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THE EFFECT OF MORPHINE ON VAGAL INHIBITION OF THE HEART

BY

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The action of morphine (0.1 to 100 mg./kg.) on the cardiac slowing produced by stimulation of the right vagus nerve varied in the four species investigated. In the guinea-pig, morphine had no inhibitory effect and in the cat the effect was small, but in the rat and the rabbit stimulation of the vagus slowed the heart much less after administration of morphine than before. Further, in the last two species morphine delayed the onset of cardiac slowing. Nalorphine, which given alone had a slight morphine-like action, partly reversed the effect of morphine.

Small concentrations of morphine are known to inhibit the muscular contractions involved in both the preparatory and emptying phases of the peristaltic reflex in the guinea-pig ileum (Trendelenburg, 1917; Schaumann, 1955; Kosterlitz and Robinson, 1955, 1957). It seemed, however, that a detailed analysis of the peripheral effects of morphine might be easier in a preparation in which the anatomical arrangement of nervous structures was simpler than that in gut and also that it would be useful to study what happened when such nervous pathways mediated an inhibitory rather than an excitatory effect. For these reasons the inhibition of the sinoauricular node by vagal stimulation was chosen.

METHODS

Four species were used, namely, the cat, guinea-pig, rat, and rabbit. Cats were anaesthetized with ether and spinal preparations made by a modified Dale technique (Kosterlitz, Krayer, and Matallana, 1955); at least 1 hr. elapsed before the start of the experiment. All other animals were anaesthetized with a solution of 10% urethane and 1% chloralose (w/v) injected intraperitoneally. Rats were given 7.5 ml./kg. and the other animals 5 ml./kg.

The trachea was cannulated and, except in the rats, artificial respiration applied. In the cats, both stellate ganglia were removed through the first intercostal space. The vagus nerve on the left side was cut; that on the right side was exposed as far as the ganglion nodosum, and care was taken to keep the blood supply to the nerve intact. The area was then flooded with warm liquid paraffin. The nerve was ligated and cut, and the distal end was placed on the stimulating electrodes. It was stimulated with rectangular pulses from a Grass stimulator, using a RF-coupled output stage for isolating the stimuli from earth. The pulse duration was 0.1 msec. and the voltage was selected to give a supramaximal stimulus; this voltage was then maintained throughout the experiment. In experiments in which the vagus was stimulated at one frequency only, this was so chosen as to reduce the unstimulated or resting heart rate by about one third. When stimulus frequency/response curves were constructed, frequencies high enough to produce rhythms other than sinoauricular were excluded.

Recording.—The blood pressure in the left femoral artery was measured with a condenser manometer and recorded with the electrocardiogram by a pen oscillograph.

The resting heart rate was counted from the electrocardiogram for a period of 10 sec. at the beginning of each successive minute, except immediately after a period of stimulation. The vagus nerve was stimulated during every third minute for 30 sec. or every fourth minute for 60 sec., and the heart rate was counted from the 15th to the 25th sec. after the beginning of stimulation; when the stimulation lasted for 60 sec. a second count was taken from the 45th to the 55th sec. The heart rate was plotted against time (Fig. 1). To facilitate interpretation of the results, the average resting heart rate (the mean of the two counts immediately before stimulation) and the maximum fall in rate during stimulation were each plotted against time (Figs. 2 and 3). When stimulus frequency/response curves were determined, the fall in rate was plotted as % of the resting heart rate against the logarithm of the stimulus frequency. Before the administration of morphine two superimposable control curves were obtained. Then morphine was injected and the series of observations was repeated.

Drugs.—All injections of morphine hydrochloride or nalorphine hydrobromide were made into the right femoral vein; the doses, which varied from 0.05 to 100 mg./kg., refer to the salts in aqueous solution.

Results

Cat.—In 8 experiments on cats, the stimulus frequency varied between 0.3 and 3/sec. but was kept constant throughout any one experiment. Morphine in doses of 0.1 to 10 mg./kg. had no lasting effect on the resting heart rate; in some preparations the larger doses (5 to 10 mg./kg.) caused a transient rise in heart rate and arterial blood pressure which was assumed to be due to a liberation of catechol amines (Fig. 1). In most experiments after injection of morphine, there was a reduction in the cardiac slowing on stimulation of the vagus (Fig. 1); this, however, was small and, on the average, a dose of 1 mg./kg. reduced the effect by 18%.

Guinea-pig.—In 5 experiments on guinea-pigs there was no evidence that morphine, in doses of 0.1 to 5 mg./kg., reduced the cardiac slowing caused by vagal stimulation. A difficulty in some of these experiments was a tendency for the resting rate to rise after injection of morphine; nevertheless, when this occurred there was no diminution of the vagal effect. In the experiment shown in Fig. 2*a* the resting rate did not change significantly and the effect of vagal stimulation was, if anything, enhanced by morphine.

Rat.—Twelve experiments were performed on rats. After morphine, in doses of 0.1 to 2.5 mg./kg., there was an immediate sharp decrease in the degree of slowing produced by stimulating the vagus at a given frequency (3 to 15/sec.) (Fig. 2*b*). Although in some experiments recovery was fairly rapid and complete, in others it was not apparent within 1 hr. That this was not necessarily due to a failure of the nerve was clear from the fact that the morphine-antagonist, nalorphine, produced at least partial recovery an hour or more after the injection of morphine in some, though not in all, experiments.

Since morphine in doses larger than 1 mg./kg. depressed respiration severely, a small dose of nalorphine was given before the injection of the

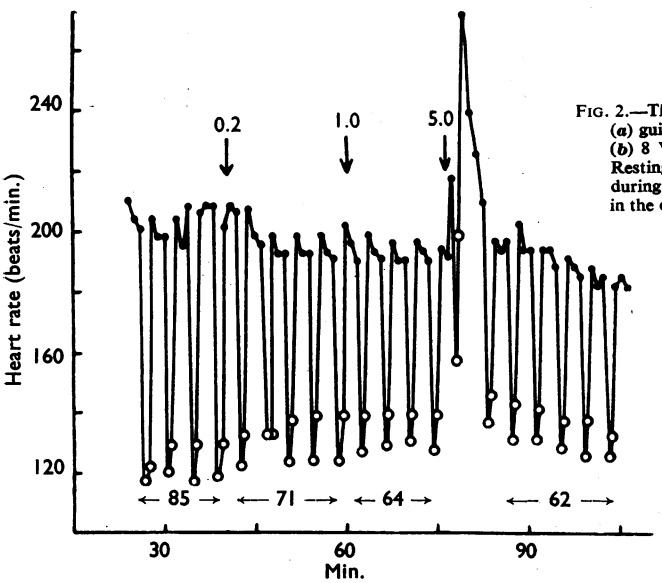

FIG. 1.—The effect of morphine on vagal inhibition of the heart in the cat. Spinal preparation, stellate ganglia removed. ●——●, resting heart rate; O——O, heart rate during vagal stimulation (12 V., 0.1 msec., 3/sec., every 4 min. for 60 sec.). At the arrows, morphine was injected in the doses indicated (mg./kg.). The numerals below the tracing give the average slowing (beats/min.) produced by vagal stimulation.

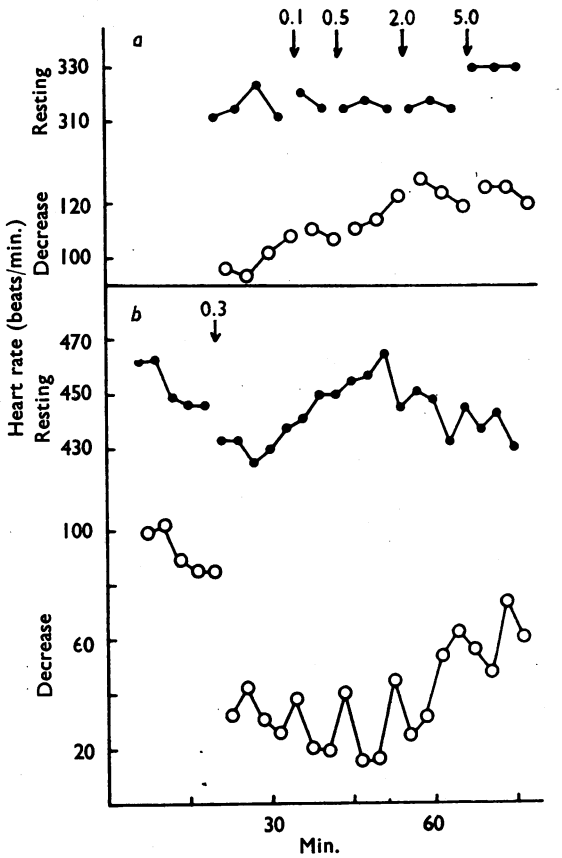

FIG. 2.—The effect of morphine on vagal inhibition of the heart in: (*a*) guinea-pig; (*b*) rat. Stimulus: (*a*) 15 V., 0.1 msec., 7/sec.; (*b*) 8 V., 0.1 msec., 3/sec., every 3 min. for 30 sec. ●——● Resting heart rate; O——O maximum decrease in heart rate during vagal stimulation. At the arrows, morphine was injected in the doses indicated (mg./kg.).

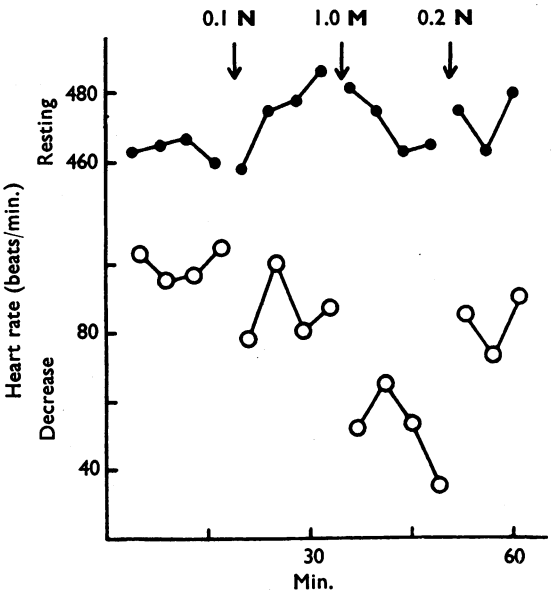

FIG. 3.—The effects of nalorphine and morphine on vagal inhibition of the heart in the rat. Stimulus: 8 V., 0.1 msec., 6/sec., every 3 min. for 30 sec. ●——● Resting heart rate; O——O maximum decrease in heart rate during vagal stimulation. At the arrows, nalorphine (N) or morphine (M) was injected in the doses indicated (mg./kg.).

larger doses of morphine. In 2 of these experiments, nalorphine had no effect on the response to vagal stimulation, whereas in 3 others a morphine-like effect was noted. After a preliminary injection of nalorphine (Fig. 3), morphine, in doses up to twice that of the nalorphine, did not inhibit vagal slowing; but larger doses of morphine did, although respiration remained relatively unaffected.

It was observed that, quite apart from the effect of morphine on the degree of slowing, the onset of this was always markedly delayed. When the vagus was stimulated at 40/sec., morphine scarcely affected the degree of slowing, its only action being to produce a delay in onset (Fig. 4).

Rabbit.—In 4 out of 20 experiments on rabbits the method of assessing the results was the same as in the other species. The effects of morphine and nalorphine were similar to those obtained in the rat.

In the course of these experiments we noticed that, in the rabbit, the resting heart rate remained constant much longer than in the rat and that the vagal responses were reproducible for long periods. For these reasons we chose the rabbit for a more detailed investigation of the stimulus frequency/response curves. The degree of cardiac slowing, expressed as % of the resting heart rate, was plotted against the stimulus frequency, which

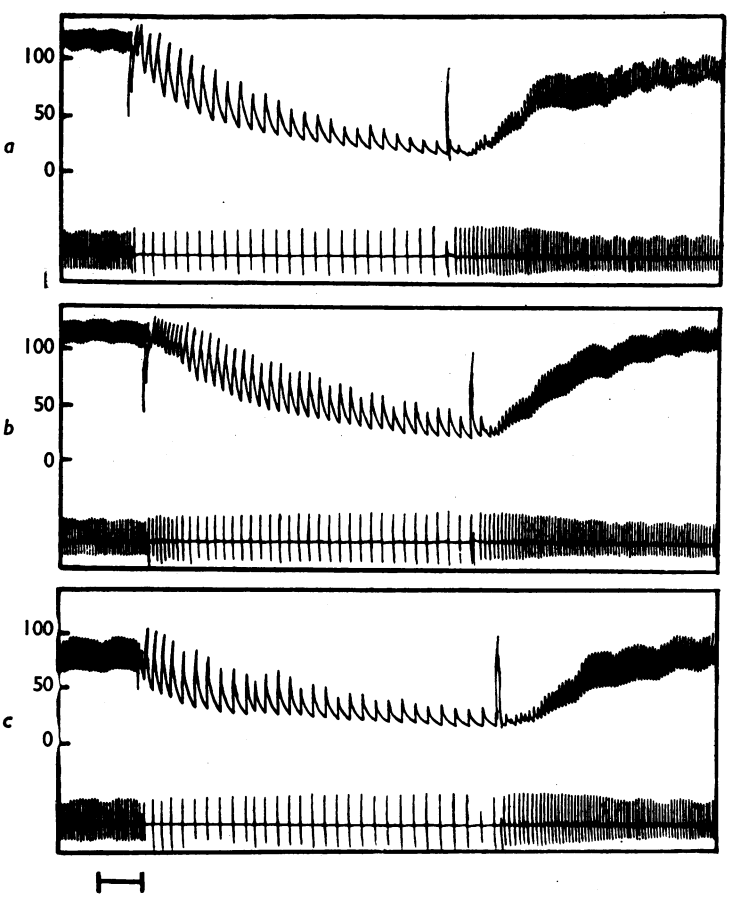

FIG. 4.—The delay caused by morphine on the onset of cardiac slowing after vagal stimulation. Rat. Stimulus: 8 V., 0.1 msec., 40/sec., between signals. (*a*) control. Between (*a*) and (*b*) 0.1 mg./kg. nalorphine was injected, without effect on the responses, followed by 1 mg./kg. morphine. Between (*b*) and (*c*) 2 mg./kg. morphine was injected without altering the responses shown in (*b*) followed by 2 doses of nalorphine, 0.2 and 0.5 mg./kg., respectively. Upper of each pair of traces: blood pressure mm. Hg; lower: electrocardiogram. Time: 2 sec.

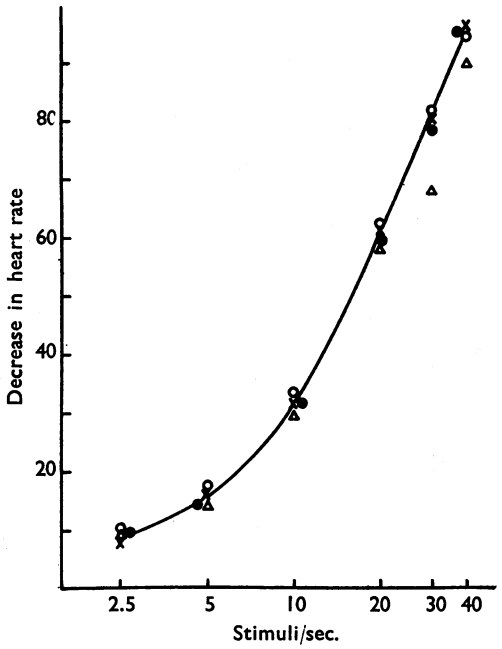

FIG. 5.—Stimulus frequency/response curve showing the effects of vagal stimulation on the heart rate in the rabbit. ●——● At beginning of the experiment; O——O after 48 min.; X——X after 120 min.; Δ——Δ after 187 min. Mean resting heart rates 300, 300, 300, and 326 min., respectively. The vagus was stimulated every 3 min. for 30 sec. Ordinate, decrease in heart rate expressed as % of resting rate.

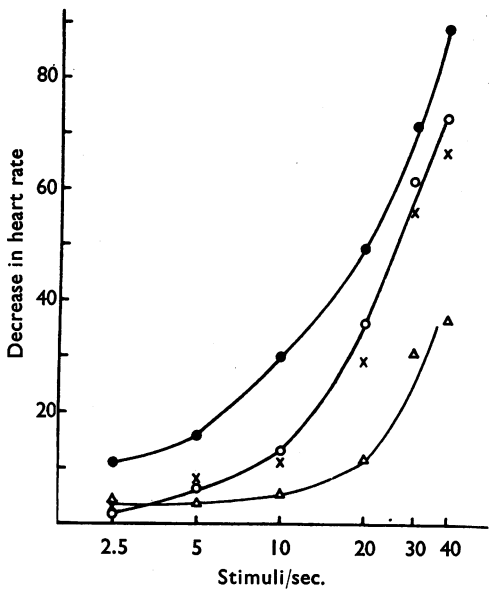

FIG. 7.—The effects of morphine (1 mg./kg.) at different intervals after injection on vagal inhibition of the heart in the rabbit. ●——● Control; O——O mean of values obtained between 18 and 51 min. after injection; X——X 73 to 88 min. after injection; Δ——Δ 164 to 179 min. after injection. Mean resting heart rates 301, 302, 320, and 242 min., respectively. The vagus was stimulated every 3 min. for 30 sec. Ordinate, as in Fig. 5.

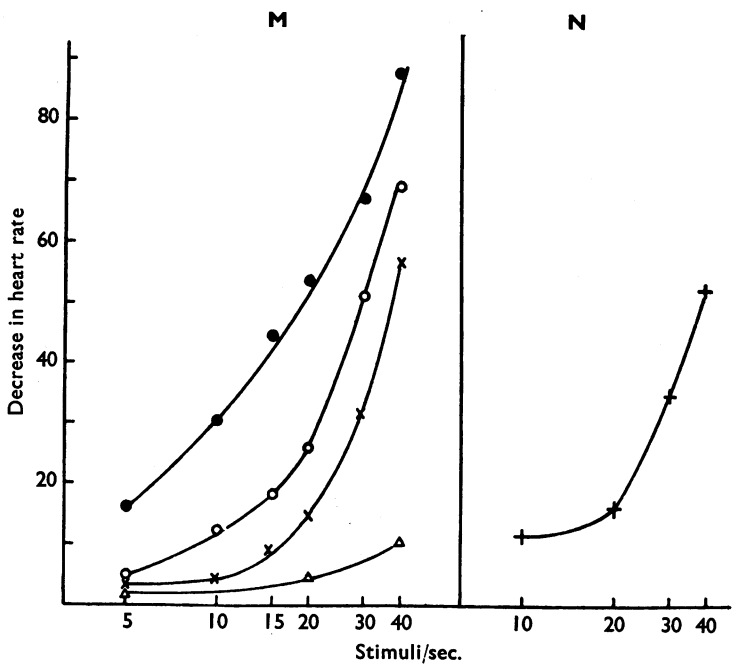

FIG. 6.—The effect of morphine (M) and nalorphine (N) on vagal inhibition of the heart in the rabbit. ●——● Control; O——O after 1 mg./kg. morphine; X——X after additional 10 mg./kg. morphine; Δ——Δ after additional 100 mg./kg. morphine; +——+ after additional 24 mg./kg. nalorphine. Mean resting heart rates 292, 293, 276, 251, and 292 min., respectively. The vagus was stimulated every 3 min. for 30 sec. Ordinate, as in Fig. 5.

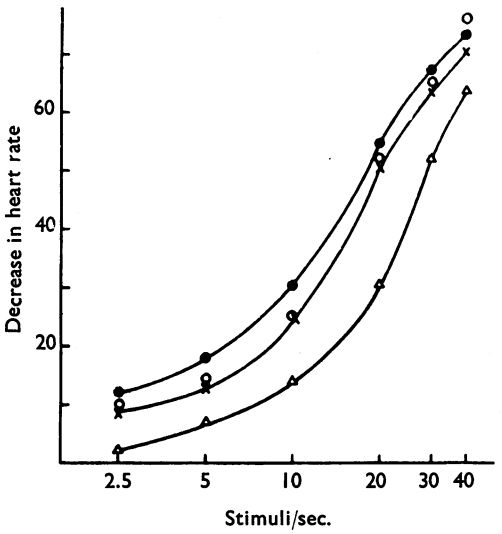

FIG. 8.—The effects of nalorphine followed by morphine on vagal inhibition of the heart in the rabbit. ●——● Control; O——O after 0.5 mg./kg. nalorphine; X——X after additional 5 mg./kg. nalorphine; Δ——Δ after additional 10 mg./kg. morphine. Mean resting heart rates 298, 296, 292, and 294 min., respectively. The vagus was stimulated every 3 min. for 30 sec. Ordinate, as in Fig. 5.

ranged from 0.5 to 40/sec. Stimulation at 40/sec. often led to complete, or almost complete, inhibition of the heart. When this was not so, higher frequencies were usually not more effective and often caused vagus escape and nodal rhythm. The shape of the response curves was usually concave upwards, with the greatest curvature at the lower frequencies; in a small number of experiments S-shaped curves were obtained. When such stimulus frequency/response curves were repeated at intervals of 1 hr. or so, without the administration of morphine, they were practically identical for at least 3 hr. (Fig. 5). The stimulus frequency required to cause a 50% fall in the resting heart rate lay between 10 and 20/sec., with a mean of 14.6/sec.

Morphine, above the threshold dose of 0.1 mg./kg., depressed the response to vagal stimulation at all frequencies (Fig. 6). The inhibitory action of morphine in doses up to 10 mg./kg. was more marked at the lower than at the higher rates of stimulation. The ease with which these results could be interpreted depended to a great extent on whether or not the resting heart rate remained constant. Doses of morphine up to 1 mg./kg. had no significant effect on the resting heart rate for about 1 hr. after administration. During this period the inhibition of vagal slowing was unchanged. However, it was not unusual for the resting heart rate to slow considerably 2½ to 3 hr. after giving morphine, when the inhibitory effect on vagal slowing became much more pronounced (Fig. 7). With large doses of morphine (100 mg./kg.) this marked fall of the resting heart rate and inhibition of vagal slowing occurred during the first few minutes after administration; both these effects were partly reversed by nalorphine (Fig. 6).

Nalorphine given alone had a slight morphine-like effect which, however, was not enhanced by increasing the dose (Fig. 8). We could not decide from the available evidence whether nalorphine, given first, protected against subsequent doses of morphine.

DISCUSSION

Four species were studied. In the guinea-pig, morphine did not reduce the cardiac slowing caused by vagal stimulation; in the cat the effect was relatively small. In the rat and rabbit, on the other hand, stimulation of the vagus produced much less slowing of the heart after morphine than before, and there was also a distinct delay in the onset of such slowing as did occur. Large doses appeared to have a more complex action than small doses in that they not only diminished the cardiac slowing due to vagal stimulation but also led to a fall in the resting, non-stimulated, heart rate. Nalorphine reversed, at least in part, the effects of small or large doses of morphine.

The inhibitory action of morphine on the effect of vagal stimulation might occur at a number of sites, but lack of experimental evidence must render any attempt at interpretation speculative, especially when one takes into account the species differences shown in this paper and known differences in the responses of various structures within any one animal. Thus in the guinea-pig, the peristaltic reflex was inhibited by morphine whereas the vagal slowing was not; on the other hand, in the rabbit, where cardiac slowing due to vagal stimulation was morphine-sensitive, Schaumann (1955) found that the preparatory phase of the peristaltic reflex in the jejunum was not inhibited by morphine.

No evidence is available as to whether or not morphine affects conduction in the vagus nerves of the rat or the rabbit. However, J. W. Thompson (personal communication) found that morphine (10^{-3}) failed to produce any alteration in the resting or action potentials, or in conduction velocity, in the desheathed sciatic nerve of the frog. As far as ganglionic transmission is concerned, no direct evidence is available for the

rabbit or the rat, but Hebb and Konzett (1950) and Trendelenburg (1957) found that morphine did not block transmission in the superior cervical ganglion of the cat. A third possibility is that the effect is produced at the postganglionic nerve endings either by interfering with the formation, release or destruction of acetylcholine, or by altering the sensitivity of the sinoauricular node to acetylcholine. There is no evidence for an increase in destruction of acetylcholine; on the contrary, morphine reduces the activity of brain and serum cholinesterase (Wikler, 1950). Paton (1956, 1957) and Schaumann (1956) both found that morphine reduces acetylcholine release from the guinea-pig ileum stimulated either electrically or by distension. But there is, as yet, no evidence about what occurs at the vagal endings round the sinoauricular node.

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