Performance was tested 1 and 4 h after injection, though with 30 mg/kg oxprenolol the monkeys failed to respond to or to complete the task at 1 hour. The data were analysed by analysis of variance.

Total response time was increased at 1 h with 20 and 25 mg/kg oxprenolol ($P<0.05$ and 0.001 respectively) and with 20, 25 and 30 mg/kg metoprolol ($P<0.01$, 0.001 and 0.001 respectively). Quadratic equations were fitted to the data for each drug, but, as the equations did not differ, the data were combined. The curve was forced through the origin to give the relation for increase in total response time with dose as 0.176 $(mg/kg)^2 - 1.63$ (mg/kg). Total response times at 4 h were also increased, and this effect was observed with all doses above 15 mg/kg metoprolol and 20 mg/kg oxprenolol ($P<0.01$).

Analysis of accuracy of response was carried out by combining the data for 5 and 10 mg/kg, 15 and 20 mg/kg and 25 and 30 mg/kg. At 1 h accuracy of response was impaired with 5 and 10 mg/kg ($P<0.01$) and 15 and 20 mg/kg ($P<0.01$) oxprenolol, and with 15 and 20 mg/kg ($P<0.05$) and 25 and 30 mg/kg ($P<0.001$) metoprolol. At 4 h accuracy of response was impaired with 25 and 30 mg/kg oxprenolol ($P<0.001$), but with metoprolol the effect was observed throughout the dose range ($P<0.01$), even though with 5–10 mg/kg no effect was observed 1 h after injection.

These results suggest that the β-adrenoceptor antagonists modify delayed differentiation in a way different from that observed with barbiturates and benzodiazepines. With barbiturates and benzodiazepines impaired differentiation is observed only when total response time is increased, but with metoprolol and oxprenolol accuracy of response may be impaired without prolongation of the total response time.

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Cocaine and amphetamine as discriminative stimuli in rats

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Amphetamine can serve as a discriminative stimulus since rats can be trained to make different behavioural responses depending on whether they have received the drug or saline. Little is known about the discriminative stimulus properties of cocaine, which has therefore been compared directly with amphetamine using the procedure described by Kuhn, Appel and Greenberg, 1974. Initially, rats were trained to press bars for water reinforcement; a tandem schedule of reinforcement was used in which, after a variable interval of time (mean = 1 min) in which bar-pressing had no consequences, the 10th bar-press was reinforced. Half of the rats were then reinforced for pressing the left bar when drugged and the right bar after saline. To balance out position preferences, these contingencies were reversed in the remaining rats. Four rats were trained with (+)-amphetamine sulphate (1.0 mg/kg, i.p.) injected 30 min before 30 min training sessions. Another 4 rats were trained with cocaine hydrochloride (10.0 mg/kg, i.p.) injected 15 min before sessions.

Amphetamine, but not cocaine, increased the overall rate of responding by about 32% ($P<0.05$); however, choice of the correct bar developed at about the same rate for both drugs. After 30–35 training sessions, discriminative control by the drugs was confirmed in brief (5 min) test sessions in which no responses were reinforced. Responding on the bar previously appropriate for amphetamine was $91.4 \pm 5.3\%$ after amphetamine, as compared with $6.4 \pm 4.9\%$ after saline (means $\pm$ s.e. mean $P<0.01$). The corresponding results with cocaine were $85.6 \pm 6.9\%$ and $5.4 \pm 1.5\%$ ($P<0.01$).

Dose-response curves were then established by injecting various doses of amphetamine or cocaine in balanced sequences before test sessions. ED_{50} values were defined as doses producing 50% responding on the bar appropriate for drug. The ED_{50} was 0.30 ± 0.07 mg/kg for amphetamine and 2.8 ± 0.4 mg/kg for cocaine (means $\pm$ s.e. mean). The dose-response curves were then determined again but this time, amphetamine was administered to the rats trained with cocaine, and *vice versa* (crossover phase). In adequate doses, both amphetamine and cocaine produced responding on the bar appropriate for the training drug, suggesting a close similarity between their discriminative stimulus properties. However the ED_{50} values were now 0.62 ± 0.18 mg/kg for amphetamine and 10.1 ± 2.7 mg/kg for cocaine, significantly higher than in the first phase of the experiment ($P < 0.05$). The changes in potency can be accounted for either by the development of tolerance or by differences in the discriminative effects of the two drugs. Generally, it is very difficult to develop tolerance to the discriminative effects of drugs (Jones, Grant & Vospalek, 1976; York & Winter, 1975). The present results therefore indicate the possible importance of complete cross-over designs in combination with ED_{50} determinations when attempting to classify drugs according to their discriminative properties.

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Influence of morphine dependence and withdrawal on circling behaviour in rats with unilateral nigral lesions

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Changes in brain dopamine may be involved in certain behavioural manifestations of morphine dependence and abstinence (Gianutsos, Hynes, Puri, Drawbaugh & Lal, 1974; Kuschinsky & Hornykiewicz, 1974; Iwamoto, Loh & Way, 1976; Lal, 1975). One possibility is that dopamine receptors become 'supersensitive' after chronic morphine administration. We report some behavioural tests of striatal dopamine receptor sensitivity during different stages of morphine dependence.

Male hooded rats with unilateral electrolytic lesions of the substantia nigra were used; the co-ordinates of the lesions were A: 2.8; L: 2.3; V: 2.5 (De Groot, 1959). Rats ($n=8$) were selected from a pool of animals displaying 'circling' behaviour ipsilateral to the side of lesioning after doses of apomorphine, a direct dopamine agonist. Circling behaviour was recorded automatically, the number of whole rotations in each direction being accumulated and printed periodically.

The first set of experiments examined whether the base-line response to apomorphine remained stable over time. Three dose-response curves were therefore obtained at intervals of one month. Doses of apomorphine HCl in these and all subsequent tests were 0, 0.25, 0.5 and 1.0 mg/kg, s.c., each rat receiving every dose according to a Latin-square design with an interval of 2–3 days between doses. Circling behaviour was recorded for 90 min after injection with apomorphine. The drug induced ipsilateral turning in a dose-related manner and there was no significant difference between the first curve and its two replications ($F = 1.98$, d.f. 2,77).

The rats were then injected daily with morphine HCl (10 mg/kg, i.p.) for two weeks and their circling response to apomorphine was recorded both when they were in a state of 23 h withdrawal and also starting 60–90 min after the injection of morphine. Withdrawal from this dose of morphine significantly increased apomorphine-induced circling behaviour ($F = 9.69$, d.f. 1,49, $P < 0.01$—the analysis of variance comparisons here and subsequently refer to the final baseline curve obtained with apomorphine). Testing in the presence of morphine also resulted in increased circling ($F = 7.24$, d.f. 1,35, $P < 0.01$).

The dose of morphine was increased and then maintained at 100 mg kg^{-1} day^{-1} for the next 22 days. The rats were retested with apomorphine as before, i.e. in withdrawal 23 h or 60–90 min after morphine. There was a further increase in circling behaviour both in withdrawal ($F = 20.03$, d.f. 1,49, $P < 0.001$) and in the presence of morphine ($F = 24.77$, d.f. 1,35, $P < 0.0001$). The nature of increased circling was,