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Cardiovascular effects of morphine, pethidine, diamorphine and nalorphine on the cat and rabbit

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Summary

1. The predominant effect of morphine, diamorphine, pethidine or nalorphine on the blood pressure of the anaesthetized cat or rabbit is hypotension although, occasionally, a pressor action may predominate or intervene.

2. Possible mechanisms of the depressor phases of action have been studied on cardiac and vascular preparations both *in situ* and *in vitro*.

3. While in the whole animal, catecholamine release from the adrenal medulla and histamine liberation may be implicated in the responses, the vasodilator and vascular relaxant actions of morphine and, probably, pethidine, nalorphine and diamorphine on the isolated preparations are not mediated by the liberation of known peripheral transmitters or autacoids or by interaction with their specific receptors.

Introduction

The actions of narcotic analgesics and their antagonists on the circulation have been reviewed by Eckenhoff & Oech (1960). In man, the cardiovascular effects of conventional doses of morphine are usually insignificant but the drug may induce a marked hypotension, principally due to vasodilation, in particular circumstances, for example head-up tilting, haemorrhagic shock. Pethidine, nalorphine and levallorphan elicit similar responses. Although nalorphine or levallorphan antagonizes the fall in blood pressure produced by an immediately preceding injection of morphine or pethidine, neither necessarily prevents the cardiovascular effects of an immediately succeeding injection.

When morphine or pethidine is administered intravenously to anaesthetized laboratory animals, the predominant effect is hypotension although this may be preceded or interrupted by an evanescent pressor effect due to the release of catecholamines from the adrenal medulla in some species (for example, cat, 4 mg/kg morphine: Evans, Nasmyth & Stewart, 1952). The depressor response to 2–5 mg/kg of these substances typically consists of an initial, rapid fall, chiefly due to histamine release in the cat (Feldberg & Paton, 1951; Evans *et al.*, 1952; Kayaalp & Kaymakçalan, 1966) and the dog (Van Arman & Sturtevant, 1958), followed by a longer period of hypotension during which the blood pressure slowly recovers. During the latter period, which may be protracted after large doses of morphine, the preparation shows tachyphylaxis to the depressor effect of this drug, and this state of hyposensitivity is still present even if the blood pressure is artificially raised to its original level (Schmidt & Livingston, 1933). Moreover, even after the pressure has recovered naturally, the depressor response to a given dose of morphine is con-

siderably less, for a long time, in all species studied (for example, 5–24 h in the rat: Evans *et al.*, 1952).

The primary object of the present experiments was to study the mechanisms involved in the cardiovascular changes produced by morphine in the cat and rabbit. But the immediate occurrence of a prolonged decrease in sensitivity following the initial morphine injection made pharmacological analysis difficult. Accordingly, pethidine and diamorphine, which do not induce such prolonged tachyphylaxis, were studied alongside morphine in the anaesthetized animal.

When isolated cardiovascular tissues are used, the insensitivity to morphine is of much shorter duration, and the actions of all the drugs involved were studied on a variety of preparations, including the guinea-pig heart and isolated parts of the peripheral circulation of the cat and the rabbit. On the perfused, isolated hearts of the common laboratory animals, morphine may stimulate the heart transiently at lower concentrations but the dominant effect is cardiac depression (Gruber & Robinson, 1929; Schmidt & Livingston, 1933). The principal action of morphine on isolated blood vessel preparations is vasodilation. The extent to which this vascular response is mediated via peripheral transmitters or tissue autacoids or their specific receptors was analysed, chiefly using arterial and venous strips.

In all preparations nalorphine was studied in parallel with morphine, pethidine and diamorphine; a few observations were made on the effects of pentazocine, a preliminary account of the findings has been published (Grundy, 1968).

Methods

Anaesthetized animals

Thirteen adult cats were anaesthetized by intraperitoneal injection of either chloralose (80 mg/kg) or sodium pentobarbitone (30 mg/kg); four rabbits were given urethane (2 g/kg) by the same route. Subsequently, drugs were administered into a jugular vein. Carotid or femoral arterial pressure was recorded either on a kymograph via a mercury manometer or on a pen recorder using an Ether transducer (BP 15) (1 mmHg≡1·333 mbar). In some animals the electrocardiogram (E.C.G., lead II) was monitored from subcutaneous needle electrodes. When drugs depressed respiration significantly, artificial respiration, of similar depth and rate to that originally spontaneously present, was applied by means of a Palmer rubber bellows respiration unit. In one cat and one rabbit, towards the end of the experiment, an anterior thoracotomy, sufficiently large to observe the heart directly, was made.

Fourteen cat hind limb perfusions were set up as follows. After intravenous injection of 2,000 μg/kg heparin, a thin nylon cannula (No. 00 Portex) was inserted into the lateral circumflex femoral artery and advanced proximally until its tip reached the junction with the femoral artery, and the femoral vein blood was long-circuited through a drop-chamber (Hilton, 1952). Occlusion of the limb vessels during cannulation was kept to a minimum. The process was carried out separately on the two legs, one of which had been previously skinned, had a tight ligature bound round its ankle and the skin resewn to cover the limb. The drop-chamber reservoir contained 50 ml 0·9% NaCl and 10 ml dextraven (10% Dextraven 150 in 5% dextrose). Drops were monitored either through a phototransistor or by electrical contact and the information passed to a Thorp impulse counter, resetting every 10 s.

which recorded on a kymograph. Subsequently, 1,000 μg/kg heparin was given every 2 hours. Drugs were injected intraarterially in 0·01–0·05 ml volumes and washed in with 0·05 ml 0·9% NaCl. Simultaneous recordings of carotid blood pressure were taken.

Isolated preparations

The methods used were essentially those of Fogelman & Grundy (1970). In the guinea-pig heart, drugs were generally injected at not less than 10 min intervals. The perfused rabbit ear and perfused rabbit ear artery preparations were as usual. Drugs were applied to spiral strips from the rabbit portal, posterior caval and pulmonary veins, descending thoracic aorta and pulmonary artery at intervals of 30 min–1 hour. Krebs-Henseleit solution (modified by the addition of ascorbic acid, 0·22 mM, and disodium edetate, 0·03 mM) was used in most experiments with the perfused ear artery and vessel spiral strips but similar results were obtained when Krebs-bicarbonate and the Krebs solution of Hughes & Vane (1967), respectively, were used in these preparations.

Drugs used

Acetylcholine perchlorate (B.D.H.); (−)-adrenaline bitartrate (B.D.H.); atropine sulphate (B.D.H.); diamorphine hydrochloride (May & Baker); histamine acid phosphate (B.D.H.); isoprenaline sulphate (Burroughs Wellcome); mepyramine maleate (B.D.H.); methysergide bimaleate (Sandoz); morphine hydrochloride (May & Baker); nalorphine hydrobromide (Burroughs Wellcome); (−)-noradrenaline bitartrate (Koch-Light); pentazocine (Sterling-Winthrop); pethidine hydrochloride (Roche); phentolamine methyl sulphate (B.D.H.); propranolol hydrochloride (I.C.I.); vasopressin (Pitressin, Parke Davis). Concentrated drug solutions were made in deionized water, stored at 8° C and diluted freshly as required. Pentazocine was dissolved in one equivalent of lactic acid and the pH adjusted to 6·8 with NaOH. Doses and concentrations are expressed as those of the free drug.

Results

Effects on anaesthetized animals

The blood pressure responses of a chloralosed cat to doses of pethidine (0·1–5 mg/kg) are shown in Fig. 1. The lower doses produced a sharp pressor effect which could be repeated every 5–10 min: intermediate doses gave a biphasic response of relatively short duration and repeatable at 15 min intervals: 5 mg/kg pethidine caused an immediate fall of blood pressure preceding a prolonged hypotensive phase, at the end of which the entire response could be replicated. Thresholds for the above effects varied in different cats but the values shown in Fig. 1 are typical. Similarly, the progression of effects with increasing doses of pethidine was usually, but not invariably, in the order described. In two cats, only depressor responses were obtained over a range of doses from 0·1–5 mg/kg. Associated phenomena included respiratory depression with high doses, but the effects on the blood pressure were similar whether the cat was breathing spontaneously or on artificial respiration. The pressor phase could be abolished by bilateral ligation of the adrenal blood vessels, an operation which also tended to potentiate the prolonged

depressor phase, especially if the blood pressure was high. The pressor and immediate depressor actions could be mimicked by adrenaline and histamine, respectively, and the biphasic response to 1 mg/kg pethidine by a combined injection of adrenaline and histamine (Fig. 1). Over 4–8 h periods, the pressor effect tended to fade and usually gradually increasing doses of pethidine were required to produce the same depressor actions (Fig. 1, third row). Over the dose range studied the drug did not induce any significant changes in heart rate. Similar results were obtained both in cats anaesthetized with pentobarbitone (Fig. 2B) and in rabbits under urethane anaesthesia, although in the latter species responses were usually rather weak.

Diamorphine produced effects comparable to those of pethidine, and its pressor phase was also abolished by ligation of the adrenal vessels. It was more potent as a hypotensive agent (Fig. 1) and even more as a respiratory depressant: with higher doses (2–5 mg/kg), twitches of the skeletal musculature, which were uncommon with pethidine, were a noticeable feature.

The actions of morphine on blood pressure (Fig. 1) and respiration were generally intermediate between those of diamorphine and pethidine. The cardiovascular responses differed markedly, however, in that the first dose of morphine induced a period of autohyposensitivity which lasted for several hours unlike pethidine and diamorphine, which showed only short periods of tachyphylaxis (5–30 min depending on the dose).

Nalorphine had a weaker agonist action than pethidine on the blood pressure (Figs. 1 and 2). Generally, it had a negligible effect on pethidine (Fig. 2A) or diamorphine (in doses 0·2–1 times that of the nalorphine) administered 1–4 min later; in about 20% of the tests, however, nalorphine had some antagonist action. It never abolished the cardiovascular responses to morphine. The antagonism of the circulatory effects of pethidine, diamorphine or morphine by nalorphine was

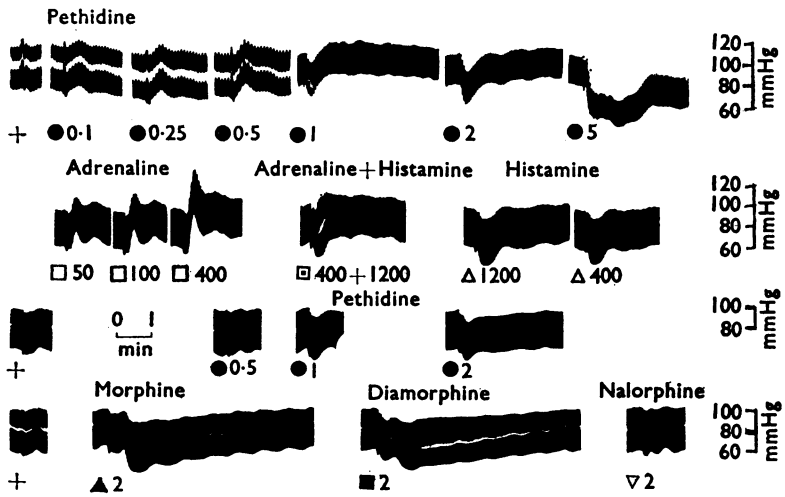

FIG. 1. Cat 2·7 kg; chloralose anaesthesia. Blood pressure responses to: top row, gradually increasing doses (mg/kg) of pethidine (●) given at 15 min intervals; second row, doses (ng/kg) of adrenaline (□), histamine (△) and a mixture of 400 ng/kg adrenaline and 1,200 ng/kg histamine (⊡); third row, three of the original pethidine doses repeated 4 h later; bottom row, 2 mg/kg morphine (▲), diamorphine (■) and nalorphine (▽) for comparison with the highest dose of pethidine used in the third row. Control injections (+) of 0·9% NaCl. Artificial respiration was applied after the third pethidine injection (top row) onwards.

much more marked when the latter drug was given to a cat or a rabbit during the prolonged depressor phase induced by one of these agonists. Then (see Fig. 2B), the initial agonist response to nalorphine was immediately followed by a rapid recovery of the blood pressure to its pristine level. Figure 2B further shows, first, that this antagonistic effect of nalorphine is independent of any respiratory improvement, as the cat was on artificial respiration and, second, the negligible action of the antagonist on a subsequent dose of pethidine.

Pentazocine (0·25–2 mg/kg) was rather similar to nalorphine in its overall cardiovascular effects. It had a weak agonist action and was a good antidote after pethidine but, given first, it neither antagonized 0·25–1 times its own dose of pethidine nor blocked the hypotension produced by an equal dose of morphine. In one cat, 1 mg/kg nalorphine, given 1 min before, reversed the pure depressor effect of 0·1 mg/kg pethidine and later, similarly administered, partially blocked the fall of blood pressure caused by 0·5 mg/kg pentazocine.

Histamine, over a range of 0·1–50 μg/kg, in both cats and rabbits, could simulate the cardiovascular effects of pethidine (0·1–10 mg/kg). In cats, hypotension was the most common response but this could be interrupted or overshadowed by a pressor effect: sometimes the responses varied, independently of the level of blood pressure, during the course of the experiment. In rabbits, as the dose of histamine was increased, the usual transition pressor→biphasic→depressor response was seen, except in one animal where the pressor phase was not prominent. Large doses of mepyramine (1,000–5,000 times those of histamine) were required to antagonize the latter's cardiovascular actions and, even then, the block was sometimes only partial.

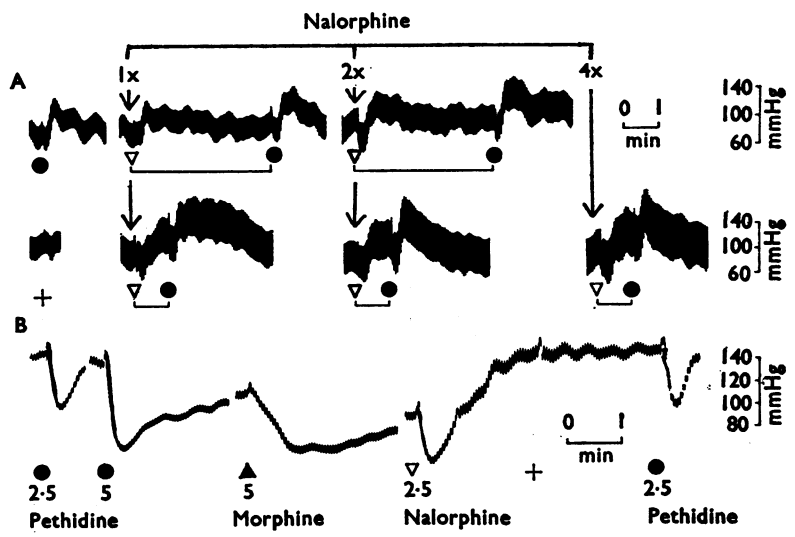

FIG. 2. A, Cat 3·3 kg ; chloralose anaesthesia ; artificial respiration. Blood pressure responses to nalorphine (▽) given in gradually increasing doses either 4 min (upper row) or 1 min (lower row) before a constant dose (●, 0·5 mg/kg) of pethidine given at 15 min intervals. The doses of nalorphine are expressed as multiples (1×, 2× or 4×) of the pethidine dose. B, Cat 2·8 kg ; pentobarbitone anaesthesia ; artificial respiration. Effects on the blood pressure of two doses of pethidine (●, 2·5 and 5 mg/kg) and morphine (▲, 5 mg/kg). Nalorphine (▽, 2·5 mg/kg), after an agonist action, produced recovery of the blood pressure but left the response to a subsequent injection of pethidine (●, 2·5 mg/kg) unaffected. Intervals between tracings, 6, 7·5 and 6 min respectively. Control injections (+) of 0·9% NaCl.

Such large doses of mepyramine usually failed to affect the pethidine or diamorphine responses but, occasionally, they produced some antagonism (Fig. 3). The actions of morphine (2·5–5 mg/kg) on the blood pressure were never abolished by doses of mepyramine up to 5 mg/kg.

From Fig. 3 it will be seen that the E.C.G. responses to pethidine differed from those to histamine in showing a marked, but transient, initial increase in amplitude. However, the injection of a mixture of histamine and adrenaline could simulate both the blood pressure (Fig. 1) and also the E.C.G. effects of 1 mg/kg pethidine. Adrenaline, from a threshold of 10 ng/kg to 2 μg/kg, produced a pressor action without any change of heart rate. Following anterior thoracotomy, in the rabbit 2·5 mg/kg histamine produced enlargement of the right ventricle whilst the same doses of pethidine caused slight dilation of the heart and of diamorphine or nalorphine no visible effect; in the cat, 5 mg/kg pethidine, diamorphine or morphine caused an immediate, but short-lived, increased force of cardiac contraction.

In more than 120 observations on the perfused cat hind limb there was no significant difference between the results on skinned and non-skinned limbs. Pethidine, from a threshold of 0·5–1 mg up to 2·5 mg, most commonly produced vasodilation without any rise in systemic blood pressure, although in about 25% of the cases there was a vasoconstrictor element in the response. Morphine and nalorphine usually had higher thresholds (1–2 mg) but more commonly gave pure dilator effects. Nalorphine, given 3–5 min before an equal dose of pethidine or morphine, only occasionally showed slight antagonist action.

Effects on isolated preparations

Guinea-pig heart. Only six preparations were studied, one of which showed some tachyphylaxis even if each dose of pethidine or morphine was separated by 30 minutes. Over a range of doses from 10 μg to 2 mg the predominant effect was depression of the heart, the order of potency being pethidine>diamorphine>morphine and

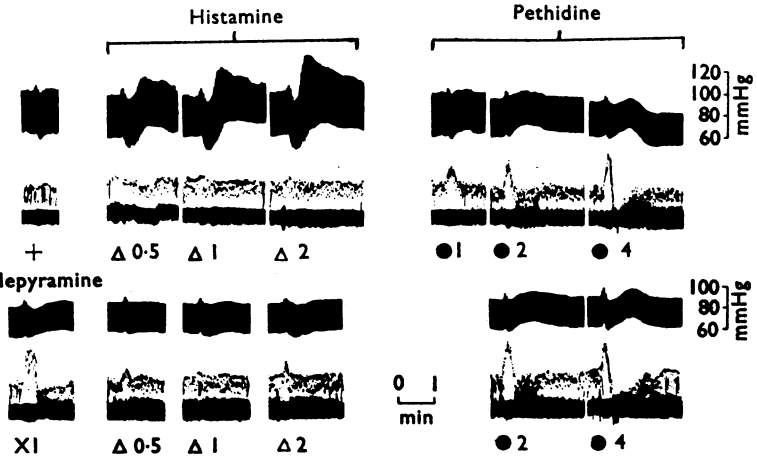

FIG. 3. Cat 2·35 kg; chloralose anaesthesia; artificial respiration. Effects of doses of histamine (△, in μg/kg) and pethidine (●, in mg/kg) on the blood pressure and electrocardiogram (E.C.G., lead II) before (upper vertical pairs of tracings) and after (lower pairs) mepyramine (×, 1 mg/kg). Each vertical pair of tracings shows blood pressure (above) and E.C.G. Control injection (+) of 0·9% NaCl.

nalorphine (Fig. 4A). Pethidine usually decreased the amplitude of contraction at a threshold of about 10 μg ; higher doses gave greater falls of amplitude, often interspersed with bradycardia and cardiac irregularities, and could be followed by atrioventricular block. Diamorphine produced similar effects at approximately three times the dose of pethidine. Threshold doses of morphine sometimes produced a transient initial stimulation but generally this drug acted as a weak myocardial depressant. This is shown in Fig. 4A, which also illustrates the rapid development of a high degree of hyposensitivity to and the production of cardiac irregularities by morphine. Nalorphine was rather similar in potency to morphine: it did not antagonize the cardiac depression produced by 25–100 μg pethidine when given 1–2 min before the agonist in doses of 50–500 μg. Figure 4B shows that nalorphine could sometimes produce antagonism when given after, though not when administered before, an equal dose of pethidine.

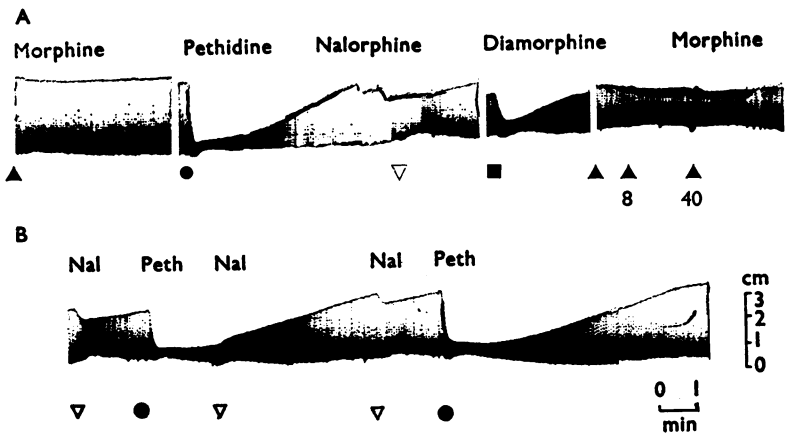

FIG. 4. Effects of drugs on a Langendorff preparation of the guinea-pig heart. A, 2 mg doses of morphine (▲), pethidine (●), nalorphine (▽), diamorphine (■) and, then, morphine again were given at 30 min intervals. Forty-eight seconds after the second morphine injection, 8 mg morphine was given and 1 min 44 s later, 40 mg morphine. All volumes of injection were $\leqslant$0·2 ml except the final morphine dose which was in 1 ml. B, Effects of 2 mg nalorphine (Nal, ▽) injected before, during the cardiac depressant action of and after recovery from the same dose (2 mg) pethidine (Peth, ●). This dose of pethidine was repeated 1 min 44 s after the last nalorphine injection.

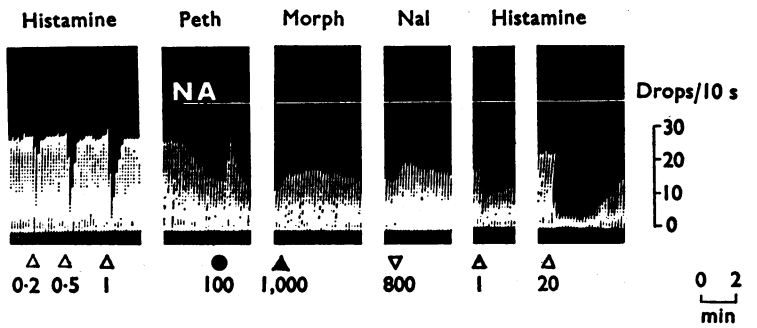

FIG. 5. Effects of drugs on the flow of perfusion fluid through a rabbit ear preparation. In the first tracing, the responses to lower doses (0·2–1 μg) of histamine (△) are shown. Subsequently, 50 ng/ml noradrenaline was added to the perfusate (NA and white horizontal line) to provide a background of vasoconstriction during which doses, in μg, of pethidine (Peth, ●), morphine (Morph, ▲), nalorphine (Nal, ▽) and histamine (△ ; including a higher dose, 20 μg) were administered.

TABLE 1. *Effective agonist and corresponding antagonist quantities, expressed as doses (in μg) on the perfused rabbit ear and as final bath concentrations (in g/ml) on two rabbit vessel strip preparations*

Agonist (Ag)	Perfused rabbit ear				Portal venous strip				Thoracic aortic strip				Antagonist (Antag)
		Dose (μg)		Antag / Ag ratio		Final bath concn. (g/ml)		Antag / Ag ratio		Final bath concn. (g/ml)		Antag / Ag ratio	
	Response	Ag	Antag		Response	Ag	Antag		Response	Ag	Antag		
Noradrenaline	C	0·05	5	100	C	10^{-7}	10^{-6}	10	C	10^{-7}	10^{-6}	10	Phentolamine
5-Hydroxytryptamine	C	0·05	200*	4,000	C	10^{-7}	10^{-6}*	10	C	5×10^{-8}	10^{-6}*	20	Methysergide
Histamine	C	0·5	0·5	1	C	5×10^{-7}	5×10^{-7}	1	C	10^{-6}	10^{-6}	1	Mepyramine
Nicotine	X				C	5×10^{-4}	5×10^{-4}	1	X				Pentolinium
Acetylcholine	R	0·5	0·5	1	C	10^{-6}	10^{-6}	1	C	10^{-5}	10^{-5}	1	Atropine
Isoprenaline	R	0·1	5	50	C†	10^{-5}	10^{-6}	0·1	C	5×10^{-6}	5×10^{-6}	1	Phentolamine
					R†	10^{-6}	10^{-6}	1					Propranolol

Responses: C, vasoconstriction or contraction (of vessel strip); R, vasodilation or relaxation (strip); X, variable response. * Higher doses of methysergide alone could produce prolonged vasoconstriction or contraction (strip); † see Fogelman & Grundy (1970).

Perfused rabbit ear. In thirteen preparations, pethidine (40–200 μg), nalorphine (60–1,000 μg) and morphine (100–2,000 μg) produced vasodilation, which was shown most clearly on a stable background of moderate vasoconstriction achieved by the addition of a suitable concentration of noradrenaline to the perfusion fluid. Figure 5 shows representative dilator effects of these drugs. Tachyphylaxis could occur if pethidine or nalorphine was given more often than every 6 min or if morphine was repeated within 30 minutes. Nalorphine, given 1–5 min previously, did not antagonize an equidilator dose of morphine or pethidine. Table 1 shows effective doses of five agonists on this preparation and the amounts of 'specific' antagonists necessary to block these effects. These doses of antagonists did not modify the responses to the subsequent administration of vasodilator doses of morphine, pethidine or nalorphine. The following 'cross-antagonisms' were noted: the effect of 5-hydroxytryptamine could be antagonized by 4,000 times its dose of morphine; acetylcholine vasodilation was blocked by pethidine (200–400 times in excess); and histamine action was prevented by 100 or 1,000 times its dose of pethidine or nalorphine, respectively. From Fig. 5 it can be seen that the constrictor effect of 1 μg histamine occurred either in the absence or in the presence of a vasoconstrictor perfusion and that a large dose (20 μg) of this drug still produced overall constriction of the ear vessels.

Perfused rabbit ear artery. Similar results were obtained in arteries prepared from innervated or previously denervated ears. In about 100 observations on eight preparations, pethidine (0·1–2 mg) and 2–8 mg nalorphine, morphine or diamorphine produced arterial dilation when tested on a background of vasoconstrictor tone induced by noradrenaline. A representative series of tracings is shown in Fig. 6 and it will be seen that, although the effective doses required are greater than those necessary in the whole ear (Fig. 5), the relative dose-ratios (pethidine : nalorphine : morphine) are similar; periods of tachyphylaxis were also comparable. In a single test, nalorphine did not antagonize the effects of an equal dose of morphine given 5 min later. The effective doses of noradrenaline, histamine and their antagonists

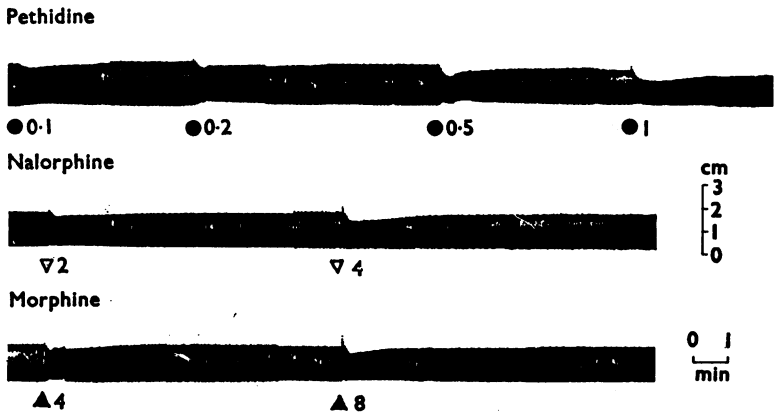

FIG. 6. Rabbit ear artery kept in stable, moderate vasoconstrictor tone by the addition of 50 ng/ml noradrenaline to the perfusion fluid: flow rate 15 ml/minute. Effects of doses (in mg) of pethidine (●), nalorphine (▽) and morphine (▲) on the perfusion pressure; a fall in the tracing profile indicates a decrease in pressure. The cm scale represents the height of the tracing. Artifacts on injection are volume effects ($\leqslant$0·2 ml, except for the last morphine injection which was 0·4 ml). The ear from which this preparation was made had been denervated 6 days previously.

and of 5-hydroxytryptamine were similar to those in the whole ear (see Table 1) but the effective dose of isoprenaline was increased about a 1,000-fold and that of acetylcholine even more, as no response could be obtained with a dose of 2 mg.

Rabbit venous and arterial strips. Most experiments, over 3,000 observations, were performed on strips of portal vein and thoracic aorta. As shown in Fig. 7, morphine, pethidine, nalorphine and diamorphine caused relaxation of these vessels when administered on the plateau of a moderate contraction produced by phenylephrine. Similar effects occurred if the initial contraction had been elicited by noradrenaline or 5-hydroxytryptamine. The usual ranges of final bath concentrations (μg/ml) to induce vessel relaxation under these conditions were: pethidine, 1–60; nalorphine, 20–1,200; morphine, 100–1,200. Sometimes, on the portal vein, the smaller concentrations of pethidine, morphine or nalorphine could produce contraction either alone or as a prelude to relaxation (for example, for morphine, see Figs. 7, 9A and 11A) and morphine could increase the amplitude of spontaneous activity of the vessel in company with either overall contraction or relaxation.

When administered to strips of portal vein without preliminary contraction (compare Figs. 8B, C, D, 9B and 11B), lower concentrations (usually $1–2 \times 10^{-4}$ g/ml) of morphine produced contraction, often with a marked increase in amplitude, but at higher concentrations ($0{\cdot}5–1 \times 10^{-3}$ g/ml) some relaxation and loss of spontaneous movement most commonly occurred. The uncontracted thoracic aorta responded only to the higher concentrations of morphine and then with a weak relaxation. None of the above effects, contractile or relaxant, due to morphine or pethidine was antagonized by nalorphine, in equal doses, added to the bath 1–4 min previously. Pulmonary arterial strips were at least as sensitive as those from the thoracic aorta and gave similar results. On the other hand, preparations from the pulmonary vein and the posterior caval vein (either thoracic or abdominal—distal to the renal veins) were unresponsive even to noradrenaline, except on one occasion.

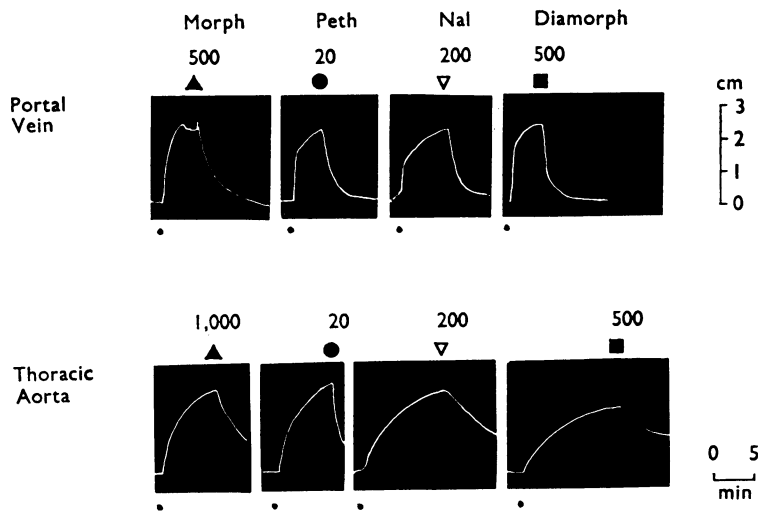

FIG. 7. Effects of administrations (numbers above indicate final bath concentrations in μg/ml) of morphine (Morph, ▲), pethidine (Peth, ●), nalorphine (Nal, ▽) and diamorphine (Diamorph, ■) on spiral strips of rabbit portal vein (upper row) and thoracic aorta following contraction of the vessel with phenylephrine (•, 1×10^{-3} g/ml, final bath concentration) at 30 min intervals.

In this case (after contraction of a strip of the abdominal posterior caval vein by noradrenaline) morphine, pethidine and nalorphine produced relaxation and the latter did not antagonize the effects of an equal dose of morphine or pethidine.

Table 1 shows suitable agonist and 'specific' antagonist concentrations for the portal venous and thoracic aortic preparations. After contraction of the vessels with phenylephrine, these six antagonists blocked the effects of their own agonists but failed to modify the relaxant actions of morphine, pethidine and nalorphine not only when given in the amounts shown in Table 1 (for example, Figs. 8A and 10B, C), but also when given against pethidine or, even, morphine in equal doses. On the uncontracted portal vein, mepyramine (5×10^{-7}–2×10^{-6} g/ml) produced a contraction, often accompanied by an increase in the amplitude of spontaneous movement, and abolished the action of an equal dose of histamine but did not have any effect on the contractile responses to an equal concentration of pethidine, or 1×10^{-4} g/ml morphine (Fig. 8B). However, from 5×10^{-6} g/ml upwards, mepyramine induced contraction of the vein which was invariably accompanied by a decrease in spontaneous activity and, in these higher concentrations, it also antagonized an equal dose of pethidine or 5×10^{-4} g/ml morphine (Fig. 8C, D). The absolute dose of mepyramine, rather than its amount relative to that of pethidine or morphine, appeared to be the necessary factor for antagonism to these substances indicating,

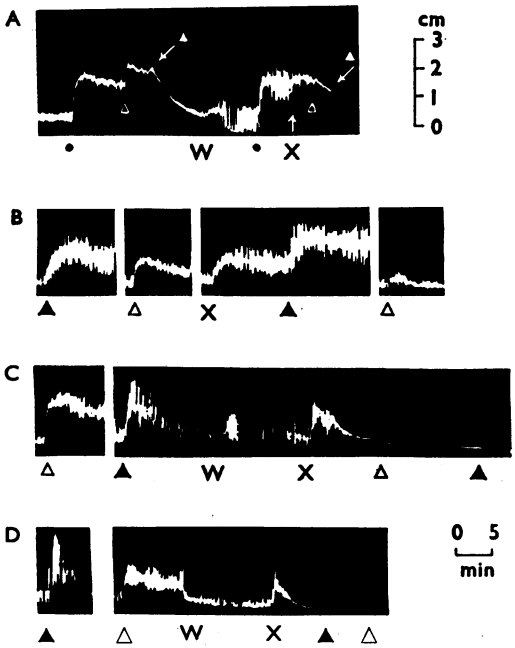

FIG. 8. Mepyramine—morphine antagonism on rabbit portal venous strips. A, Following contraction of the vessel with phenylephrine (•, 1×10^{-8} g/ml, final bath concentration), histamine (△, 5×10^{-7} g/ml) and morphine (▲, upper diagonal arrow, 5×10^{-4} g/ml) were given. The cycle was repeated with the interposition of mepyramine (×, lower vertical arrow, 5×10^{-7} g/ml). B–D, Initially uncontracted venous strip; morphine and histamine before and after mepyramine. Morphine (▲) concentrations were 1×10^{-4} g/ml (B) and 5×10^{-4} g/ml (C and D). Histamine (△) and mepyramine (×) concentrations were equal and were 5×10^{-7} g/ml (B) and 5×10^{-6} g/ml (C and D). The order of the morphine and histamine administrations was opposite in C and D. Time intervals between the two morphine additions in each row were A, 25 min; B, 90 min; C, 48 min; and D, 56 minutes. In B, the last histamine addition was 35 min after the dose of mepyramine. W indicates washout.

in this situation, a non-specific action. Figure 9 shows the effects of a series of increasing concentrations of morphine or histamine applied to the portal vein or thoracic aorta either in the presence or in the absence of phenylephrine. On the contracted preparations (Fig. 9A), the threshold concentration of histamine (5×10^{-8} g/ml) produced contraction of both vessels whilst the threshold concentration of morphine on the vein (1×10^{-4} g/ml) caused venous contraction but did not affect the aorta: intermediate concentrations of histamine and morphine evoked responses from both vessels, the former invariably producing contraction and the latter relaxation: the highest concentrations of histamine relaxed the vessels if given at the end of a cumulative series but, if such concentrations were given immediately after the phenylephrine administration, they caused contraction. Similar results were obtained on the non-contracted vessels (Fig. 9B) except that here histamine was not administered in those high concentrations sufficient to relax the already contracted preparation.

Morphine is an antagonist, albeit much weaker than methysergide, of the contractions produced in both the portal vein (Fig. 10A) and the thoracic aorta by 5-hydroxytryptamine. In nine preparations, the range of concentration ratios (an-

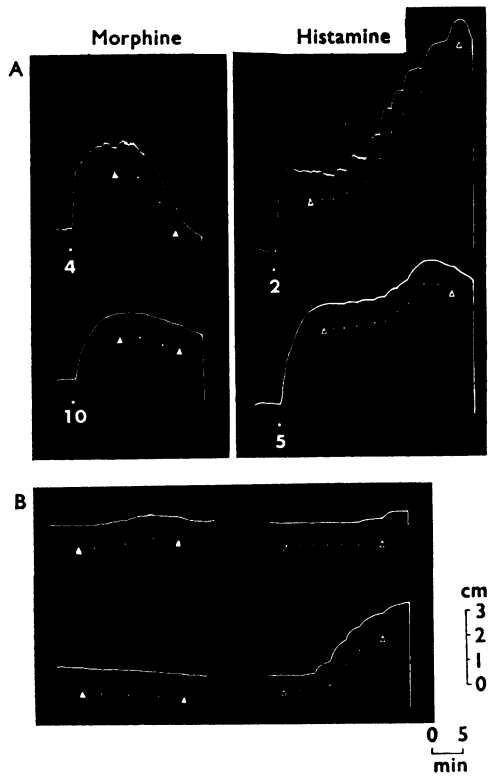

FIG. 9. Effects of gradually increasing concentrations (from threshold) of morphine (▲——▲, including intervening dots) and histamine (△——△, including intervening dots) on the portal vein (upper tracing of each vertical pair) and thoracic aorta (lower tracing) applied either alone (B) or following contraction of the vessels (A) with phenylephrine (numbered white dots, number indicates final bath concentration $\times 10^{-8}$ g/ml). Successive concentrations were: morphine, A, 1×10^{-4}, 2×10^{-4}, 2×10^{-4} and 4×10^{-4} g/ml; B, 5×10^{-5}, 1, 2 and 5×10^{-4} and 1×10^{-3} g/ml: histamine, A, 1, 2 and 5×10^{-8}, 1, 2 and 5×10^{-7}, 1×10^{-6}, 1×10^{-5}, 1, 2 and 4×10^{-4} g/ml; B, 1×10^{-8}, 1, 2 and 5×10^{-7}, 1, 2 and 5×10^{-6} g/ml. Vertical lines at right edges of tracings indicate washout.

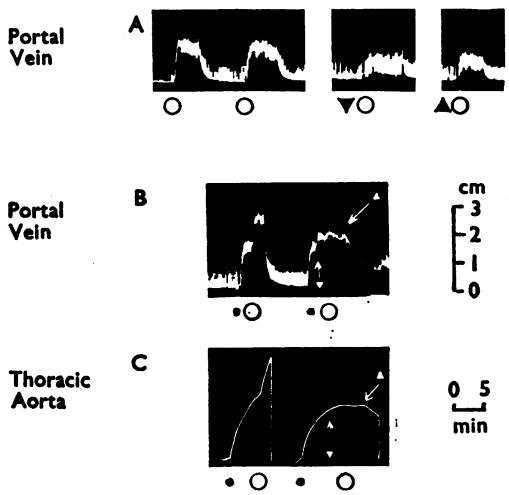

FIG. 10. 5-Hydroxytryptamine-morphine interactions on rabbit vessel strips. A, Strip of portal vein. Antagonism of 5-hydroxytryptamine (○, 1×10^{-7} g/ml, final bath concentration) contractions, given every 10 min, by either methysergide (▼, 1×10^{-7} g/ml) or morphine (▲, 2×10^{-6} g/ml) given 90 s previously. B, Strips of portal vein and C, strips of thoracic aorta. Following contraction of the vessel with phenylephrine (•, 1×10^{-8} g/ml), a concentration of 5-hydroxytryptamine (○, 1×10^{-7} g/ml to the vein, 5×10^{-8} g/ml to the aorta) was applied; in the next cycle, methysergide (▼, lower vertical arrow, 1×10^{-6} g/ml) was given before and morphine (▲, upper diagonal arrow 5×10^{-4} g/ml) after the 5-hydroxytryptamine.

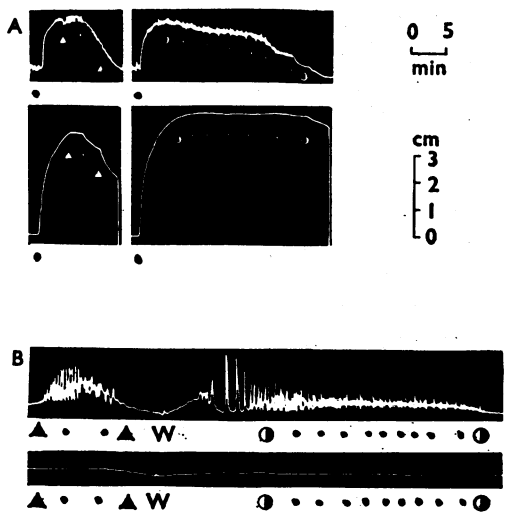

FIG. 11. Effects of gradually increasing concentrations of morphine (▲——▲, including intervening dots) and vasopressin (◑——◑, including intervening dots) on the portal vein (upper tracing of each vertical pair) and thoracic aorta (lower tracing) applied either alone (B) or following contraction of the vessels (A) with phenylephrine (•, 2×10^{-8} g/ml, final bath concentration). Successive concentrations were: morphine, A, 2, 5 and 10×10^{-4} g/ml; B, the same followed by 2×10^{-3} g/ml: vasopressin, A, 0·1, 0·5, 2, 10, 40, 100, 200 and 400 mU/ml; B, 1 (sic), 0·1, 0·2, 0·5, 1, 2, 5, 10, 20, 40 and 100 mU/ml. W indicates washout.

tagonist: 5-hydroxytryptamine) to abolish the agonist responses in both vessels were: methysergide, 1–20:1; morphine, 50–200:1. Following phenylephrine contraction of either vessel, the relaxant effects of morphine could still be elicited after a dose of methysergide which blocked completely the contractions caused by 5-hydroxytryptamine (Fig. 10B, C) or, even, after a concentration of methysergide equal to that of the morphine (*vide supra*).

A comparison of the effects of morphine and vasopressin on the vessel strips is shown in Fig. 11. When given alone to the preparations (Fig. 11B), morphine produced an initial contraction with a greatly augmented amplitude of spontaneous movement at a threshold concentration (2×10^{-4} g/ml) on the vein and caused relaxation in both vessels at $1–2 \times 10^{-3}$ g/ml, while a series of concentrations of vasopressin caused a progressive decrease in the spontaneous activity of the vein but had no effect on the aorta. When given to vessels already contracted by phenylephrine, as shown in Fig. 11A, morphine produced contraction initially in the vein and, at higher concentrations ($0{\cdot}5–1 \times 10^{-3}$ g/ml), relaxation in both vessels whereas vasopressin relaxed the vein and artery from thresholds of 100 and 200 mU/ml, respectively.

Discussion

In the anaesthetized cat we found, like previous workers, that 0·1–10 mg/kg of morphine, pethidine, diamorphine and nalorphine, given intravenously, could produce one or more facets of a triphasic response on the blood pressure. These were, namely, a transient pressor effect and a more durable depressor phase which, at high doses, was preceded by a sharp, immediate fall of pressure. The most common order of potency was diamorphine>morphine>pethidine$\gg$nalorphine. Although the rabbit anaesthetized with urethane gave similar results with all these drugs, it was less sensitive by up to one order of magnitude and, occasionally, even less responsive, as found by Schmidt & Livingston (1933) for the rabbit under ether. Like all previous workers, we found that the initial dose of morphine induced a prolonged hyposensitivity and, therefore, pethidine and diamorphine, which showed only short periods of tachyphylaxis, were preferred for analytical procedures in the whole animal.

Catecholamine liberation was undoubtedly involved in the pressor phases of action produced by pethidine and diamorphine, as these responses were abolished by adrenal vessel ligation. However, the same manoeuvre could also potentiate the depressor phase, especially if the blood pressure was high (so that vasodilation —*vide infra*—could manifest itself more readily), which suggests that catecholamine liberation was also occurring over a significant period of the more prolonged response. The same conclusion might be drawn from the observation that, on one occasion, nalorphine reversed the depressor effect of pethidine. Evans *et al.* (1952) obtained direct evidence of catecholamine release from the adrenal medulla by morphine in the cat and, as the initial rise of blood pressure can be very marked in spinal cats (Kalyaalp & Kaymakçalan, 1966), any reflex or central contribution to the mechanism is not essential.

The gradual development of tachyphylaxis to the pressor response of morphine can be ascribed to a continuous depletion of the adrenal medulla by sympathetic activation (Outschoorn, 1952) and repeated administration of morphine and its allies,

possibly in association with hyposensitization to adrenaline and noradrenaline (Contreras & Huidobro, 1970). The fact that we have never seen any significant change in heart rate accompanying the blood pressure effects produced by morphine, pethidine, diamorphine and nalorphine, even when the heart has been observed to be contracting more forcibly in a thoracotomized cat, might appear to argue against any participation of adrenal medullary hormones in the responses. However, the direct effect of adrenaline on cardiac frequency can be ' reflexly antagonized via the baroreceptor mechanism during infusion into the intact animal at rates which raise systemic arterial pressure' (Haddy & Scott, 1966). Further, the adrenal medullary outputs (resting (0·1 μg/kg)/min and strongly reflexly activated (2–3 μg/kg)/min) quoted by Mellander & Johansson (1968) for the cat indicate that the dose of adrenaline (400 ng/kg) which we used to mimic the pressor element of the pethidine response (Fig. 1) was rather low and we found that a single intravenous dose up to 2 μg/kg adrenaline did not produce any change in heart rate. Except at very high rates of intravenous infusion, adrenaline causes a fall in total peripheral resistance in the intact animal (Haddy & Scott, 1966), which might be offset, or even over-compensated, by the marked vasoconstriction due to the noradrenaline content of the adrenal medullary secretion. So, the initial rise in blood pressure produced by morphine and its allies must be considered to be mediated by the liberation of adrenal medullary hormones which then, possibly, increase the total peripheral resistance but certainly exert a positive inotropic effect. We have observed this increased force of cardiac contraction directly in the thoracotomized cat following 5 mg/kg pethidine, diamorphine or morphine, given intravenously. Such a dose, resulting in the immediate passage of about 750 μg through the coronary circulation of a 3 kg cat, is within the range for depression of the isolated guinea-pig heart (which, according to Schmidt & Livingston (1933), has a similar sensitivity to morphine as the heart of the cat) by pethidine and diamorphine and above our range for transient stimulation by morphine (but see Gruber & Robinson, 1929). A contribution to the pressor effect by direct cardiac stimulation due to morphine or its allies is, therefore, improbable.

The effects of histamine on the blood pressure (Rocha e Silva, 1966) are species specific—characteristically producing, in the cat, a depressor response which may be interrupted by a rise in pressure due to sympathetico-adrenal discharge and constriction of the large vessels (arterial and venous), and in the rabbit a pressor response due to overall vasoconstriction, gradually reverting, as the dose is increased, to a hypotensive effect caused by the excessive pulmonary vasoconstriction lowering left ventricular output—and can also vary with the type of anaesthesia, in different animals and, as we noted, in an individual animal with time. These actions are in many ways similar to those produced by morphine and its allies on the cardiovascular systems of the cat and the rabbit, and there is little doubt that histamine can be implicated in the responses under discussion. Feldberg & Paton (1951) showed that there was an increase in the plasma histamine at an early stage of the prolonged depressor response produced by 2·4 mg/kg morphine in a cat anaesthetized with chloralose, and Van Arman & Sturtevant (1958) showed a similar effect during the fall of blood pressure following a dose of 4 mg/kg pethidine to a dog under pentobarbitone. Whilst Van Arman & Sturtevant (1958) could block their depressor response with diphenhydramine (dose not stated), Feldberg & Paton (1951) and Evans *et al.* (1952) found mepyramine ineffective. Undoubtedly, part of this difficulty is due to the large dose of mepyramine required, as Kayaalp &

Kaymakçalan (1966) have shown; but even they, using 10 mg/kg mepyramine, could only block the transient response to 3 mg/kg morphine (in a nalorphine-treated cat), and this suggests that histamine is not greatly implicated in the prolonged depressor response.

In fine it is our opinion that the immediate depressor effects are in large part due to histamine but that this substance makes little contribution to the prolonged hypotensive effect seen especially with higher doses. The evidence for this standpoint is as follows. The effects of a relatively low dose of pethidine (1 mg/kg) can be simulated both in respect of blood pressure and E.C.G. by a mixture of adrenaline and histamine, and the depressor phase can be blocked by a very large dose of mepyramine (Van Arman & Sturtevant, 1958); our dose was obviously inadequate. Histamine can, of course, cause the liberation of catecholamines in the cat but as morphine and its congeners usually produced pressor effects before depressor effects, they are unlikely to be indirectly activating the adrenal medulla via histamine. It is unnecessary to postulate that the endogenous histamine released by morphine is only antagonized with difficulty and by a great excess of mepyramine because it is liberated very close to the receptor, since exogenously administered histamine also requires large doses of the antihistamine and even then may not be fully antagonized. The slight heart dilation observed when 5 mg pethidine was given to a thoracotomized rabbit weighing 2 kg is not considered to be due to pulmonary vasoconstriction secondary to histamine release for two reasons. First, pethidine effects are consistent with the liberation of about one-thousandth of its dose of histamine (see Figs. 1 and 3); that is, 5 mg pethidine produces a depressor effect similar to about 5 μg histamine: this dose of histamine is far too low to produce sufficient pulmonary vasoconstriction to cause a fall of blood pressure in most rabbits. Second, of 5 mg pethidine given intravenously about one-twentieth, that is 250 μg, would immediately pass through the coronary circulation and this dose, in the perfused guinea-pig heart produces a marked myocardial depression. The latter is the most likely cause of the slight cardiac dilation seen in the rabbit following a 2·5 mg/kg dose of pethidine.

With regard to the significance of histamine liberation during the prolonged depressor phase, we agree with Feldberg & Paton (1951), who consider that ' Release of histamine into the blood stream therefore can account only partly for the depressor action of morphine '. Most workers, including ourselves, find little evidence of antagonism by mepyramine of the prolonged depressor action due to the larger doses of morphine and, more significantly, Kayaalp & Kaymakçalan (1966) found 2–4 mg/kg morphine given to cats treated with 10 mg/kg mepyramine to cause a slowly developing fall of blood pressure. On the negative side, there is some evidence (*vide infra*) that the prolonged depressor phase is due to direct peripheral vasodilation with a possible contribution from cardiac depression at extremely high doses. Tachyphylaxis to the immediate depressor action could be due to histamine depletion, and the lessening of the prolonged hypotensive phase with time due to a gradual decrease in blood pressure making the drug induced vasodilation less effective (although, see **Introduction**, Schmidt & Livingston (1933) still found hyposensitivity after artificial restoration of the blood pressure). The depressor effects might not be compensated so well as in the conscious animal owing to depression of the vasomotor centre either by the anaesthetic or by morphine (Evans *et al.*, 1952; Kayaalp & Kaymakçalan, 1966).

As in man (see **Introduction**), it was found that in the cat and the rabbit, while nalorphine did not generally prevent the cardiovascular effects of a subsequent injection of pethidine, diamorphine or, probably, morphine to any marked degree, it could antagonize quite efficiently the prolonged depressor phase produced by any one of these substances. Similar observations have been made by Kayaalp & Kaymakçalan (1966) and Martin & Eisenman (1962). As the antagonism still occurs in artificially respired cats, the cardiovascular improvement is not wholly due to respiratory amelioration. The facts that the depressor antagonism was preceded by a small hypotensive response and that nalorphine alone is usually a much less potent effector than morphine, pethidine and diamorphine on the cardiovascular system, suggest that antagonism is due to a weak agonist action. Pentazocine probably has a similar effect. On the isolated guinea-pig heart, nalorphine also shows weak agonist action—improving the amplitude of contraction depressed by pethidine, but having little effect if given beforehand.

The prolonged depressor effects of morphine, pethidine, diamorphine and nalorphine could be caused by changes in heart action and/or peripheral resistance. Let us examine the cardiac effects first. For pethidine or diamorphine, a suitable dose to produce prolonged hypotension is 5 mg/kg, which, in a 3 kg cat, would give an immediate dose of 750 μg round the coronary circulation—quite sufficient to cause a marked decrease in the amplitude of cardiac contraction in the isolated guinea-pig heart. This effect could contribute to the prolonged hypotension produced by pethidine or diamorphine. Morphine is much more benign on the heart (Gruber & Robinson, 1929 ; Thorp, 1949). Schmidt & Livingston (1933), using a myocardiograph and a cardiometer on a dog heart *in situ*, showed that there was no significant diminution in strength or output of the heart at the height of the depressor response to 2 mg/kg morphine. They concluded that the myocardial depressant action of morphine was not a prominent feature in the whole animal unless large or repeated doses had been administered. I agree with this conclusion and confirm that high doses produced bradycardia and cardiac irregularities not only with morphine but also with pethidine and diamorphine.

The extent to which the peripheral vasodilation produced by morphine in the anaesthetized animal is due to central vasomotor depression can be determined to some extent by high spinal section but it must be remembered that the absence or diminution of the depressor response subsequently does not necessarily prove the original involvement of a central effect, as the lower vasomotor tone in the spinal animal would render a peripheral vasodilator less effective. Nevertheless, Evans *et al.* (1952) and Kayaalp & Kaymakçalan (1966) consider depression of the vasomotor centre to be an important element in the depressor response to morphine. I have not studied this particular aspect of the problem, but can state unequivocally that even if it does occur, it is not the only factor. Peripheral vasodilation undoubtedly occurs in the perfused cat hind limb and it is active in nature as it is unaccompanied by any rise in the systemic blood pressure. This confirms the plethysmographic findings of Schmidt & Livingston (1933) on the cat hind limb which increased in volume during the depressor effect of an intravenous injection of morphine or, following intraarterial injection into the leg, in the absence of any marked change of blood pressure. These effects were uninfluenced by acute denervation of the limb as also were those of Gruber, Hart & Gruber (1941) who noted an increased volume of the dog leg concurrently with the hypotensive response to 5 mg/kg pethidine. I found no difference between the effects on skinned and non-skinned limbs

indicating that possibly skin and, certainly, skeletal muscle vessels are involved in the vasodilation. The possibility that histamine might have been implicated in this response was not eliminated. However, on the perfused rabbit ear, the vasodilation produced by pethidine, morphine or nalorphine was not antagonized by a dose of mepyramine which completely blocked the effects of exogenous histamine. Further, if the dilator effect of morphine and its allies is due to the liberation of endogenous histamine not susceptible to antagonism by mepyramine, how is this explicable when histamine produces vasoconstriction in this preparation whether injected alone or during a vasoconstrictor infusion, whether in low or in high doses? The vasodilator actions of pethidine and nalorphine were not modified, nor that of morphine prevented, by antagonists for α- or β-adrenoceptors or muscarinic cholinoceptors. The well known antimuscarinic and antihistaminic actions of pethidine (Schild, 1947) were confirmed: nalorphine also appeared to have a slight action against histamine. Methysergide and morphine were equally 'specific' as 5-hydroxytryptamine antagonists, the effective dose of either being about 4,000 times the agonist dose. The perfused rabbit ear artery, whilst as sensitive as the whole ear to vasoconstrictors, showed less responsiveness to morphine and its allies, isoprenaline and acetylcholine by factors of ten, a thousand and greater than four thousand, respectively. Such a wide variation in the responses to vasodilator agents suggests that it is not only a difference in background constrictor tone which is affecting the sensitivity but also, that morphine is dilating the artery less than the other components of the peripheral circulation. This would be in keeping with the observation that the hypotension due to morphine and pethidine is exacerbated by head-up tilting or haemorrhagic shock (see **Introduction**) which suggests marked venodilation.

Whilst the pulmonary artery provided a useful alternative to the thoracic aorta, at least for the drugs used in the present investigation, we found the pulmonary and posterior caval veins to respond very poorly, if at all. The relaxation by morphine, pethidine, diamorphine and nalorphine of strips of portal vein or thoracic aorta is shown best, as in other preparations, on a background of vasoconstrictor tone. The effects of morphine or pethidine are not antagonized by concentrations (equal in amount to those of morphine or pethidine, respectively) of phentolamine, propranolol, atropine, pentolinium, mepyramine or methysergide. There is no evidence that morphine acts directly upon α- or β-adrenoceptors. On the cholinergic side, the effects of nicotine are complex (Hughes & Vane, 1970) whilst acetylcholine causes contraction of either vessel when given alone but can relax vessels which have been fairly strongly contracted by phenylephrine. Morphine or pethidine, on the whole, would need to mimic acetylcholine, an action which is opposite to the usual depressant effects of morphine at cholinergic synapses (Paton, 1957; Schaumann, 1957; Kosterlitz & Taylor, 1959; Kennedy & West, 1967) or the antimuscarinic effects of pethidine.

In relation to histamine receptors, morphine has been preferred to pethidine because of the known antihistamine action of the latter. One suggestion is that morphine relaxes the vessel strips via the intermediation of histamine. Mepyramine abolishes the response to an equal dose of histamine yet at 1,000 times this dose (that is, equal to the morphine concentration) mepyramine does not affect the response to morphine. But this is not conclusive, since the histamine liberated endogenously by morphine may, for some reason, be resistant to mepyramine

blockade. However, exogenous and endogenous histamine must have similar qualitative effects and, therefore, if morphine and exogenous histamine have qualitatively different actions, morphine cannot be acting solely by liberating the autacoid. This is the case. On the perfused rabbit ear and on the two vessel strips, morphine and histamine have diametrically opposite major actions. There are two superficial similarities but these are fallacious. First, a huge dose of histamine, given at the end of a series of doses to a strip of portal vein initially contracted with phenylephrine, can cause relaxation. This is due to desensitization, however, as when such a dose is given first in the series, that is, immediately after the phenylephrine, it produces contraction. Second, the lowest effective concentration of morphine on the portal vein, alone or after phenylephrine, can produce contraction like histamine, but at this same concentration the effects of morphine and histamine on the thoracic aortic strips are almost invariably exactly opposite.

Gyermek (1961) suggested that morphine might act by antagonizing tone due to endogenous 5-hydroxytryptamine. There is no evidence that such tone exists in the isolated vessel strip. However, in the whole animal, circulating (hormonal) 5-hydroxytryptamine could act on vascular receptors and this effect be antagonized by morphine. This action would be via receptors for exogenous 5-hydroxytryptamine. Such receptors do exist in the preparations used in this study but how specific they are for 5-hydroxytryptamine and how homogeneous among themselves is problematical. For example, Savini (1956) on the perfused rabbit ear found lysergic acid diethylamide, but not morphine, to be an effective antagonist of 5-hydroxytryptamine with a negligible action against adrenaline and noradrenaline. On the other hand, using the rabbit thoracic aorta, Wurzel (1966) showed that both lysergic acid diethylamide and morphine were ineffective against 5-hydroxytryptamine. Our experiments indicate that methysergide, whilst of similar potency to morphine as a 5-hydroxytryptamine antagonist on the perfused rabbit ear (*vide supra*), is a much more specific inhibitor of 5-hydroxytryptamine action on the portal vein and thoracic aorta but that even when present in large doses it fails to prevent the relaxant action of morphine on these two vessel strip preparations.

On all the above evidence, it is considered that morphine, and probably pethidine, diamorphine and nalorphine, exert their relaxant and vasodilator effects on the isolated preparations studied independently of mechanisms related to known peripheral transmitters and tissue autacoids, although some mode of action which might be relatively non-specific with regard to receptors, for example, membrane stabilization, has not been precluded.

Sutter (1965) found vasopressin to be without effect on the rabbit portal vein at up to 100 mU/ml ; Hughes & Vane (1967) obtained relaxation with 10–100 mU/ml. I confirm the latter action, which can also be shown on the vein contracted with phenylephrine under which condition higher concentrations of vasopressin also relax the thoracic aorta. The most interesting observation with vasopressin, however, was that it caused a decrease in the amplitude of the spontaneous movement of the uncontracted portal vein. This is the exact opposite of morphine which, usually near threshold, regularly increased this spontaneous movement, even on occasions whilst relaxing the vessel following phenylephrine. This phenomenon may well be the key to the mode of action of morphine which, however, for the moment must remain a member of the heterogeneous group, the direct peripheral vasodilators.

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REFERENCES

CONTRERAS, E. & HUIDOBRO, F. (1970). Hyposensitivity to drugs induced by morphine and some related substances in the cat. *Br. J. Pharmac.*, **39**, 789–797.

ECKENHOFF, J. E. & OECH, S. R. (1960). The effects of narcotics and antagonists upon respiration and circulation in man. *Clin. Pharmac. Ther.*, **1**, 483–524.

EVANS, A. G. J., NASMYTH, P. A. & STEWART, H. C. (1952). The fall of blood pressure caused by intravenous morphine in the rat and the cat. *Br. J. Pharmac. Chemother.*, **7**, 542–552.

FELDBERG, W. & PATON, W. D. M. (1951). Release of histamine from skin and muscle in the cat by opium alkaloids and other histamine liberators. *J. Physiol., Lond.*, **114**, 490–509.

FOGELMAN, F. & GRUNDY, H. F. (1970). A comparison of the cardiovascular actions of AQ 110 with those of isoprenaline and salbutamol. *Br. J. Pharmac.*, **38**, 416–432.

GRUBER, C. M., HART, E. R. & GRUBER, C. M. jun. (1941). The pharmacology and toxicology of the ethyl ester of 1-methyl-4-phenyl-piperidine-4-carboxylic acid (Demerol). *J. Pharmac. exp. Ther.*, **73**, 319–334.

GRUBER, C. M. & ROBINSON, P. I. (1929). Studies on the influence of morphine, papaverine and quinidine upon the heart. *J. Pharmac. exp. Ther.*, **37**, 429–449.

GRUNDY, H. F. (1968). The actions of morphine, pethidine and nalorphine on some blood vessel preparations. *Br. J. Pharmac.*, **34**, 208–209*P*.

GYERMEK, L. (1961). 5-Hydroxytryptamine antagonists. *Pharmac. Rev.*, **13**, 399–439.

HADDY, F. J. & SCOTT, J. B. (1966). Cardiovascular pharmacology. *A. Rev. Pharmac.*, **6**, 49–76.

HILTON, S. M. (1952). A perspex drop-chamber. *J. Physiol., Lond.*, **117**, 48–49*P*.

HUGHES, J. & VANE, J. R. (1967). An analysis of the responses of the isolated portal vein of the rabbit to electrical stimulation and to drugs. *Br. J. Pharmac. Chemother.*, **30**, 46–66.

HUGHES, J. & VANE, J. R. (1970). Relaxations of the isolated portal vein of the rabbit induced by nicotine and electrical stimulation. *Br. J. Pharmac.*, **39**, 476–489.

KAYAALP, S. O. & KAYMAKÇALAN, S. (1966). A comparative study of the effects of morphine in unanaesthetized and anaesthetized cats. *Br. J. Pharmac. Chemother.*, **26**, 196–204.

KENNEDY, B. L. & WEST, T. C. (1967). Effect of morphine on electrically-induced release of autonomic mediators in the rabbit sinoatrial node. *J. Pharmac. exp. Ther.*, **157**, 149–158.

KOSTERLITZ, H. W. & TAYLOR, D. W. (1959). The effect of morphine on vagal inhibition of the heart. *Br. J. Pharmac. Chemother.*, **14**, 209–214.

MARTIN, W. R. & EISENMAN, A. J. (1962). Interactions between nalorphine and morphine in the decerebrate cat. *J. Pharmac. exp. Ther.*, **138**, 113–119.

MELLANDER, S. & JOHANSSON, B. (1968). Control of resistance, exchange, and capacitance functions in the peripheral circulation. *Pharmac. Rev.*, **20**, 117–196.

OUTSCHOORN, A. S. (1952). The hormones of the adrenal medulla and their release. *Br. J. Pharmac. Chemother.*, **7**, 605–615.

PATON, W. D. M. (1957). The action of morphine and related substances on contraction and on acetylcholine output of coaxially stimulated guinea-pig ileum. *Br. J. Pharmac. Chemother.* **12**, 119–127.

ROCHA E SILVA, M. (1966). Action of histamine upon the circulatory apparatus. In: *Handbook of Experimental Pharmacology*, Vol. XVIII/I, pp. 238–293. Berlin: Springer.

SAVINI, E. C. (1956). The antagonism between 5-hydroxytryptamine and certain derivatives of lysergic acid. *Br. J. Pharmac. Chemother.*, **11**, 313–317.

SCHAUMANN, W. (1957). Inhibition by morphine of the release of acetylcholine from the intestine of the guinea-pig. *Br. J. Pharmac. Chemother.*, **12**, 115–118.

SCHILD, H. O. (1947). pA, A new scale for the measurement of drug antagonism. *Br. J. Pharmac. Chemother.*, **2**, 189–206.

SCHMIDT, C. F. & LIVINGSTON, A. E. (1933). The action of morphine on the mammalian circulation. *J. Pharmac. exp. Ther.*, **47**, 411–441.

SUTTER, M. C. (1965). The pharmacology of isolated veins. *Br. J. Pharmac. Chemother.*, **24**, 742–751.

THORP, R. H. (1949). The pharmacology of the optical isomers of amidone (2-dimethylamino-4: 4-diphenylheptan-5-one). *Br. J. Pharmac. Chemother.*, **4**, 98–104.

VAN ARMAN, C. G. & STURTEVANT, F. M. (1958). Release of histamine by meperidine. *Fedn Proc.*, **17**, 416.

WURZEL, M. (1966). Serotonin receptor in rabbit artery. *Am. J. Physiol.*, **211**, 1424–1428.

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