THE ACTION OF MORPHINE AND MORPHINE-LIKE ANALGESICS APPLIED ON THE INTRALUMINALLY PERISTALTIC REFLEX OF THE ISOLATED GUINEA PIG ILEUM

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Morphine and morphine-like analgesics inhibit peristalsis of the isolated guinea pig ileum, when introduced into its lumen. Their effects were parallel to their relative analgesic potencies. Since suitable doses of morphine did not inhibit the responses to nicotine and to 5-HT, it is thought that the inhibitory action of morphine and related drugs, involves the afferent part of the peristaltic reflex. Peristalsis, previously abolished by intraluminal morphine, can be restored by 5-HT by the same route. That the inhibitory action of the intraluminal morphine upon the peristalsis may be caused, at least partly, by its antagonism towards intrinsic 5-HT and may take place on the same mucosal receptors, is discussed.

TRENDELENBURG[1] has described the inhibitory action of morphine on the peristaltic reflex of the isolated guinea pig ileum. Since then the action of morphine upon the isolated guinea pig ileum has been analysed by several authors [2–9]. When morphine was added to the bath in which the segment was suspended, the results indicated that it acted on the postganglionic fibres of the intramural nervous system, inhibiting the neuromuscular transmission[6–9], or the synaptic transmission of impulses[2].

Recently the role of 5-hydroxytryptamine (5-HT) in the initiation of peristalsis has been described by Bülbring and Lin[10,11]. Introduced into the lumen of the isolated guinea pig ileum, 5-HT was found to stimulate peristaltic movement while morphine[5] and morphine-like analgesics[12] have been described as potent inhibitors of 5-HT action upon the guinea pig ileum when added to the bath. It seemed, therefore, attractive to study in the bath the action of morphine and some related analgesics upon peristalsis under conditions used by Bülbring and Lin[10,11].

METHOD

A modification of Trendelenburg's original method by Beleslin and Varagić[13], which allowed the introduction of drugs into the lumen and also the washing of the lumen, was used throughout the present experiments. The segments of the guinea pig ileum were suspended in a 20 ml. bath, containing Tyrode solution kept at 36° and aerated with O_2.

The following drugs were used: morphine hydrochloride, dihydromorphinone hydrochloride, codeine phosphate, pethidine hydrochloride, 5-hydroxytryptamine creatinine sulphate and nicotine hydrogen tartrate. All the drugs, except nicotine and 5-HT in some experiments, were injected into the lumen of the isolated segments, in 0·1 ml. volume,

diluted with Tyrode solution. All the doses and concentrations refer to the salts used.

RESULTS

The Action of Morphine in the Lumen

The introduction of 0·1 to 5μg. of morphine into the lumen was found to inhibit the peristalsis elicited by raising the intraluminal pressure. If the volume of the suspended segment is estimated to be approximately 0·5 to 1 ml., then the actual effective concentration of morphine might be estimated to be 10^{-7} to 10^{-5} g./ml.

As in experiments described by Kosterlitz and others[14], two separate phases of the longitudinal muscle contraction during peristalsis were distinguished. A slow increase in tone of the longitudinal muscle in response to the raised intraluminal pressure was followed by a secondary, rapid contraction, which was immediately followed by the emptying of the segment. When injected in threshold doses, morphine inhibited first the rapid, secondary contraction and the emptying phase to the same degree. The inhibition of the primary, slow longitudinal contraction became evident only when the dose of morphine was increased. By increasing the dose sufficiently it was abolished completely.

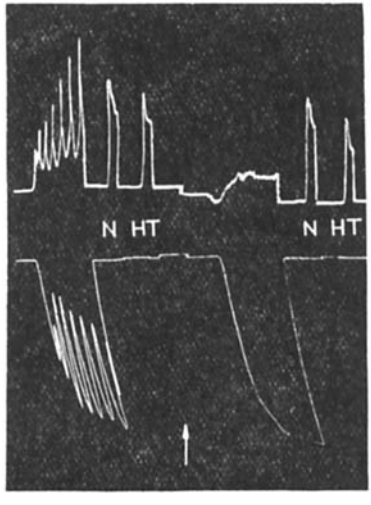

FIG. 1. The inhibition of the persitaltic reflex by the intraluminal application of morphine, without the inhibition of the response to nicotine and to 5-HT. At N, 40 μg. of nicotine, and at HT, 4 μg. of 5-HT was added to the bath and allowed to act for 30 seconds. At arrow, 1 μg. of morphine was injected into the intestinal lumen. Upper tracing, longitudinal muscle; Lower tracing, circular muscle.

Morphine inhibition of the peristaltic reflex was reversible and lasted for 10 to 60 minutes after washing out, depending on the dose used and on the duration of the contact. In some experiments the inhibitory effect of morphine wore off in spite of its continuous presence in the lumen of the isolated segment.

To obtain some evidence on the possible site of action of morphine in the lumen, its inhibitory action on peristalsis was compared with its action on the response to nicotine and to 5-HT added to the bath. Thus, between two records of the peristalsis, nicotine, 15 to 20 μg., and 5-HT, 2 to 5 μg., were added to the bath and the intraluminal pressure raised again, causing contractions of the longitudinal muscle comparable to the peristaltic contractions of the longitudinal muscle. By adjusting the dose of morphine, the peristalsis could be inhibited or abolished, while the action of nicotine and that of 5-HT remained unchanged (Fig. 1).

However, with higher doses of morphine, the effects of nicotine and of 5-HT were also inhibited or abolished.

The Action of Morphine-like Analgesics

Dihydromorphinone, pethidine and codeine inhibited peristalsis when introduced into the lumen of the isolated segment in suitable doses (Fig. 2). Dihydromorphinone was found to be approximately five times

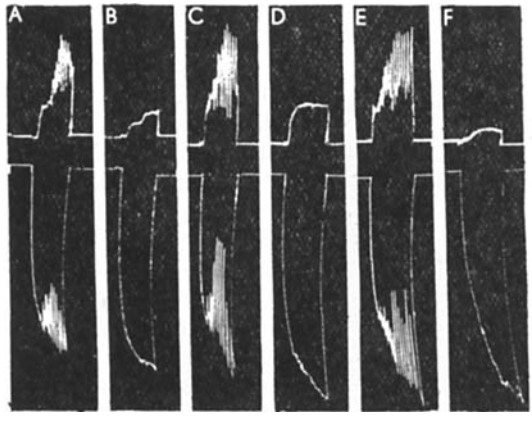

FIG. 2. Comparison of inhibitory activities of morphine and some related drugs on the peristaltic reflex. At A, C and E control records. Between A and B, 1 μg. of morphine; between C and D, 20 μg. of codeine; and between E and F, 0·2 μg. of dihydromorphinone was introduced into the lumen of the intestine. After B, D and F the drugs were washed out. Upper tracing, logitudinal muscle; Lower tracing, circular muscle.

as potent as morphine, and the inhibitory activity of pethidine and codeine was 1/10 and 1/50 to 1/20 respectively (morphine = 1). These data indicated a parallelism of inhibitory action with relative analgesic potencies.

The Influence of 5-HT on the Inhibitory Action of Morphine

It has been shown that 5-HT added to the lumen of the isolated guinea pig ileum stimulated peristalsis under normal conditions[10,11], as well as when the reflex had been depressed by cooling[13]. In the present experiments, peristalsis previously inhibited by morphine in the lumen was restored by 5-HT by the same route. As can be seen from Figure 3, both the preparatory and the emptying phase of the peristaltic reflex were stimulated immediately after 5-HT was introduced into the lumen. However, with a higher dose of morphine, peristalsis was abolished, and could not be restored by the addition of a higher dose of 5-HT.

Figure 4 shows that 5-HT in the lumen, caused a contraction of the longitudinal muscle of the segment which was previously paralysed by morphine, and the intraluminal pressure of which had been raised before the addition of the 5-HT. This contraction disappeared as soon as the pressure was decreased, in spite of the presence of 5-HT in the lumen.

Discussion

We have shown that morphine and morphine-like analgesics introduced intraluminally into the isolated guinea pig ileum inhibit peristalsis. That the addition of morphine to the bath abolishes this reflex has been known since Trendelenburg's demonstration[1]. Schaumann[6] has shown that morphine, added to the bath abolished not only peristalsis, but also the contraction of the longitudinal muscle caused by nicotine. This led him to suggest that morphine acted on the efferent part of the peristaltic reflex. Later, morphine was found to inhibit acetylcholine formation from cholinergic nerve endings of the autonomic intestinal nervous system[7–9].

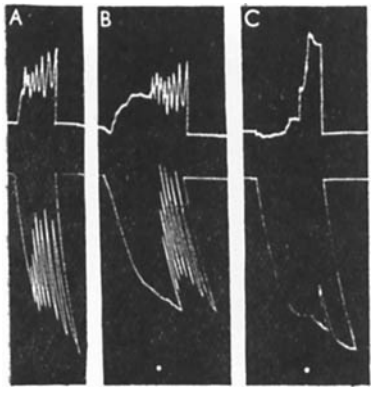

Fig. 3. Effect of intraluminal injection of 5-HT on the inhibitory action of intraluminal morphine upon the peristalsis. At A control record. Between A and B, 1 μg. and between B and C, 10 μg. of morphine was introduced into the intestinal lumen. At white dot in B, 5 μg., and in C, 50 μg. of 5-HT was applied into the lumen.

The present experiments have shown that morphine can inhibit peristalsis without any depression of the response to nicotine or to 5-HT. The response to nicotine is due to the stimulation of intramural ganglia, and according to Gaddum and Hameed[15] the effect of 5-HT upon the isolated guinea pig ileum is also exerted upon intestinal ganglia. But it is supposed that these drugs act upon different ganglionic receptors[15]. Trendelenburg[16] has found that morphine inhibited the stimulating effect of 5-HT upon the superior cervical ganglion of the cat, leaving the effect of nicotine intact. Therefore, both the nicotine and 5-HT were used as controls in the present experiments. The failure of morphine to inhibit the action of either nicotine or 5-HT upon the gut, while abolishing the peristaltic reflex, suggests that this drug, applied into the lumen of the intestine, was acting on afferent nervous structures of the peristaltic reflex. However, higher doses of morphine, applied by the same route, inhibited not only the peristalsis, but also the effects of both nicotine and 5-HT. This finding may be explained on the assumption, that if higher doses of morphine were applied into the lumen, the drug diffused from the lumen to the outside and affected either the ganglia or the postganglionic fibres of the intestinal cholinergic nervous system.

The experiment presented in Figure 4 indicates that the intestinal ganglia were not involved either in the inhibitory action of intraluminal morphine or in the stimulatory action of 5-HT. It also shows that the longitudinal contraction of the segment, which is normally elicited by raising the intraluminal pressure, can be abolished by morphine in the lumen and restored by intraluminal 5-HT. This contraction, produced by raising the intraluminal pressure, has been shown not to involve intramural intestinal ganglia[6,17]. Thus, the experiment presented in Figure 4 could be interpreted as meaning that the restoring action, which 5-HT exerted upon peristalsis in the present experiments, was not caused by facilitating ganglionic transmission, in the sense of findings made by Trendelenburg[16]. Thus, it seems plausible to suppose that this action of 5-HT is exerted somewhere in the afferent part of the peristaltic reflex, probably by sensitising to intraluminal pressure the receptors of the intestinal mucosa, which are involved in the initiation of the peristaltic reflex. The antagonism between morphine and 5-HT might take place on the same 5-HT sensitive receptors, which have been shown to be involved in the peristaltic reflex[11].

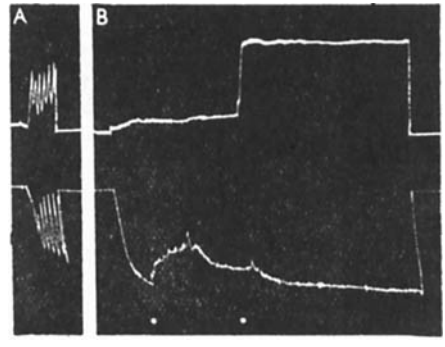

FIG. 4. Sensitation of the intestinal segment paralysed by morphine, to the raised intraluminal pressure, by the intraluminal introduction of 5-HT. At A, control record. Between A and B, 1 μg. of morphine was introduced into the intestinal lumen. At first white dot 1 μg. and at the second 5 μg. of 5-HT was introduced by the same route. Note the reappearance of the contraction of the longitudinal muscle after the addition of 5-HT and its disappearance on the decrease of the intraluminal pressure.

Bülbring and colleagues[11,18] have found that the intraluminal introduction of cocaine (10^{-4}) and procaine (10^{-3}), abolished the peristaltic reflex but it does not seem probable that the inhibitory action of morphine on peristalsis is due to a local anaesthetic effect, since the inhibitory concentrations of morphine used were below those of cocaine[18].

The question arises whether the inhibition of the peristalsis caused by morphine, can be ascribed, at least partly, to the antagonistic action of this drug towards the intrinsic 5-HT. The latter substance has been shown to sensitise the pressure receptors of the intestinal mucosa[11]. Morphine-like analgesics in the bath have been shown to inhibit the effect of 5-HT upon the isolated guinea pig ileum, their activity being parallel to their analgesic potencies[12]. Also when the 5-HT antagonists, LSD and BOL, are introduced into the lumen the opposite effects to those of 5-HT are produced[10,11].

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