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Morphine has no direct effect on PGE_2-stimulated cyclic AMP production by rat isolated enterocytes

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The antidiarrhoeal actions of the opiates have been assumed to result from their effects on intestinal motility. However, it now appears likely that their ability to inhibit the secretion of water and electrolytes by the intestine is important in their constipating action, although it is still not known whether they act directly on the transporting cells (Powell 1981). When administered in vivo, morphine prevents prostaglandin-induced intestinal fluid secretion together with the rise in cyclic (c)AMP levels measured in mucosal scrapes (Beubler & Lembeck 1980). In the in vivo preparation, however, it is not possible to determine whether morphine acts directly on the enterocyte or via an intermediate link. One way to investigate this problem is to determine the actions of morphine on enterocytes that have been isolated from the small intestine and this was the aim of the present study.

The influence of morphine on intestinal cAMP production was determined in a mixed population of villous and crypt enterocytes using the method described by Hardcastle et al (1980). In this preparation PGE_2 enhanced cAMP levels ($P < 0.001$) and a concentration of 1.13×10^{-5} M was just sufficient to induce a maximum response. Morphine, at concentrations from 10^{-8} to 10^{-4} M, had no effect on either basal or prostaglandin-stimulated cAMP production ($P > 0.05$ in all cases) by these isolated enterocytes (Fig. 1).

The finding that morphine does not affect basal or prostaglandin-stimulated cAMP production in isolated enterocytes is in contrast to the results obtained in vivo by Beubler & Lembeck (1980). This suggests that the opiate is not acting directly on the transporting cells to alter nucleotide production but is acting via an intermediary pathway. Several factors suggest that the site of opiate action in the intestine is the neural elements within the gut wall. Opiate receptors are thought to be confined to nervous tissue and it has been shown in the intestine that opiates can alter the firing pattern of myenteric plexus neurons (Dingledine et al 1974). In addition, the anti-secretory effects of enkephalin in rabbit ileum can be blocked by tetrodotoxin (Dobbins et al 1980). If the opiates do act at the nerve plexi to alter mucosal cAMP levels rather than directly on the enterocyte there must be some intermediary pathway linking these two sites. The nature of this link has yet to be determined but could involve the release of an agent that inhibits secretion or a reduction in the release of an agent that stimulates secretion. Substances which stimulate (acetylcholine, 5-HT, VIP) and inhibit (somatostatin) secretion are present within the gut wall and it will be necessary to investigate their involvement in the opiate response.

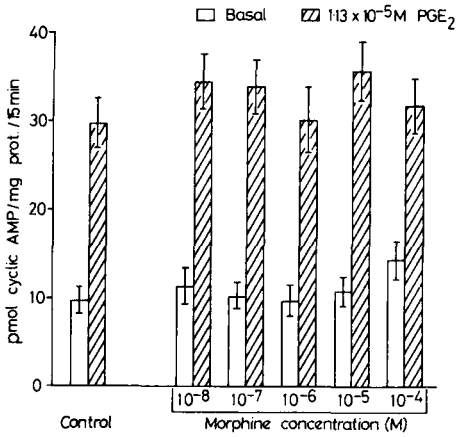

FIG. 1. Effect of morphine sulphate on cAMP production by isolated enterocytes in the absence (basal) and presence of PGE_2 (1.13×10^{-5} M). Each point represents the mean ±1 s.e.m. of 5 separate experiments each performed in triplicate.

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