Abolition of the morphine effect on body temperature in midbrain raphe lesioned rats

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The hyperthermia and the hypothermia elicited by 5 mg/kg, i.p. or 30 mg/kg i.p. of morphine in rats are abolished by a previous lesion of the midbrain raphe resulting in a lowering of forebrain 5-HT and 5-hydroxyindolacetic acid. Lesions lateral to the midbrain raphe which do not modify brain 5-HT are without effect on body temperature changes induced by morphine. Animals lesioned in the midbrain raphe are still able to respond with a hyperthermia or with a hypothermia when they are treated respectively with 2,4-dinitrophenol or phentolamine.

Both an increase and a decrease of body temperature have been reported to occur after doses of morphine, depending on species and doses (Eichenberger, 1966; Reynold & Randall, 1957). In rats, morphine in low doses produces hyperthermia and in high doses, hypothermia (Chodera, 1963; Gunne, 1960; Lotti, Lomax & George, 1965).

The action of morphine on the anterior hypothalamus was claimed to be responsible for the changes in body temperature (Banerjee, Feldberg & Lotti, 1968; Lotti & others, 1965) and it has been suggested that brain 5-hydroxytryptamine (5-HT) might be involved in this effect (Banerjee & others, 1968; Medon, Haubrich & Blake, 1969). The lesion of midbrain raphe area (MR), which selectively lowers the 5-HT content in the forebrain without affecting the concentrations of noradrenaline and dopamine (Kostowski, Giacalone & others, 1968) has been shown to antagonize the analgesic effect of morphine (Samanin, Gumulka & Valzelli, 1970).

We have investigated the effects of morphine on temperature in these experimental conditions, and have compared the effects with those of 2,4-dinitrophenol and phentolamine which are known to produce temperature modifications without apparently interfering with brain-5-HT activity or metabolism.

MATERIALS AND METHODS

Female Sprague Dawley rats, 170 ± 10 g, were kept individually in special cages to minimize the movements of the animals, at a constant room temperature (22° ± 1) and relative humidity (60%). Body temperature was estimated by inserting a thermocouple into the rectum at 10 a.m. immediately before injection of drug and at 30 min intervals for 3 h.

Animals lesioned in the MR were prepared as described by Kostowski & others (1968). Groups of animals lesioned laterally to the MR were used as additional controls. In animals, taken randomly, the concentrations of 5-HT and 5-hydroxyindolacetic acid (5-HIAA) in the forebrain were determined spectrofluorometrically (Giacalone & Valzelli, 1969). Treatments and biochemical determinations were made one week after surgery.

The drugs used were: morphine hydrochloride (5, 10, 20 and 30 mg/kg, i.p.); 2,4-dinitrophenol (30 mg/kg, s.c.); phentolamine (5 mg/kg, i.p.). A group of control rats received corresponding volumes of saline.

Table 1. *Effect of morphine, 2,4-dinitrophenol and phentolamine on body temperature in sham, lateral midbrain raphe (LMR), or midbrain raphe (MR), lesioned rats.*

Experimental groups (mg/kg)	No. rats	Body temperature (°C ± s.e.) after injection (min)						
		0	30	60	90	120	150	180
Sham lesioned								
Saline	10	37·6 ± 0·1	37·6 ± 0·1	37·5 ± 0·2	37·5 ± 0·1	37·5 ± 0·1	37·6 ± 0·1	37·5 ± 0·1
Morphine (5 i.p.)	10	37·7 ± 0·1	37·8 ± 0·2	38·1 ± 0·2	38·4 ± 0·1*	38·3 ± 0·1*	37·9 ± 0·1	37·7 ± 0·1
Morphine (10 i.p.)	10	37·7 ± 0·1	37·2 ± 0·3	37·1 ± 0·2**	37·4 ± 0·3	37·5 ± 0·3	37·4 ± 0·3	37·6 ± 0·3
Morphine (20 i.p.)	10	37·8 ± 0·1	37·0 ± 0·3**	36·1 ± 0·4*	35·9 ± 0·5*	36·8 ± 0·4**	37·4 ± 0·3	37·7 ± 0·2
Morphine (30 i.p.)	8	37·8 ± 0·2	36·7 ± 0·4*	35·9 ± 0·4*	35·6 ± 0·5*	35·3 ± 0·6*	36·0 ± 0·4*	36·6 ± 0·4*
Dinitrophenol (30 s.c.)	8	37·8 ± 0·2	38·7 ± 0·2*	39·6 ± 0·2*	39·6 ± 0·1*	39·4 ± 0·1*	39·2 ± 0·1*	38·7 ± 0·2*
Phentolamine (5 i.p.)	8	37·9 ± 0·2	36·7 ± 0·2*	36·3 ± 0·3*	36·1 ± 0·3*	36·1 ± 0·3*	36·3 ± 0·3*	36·4 ± 0·3*
LMR lesioned								
Saline	8	37·7 ± 0·2	37·6 ± 0·2	37·6 ± 0·1	37·6 ± 0·2	37·7 ± 0·2	37·8 ± 0·1	37·7 ± 0·2
Morphine (5 i.p.)	8	37·8 ± 0·1	37·8 ± 0·1	38·2 ± 0·1	38·4 ± 0·1*	38·3 ± 0·1*	37·9 ± 0·1	37·9 ± 0·1
Morphine (30 i.p.)	10	37·8 ± 0·1	36·7 ± 0·2*	35·6 ± 0·3*	35·0 ± 0·3*	34·7 ± 0·3*	35·5 ± 0·4*	36·3 ± 0·3*
Dinitrophenol (30 s.c.)	8	37·8 ± 0·3	38·7 ± 0·2**	39·3 ± 0·3*	39·3 ± 0·2*	38·9 ± 0·1*	38·6 ± 0·2*	38·6 ± 0·2**
Phentolamine (5 i.p.)	8	37·9 ± 0·1	37·0 ± 0·2*	36·3 ± 0·2*	35·8 ± 0·3*	36·0 ± 0·3*	36·1 ± 0·3*	36·3 ± 0·3*
MR lesioned								
Saline	8	37·8 ± 0·2	37·6 ± 0·3	37·7 ± 0·2	37·8 ± 0·2	37·8 ± 0·1	37·7 ± 0·2	37·6 ± 0·1
Morphine (5 i.p.)	10	37·8 ± 0·1	37·7 ± 0·2	37·8 ± 0·2	37·8 ± 0·2	37·8 ± 0·2	37·6 ± 0·1	37·6 ± 0·1
Morphine (30 i.p.)	8	37·6 ± 0·2	37·6 ± 0·3	37·0 ± 0·4	37·1 ± 0·5	37·2 ± 0·5	37·3 ± 0·4	37·6 ± 0·3
Dinitrophenol (30 s.c.)	8	37·7 ± 0·2	38·6 ± 0·2*	39·4 ± 0·2*	39·2 ± 0·3*	39·1 ± 0·3*	38·9 ± 0·2*	38·7 ± 0·2*
Phentolamine (5 i.p.)	8	37·9 ± 0·2	36·7 ± 0·2*	36·0 ± 0·3*	35·9 ± 0·4*	36·1 ± 0·4*	36·2 ± 0·4*	36·6 ± 0·3*

* = $P < 0.01$ in respect to animals treated with saline (*t*-test).
** = $P < 0.05$ in respect to animals treated with saline.

Table 2. *Forebrain concentration of 5-HT and 5-HIAA in normal, lateral midbrain raphe (LMR) and midbrain raphe (MR) lesioned rats.*

	Brain content	
Experimental group	5-HT μg/g ± s.e.	5-HIAA μg/g ± s.e.
Normal	0·38 ± 0·01	0·22 ± 0·01
LMR lesioned	0·34 ± 0·01	0·21 ± 0·01
MR lesioned	0·13 ± 0·01*	0·10 ± 0·01*

* = $P < 0.01$ in respect to normal rats (*t*-test).
The figures represent the average of at least 4 rats per group.

RESULTS

Morphine given intraperitoneally had a dual effect on body temperature dependent on dose (Table 1). The 5 mg/kg dose produced a moderate increase of temperature, reaching a significant peak at 90 and 120 min from injection to return to normal values at the end of the experiment (3 h). A slight decrease of body temperature was observed with the 10 mg/kg dose, whereas a marked hypothermia occurred when 20 or 30 mg/kg were injected. Similar results were obtained when the 5 and 30 mg/kg doses were given to the animals lesioned laterally to the MR, but when the two doses of morphine were administered to MR lesioned rats, there was no significant change in body temperature (Table 1, Fig. 1).

In contrast, the marked hyperthermia produced by 2,4-dinitrophenol and the hypothermia induced by phentolamine were similar in sham lesioned as well as in MR or in lateral MR lesioned animals (Table 1).

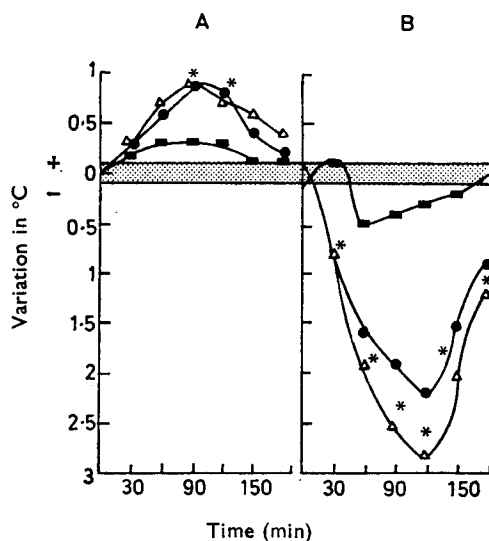Table 2 shows the concentrations of 5-HT and 5-HIAA in the forebrain one week

FIG. 1. Change in rectal body temperature after administration of morphine hydrochloride at 5 or 30 mg/kg, i.p. in sham lesioned (●———●), midbrain raphe lesioned (■———■) and lateral midbrain raphe lesioned (△———△) rats. The statistical signficance is calculated in respect to corresponding untreated rats.

after the lesion. There was a marked decrease of both indoles in the MR lesioned animals, whereas no significant changes occurred in the animals with a lateral MR lesion.

DISCUSSION

It has been suggested that brain monoamines may play a role in the hypothalamic regulation of body temperature (Corrodi, Fuxe & Hökfelt, 1967; Feldberg & Lotti, 1967; Feldberg & Myers, 1963, 1964, 1965). Morphine is known to influence the hypothalamic heat-regulatory mechanism by producing hyper- or hypothermia according to animal species and doses (Eichenberger, 1966; Reynolds & Randall, 1957). The administration of morphine into the lateral ventricles or into the anterior hypothalamus of various species causes changes in body temperature which resemble those seen after similar administration of 5-HT (Banerjee & others, 1968; Feldberg & Lotti, 1967; Feldberg & Myers, 1965; Lotti & others, 1965). Moreover morphine is known to act on the brain serotoninergic system in various ways (Haubrich & Blake, 1969; Lee & Fennessy, 1970; Türker & Akçasu, 1962; Way, Loh & Shen, 1968).

Our results are similar to those of Lotti & others (1965) that there is a dual effect of morphine on body temperature of rats. Lesion of the MR destroys the serotoninergic terminals in the forebrain (Kostowski & others, 1968). Samanin & others (1970) have shown that this lesion will abolish the analgesic action of morphine. We now report that the hypothermic and hyperthermic actions of morphine are similarly affected by this procedure, whilst a lesion made lateral to the MR does not influence morphine's action. That animals with a MR lesion may still respond with changes of body temperature is demonstrated by the finding that 2,4-dinitrophenol and phentolamine maintain their respective hyper- or hypothermic activity.

In conclusion these studies are in agreement with the hypothesis that, as with its analgesic action, morphine modifies body temperature by interacting with brain 5-HT (Banerjee & others, 1968; Medon & others, 1969).

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