REVISTA ESPAÑOLA DE FISIOLOGIA, 39, 467-470. 1983

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Increase of the Hypothermic Effect of Morphine in Restraint Guinea-Pigs

The effects of morphine on body temperature are complex and subject to many experimental variables and environmental factors including temperature (6). In most mammals, morphine induces hypothermia (2). However, in the rat the administration of morphine induces a biphasic effect which is dependent on dose and degree of restraint of the animals (6, 8). Both effects of morphine in rats were antagonized by naloxone (8, 9). In the guinea-pig, a dose dependent increase (5) as well as a decrease in body temperature (4) has been reported following morphine administration. In the present study we have shown a hypothermic effect of morphine in guinea-pigs, which is increased in restraint animals and reversed by naloxone administration.

Male and female tricolor guinea-pigs (300-350 g) were used. Moderate restraint was obtained by placing the animals in small plexiglass restraining cages (18 × 8 × 8). Where no restraining was required, each guinea-pig was housed singly in a standard cage (22 × 14 × 25 cm) with a wire top. Temperature was measured with a Thermistor probe (Yellow Springs Instrument 402) inserted 6-7 cm into the rectum and monitored on a multi-channel recorder. Temperature was recorded continuously at room temperature (22-24°C) for a period of six hours. Drugs were dissolved in 0.9% NaCl and sterilized by filtration through a Millipore filter. Morphine sulphate was injected intraperitoneally (i.p.) or into the third cerebral ventricle (i.c.v.). Using standard stereotaxic procedures, a David-Koff cannula was implanted into the third ventricle under sodium pentobarbitone anaesthesia (35 mg/kg i.p.). The coordinates were obtained from the stereotaxic atlas of the guinea-pig brain (7). At the end of the experiment the ventricular location of the cannula was routinely verified by histology. Naloxone was administered subcutaneously (s.c.) at a dose of 10 mg/kg.

Morphine administration (50 mg/kg i.p.) to unrestraint guinea-pigs, consistently produced a hypothermic effect with a maximum mean decline in temperature of —1.3 ± 0.1°C. After such decrease, body temperature returned to the control values at 3 h post-injection. The unrestraint controls, injected with saline alone, showed no changes in temperature during the 6 h recording period. When restraint guinea-pigs received the same dose of morphine i.p. a more pronounced hypothermia was observed in all animals, with a maximum mean decrease of 2.4 ± 0.2°C. The restraint animals receiving saline showed a slight and gradual decline of core temperature throughout the experiment. When comparing the hypothermic

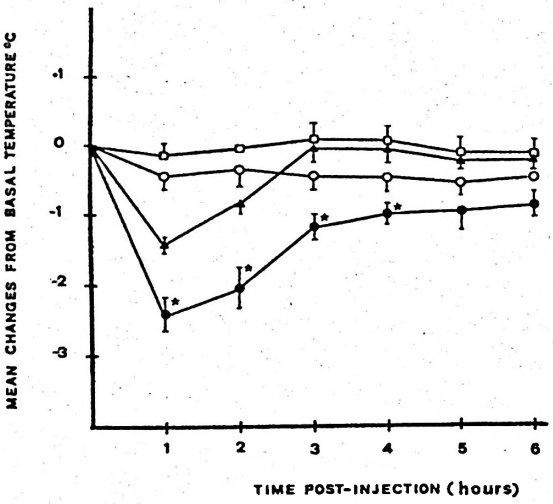

Fig. 1. *Temperature changes produced by i.p. morphine 50 mg/kg) in free moving (▲) and restraint (●) guinea-pigs.*

Open square and circles represent saline controls unrestraint and restraint guinea-pigs respectively. Each curve shows the mean temperature values of six animals over a 6 h period. For the sake of clarity not all SEM were included. Asteriscs (*) indicate p values of 0.02 when comparing the effect of morphine in restraint and unrestraint guinea-pigs.

effects of morphine i.p. in restraint and unrestraint animals, it is apparent that in every time point the effects in the restraint animals were significantly enhanced than those in the unrestraint guinea-pigs (fig. 1). The p values for 1 to 4 h were < 0.02. In another series of experiments, unrestraint animals received 50 μg of morphine or an identical volume of saline i.c.v. The hypothermic effect was comparable in magnitude to that observed when morphine was administered systemically. The unrestrained controls receiving i.c.v. saline showed negligible changes in core temperature throughout the 6 h recording period. Treatment with naloxone (10 mg/kg s.c.) 30 min before morphine administration i.p. or i.c.v. abrogated the hypothermic effect of morphine by both routes of administration. However, the controls receiving the same dose of naloxone showed no detectable changes in body temperature during the 6 h recording.

The present study shows a potentiation of the hypothermic effect of systemic administration of morphine in restraint guinea-pigs. Although the magnitude of the morphine-induced hypothermia in restraint guinea-pigs was different from the unrestraint animals, the time course of hypothermia was comparable. However, the restraint animals had an incomplete recovery of core temperature, within the 6 h study period. In contrast with this finding, FRENCH (3) reported that rats restrained responded to morphine, with a pronounced hypothermia and when the same dose of morphine was administered to unrestrained freely moving

Table 1. *Effects of naloxone (10 mg/kg) injected s.c. on the hypothermic response to morphine administered to conscious restraint and unrestraint guinea pigs.*

All experiments were recorded over a six hour period. Naloxone was administered 30 min before morphine or saline. Results are the mean values of 6 experiments ± S.E.M. Route: a) i.p. b) i.c.v.

Group	Morphine dose	Maximum decrease at 1 h (°C±SEM)	Temperature at 6 h
Restraint			
Morphine	50 mg/kg[a]	—2.4±0.2	37.6±0.2
Morphine + Naloxone	50 mg/kg[a]	—0.4±0.2	38.5±0.2
Saline	none[a]	—0.3±0.2	37.9±0.2
Unrestraint			
Morphine	50 mg/kg[a]	—1.3±0.1	38.5±0.1
Morphine + Naloxone	50 mg/kg[a]	—0.3±0.3	38.6±0.1
Saline	none[a]	—0.1±0.2	38.3±0.2
Morphine	50 μg[b]	—1.9±0.3	37.4±0.1
Morphine + Naloxone	50 μg[b]	—0.3±0.1	38.7±0.1
Saline	none[b]	—0.1±0.2	38.5±0.2

rats a marked hyperthermia resulted. A similar hypothermic effect was observed after i.c.v. morphine administration, which suggests that the hypothermic effects of morphine could be mediated by a central mechanism. These results supports, the finding of BALDINO *et al.* (1), who reported that morphine excited warm-sensitive cells, which are assumed to mediated heat dissipation responses and inhibited cold sensitive cells, which are assumed to mediated heat-gain responses, these effects are consistent with the thermal effect produced by morphine in this study. However, in both systemic and central morphine administration, the hypothermic effect could be prevented by pretreatment with naloxone. These findings suggest that the hypothermic effect induced by morphine in all instances is meadiated by a naloxone-sensitive mechanism. Our hypothesis for the restraint-induced potentiation of hypothermia is that it may be related to a stress-induced release of endogenous opiate-like factors.

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(Received on January 26, 1983)

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