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,

however, different in the treated and withdrawn states. In withdrawal there was an increase in the slopes of the dose-response curves. The difference between the slopes in withdrawal from 100 mg/kg morphine (86.69 ± 19.98 turns/log unit dose) and control (38.69 ± 8.56 turns/log unit dose) was significant ($t = 2.21$, d.f. 21, $P < 0.05$). In contrast, the slope values obtained in the presence of 10 and 100 mg/kg morphine were not changed; they were 41.94 ± 9.06 and 36.81 ± 14.08 turns/log unit dose respectively. In dependent rats morphine by itself induced ipsilateral circling. Thus, in the presence of morphine an apparent increase in the sensitivity to apomorphine reflected the summation of an unchanged net response to apomorphine with a dose-related increase in circling due to morphine.

The enhanced response to apomorphine in morphine abstinence appears to be related to the level of dependence and it may reflect a change in the sensitivity of one or more populations of dopamine receptors.

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Effect of a potent synthetic opioid pentapeptide in some anti-nociceptive and behavioural tests in mice and rats

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The anti-nociceptive action of the two endogenous morphine-like pentapeptides, methionine- and leucine-enkephalin (Hughes, Smith, Kosterlitz, Fothergill, Morgan & Morris, 1975) is extremely weak and transient and is only apparent after injection into the brain (Büscher, Hill, Römer, Cardinaux, Closse, Hauser & Pless, 1976; Belluzzi, Grant, Garsky, Sarantakis, Wise & Stein, 1976). Synthetic pentapeptides with increased opiate receptor affinity (Chang, Fong, Pert & Pert, 1976) and with a longer duration of anti-nociceptive action have been reported (Pert, 1976). A potent synthetic opioid pentapeptide analogue of leucine-enkephalin has recently been found having potency ratios relative to morphine of 1227 in the isolated mouse vas deferens and 1.95 in the isolated guinea-pig ileum preparation (Beddell, Clark, Hardy, Lowe, Ubatuba, Wilkinson, Miller, Chang & Cuatrecasas, unpublished observations). We have now undertaken some comparative studies on this peptide, Tyr.D-Ala.Gly.Phe.D-Leu (BW 180C) and morphine injected intracerebroventricularly (i.c.v.) in some behavioural and antinociceptive studies in mice and rats.

Anti-nociceptive studies were undertaken in mice using standard stimuli: thermal (hot plate at 55°C), mechanical (tail clip) and chemical (phenylbenzoquinone induced writhing). The ED_{50} values (μg/mouse) at 20 min after drug in the three tests were respectively 0.10, 0.07 and 0.007 μg for BW 180C and 0.33, 0.21 and 0.015 μg for morphine. The anti-nociceptive action of the peptide was of shorter duration than that of morphine. Simultaneous treatment with the specific morphine antagonist naloxone (78 μg/kg, s.c.) produced a parallel shift of the dose-response curves for both morphine and the peptide in the hot-plate test.

Behavioural and locomotor activity studies in mice (5 or 6 groups, $n = 4$, per treatment) revealed that both the peptide and morphine (i.c.v.) increased locomotor activity as measured by ultrasonic activity monitoring equipment (6 channel; C.F. Palmer, High Wycombe). Activity was significantly increased ($P \leqslant 0.01$) by the peptide at doses $\geqslant 0.04$ μg and by morphine at $\geqslant 0.3$ μg. The effect of the peptide was less persistent than that of morphine. The hyperactivity induced by the peptide in mice may reflect an increased dopaminergic transmission as has been suggested for