tion (Petty & Reid, 1977) is thus accompanied by a decrease in tyrosine hydroxylase in the hypothalamic terminals, and an increase in the activity of this enzyme in the cell body regions of the brainstem. This could represent an increase in synthesis to compensate for an increase in noradrenergic neuronal activity. The elevation of PNMT activity at 7 and 28 days in the brainstem suggests that adrenaline formation in these neurones is increased during the development of renovascular hypertension. These studies support the hypothesis that during the development of renovascular hypertension there are localized increases in activity of noradrenaline and adrenaline containing neurones in the brain.

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Stimulus-response relationships in ileum preparations from normal and morphine treated guinea pigs

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The longitudinal muscle – myenteric plexus preparation from morphine pretreated guinea pigs shows reduced sensitivity to opiate induced inhibition of electrically stimulated acetylcholine release (Goldstein & Schulz, 1973). This reduction in opiate sensitivity is not associated with a change in opiate receptor binding properties (Cox & Padhya, 1977). Thus tolerance results from an alteration in neuronal function subsequent to the drug-receptor interaction, and may be reflected in general changes in neuronal properties. The relationship between the strength or duration of the electrical stimulus and the contractile response has therefore been examined in ileum preparations from untreated and 3 day morphine pretreated (Cox & Padhya, 1977) guinea pigs. Stimulus duration (ms)-response (tension generated, g) curves at constant voltage (80 V), or stimulus strength (V)-response curves at constant pulse duration (1 ms) were constructed in the absence of added drug, and in the presence of normorphine.

The normorphine concentration required to reduce by 50% the contractions elicited by 80 V, 0.25 ms stimuli was increased about three fold following morphine pretreatment. In preparations from both normal and morphine pretreated guinea pigs, stimuli of longer than 0.25 ms induced contractions that could not be completely inhibited by normorphine at a concentration (1 μM) approximately ten fold higher than its IC_{50} in normal preparations (Figure 1). No further inhibition could be obtained with higher normorphine concentrations. However, these residual contractions were completely inhibited by tetrodotoxin (300 nM) or by atropine (100 nM). The stimulus sensitivity and maximum tension generated by the opiate insensitive mechanism was not changed by morphine pretreatment (Figure 1).

In contrast, the normorphine suppressible component of the total response to electrical stimulation was consistently greater following morphine pretreatment (Figure 1). Under stimulus conditions giving maximum contractions, the opiate insensitive responses represented 44 ± 3% (n = 8) of the maximum responses in control preparations and 27 ± 4% (n= 8) in morphine pretreated preparations. Addition of normorphine (100 nM) to pretreated strips reduced the magnitude of the total response to a level comparable to that in control preparations (Figure 1).

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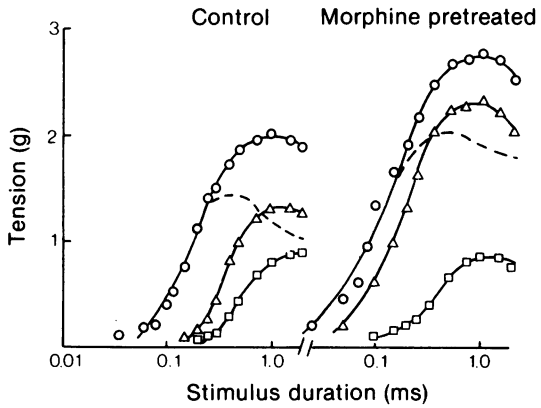

Figure 1 Stimulus duration-response curves for ileum preparations from control and morphine pretreated guinea pigs. 80 V stimuli were applied at 0.1 Hz. Each point represents the mean value of five consecutive contractions; (○), no drug added; (Δ), normorphine, 100 nM; (□), residual responses in the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