compare its action to those of dopamine, applied to the same neurone.

Male Sprague-Dawley rats (150–300 g), anaesthetized with urethane (1.2–1.5 g/kg), were used. Five-barrelled micro-electrodes, with an additional single recording barrel attached, the tip of which extended 15 μ beyond the tips of the drug-containing barrels (Crossman, Walker & Woodruff, 1974) gave improved signal/noise ratio and reduced current-induced alteration of neurone firing rate. The cortex overlying one caudate nucleus was exposed and the electrode passed through the cortex into the caudate (stereotaxic co-ordinates: A 8.5, L 2.0–2.5, V + 2.0–0; atlas of Konig & Klippel, 1963).

Drugs used were: dopamine-HC1 (0.5 M, pH 4.5, Sigma), morphine-HC1 (0.031 M, pH 4.5, Macfarland Smith Ltd.), levorphanol tartrate (0.026 M, pH 4.5, Roche), dextrorphan tartrate (0.026 M, pH 4.5, Roche), naloxone-HC1 (0.021 M, pH 4.5, Endo), α-flupenthixol (0.04 M, pH 4.0, Lundbeck), and DL-homocysteic acid (0.2 M, pH 8.0, Koch-Light).

Out of 94 neurones tested, dopamine depressed the activity of 85 and morphine depressed 45; dopamine excited 8 cells, of which morphine excited four. Naloxone antagonised the depressant effect of morphine on 14 out of 15 cells while having no effect on the response to dopamine. Levorphanol depressed the activity of all cells to which it was applied (13) and naloxone blocked this effect in 11 (out of 13). Dextrorphan produced depression of 14 out of the 20 cells on which it was tested, but this effect was not modified by naloxone. The dopamine antagonist, α-flupenthixol, was tested on 4 cells; in three cases it blocked the effects of dopamine but it had no effect on responses to morphine. In a few cases dopamine responses appeared to be reduced following application of morphine.

Since the depression of rat caudate neurones produced by iontophoretic morphine and levorphanol could be reversed or prevented by naloxone, whereas that produced by dextrorphan was not, this action of morphine may be stereo-specific. On the other hand the finding that opiate- or dopamine-antagonists selectively blocked the response to either morphine or dopamine, respectively, without modifying the response to the other compound applied to the same neurone, suggests that separate receptors may mediate these effects.

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## Behavioural changes following olfactory bulbectomy in rats: a possible model for the detection of antidepressant drugs

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The battery of animal tests available to pharmacologists to detect 'antidepressant activity' of drugs is still very unspecific and yields many false positives and negatives. One such false negative was 1,2,3,4,10, 14b-hexahydro-2-methyldibenzo [c,f,]-pyrazino-[1,2-a]azepine monohydrochloride (Org GB 94) a tetracyclic with potent 5-HT and histamine antagonistic properties (Van Riezen, 1972). However, human studies have revealed that this drug has an antidepressant activity similar to and more potent than that of amitriptyline (AMI; Itil, Polvan & Hsu, 1972).

Over the last few years bilateral olfactory bulbectomy has been shown to cause many behavioural changes including increased motor activity (Ueki, Nurimoto & Ogawa, 1972), and decreased acquisition of behavioural tasks involving both reward and avoidance training (Marks, Remley, Seago & Hastings, 1971). Cairncross & King (1971) showed that behavioural deficits resulting from bulbectomy may be reversed by subchronic treatment with AMI. The following experiments were performed to investigate whether this reversal is specific for all antidepressants.

Male Sprague-Dawley rats (175–225 g) were anaesthetized with pentobarbitone sodium and subjected to either olfactory bulbectomy (OB) by means of bilateral aspiration, or to sham-operation (SO). After a two week recovery period, groups of OB and

SO rats were chronically treated (i.p.) with either saline, AMI (3 or 10 mg $kg^{-1}$ $day^{-1}$), Org GB 94 (5 or 15 mg $kg^{-1}$ $day^{-1}$), chlorpromazine (1 or 3 mg $kg^{-1}$ $day^{-1}$), chlordiazepoxide (10 or 20 mg $kg^{-1}$ $day^{-1}$), (+)-amphetamine (1 or 3 mg $kg^{-1}$ $day^{-1}$) and lithium sulphate (1 or 3 mEq $kg^{-1}$ $day^{-1}$). After 7 days of pretreatment motor activity was recorded in the open field test for a 2.5 min period. From day 8 onwards the rats were food deprived. Acquisition of appetite motivated behaviour was studied during 20 daily trials on days 11 and 12. A two compartment box was used. The rats were placed in one compartment and the time taken by the animals to reach a food cup on the back wall of the other compartment was recorded. Acquisition of passive avoidance behaviour was tested on day 13 by electrifying the floor of the 'food' compartment. Rats were considered as exhibiting passive avoidance when they remained in the safe compartment for 20 seconds.

Amphetamine increased, whereas chlorpromazine and chlordiazepoxide decreased open field activity in SO as well as in OB rats. The antidepressants, and to a lesser extent lithium, reduced activity in OB rats but had little effect on SO rats. AMI and ORG GB 94 also had distinct effects on acquisition. Bulbectomy produced deficient acquisition of appetite motivated and avoidance behaviour and the antidepressants reversed this deficit. However, they worsened the performance of the SO rats. A similar result was obtained with rats treated with amphetamine but not with those receiving chlorpromazine, chlordiaze poxide and lithium.

It is concluded that the OB rat is a possible model for the detection of antidepressant drugs. Using more than one behavioural test, the effects of antidepressants can easily be differentiated from those of other psychotropic compounds.

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## Plasma concentrations in the monkey *(Macaca mulatta)* of six related benzodiazepines after intraperitoneal injection

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Recent studies in the monkey (*Macaca mulatta*) on the behavioural activity of benzodiazepines have been concerned with effects on delayed differentiation and spatial delayed alternation (Nicholson & Wright, 1974, 1976). We have determined the concentrations of six related benzodiazepines in monkeys from the same population. The compounds studied were: medazepam, diazepam, *N*-desmethyldiazepam (nordiazepam) and oxazepam, which are metabolized one to another in that order, plus clorazepate (a precursor of nordiazepam) and temazepam, an intermediate in metabolism of diazepam to oxazepam (Robin, Curry & Whelpton, 1974). Concentrations were determined by solvent extraction and gas-chromatography (de Silva & Puglisi, 1970). Eight monkeys were used, in groups of six for each drug, so that each monkey took part in not less than two, and up to six, trials with at least one month between trials.

Five of the six compounds have similar molecular weights (range 271–291) and their doses were 3.0 mg/kg. In contrast, clorazepate, with its molecular weight 1.4–1.5 times that of the others (409) was given at 4.5 mg/kg. Doses were in 5 ml polyethylene glycol. Samples were taken from the saphenous vein into heparin anticoagulant tubes.

Highest mean concentrations of unchanged drug were mostly at the initial time point ($\frac{1}{2}$ h). The exception was nordiazepam (1 h), (Table 1). The only compound quantitatively assessable when occurring as a metabolite was nordiazepam (after medazepam, diazepam and chlorazepate) though traces ($< 0.05$ µg/ml) of diazepam following medazepam, of temazepam following diazepam and oxazepam, and of oxazepam following medazepam, diazepam and chlorazepate, were detected.