EFFECT OF MORPHINE ON CHOLINERGIC RECEPTORS

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Morphine and other opium alkaloids are widely used for their potent analgesic and intestinal activity, although there is still no agreement about their mode of action. Cholinergic mechanism appears to play some role in the action of morphine. It is suggested that probably the anticholinesterase activity is responsible for its central actions, but it is a relatively feeble inhibitor and more potent anticholinesterase does not reproduce its effect (5). Recent work has shown that the specific paralysing effect of morphine on the guineapig intestine can be explained by an inhibition of the release of acetylcholine apparently by inhibiting the excitatory process which releases acetylcholine from nerve endings (6). Beleslin and Polak (1) showed that morphine has a similar effect on the central nervous system.

The present experiments were undertaken to study the probable mode of action of morphine on cholinergic receptors.

MATERIALS AND METHODS

One per cent stock solution of morphine hydrochloride was diluted to required concentration at the time of each experiment. Five experiments were done with each type of muscle preparation, taken from different animals.

Isolated frog heart was perfused through a venous cannula put in the sinus venosus. Acetylcholine (0.5-1.5μg) was injected through an indwelling polyethylene tube, and the responses were recorded. Heart was then perfused with Ringer solution containing morphine hydrochloride (0.2 *mg/ml*) till the maximum effect of the drug was produced. Subsequently, the effect of the same dose of acetylcholine was studied in the presence of morphine.

Isolated rabbit intestine was put up as usual. Submaximal concentrations, elicited by 90 second contact with acetylcholine (1.5-2.0μg), were recorded. Morphine (0.2 *mg/ml*) was added in the bath and was allowed a contact of 5 minutes before repeating the same dose of acetylcholine.

The frog rectus abdominis muscle preparation was made by the method of Burn (4). Concentrations of acetylcholine (4.5-5.5 μg) causing submaximal effects, were allowed a contact of 2 minutes and the contractions were recorded isotonically by a weighted gimbal lever. Morphine (0.2 *mg/ml*) was added to the bath and allowed a contact of 5 minutes before repeating the same dose of acetylcholine.

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The isolated rat phrenic nerve diaphragm preparation was made by the method of Bulbring (3). Single maximal shocks were delivered to the nerve or muscle by a Grass stimulator and the effect of morphine (1.5 *mg/ml*) on the responses of the nerve and muscle to electrical stimuli were studied.

OBSERVATIONS

Frog heart perfusion—Acetylcholine caused a mean reduction of 41.6 per cent in the amplitude of contraction which became 17.82 per cent in the presence of morphine hydrochloride. The acetylcholine response was found to be reduced to an extent of 55.9 per cent by morphine.

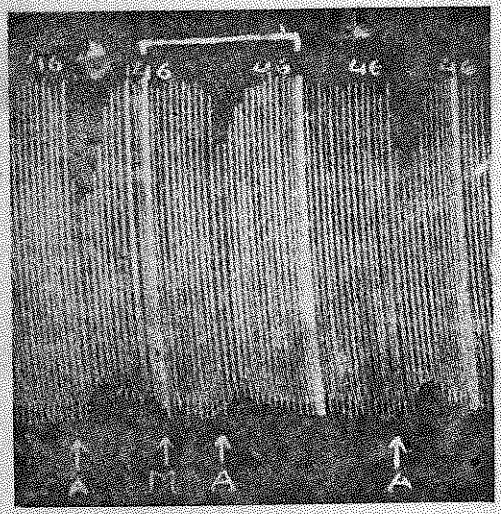

Fig. 1 : *Frog heart perfusion. A, acetylcholine* (0.75µg). *Bracket indicates the perfusion with M, morphine hydrochloride* (0.2 *mg/ml*). *Heart rate per minute is indicated above the tracings. Time interval* 3 *sec.*

Fig. 2 : *Isolated rabbit intestine. A, acetylcholine* (2.5µg). *Dot indicates wash. M, morphine hydrochloride* (0.2 *mg/ml*).

Morphine itself had no effect on the rate and amplitude of contraction of the heart (Fig. 1).

Intestinal muscle—Acetylcholine caused an average contraction of 70.6 *mm* of the intestinal muscle which was reduced to 51.6 *mm* in presence of morphine. The acetylcholine response was thus blocked by 29.46 per cent in the presence of morphine.

Morphine did not produce any direct action on the intestinal muscle and the recovery of the acetylcholine response was complete (Fig. 2).

Frog rectus abdominis muscle—The average contraction of rectus muscle after acetylcholine was 33.8 *mm* which became 21.4 *mm* after morphine. The acetylcholine response was thus blocked by 31.26 per cent by morphine (Fig. 3).

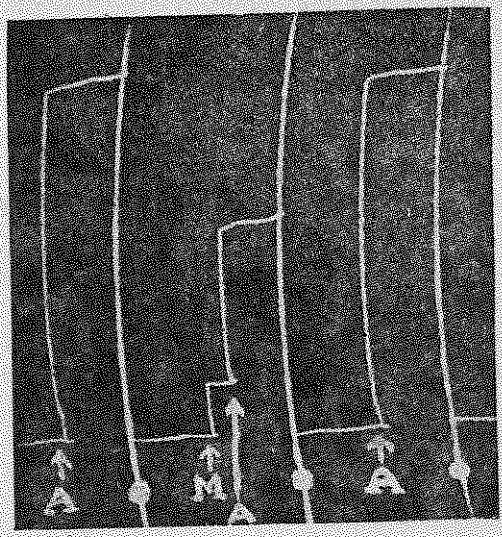

Fig. 3 : *Isolated frog rectus. 'A' acetylcholine* (5.0μg). *Dot indicates wash. 'M' morphine hydrochloride* (0.2 *mg/ml*).

Rat phrenic diaphragm—Morphine (1.5-2.5 *mg/ml*) was found to block the neuromuscular transmission. It also reduced the response of muscle to direct stimulation (Fig. 4). The morphine induced block was not modified by neostigmine (4 $\mu g/ml$).

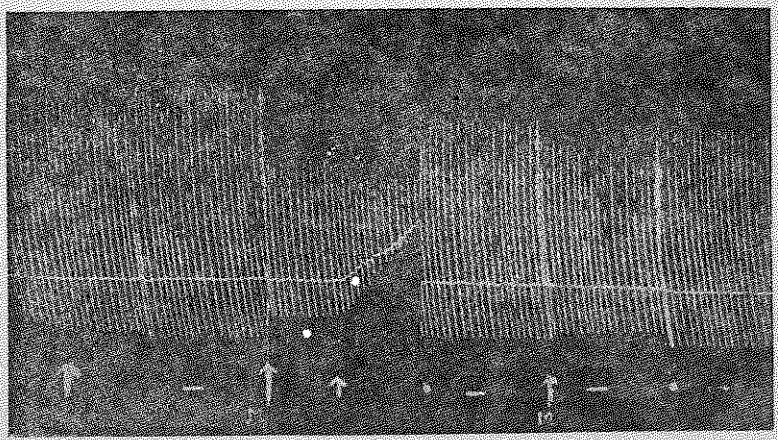

Fig. 4 : *Isolated rat phrenic nerve diaphragm. The twitches arising from direct stimulation (—) of muscle are greater in amplitude than the indirect response. Dot represents wash. M, morphine hydrochloride* (1.5 *mg/ml*).

DISCUSSION

The present study reveals that morphine possesses an anti-acetylcholine action on cardiac, smooth and skeletal muscles. The anti-acetylcholine effect of morphine can be explained probably on the basis of (*i*) inhibition of synthesis, (*ii*) prevention of release of acetylcholine from its bound form, (*iii*) due to less utilisation of acetylcholine by cholinergic receptors or as a result of a decreased excitability of the receptors due to some cellular changes produced by the drug.

Morphine has been reported to possess an insignificant effect on the synthesis of acetylcholine (7, 6). However, Kosterlitz and Robinson (4) and Paton (5) have reported that morphine inhibits the release of acetylcholine in guineapig intestine, which may be due to the depression of nervous mechanism involved in the peristalsis, possibly by reducing the excitability of post-ganglionic structures (6).

Morphine diminishes the skeletal muscle response to indirect as well as direct stimuli. This action of morphine may be due to some direct action on the receptors or on the contractile mechanism, thereby decreasing their excitability or causing a lesser utilisation of acetylcholine by the cholinergic receptors. Similar results with the cardiac and intestinal smooth muscles are also indicative of anti-acetylcholine action.

SUMMARY

Morphine is found to possess an anti-acetylcholine action on cardiac, smooth and skeletal muscles. It blocked the response of skeletal muscle to direct and indirect electrical stimulation. It is suggested that the anti-acetylcholine action of morphine may be due to some direct action on cholinergic receptors or muscle contractile mechanism.

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