however, different in the treated and withdrawn states.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isolated guinea-pig ileum preparation (Beddell, Clark, Hardy, Lowe, Ubatuba, Wilkinson, Miller, Chang & Cuatrecasas, unpublished observations).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

morphine (Kuschinsky, 1976). This suggestion is supported by the finding that the known dopamine antagonist, chlorpromazine (5 mg/kg, i.p.) given 1 h previously abolished the increased activity induced by the peptide (0.15 μg) and by morphine (0.6 μg).

The effect of the peptide (i.c.v.) on the EEG of conscious rats was studied in animals (male 300 to 350 g) chronically implanted with skull electrodes and intraventricular cannula (Goff, Miller, Smith, Smith & Wheatley, 1975). The peptide at 5 μg ($n=2$) induced EEG spiking of almost immediate onset followed by facial and forelimb clonus 6 min later. Spiking continued for at least 45 min but the clonus was of shorter duration (9 and 30 min respectively for each rat). Morphine is known to induce EEG spiking when injected directly into the brain of rats (Teitelbaum, Blosser & Catravas, 1976).

Our studies on BW 180C provide further evidence that synthetic opioid pentapeptides which are less labile than endogenous enkephalins possess an anti-nociceptive action similar to that of morphine (Pert, 1976). Additionally, our studies have revealed that these peptides may also possess a similar behavioural profile to morphine.

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Reversal of morphine-induced suppression of active avoidance behaviour by the tetracyclic antidepressant mianserin

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The antidepressant drug mianserin (Org GB 94) has been shown to effectively antagonize in rats the catatonia (both muscle rigidity and akinesia) produced by morphine (Preston, unpublished observations). The present study was undertaken to examine if mianserin would also antagonize other behavioural effects of morphine. It has been reported that morphine depresses avoidance responses in rats (Verhave, Owen & Robbins, 1959). We have therefore tested whether mianserin and some other antidepressants or 5-hydroxytryptamine (5-HT)-receptor blocking agents antagonize the incapacitating effect of morphine on the performance of a two-way active avoidance response.

For each experiment 50 or 60 male Wistar rats (weighing 200–250 g) received avoidance training in automated shuttleboxes. During a trial a light in the lid of the box signalled impending electric shock to the feet through the grid floor. A rat could prevent onset of the shock by moving to the opposite side of the box within the first 6 s of illumination (avoidance). Shuttling after the onset of shock caused the current to shut off (escape); failure to escape led to 25 s of shock. Trials took place once a minute. In addition to the number of avoidances and escapes, the number of intertrial responses was also recorded.

The training schedule was as follows: days 1, 2 and 3: 50 trials per day; day 4: 25 trials. On day 5, rats were randomly allotted to groups (9–10 rats per group) which received either placebo s.c. + placebo i.p., 10 mg/kg morphine s.c. + placebo i.p., or 10 mg/kg morphine s.c. + test drug i.p. All injections were given 40 min before the start of the test session of 25