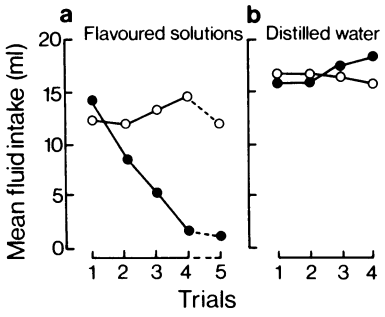

Figure 1 Aversive conditioning with dexamphetamine (1.0 mg/kg) in rats ($n=8$). (a) The mean consumption in 15 min of flavoured solutions paired with dexamphetamine (1.0 mg/kg i.p.) fell progressively (●, $P<0.001$), whereas the consumption of the control flavour was relatively constant (○). (b) There was a small but significant ($P<0.001$) compensatory increase in the mean 15 min water intake on the days after drug administrations (●), as compared with the days after intraperitoneal saline (○). The vertical bars indicate s.e. mean.

Solutions with synthetic 'chicken' and 'lemon' flavours were modified from Lovett & Booth (1970). After rats were adapted to restricted access to water, a flavour was presented for 15 min on every second day. Immediately afterwards, either dexamphetamine sulphate or saline was injected intraperitoneally. Thus, for half of the rats in an experiment, 'chicken' was repeatedly paired with dexamphetamine and 'lemon' with saline, and *vice versa* for the remaining rats. Water was available for restricted periods between flavour presentations.

The conditioning of flavour aversion with dexamphetamine (1.0 mg/kg) is shown in Figure 1 (trials 1–4). The aversion, which was confirmed when both flavours were presented simultaneously (trial 5), was not affected by delaying injections until 45 min after flavour presentations, or by providing spatial as well as flavour cues. Lower doses of dexamphetamine (0.10–0.32 mg/kg) yielded weaker aversions, but even smaller doses (0.025–0.05 mg/kg) did not enhance flavour intake. Severe deprivation combined with highly palatable flavours may have precluded any further enhancement by the drug. However, manipulations of palatability and deprivation also failed to reveal enhanced intake. The apparent aversive property of dexamphetamine has therefore proved robust to several variations in procedure and it appears to date that neither the dose level nor a 'ceiling' effect can account for the absence of a positive reinforcing action in this type of experiment.

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Actions and interactions of morphine and dopamine on single neurones in the rat caudate nucleus

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Acetylcholine, 5-hydroxytryptamine, noradrenaline and dopamine have all been implicated in both the acute and chronic effects of morphine, but it is not at all certain which, if any, of these neurotransmitters in brain is involved in the central actions of the drug. However, dopamine is of special interest as binding studies have shown that some areas with high opiate-binding capacity (Pert & Snyder, 1973, 1975) also contain a high proportion of dopamine-sensitive neurones, e.g. the striatum, and this structure also contains relatively high levels of the endogenous morphine-like substance, enkephalin (Hughes, 1975). We have therefore used the microiontophoretic technique to study the effects of morphine on single neurones in the caudate nucleus of the rat and to

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