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ROLE OF ADRENAL MEDULLA IN MORPHINE-INDUCED HYPERTHERMIA THROUGH CENTRAL ACTION

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1 The role of the adrenal glands, in morphine-induced hyperthermia was studied in normal, chemically-sympathectomized, adrenalectomized, adrenal-demedullated or splanchnicotomized rats.

2 In restrained female rats, 5 mg/kg morphine produced hyperthermia whereas 20 mg/kg and 40 mg/kg produced hypothermia.

3 After adrenalectomy, 5 mg/kg morphine did not produce hyperthermia.

4 After adrenal-demedullation or adrenal-denervation (splanchnicotomy), 5 mg/kg morphine did not produce hyperthermia.

5 The results suggest that, in the rat, the adrenal medulla plays an important role in morphine-induced hyperthemia, and that morphine acts centrally to stimulate the medulla.

Introduction

It has been demonstrated that, in restrained rats, low doses of morphine usually produce hyperthermia while high doses produce hypothermia (Gunne, 1960; Lotti, Lomax & George, 1965). Research strongly suggests that morphine works centrally to induce hyperthermia in the rat (Lotti, *et al.*, 1965; Cox, Ary, Chesarek & Lomax, 1976). However, the complete mechanism through which morphine induces hyperthermia is still uncertain. The adrenal, which has been shown to play a significant role in several actions of morphine (Wallenstein, 1979, 1981; Wallenstein & Wang, 1979), secretes several thermogenic hormones.

The purpose of the present investigation was to study whether the adrenal glands are an important part of the physiological mechanism activated by morphine to induce hyperthermia in the rat. Morphine was administered to groups of either normal, guanethidine-pretreated, adrenalectomized, adrenal-demedullated or adrenal-denervated rats. It was found that the adrenal medulla played a significant role in morphine-induced hyperthermia in the rat, and that morphine exerted its effect on the medulla through a central action.

Methods

Female Sprague-Dawley rats (Charles River, Wilmington, Mass.), weighing between 200–300 g, were used. Within any one experimental group, the weight range was never greater than 50 g. The animals were housed under an artificial lighting regimen of 12 h of light (08 h 00 min–20 h 00 min) alternating with 12 h of darkness at an ambient temperature of 24 ± 1°C; 51 ± 2% relative humidity. Food and water were available *ad libitum* except during periods of restraint when no food or water was available. Adrenalectomized rats were maintained on saline (0.9% w/v NaCl solution) and food between testing periods.

Surgery

Adrenal glands were removed by a dorsal approach in rats anaesthetized with sodium pentobarbitone (45–60 mg/kg, i.p.). Another group underwent a sham operation. Adrenal demedullation and adrenal denervation (splanchnicotomy) were performed by ARC Sprague Dawley (Madison, WI). The viability of the adrenal cortex in these animals was demonstrated by their ability to survive without having to be maintained on saline. All groups were allowed to recover for 7 days before being tested.

Chemical sympathectomy was performed on new born animals following the method of Angeletti, Levi-Montalcini & Caramia (1972). Litters were divided into experimental and control groups. One group was injected with guanethidine (20 mg/kg, s.c.) every second day for 3 weeks. Control animals received saline injections. The guanethidine-pretreated, but not the saline-injected, animals developed ptosis. Testing began when the animals reached 200–250 g body weight.

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Procedure

Testing occurred in a dimly-lit (40 watt fluorescent bulb, covered with a red filter), sound-attenuating room. The ambient temperature was between 21–24°C. Each rat was placed in a plastic restraining tube (Arthur Thomas, model 1123-C30). The inner space was decreased with plexiglass bars so that the tube was tight enough to permit only head movements. Animals were allowed to adapt to restraining holders for 1 h before morphine administration. Body temperature was measured with a thermistor probe (Yellow Springs Instrument, type 402) inserted 6–8 cm beyond the anal orifice and taped to the base of the tail. The thermistor cable was connected to a YSI tele-thermometer. Readings were taken every 15 min for the 60 min before and for at least 5 h after each injection. Except for the time of injection, the animals were isolated from the investigator by the sound-attenuating room. Five to eight rats were used for each test.

Results

The body temperature of rats injected with saline showed a slow mean decrease over 5 h of restraint (Table 1). A dose of 5 mg/kg morphine produced an increase in body temperature which was statistically significant ($P < 0.01$; Student's t test) when compared to the effect of saline alone. In contrast, 20 mg/kg and 40 mg/kg morphine produced statistically significant decreases in body temperature (Table 1).

Effect of guanethidine pretreatment

To investigate whether the mechanism underlying the hyperthermia included part of the peripheral neural sympathetic system, morphine was administered to rats which had been chemically sympathectomized through a series of guanethidine injections (guanethidine destroys only postganglionic adrenergic neurones). In both saline-pretreated (series of saline injections) and guanethidine-pretreated rats, 5 mg/kg morphine produced the usual hyperthermia (Table 1).

Effect of adrenalectomy

Seven days after the operations, both sham-operated and adrenalectomized female rats showed body temperatures which were not significantly different from those recorded from the non-operated control groups under the same testing conditions (Table 1). In the sham-operated rats, 5 mg/kg morphine produced a significant increase in body temperature (Table 1). In contrast, in the adrenalectomized rats, 5 mg/kg morphine did not have a significant effect on body temperature (Table 1).

Effect of adrenal demedullation

To investigate whether the adrenal medulla plays a role in morphine-induced hyperthermia, saline or 5 mg/kg morphine was administered to adrenal-demedullated rats. The saline-administered rats showed a slow decrease in body temperature which was not significantly different from that produced in non-operated rats (Table 1). The rats which received 5 mg/kg morphine did not show the usual hyperthermia, but instead showed a slow decrease in body temperature which was not significantly different from that recorded from either the non-operated rats or the saline-administered demedullated rats (Table 1).

Effect of adrenal denervation

To investigate if morphine acted on the adrenal medulla centrally or peripherally, saline or 5 mg/kg morphine was administered to adrenal denervated rats. The saline-administered rats showed a slow decrease in body temperature which was not significantly different from that produced in non-operated rats (Table 1). The rats which received 5 mg/kg morphine did not show the usual hyperthermia but instead underwent the same slow decrease in body temperature as recorded from the saline-administered non-operated rats.

Discussion

In the present study, 5 mg/kg morphine produced a significant increase in body temperature while 20 mg/kg and 40 mg/kg morphine produced a significant decrease in body temperature. These results agree with those of other investigators (Gunne, 1960; Lotti *et al.*, 1965).

A dose of 5 mg/kg morphine also induced hyperthermia in guanethidine pretreated rats. Guanethidine pretreatment destroys all postganglionic sympathetic neurones but does not affect the adrenal medulla (Kvetnansky, Weise, Thoa & Kopin, 1979). These results suggest that morphine-induced hyperthermia in the rat is not dependent on peripheral thermoregulatory phenomena such as cutaneous vasoconstriction. In contrast, 5 mg/kg morphine did not produce hyperthermia in adrenalectomized rats. Adrenal demedullation also blocked the hyperthermia usually produced by 5 mg/kg morphine in rats. (The ability of the demedullated rats to survive on tap water indicates that the adrenal cortex remained

Table 1 Effect of pretreatments on morphine-induced changes in body temperature in rat

Morphine (mg/kg)	*Time (h after morphine administration)* 1.0	2.0	3.0	4.0
	No pretreatment			
0[a]	−0.3±0.2[b]	−0.6±0.2	−0.9±0.3	−0.9±0.3
5	0.7±0.1**	0.9±0.3**	0.1±0.4*	−0.6±0.4
20	−0.1±0.1	−1.2±0.2*	−1.2±0.2	−1.2±0.3
40	−1.9±0.3**	−3.2±0.3***	−3.7±0.8*	−3.0±1.0
	Guanethidine pretreatment			
5[c]	0.6±0.1*	0.7±0.2*	−0.2±0.3	−0.6±0.3
5[d]	0.8±0.1**	0.6±0.2*	0.2±0.2*	0.1±0.2*
	Sham-adrenalectomized			
0[a]	−0.3±0.2	−0.4±0.2	−0.7±0.1	−0.9±0.2
5	0.8±0.1	0.9±0.3**	0.2±0.3	−1.1±0.4
	Adrenalectomized			
0	−0.1±0.5	−0.4±0.4	−0.6±0.4	−0.8±0.4
5	−0.4±0.3	−0.6±0.4	−1.0±0.5	−1.2±0.5
	Adrenal demedullated			
0	−0.1±0.1	−0.3±0.1	−0.3±0.2	−0.8±0.2
5	−0.3±0.1	−0.3±0.2	−0.5±0.3	−0.6±0.3
	Adrenal-denervated			
0	−0.3±0.1	−0.5±0.1	−0.6±0.3	−0.5±0.2
5	−0.3±0.2	−0.6±0.1	−0.8±0.2	−1.1±0.3

Body temperature given as °C mean ± s.e.mean.
[a]Saline injection; [b]change in body temperature when compared to 5 min before morphine or saline administration; [c]sham injections of saline; [d]multiple dose pretreatment with guanethidine while new born (see Methods).
*$P<0.05$; Student's *t* test; **$P<0.01$; ***$P<0.001$.

functional in these animals.) These results suggest that the adrenal medulla plays an important role in morphine-induced hyperthermia in the rat. Morphine has been shown previously to increase catecholamine release from the adrenal medulla (Gunne, 1963; Anderson & Slotkin, 1975). These hormones have a non-shivering thermogenic function (Banet, Hensel & Liebermann, 1978) which is probably mediated by action on brown adipose tissue in the rat (Foster, Depocas & Frydman, 1980). Adrenal denervation also blocked the morphine-induced hyperthermia in the present study. This indicates that morphine acted centrally to stimulate the adrenal medulla. This concept is consistent with the results of Yoshizaki (1973) who found that adrenal denervation largely blocked morphine-induced increases in adrenaline release from the adrenal medulla.

These results appear to disagree with those of some investigators. However, differences may be explained by the multiple actions of glucocorticoids and/or differences in the strains of rat used. Holaday, Law, Loh & Li (1979) found that after pretreatment with dexamethasone, morphine induced hyperthermia in adrenalectomized rats and they suggested that adrenalectomy blocked the hyperthermia because hormones from the adrenal cortex normally influenced the metabolism of morphine, and thereby its potency. However, French (1979) has suggested that the exogenous dexamethasone interacted with ACTH which acts directly on thermoregulatory mechanisms or opiate receptors. It is also possible that the glucocorticoid administered by Holaday *et al.* (1979) stimulated calorigenic sources which were not stimulated in the present series of experiments since dexamethasone can have both direct and permissive thermogenic actions of its own (cf. Deavers & Musacchia, 1979). Hermann (1942) found that adrenalectomy did not block hyperthermia in rats given saline. These results are in conflict with both the results of the present study and those of Holaday *et al.* (1979). Additionally, in Hermann's experiments, adrenalectomy blocked morphine-induced exophthalmos. This result is in contrast to that obtained with the strain of rat used in the present study (Wallenstein, 1981). The rat strain used by Hermann was not identified; differences in results may be due to the fact that Hermann used a different rat strain, which

can be a complicating factor (McCarty, Gilad, Weise & Kopin, 1979; Kenny & Leonard, 1980). Further, Hermann administered the morphine 24 h after adrenalectomy.

In conclusion, the results indicate that the adrenal medulla plays a role in morphine-induced hyperthermia in the rat. This is probably due to the release of catecholamines from the adrenal medulla via a central stimulatory effect of morphine.

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