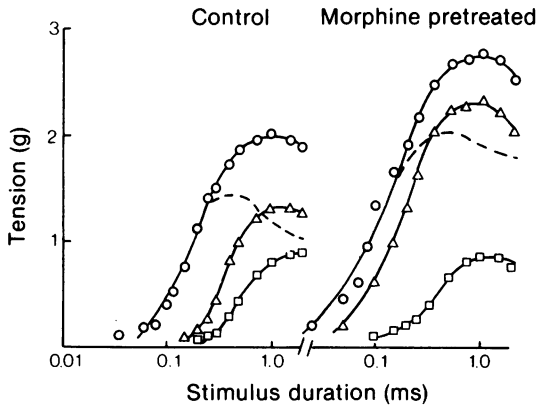

Figure 1 Stimulus duration-response curves for ileum preparations from control and morphine pretreated guinea pigs. 80 V stimuli were applied at 0.1 Hz. Each point represents the mean value of five consecutive contractions; (○), no drug added; (Δ), normorphine, 100 nM; (□), residual responses in the presence of normorphine. 1000 nM. The dashed line indicates the opiate suppressible component of the total response.

The inhibitory effects of clonidine on the contractions of the guinea-pig ileum in the morphine-dependent and withdrawn states

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The inhibitory effects of adrenaline and dopamine on the contractions of the longitudinal muscle are smaller in myenteric plexus preparations obtained from guinea-pigs implanted with morphine pellets than for control animals (Goldstein & Schulz, 1973). We intended to examine the effects of removal of morphine from the bath fluid on presynaptic α-adrenoceptors.

Guinea-pigs were implanted with two pellets containing 75 mg morphine base each; after 3 days the animals were killed and the ilea removed, washed with Krebs solution containing (0.5–2 μM) morphine and mounted for coaxial stimulation (0.5 ms, 0.1 Hz, maximal voltage) in the same solution. The sensitivity of the presynaptic α-adrenoceptors were determined by cumulative dose-response curves to clonidine.

In the presence of morphine the ED_{50} values for clonidine (20–50 nM) were 2 to 3 times higher than in preparations from control animals (Figure 1). On changing the bath fluid to morphine-free Krebs solution, the dose-response curves became quite flat indicating that the depressant effect of clonidine was almost abolished. On replacing the morphine or adding the opioid peptide, Tyr-D-Ala-Gly-Phe-D-Leu (Baxter, Goff, Miller & Saunders, 1977), the depressant effect of clonidine was restored.

Since it has been shown (Kosterlitz & Watt, 1968) that in the guinea-pig ileum, opiate and α-adrenoceptor receptors are independently and specifically stimulated by their respective agonists, the apparent interaction between clonidine and the opiate agonists in the ileum from dependent guinea-pigs is most likely to take place at points beyond the recognition sites of the receptor complexes. One possible explanation is that, in dependent preparations, adenylate cyclase activity is increased as has been shown for cultured neuroblastoma × glioma hybrid cells (Sharma, Klee & Nirenberg, 1975). Under the conditions of our experiments, clonidine would be expected to exert its normal inhibitory effect only in the presence of opiates. In the dependent state, there is increased activity of adenylate cyclase which is counteracted by the presence of opiates; withdrawal of the opiates then unmasks this increased activity.

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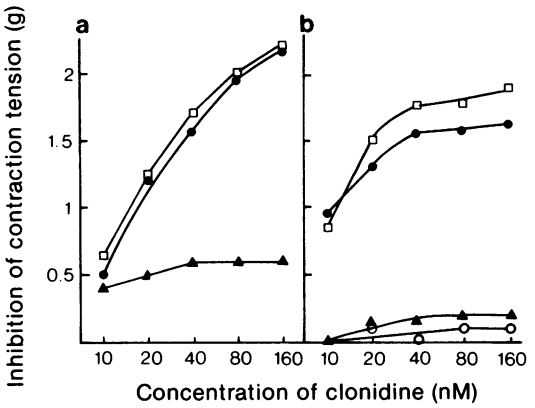

Figure 1 Coaxially stimulated ileum of morphine-dependent guinea-pig. Depression of the inhibitory effect of clonidine by withdrawal of morphine from the bath fluid and its restoration by the subsequent addition of morphine or the opioid peptide Tyr-A-Ala-Gly-Phe-D-Leu. Single typical experiments. (●), 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

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