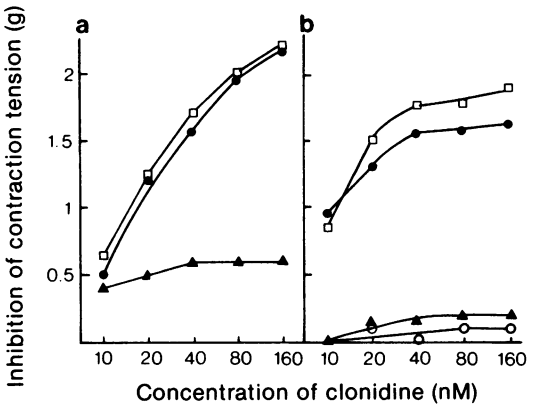

Figure 1 Coaxially stimulated ileum of morphine-dependent guinea-pig. Depression of the inhibitory effect of clonidine by withdrawal of morphine from the bath fluid and its restoration by the subsequent addition of morphine or the opioid peptide Tyr-A-Ala-Gly-Phe-D-Leu. Single typical experiments. (●), in the presence of morphine, 0.5 μM in a and 1 μM in b; (▲), 15–20 min after removal of morphine; (□), 15 min after addition of morphine (0.5 μM) in (a) and 50 min after addition of the peptide (0.09 μM) in (b); (○), 19 min after removal of the peptide.

Sexual behaviour in morphine-dependent rats

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Sexual dysfunctions can occur in opioid addicts both in the drugged and in the abstinent state (Cushman 1972; Martin, Jasinski, Haertzen, Kay, Jones, Mansky & Carpenter, 1973) but it is difficult to separate out the contribution of the opioid addiction cycle *per se*. Systematic studies of sexual behaviour in morphine-dependent animals do not seem to have been reported and we have tested whether changes, if any, in the sexual behaviour of male, morphine-dependent rats follow a similar time-course to the changes that may be seen in consummatory behaviour. In rats that are maintained on large, once daily doses of morphine, there is a phase of increased eating and drinking 2–6 h after injection, followed by a reduction in consummatory behaviour which occurs as a result of the onset of abstinence (Kumar, Mitchell & Stolerman, 1971; Kumar, Mumford & Teixeira, 1977).

Sexually naive male, hooded rats, aged 110–120 days ($n = 12$) which had been maintained on i.p. injections of morphine HCl (100 mg/kg), given at 10.00 h each day for five weeks, were compared with control rats injected with saline. The tests of sexual behaviour were done when the dependent rats were in the drugged state, 2.5 h after injection, and when the rats were abstinent, 23 h after their last injection. Morphine injections were then stopped and after two weeks of abstinence the post-addicts were again compared with the controls. Two days later, a final test was done in which both the post-addicts and the controls received a single dose of morphine (30 mg/kg) 2.5 h before the test.

The rats were individually placed in an open field (58.5 cm^2) for 5 min and then a non-dependent, receptive female was introduced. The female rats ($n = 12$) were ovariectomised and had received intramuscular injections of oestradiol benzoate (0.1 mg), 48 h and 24 h before the test and progesterone (1 mg) 6 h beforehand. The tests lasted 30 min and the measures taken included: number of contacts (defined as any orienting response to the female ending with bodily contact), duration of contacts, number of mounts and

Table 1 Sexual behaviour of morphine-dependent and control rats

Measures of sexual behaviour	*Tests I and II Dependent n=12 Drugged*	*Abstinent*	*Tests I and II Controls n=12 I*	*II*	*Test III No injections Post-Addicts*	*Controls*	*Test IV 30 mg/kg morphine Post-Addicts*	*Controls*
Mean number of contacts	83	53*	68	67	74	67	87	42**
Mean total duration of contacts (seconds)	82	186***	177	175	182	189	136	53**
Number of rats mounting	0	7**	7	9	9	8	4	1
Number of rats ejaculating	0	4*	2	7	8	6	2	0

Tests I and II. Significant differences between drugged and abstinent rats *t*-tests or Chi-square
Test IV. Significant differences between post-addicts and controls *t*-tests

* $P<0.05$
** $P<0.01$
*** $P<0.001$

number of ejaculations. The order of testing the drugged or abstinent dependent rats was counterbalanced.

Dependent, drugged rats, which were more active, made more contacts with the females but these were brief and the rats responded to the females inappropriately. There were no attempts at mounting or any other sexual interactions. However, in acute abstinence these same rats appeared to respond normally to the females and were now indistinguishable from controls (see Table 1).

After two weeks of abstinence, the post-addicts and the controls showed no differences (Test III) but when both groups were tested after an injection of morphine (30 mg/kg), the controls were sedated and their sexual behaviour was virtually suppressed. The post-addicts showed significantly less attenuation of the number and duration of contacts which indicates that there was still some tolerance to morphine 16 days after withdrawal.

The effects of morphine on eating and drinking (Kumar *et al.* 1977) and on the sexual activity of dependent rats follow different courses over time; sexual behaviour is disrupted while the rats are drugged and seems to be unaffected during acute abstinence.

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Effect in the rat of chronic morphine treatment on the behavioural response to apomorphine

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A growing body of biochemical (Kuschinsky & Hornykiewicz, 1974) evidence suggests that morphine interacts with dopamine (DA) containing neurones. Behavioural evidence for such an interaction is contradictory (Kuschinsky, 1975; Smee & Overstreet, 1976). In the present experiments the effect of chronic morphine treatment on the behavioural response to the DA agonist, apomorphine, was investigated in normal rats and in rats with bilateral lesions to the caudate DA terminals. Apomorphine in low doses induces a marked stimulation of locomotor activity in the rat.

In Experiment 1, 6 rats and their controls received escalating i.p. injections of morphine sulphate (20–40 mg/kg) for 5 days. One and five days after the last dose of morphine, the response to 0.1 mg/kg apomorphine (s.c.) was measured. Morphine injections were then reinstated twice per day in dosages up to 120 mg/kg. The response to apomorphine was again tested 1, 5 and 16 days after the last morphine injection. Motor activity was measured for 1 h after apomorphine with photocell recording methods and stereotypy was rated every 10 min with a non-linear scale which classifies motor behaviour into one of 6 characteristic topographies (Creese & Iversen, 1975). In experiment 2, essentially the same procedures were followed but in this case the effect of morphine pretreatment was studied in rats with bilateral 6-OHDA (8 μg in 2 μl each side) lesions to the caudate nucleus and their appropriate controls. At the completion of this experiment the levels of caudate DA were measured with a radio-enzymatic assay (Cuello, Hiley & Iversen, 1973).

In Experiment 1, after the second morphine treatment regime, significantly higher locomotor activity was recorded 10 and 20 min after apomorphine in the morphine treated group compared to the saline controls (24 h post morphine injection, 10′ $P<0.013$, 20′ $P<0.047$; 5 days post morphine injection, 10′ $P<0.008$, 20′ $P<0.004$). In Experiment 2, after chronic morphine treatment, the caudate lesioned animals showed a different apomorphine response from that observed in saline treated caudate lesioned animals. In the latter animals intense confined stereotypy was seen after apomorphine whereas in the morphine treated animals apomorphine stereotypy was severely disrupted by long bursts of locomotor activity.

It has been established that the mesolimbic DA system mediates locomotor responses to DA agonists (Kelly, Seviour & Iversen, 1975) and thus it is suggested that morphine interacts principally with non-striatal DA substrates to modify the apomorphine response. This is supported by the observation that locomotor activity predominates in morphine treated caudate lesioned animals, where the enhanced responsiveness of the post-synaptic striatal receptors normally results in persistent stereotyped responding to low doses of apomorphine (Kelly *et al.*, 1975).