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A comparison of the effects of morphine and pethidine upon body temperature and the reversal of reserpine's effects upon body temperature in the mouse

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The effects of morphine and pethidine upon body temperature and upon the reversal of reserpine hypothermia in the mouse were investigated. Both morphine and pethidine produced a dose-dependent fall in body temperature, that of morphine being totally antagonized by nalorphine and partially by naloxone, while that of pethidine was antagonised by naloxone and enhanced by nalorphine. Both drugs reversed reserpine-induced hypothermia. The reversal by morphine, but not by pethidine, was partially antagonized by naloxone. Adrenalectomy prevented the reversal of reserpine hypothermia by pethidine but morphine produced a partial reversal. Ganglion blockade and α-and β-blockade all prevented reversal of reserpine hypothermia by both drugs. The results are discussed with regard to differences between pethidine and morphine and possible involvement of opiate receptors.

Although the details remain controversial, it is clear that the antinociceptive activity of morphine involves systems also affected by 5-hydroxytryptamine (5-HT) and catecholamines (Way & Fu-Hsuing Shen, 1971). However, the involvement of 5-HT in the antinociceptive activity of pethidine is more debatable (Samanin, Ghezzi & others, 1973). In mice the difference between the antinociceptive activity of pethidine and morphine were most clearly demonstrated in interaction with 5-hydroxytryptophan and reserpine (Pleuvry, 1975).

The present study was designed to determine whether differences between pethidine and morphine extended to other systems believed to involve catecholamines and 5-HT. Regulation of body temperature has been ascribed to a balance of 5-HT and catecholamines in the hypothalamus (Feldberg & Myers, 1963) and reversal of reserpine-induced hypothermia has been ascribed to restoration of monoamine balance either centrally or peripherally (Cooper, 1971; Whittle, 1967). Thus we have compared the effects of pethidine and morphine on the body temperature of the mouse and on reserpine-induced hypothermia, which is reversed, in the mouse by morphine (Whittle, 1967).

METHODS AND MATERIALS

Male and female albino mice, 25–30 g, were allowed free access to food and water up to the time of experiment, and were kept at an ambient temperature of 21–22°. To investigate the effects of drugs on reserpine reversal, mice were injected with reserpine 18 h before injection of drugs under investigation.

Animals for adrenalectomy were anaesthetized with ether and adrenalectomized according to Griffiths & Farris (1942), 48 h before investigation. Control animals were prepared by carrying out the operative procedure, but not removing the adrenals. Adrenalectomized animals were given a normal diet, but drinking water was substituted with glucose in 0·9% saline. A control group given a saline injection was used with each set of drugs under investigation. All drugs were administered by intraperitoneal injection. Core temperature was measured in the oesophagus (Gerbrandy, Snell & Cranston, 1954) before the drugs were injected, and at 15 or 30 min intervals, using a thermistor (Light Laboratories, Brighton). Results are expressed as mean ± standard error and significance was calculated using the Student's *t*-test.

Drugs used were: pethidine hydrochloride (30–60 mg kg^{-1}) (Roche Laboratories); morphine hydrochloride (10–20 mg kg^{-1}) (MacFarlane Smith); naloxone hydrochloride (1–10 mg kg^{-1}) (Endo Laboratories Ltd); nalorphine hydrobromide (5–20 mg kg^{-1}) (Burroughs Wellcome & Co.); reserpine (2–5 mg kg^{-1})(BDH); propranolol hydrochloride (10 mg kg^{-1}) (May & Baker Ltd); phenoxybenzamine (30 mg kg^{-1}) (Smith, Kline & French).

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Reserpine was dissolved in a minimal quantity of glacial acetic acid and diluted to 500 μg ml^{-1} with distilled water (final pH 5·3). All other drugs were dissolved in saline. Doses in the text refer to salts.

RESULTS

Effects of pethidine and morphine on control mice

Both pethidine and morphine produce a fall in body temperature, maximal at 30 minutes with both, but more prolonged with pethidine at all dose levels (Table 1). The temperature of the saline controls dropped slowly by one degree during the experiment.

Table 1. *Effects of pethidine and morphine on the oesophageal temperature of the mouse.*

	Dose mg kg^{-1}	Maximum drop in temp. Δ °C	Duration of significant drop (min)
Pethidine	30	1·7 ± 0·4	90 min +
	45	2·8 ± 0·3	105 +
	60	3·1 ± 0·2	150
Morphine	10	1·1 ± 0·2	30
	20	2·1 ± 0·3	75

All results are mean ± standard error of at least 6 determinations.

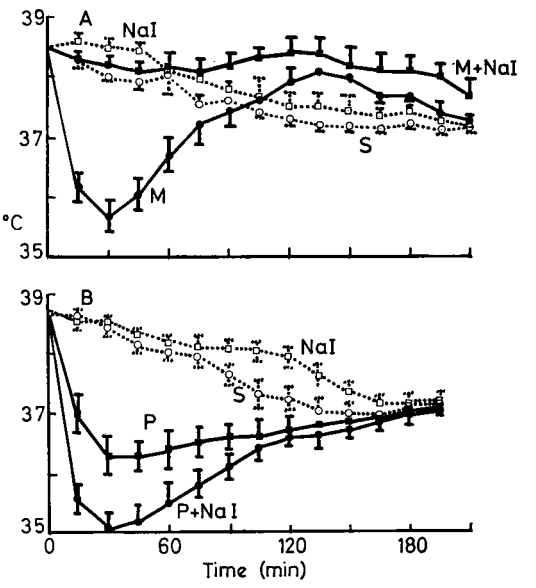

FIG. 1. The effects of nalorphine, 10 mg kg^{-1} (NaI) upon the hypothermic response of mice to: A. Morphine 20 mg kg^{-1} (M). B. Pethidine 45 mg kg^{-1} (P). Values for concurrently tested saline treated control mice (S) are included for comparison. Results are means ± standard errors of not less than 12 experiments. In these experiments nalorphine was injected at the same time as the analgesics. y axis—Oesophageal temperature (°C).

Naloxone, 1–10 mg kg^{-1}, did not significantly alter the temperature change when administered coincidentally with pethidine at any dose level. When given 15 min before pethidine 45 mg kg^{-1}, it decreased the fall in temperature ($P < 0{\cdot}05$) from 45 to 75 min after injection. This effect could not be prolonged by giving a second dose of naloxone.

Naloxone 1 mg kg^{-1} delayed the initial fall in temperature found when morphine was administered (at 15 min $P < 0{\cdot}02$ with 10 mg kg^{-1}, $P < 0{\cdot}005$ with 20 mg kg^{-1}), but the extent of the drop was the same. The effect could not be prolonged by giving a second dose of naloxone. However, naloxone, 10 mg kg^{-1}, markedly diminished the fall in temperature, as did naloxone 1 mg kg^{-1} given 15 min before morphine. Naxloxone alone, 1–10 mg kg^{-1}, had no significant effects upon body temperature in control mice.

Nalorphine, 10 mg kg^{-1}, increased the temperature drop with pethidine, 45 mg kg^{-1}, but completely prevented the fall associated with morphine, 20 mg kg^{-1} (Fig. 1). Similar results were found with nalorphine, 5 and 20 mg kg^{-1}. In some experiments nalorphine, slowed the normal fall in body temperature seen in control mice (Fig. 1 A). This was not a consistent finding however (Fig. 1 B) and it was not significant if results from 48 mice were bulked.

Effects of pethidine and morphine on body temperature in reserpinized mice

Mice which had been given reserpine, 5 mg kg^{-1}, were found to have body temperatures in the range 23°–25° 18 h later. Morphine and pethidine were equally effective in reversing this hypothermia (Fig. 2). The temperature of control animals rose by 1–2°.

Naloxone, 1 mg kg^{-1}, partially inhibited the reversal by morphine (Fig. 3) but inhibition could not be made complete by increasing the dose of naloxone to 10 mg kg^{-1} or by giving a second dose of naloxone. Naloxone had no effect on the reserpine reversal by pethidine and did not produce any reserpine reversal when given alone.

Effects of adrenalectomy on reserpine reversal

Adrenalectomized mice became markedly hypothermic when given reserpine 2 mg kg^{-1}, a dose which produced a fall of only 3°–4° in sham operated animals. Adrenalectomy prevented the normal rise in body temperature produced by handling and

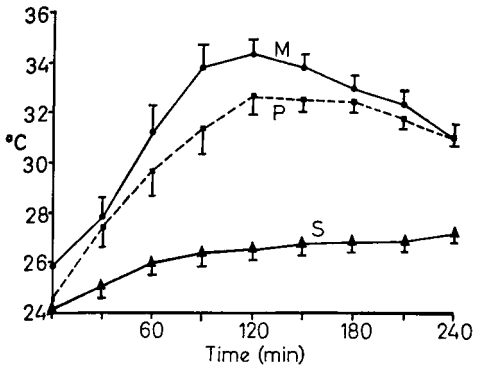

FIG. 2. The effects of morphine 20 mg kg^{-1} (M) and pethidine 45 mg kg^{-1} (P) upon the oesophageal temperature (°C) of mice pretreated with 5 mg kg^{-1} resperine for 18 h. Results are expressed as means ± standard error of not less than 12 experiments. Control animals given reserpine and saline (S) are shown for comparison.

completely prevented reversal of the hypothermia by pethidine. Morphine, 20 mg kg^{-1}, produced a partial reversal (Fig. 4) in reserpinized adrenalectomized mice.

Effects of propranolol, phenoxybenzamine and pentolinium on reserpine reversal

Reserpinized mice given propranolol, 10 mg kg^{-1}, or pretreated with phenoxybenzamine, 30 mg kg^{-1}, or pentolinium, 5 mg kg^{-1}, showed complete inhibition of the reserpine reversal of both morphine and pethidine (Table 2). All drugs prevented the rise in temperature found with handling, and control mice treated with the drugs were found to have

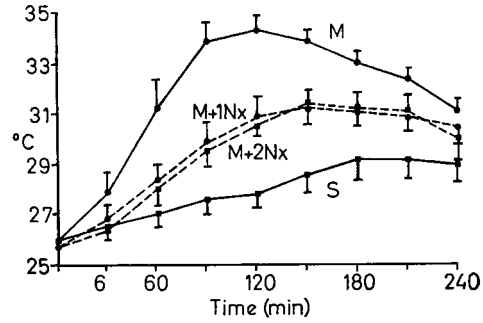

FIG. 3. The effects of one (1N×) or two (2N×) doses of naloxone 1 mg kg^{-1} upon the reversal of reserpine hypothermia by morphine 20 mg kg^{-1} (M). The first dose of naloxone was administered at time 0 and the second at 60 min after morphine injection. Results are means ± standard error of not less than 12 experiments. All mice were pretreated with 5 mg kg^{-1} reserpine for 18 h. y axis—Oesophageal temperature (°C).

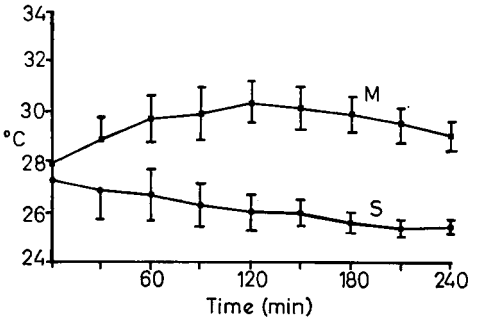

FIG. 4. The effects of morphine (M) 20 mg kg^{-1} upon the oesophageal temperature (°C) of adrenalectomized mice pretreated with 2 mg kg^{-1} reserpine for 18 h. The effects of saline (S) are shown for comparison. Results are expressed as means ± standard error of not less than 12 experiments.

temperatures lower than control mice given saline. Temperature of mice treated with phenoxybenzamine remained low, but the temperature difference in mice treated with propranolol and pentolinium was no longer significant after 45 min.

DISCUSSION

Although noradrenaline and 5-HT appear to be involved in the control of body temperature in most species, the effects of the individual monoamines appears to be species specific (Feldberg, 1968). In the cat 5-HT causes hyperthermia and catecholamines cause hypothermia, whereas in the mouse both substances cause hypothermia (Brittain & Handley, 1967). Thus it is not surprising that the effects of drugs on body temperature is also species specific. In the cat morphine causes hyperthermia (Bannerjee, Feldberg & Lotti, 1968) whilst in the rat low doses caused hypothermia and high doses caused hyperthermia (Sharkawi, 1972).

Table 2. *Effect of propranolol (10 mg kg^{-1}) phenoxybenzamine (30 mg kg^{-1}) and pentolinium (5 mg kg^{-1}) upon reserpine reversal by pethidine (45 mg kg^{-1}) and morphine (20 mg kg^{-1}) in the mouse.*

Oesophageal temperature (°C) 180 min after the injection of analgesics or saline. Means ± s.e.

	Saline	Propranolol	Pentolinium	Phenoxybenzamine
Saline	37·2 ± 0·3	36·3 ± 0·5	37·2 ± 0·17	29·2 ± 0·7
Reserpine	26·9 ± 0·4	24·2 ± 0·1*	24·6 ± 0·2*	24·5 ± 0·3*
Reserpine† + pethidine	30·9 ± 0·4	25·4 ± 0·5*	26·0 ± 0·3*	24·6 ± 0·6*
Reserpine† + morphine	33·8 ± 0·5	27·4 ± 0·3*	26·8 ± 0·4*	25·0 ± 0·3*

* Significantly different from saline values in the first column ($P < 0.001$).

† Reserpine (5 mg kg^{-1}) was administered 18 h before the test. Mice were pretreated with pentolinium for 1 h and with phenoxybenzamine for 15 min. Propranol was administered with the morphine and pethidine.

In the mouse we have found that both morphine and pethidine induce a dose-dependent hypothermia. However, in equivalent antinociceptive doses, pethidine caused a greater and more prolonged fall in oesophageal temperature. Pethidine, but not morphine, has been shown to prevent uptake of 5-HT into blood platelets (Ahtee & Saarnivaara, 1973) and neurons (Carlsson & Lindqvist, 1969). If this occurred in the hypothalamus of the mouse, where 5-HT causes hypothermia (Brittain & Handley, 1967), this could explain the enhanced hypothermic action of pethidine over morphine in the mouse. The actions of morphine upon temperature in the rat are completely antagonized by nalorphine (Lotti, Lomax & George, 1965; Sharkawi, 1972). Similarly in the mouse we have found that although nalorphine completely antagonized the hypothermic action of morphine it increased the hypothermic actions of pethidine.

Although in the dose used, nalorphine had no effect upon oesophageal temperature itself, it has both narcotic agonist and antagonist actions. Thus the actions of naloxone are more useful in determining whether the effects of pethidine and morphine upon temperature are mediated through a structurally specific opiate receptor. Given concurrently with the analgesics, naloxone delayed the fall in temperature induced by morphine and had no significant effect upon pethidine hypothermia. Repeat injections in morphine-treated mice did not alter the responses observed, but an increased dose of naloxone and pre-treatment with naloxone markedly reduced the fall. Pre-treatment of mice given pethidine by naloxone also partially prevented the fall in temperatures. Nevertheless, no dose pre-treatment regime with naloxone totally prevented the fall in temperature induced by the two analgesics, thus it is unlikely that the effect is mediated solely through opiate receptors.

The fall in temperature with morphine and pethidine was still observed in adrenalectomized mice ruling out a role of this gland in the hypothermia.

Reversal of reserpine hypothermia, in the mouse, was originally suggested as a screening method for drugs with antidepressant activity (Askew, 1963). However, Whittle (1967) demonstrated that the test was not specific for antidepressant activity as other drugs, such as morphine, had similar effects. In the present study it has been shown that pethidine as well as morphine, is capable of reversing reserpine-induced hypothermia in the mouse, but there are some differences in the mechanisms by which this occurs.

Reserpine reversal with morphine was partially inhibited by naloxone, whilst that of pethidine was unaffected. The action of naloxone was not increased by increasing the dose. Thus opiate receptors are not a prerequisite for reversal of reserpine hypothermia by the narcotic analgesics, but they may play a role in the activity of morphine in this respect.

Adrenalectomy has been reported to prevent the reserpine reversal effects of a number of compounds including desipramine (Cooper, 1971) and morphine (Cowan & Whittle, 1971). However, using mice pretreated with 2 mg kg^{-1} reserpine for 18 h, we have been unable to confirm that adrenalectomy prevents the reversal action of morphine. Adrenalectomized mice treated with reserpine and morphine exhibited a significant increase in body temperature over the appropriate control mice, although this was not as great as that seen in non-adrenalectomized mice. The reserpine reversal action of pethidine, however, was completely inhibited by adrenalectomy.

The difference between our results and those of Cowan & Whittle (1972) may be explained by two factors. Firstly, since adrenalectomized mice are more sensitive to reserpine (Somerville & Whittle, 1967) a lower dose of reserpine was used in adrenalectomized mice so that the temperature fall was not maximal and reached a plateau significantly above room temperature. This contrasts with Cowan & Whittle's mice in which temperatures after adrenalectomy and reserpine were not significantly different from room temperature. Thus it may be that the reversal of reserpine hypothermia in adrenalectomized mice, by morphine, depends upon the degree of reserpinization. Secondly, Cowan & Whittle (1972) injected morphine during the falling phase of reserpine-induced hypothermia. In this laboratory it was found that morphine was less effective in reversing reserpine hypothermia in adrenalectomized mice if administered during the falling phase of reserpine hypothermia. However, it has been shown in this study that while the reserpine-reversing effects of pethidine can be abolished by adrenalectomy, the effects of morphine are only reduced. Thus part of morphine's action must involve a mechanism not related to the adrenal gland. A similar finding has been reported for the reserpine reversal activity of chlorpromazine in the mouse (Cooper & Schnieden, 1972).

Ganglion blockade completely abolished the thermogenic effects of both pethidine and morphine in reserpinized mice. These results suggest that the mechanisms involved are not peripheral to the

ganglia. Whittle (1967) found that phenoxybenzamine, 30 mg kg^{-1}, partially prevented the reversal of reserpine hypothermia by morphine, but using the same dose we found complete inhibition of thermogenesis. However, as the temperature of control mice dropped by 10°, interpretation of these results is difficult. They would suggest that α-blockade prevents the thermogenic action of pethidine and morphine, but the specificity of phenoxybenzamine at this dose level is debatable.

Finally, we have confirmed that the thermogenic activity of morphine in reserpinized mice can be inhibited by propranolol (Whittle, 1967) and we have demonstrated that the actions of pethidine are similarly inhibited. However, whether this inhibition is related to β-blockade or to some other pharmacological activity of propranolol remains to be examined.

Thus it is shown that the actions of morphine and pethidine cannot be distinguished by the use of ganglion blockade or α- and β-receptor blockade.

It would seem that whilst the effects of morphine and pethidine upon oesophageal temperature in the control and reserpinized mouse are grossly similar, there are a number of differences in the mechanisms by which the two drugs exert their effects.

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