to 5HT-sensitive adenylate cyclase activity and that this is present on glia rather than neurones. However, a definitive connections between these sites awaits a time when the solubilisation and reconstitution of these receptors is achieved.

Implications for the 2-Deoxyglucose Method

The above evidence suggests that serotoninmimetic agents may well produce changes in glial cell function via. receptors linked to adenylate cyclase. Such a differential effect by serotonin-like agents on glial cells and neurones might well be postulated to have a marked effect on the relative amounts of glucose used by neurones and glia and, therefore, on the final meaned glucose utilisation value.

Can the ratio of glial to neuronal glucose utilisation be estimated?

The ratio of numbers of glia/neurones has been estimated as 0.5 in 100 days old rats (Brizee et al., 1964). This is in agreement with the ratio of the relative volumes of perikarya of neurones and glia which was also 0.5 (Ramon-Moliner, 1961). Furthermore, estimates of the surface areas of the dendrites of giant cells in the reticular formation suggest that the total volume of these processes may be 5 times greater than that of their cell bodies (Peters et al., 1970). Thus, the total volume of neurones and their extensions is probably appreciably higher than that of glial cells.

Several groups have estimated that neurones are responsible for between 75% and 95% of the oxygen consumption in the cortex (Elliot and Heller, 1957; Korey and Orchen, 1959; Hess, 1961). Furthermore, when the relative volumes of glia and neurones are taken into account, it can be shown that the average neuron should have a respiratory rate 16-50 times that of the average cortical neuroglial cells (Friede, 1954). It can also be estimated that even a doubling of the non-neuronal respiratory rate could only reduce the proportion of oxygen used by neurons by approximately 4% (Allen, 1957).

This information is in keeping with the data of Yarowsky et al., 1979 who showed that there was a direct linear relationship between the frequency of electrical spike activity in the superior cervical ganglion and glucose utilisation. Also, Mata et al., 1980 have observed that preparations of rat posterior pituitary, in vitro, show a dose correlation between Na^+/K^+ ATPase activity and glucose utilisation as measured by the 2-deoxyglucose technique. Because of the high density of axon terminals present in this tissue and the consequent high

ionic concentration gradients for a given amount of spike activity (Hardmann, 1966), Mata et al., 1980 concluded that the changes in glucose utilisation observed probably reflect the metabolic activity of axonal terminals.

Indirect evidence has also come from the work of Frey and Agranoff, 1983 who recently showed that the administration of berbiturate to rats with ibotenic acid lesions (a toxin which destroys neurones but leaves non-neuronal cells and blood vessels intact) had marked depressive effects on 2 deoxyglucose uptake in all areas of the brain except in the lesioned area. They suggested that the surviving non-neuronal elements formed a metabolically stable population in comparison to neurones.

In conclusion, there is evidence that glial cells have serotonin receptors some of which are probably related to serotonin-sensitive adenylate cyclase activity. This allows the possibility that neuronal and non-neuronal elements may be affected differentially by serotonin and serotonin-like compounds. However, although the glial component of total oxygen and glucose consumption is by no means negligible, it is smaller and apparently more stable than that of neurones. Therefore, it may be concluded that while a portion of the glucose utilisation effects seen in this thesis, following the administration of serotonin agonists and antagonists, were produced by the actions of these compounds on non-neuronal elements, the greater proportion of change in glucose utilisation probably reflect changes in neuronal metabolic activity.

An Estimation of the Maximum and Minimum Changes in Local Cerebral Glucose Utilisation

Siesjo (1978) states that "..... generalised seizures represent the most intense cerebral activity known .....". This statement is emphasised by the findings of Meldrum and Nilsson, 1976 who showed that the cerebral metabolic rate for oxygen use ($CMRO_2$) increased by 250% within the first minute of bicuculline-induced status epilepticus in rats. There is evidence too that cerebral glucose utilisation exceeds oxygen consumption. It was shown that bicuculline-induced seizures increased $CMRO_2$ by 267% but they increase glucose consumption by 400%.

At the other end of the scale, barbiturates produced a dose-dependent reduction in the level of consciousness and metabolic rate. This was originally shown by Kety et al., 1947-48, who obtained a 45% reduction in $CMRO_2$ during deep thiopental induced anaesthesia in humans. Of perhaps most interest are the observations of Crane et al., 1978, showing that in the rat the maximum reduction of glucose utilisation following pentobarbital administration was approximately 60%. Higher doses produced no further decrease in glucose utilisation. Thus, they postulated that there was a basal rate of glucose utilisation which was insensitive to barbiturate administration.

In the light of the inverse correlations between barbiturate dose and consciousness and barbiturate dose and electorial activity (Morzorati and Barnes, 1977), it is tempting to speculate whether the basal metabolic rate measured in the study of Crane et al., 1978 was due at least in part to the

metabolically more stable glial cells (see afore-mentioned).

In conclusion, the maximum and minimum glucose utilisation values which might be expected would lie between -60% and + 400%. The results described in this study fall within this range and are therefore worthy of consideration.

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