## Studies on the role of catecholamines in the frontal cortex

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The frontal cortex is believed to play a role as an inhibitor of behavioural stimulation (Iversen, Wilkinson & Simpson, 1971). Although it is thought that the frontal cortex modulates the activity of dopaminergic neuronal systems (Glick & Cox, 1976) the mechanisms governing this effect are obscure. The existence of dopamine (DA) (Thierry, Stinus, Blanc & Glowinski, 1972) and noradrenaline (NA) (Fuxe, 1965) terminals in this region might suggest that the catecholamines play an important role at this site. DA and NA have a behaviourally stimulant role in limbic and extrapyramidal areas, but their roles in cortical regions are unknown. In this study we have compared the effects of electrolytic and 6-hydroxydopamine (6-OHDA) lesions on the behavioural responses produced by DA agonists and antagonists.

Bilateral electrolytic (2 mA for 10 s) or 6-OHDA (8 μg/2 μl plus 20 mg/kg desipramine, i.p.) lesions were placed stereotaxically in the frontal cortex of male Porton rats (A 10.3, L ± 0.8, V + 1.5; König & Klippel, 1963).

Both types of lesion significantly enhanced the stereotypic effects of (+) – amphetamine (1.25–5.0 mg/kg, i.p., $P<0.05$). Apomorphine (0.25–1.0 mg/kg, s.c.) – induced stereotypy was unaffected by electrolytic cortical lesions, but the effects of apomorphine (0.25 and 0.5 mg/kg) were significantly reduced by prior 6-OHDA lesioning ($P<0.005$). The cataleptic state induced by fluphenazine (0.5–2.0 mg/kg, i.p.) was reduced by electrolytic lesions of the frontal cortex ($P<0.05$) but not by 6-OHDA lesions.

The intracortical injection of DA (3.12–50 μg bilateral) into this region, induced a dose-dependent state of catalepsy, with an onset of 10–20 min and a duration of at least 3 hours. At no time were any signs of hyperactive or stereotyped behaviour observed. Intracortical injections of low doses of fluphenazine (1 and 5 μg) were without significant effect on either the stereotypic or locomotor responses induced by amphetamine (5 mg/kg i.p.), while a higher dose (10 μg) significantly reduced the stereotypic component ($P<0.05$. Mann-Whitney U test).

The results suggest that catecholamines may play a large part in the inhibitory role of the frontal cortex, and imply that this area may be an important site for the control of mesolimbic and extrapyramidal systems, where stereotyped, hyperactive and cataleptic responses are thought to be initiated. The reduction of apomorphine-induced stereotypy by 6-OHDA lesions, which might be expected to promote postsynaptic receptor sensitivity and the behavioural inhibition or catalepsy produced by intracortical dopamine, suggest that this transmitter may play a major part in frontal cortical behavioural inhibition – in direct opposition to its stimulant role in other brain areas.

CJC is an MRC student.

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## The effect of desipramine on neuronal responses to tyramine and noradrenaline in the cerebral cortex

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It has been reported that the tricyclic antidepressant drug, desipramine, can both potentiate and antagonise neuronal responses to noradrenaline (Bradshaw, Roberts & Szabadi, 1974). We have now examined how neuronal responses to tyramine are affected by desipramine.

Spontaneously active single neurones were studied in the somatosensory cortex of the halothane anaesthetised rat. Drugs were applied by microelectrophoresis. The following drug solutions were used: (–)-noradrenaline bitartrate (0.05M, pH 3.0–3.5); tyramine hydrochloride (0.05M, pH 5.0); (±)-homocysteic acid (0.05M, pH adjusted to 8.0 with NaOH); desipramine hydrochloride (0.005M, pH 4.5). Our techniques have been described elsewhere (Bradshaw *et al*, 1974).

The effects of tyramine and noradrenaline were compared on 103 cells: 75 cells were excited and 26 cells were depressed by both drugs; 2 cells were excited by noradrenaline, but depressed by tyramine. The relative potencies of the two drugs were compared

on 43 cells (31 cells excited, 12 cells depressed by both drugs) on which responses of approximately identical sizes were established. Responses were regarded as approximately of equal magnitude if the ratio of the equilibrium changes in firing rate for the two responses (response to tyramine/response to noradrenaline) was $1.0 \pm 0.2$. The mean equipotent ejecting current ratio was $3.1 \pm 0.3$ (excitatory responses) and $2.8 \pm 0.5$ (depressant responses). For both excitatory and depressant responses noradrenaline had a greater apparent potency than tyramine ($t$ test: $P<0.0005$ and $P<0.005$, respectively).

The effects of continuously applied desipramine (for methods see Bevan, Bradshaw & Szabadi, 1977) were studied on 28 cells excited by both noradrenaline and tyramine. Homocysteic acid was used as a control agonist. On 26 cells desipramine could discriminate between responses to tyramine and noradrenaline: the response to tyramine was antagonised, whereas the response to noradrenaline was either potentiated (6 cells) or unaffected (20 cells). Recovery of responses to tyramine usually was only partial and occurred after 1–2 hours. On two cells responses to both monoamines were antagonised. Responses to homocysteic acid were not affected.

The effect of desipramine was studied on six cells depressed by both monoamines: on 5 of these responses to tyramine were antagonised, whereas the response to noradrenaline was either potentiated (4 cells) or unaffected (1 cell). On one cell depressant responses to both monoamines were equally antagonised by desipramine.

Tyramine is an indirectly acting sympathomimetic amine: its pharmacological effects have been attributed to the action of noradrenaline released by tyramine from sympathetic terminals (Burn & Rand, 1958). It has been reported that desipramine blocks the uptake of tyramine into sympathetically innervated tissues, and thus prevents its pharmacological actions (Brodie, Costa, Gropetti & Matsumoto, 1968). Our results are consistent with the hypothesis that a similar interaction may occur on brain cells.

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## Potentiation of monoamine responses of denervated cells by a noradrenaline uptake inhibitor (viloxazine)

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Monoamines are inactivated by reuptake into presynaptic terminals (Ross & Renyi, 1967; Coyle & Snyder, 1969). It has been suggested that tricyclic anti-depressants potentiate responses to monoamines by a mechanism dissociated from their uptake blocking ability (Bradshaw, Roberts & Szabadi, 1974). It is of interest therefore to examine the ability of an uptake inhibitor to potentiate monoamine responses following degeneration of presynaptic terminals.

Male albino Wistar rats (200–350 g) were anaesthetized with halothane (0.6%) and prepared for the recording of the spontaneous activity of cortical cells using the techniques described by Bradshaw *et al.* (1974). Drugs were applied by microiontophoresis from the following solutions: noradrenaline bitartrate (0.2M, pH 3.5); 5-hydroxytryptamine bimalinate (0.2M, pH 3.5); viloxazine hydrochloride (Vivalan, ICI Ltd.) (0.2M, pH 6.0). Ten–14 days before each experiment a unilateral electrolytic lesion was placed in the median forebrain bundle at stereotaxic coordinates AP + 3.4; lat. 1.6; vert. − 2.8 (König & Klippel, 1963). Lesions of approximately 2 mm diameter were produced with a direct current of 2 mA passed for 20 s from a bipolar stainless steel electrode. Uptake of monoamines by neocortical synaptosomes was reduced to 21% by this lesion.

Excitatory and depressant responses to 5-HT and noradrenaline were recorded from neocortical cells on both lesioned and unlesioned sides. Changes in the proportions of these responses have been reported elsewhere (Jones & Roberts, 1977a). Excitatory responses occurred much less frequently than in unlesioned cortex. Only a single study of the effect of viloxazine on an excitatory response to noradrenaline was obtained. Viloxazine potentiated this response to