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HYPERTHERMIC EFFECTS OF MORPHINE: SET POINT MANIPULATION BY A DIRECT SPINAL ACTION

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1 Rats were implanted with chronic indwelling catheters in the lumbar spinal subarachnoid space in order to study the effects of morphine on body temperature.

2 Morphine administered intrathecally produced a dose-dependent rise in body temperature that was antagonized by naloxone.

3 The rise in body temperature evoked by a given dose of morphine appeared to be independent of the environmental temperature (4°C to 32°C) and was consistently associated with coordinated thermoregulatory responses (i.e. shivering and tail vasoconstriction). The fall in body temperature observed in these hyperthermic animals, following naloxone, was associated with a vasodilatation which coincided with the fall to the premorphine temperature level.

4 Morphine administered systemically also produced hyperthermia. This was only partially reversed by intrathecal naloxone. In animals made tolerant to the hyperthermic effects of systemic morphine, the intrathecal administration of naloxone produced a fall in body temperature.

5 Naloxone alone, administered either intrathecally or systemically, had no effect upon body temperature.

6 We suggest that morphine exerts a direct, pharmacologically specific effect on the spinal cord, which results in an altered thermoregulatory set point in the rat.

Introduction

The effects of morphine on body temperature have been shown to be complex, species-dependent and subject to experimental variables such as environmental temperature and restraint. In particular, work carried out in the rat has suggested that in the unrestrained rat, maintained in a high environmental temperature, systemically administered narcotics produce a rise in body temperature. In contrast, restraint and low environmental temperatures appear to attenuate the hyperthermic response or cause morphine to produce a frank hypothermia (Herrman, 1942; Gunne, 1960; Lotti, Lomax & George, 1965a & b; Paolino & Bernard, 1968; Martin, Dryzbylik & Spector, 1977). One suggested locus for this effect is the thermoregulatory centres associated with the anterior-preoptic region of the hypothalamus (Lotti *et al.*, 1965a & b; Foster, Jenden & Lomax, 1967; Lotti, 1973; Martin & Morrison, 1977). Intracerebral injection experiments have clearly demonstrated that opiates acting only within this delimited region can in fact exert a direct and pharmacologically specific effect (i.e. antagonized by naloxone or nalorphine) on the thermoregulatory response of several species including the rat (see above) and cat (Banerjee, Feldberg & Lotti, 1968). We now present evidence that the observed temperature response produced by systemically administered narcotics may also influence body temperature by a direct action on the spinal cord.

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Methods

To study the local action of morphine in the spinal cord, rats under Nembutal anaesthesia were chronically implanted with catheters as described by Yaksh & Rudy (1976a). A polyethylene catheter was inserted into the spinal subarachnoid space through a slit in the cisternal membrane and extended to the rostral face of the lumbar enlargement. The distance from the point of insertion to the lumbar space was approximately 8.5 cm. The catheter was secured to the skull with screws and cranioplast cement. Experiments were started after a 7–10 day recovery period. All drugs injected intrathecally were dissolved in a volume of 10 μl of artificial cerebrospinal fluid. Each drug injection was immediately followed by an injection of 5 μl of the vehicle to clear the catheter.

All temperature experiments were carried out with

the animal restrained in a hemicylindrical wire mesh cage with its tail protruding from the rear. Body temperature was measured by the insertion of a YSI 401 thermistor probe (Yellow Springs Instrument Co.), 6 cm into the colon. The probe was affixed to the tail by a loose wrapping of tape. In a number of experiments, tail temperature was also assessed as a measure of vasodilitation, with a specially constructed probe consisting of the normal YSI 401 thermistor to which had been attached the disc portion of a YSI 427 thermistor probe. When the colonic probe was in place, the disc probe lay with its surface on the base of the tail, approximately 2 cm from the rectum. All temperatures were continuously monitored on a potentiometric recorder. Experiments were normally carried out at an environmental temperature of 22°C, but in a limited number of experiments, the temperature response of the animal following intrathecally injected morphine was assessed in a high (32°C) and low (4°C) temperature environment. The doses referred to in this paper are given in terms of the weight of the salt of morphine sulphate (Merck) and naloxone hydrochloride (Endo).

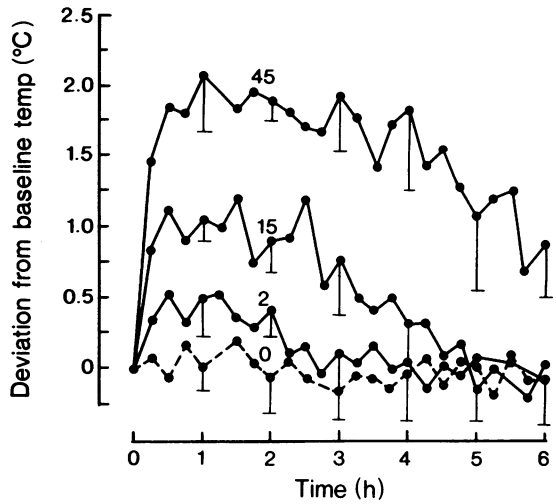

Figure 1 Mean deviation from baseline colonic temperature is plotted as a function of time after the intrathecal injection of morphine sulphate in doses of 0 to 45 μg. Each curve represents the mean response of from 4–6 rats. Vertical lines show s.e. mean.

Results

Effects of morphine in the spinal subarachnoid space

The injection of morphine into the spinal subarachnoid space of the rat produced a profound hyperthermia, the amplitude and duration of which was dose-dependent over a range of 2–45 μg. As shown in Figure 1, the hyperthermia was characterized by a relatively rapid onset at all doses, with the half maximum level of temperature rise being observed within 5–10 min after the injection. The injection of equal amounts of vehicle had no effect on the animal's body temperature. The intrathecal injection of morphine, at the doses employed, had no effect on heart rate, blood pressure or respiration and produced no signs of behavioural agitation. In view of the possibility that pyrexic effects produced by intracerebral injections may be associated with the release of prostaglandins, indomethacin was administered (5 mg/kg, i.p.) 2 h before the intrathecal injection of morphine (45 μg) in 4 rats. This amount of indomethacin, while inducing a slight hypothermia alone, had no effect on the observed morphine-induced hyperthermia.

Evidence for a set point change

To assess whether the hyperthermic action of morphine in the spinal cord resulted from a non-specific blockade of heat loss responses or activation of heat gain mechanisms, the injections of morphine were carried out at three ambient temperatures (high, 32°C; thermoneutral, 22°C and low, 4°C). As well as colonic temperature, the tail temperature was recorded whilst the animals were closely observed for signs of tremor activity. Three experiments at each ambient temperature were carried out. The data presented in Figure 2 are the results obtained from one such animal and are representative of the results observed in the other two animals. At all ambient temperatures, intrathecal morphine (45 μg) produced a uniform rise in colonic temperature of approximately 2°C. The injection of morphine was uniformly associated with a fall in tail temperature at 32°C and 22°C ambient temperature, suggesting the initiation of an active vasoconstriction. At 4°C ambient temperature, the absence of any change in tail temperature suggests that the animal was already vasoconstricted. After approximately 55 min, naloxone was administered systemically (1 mg/kg, i.p.). Naloxone produced an immediate elevation in the tail temperature concurrent with the fall in colonic temperature. The rise in tail temperature, indicated active vasodilator control by the animal. As the body temperature approached premorphine levels, the tail temperature fell. This is illustrated in the record taken at 22°C. Though tremor activity, reflecting a heat gain response, was not quantified, the presence of such tremor was most apparent in all animals following the injection of morphine in the neutral and low temperature environments. While at the low temperature, tremor activity was observable in two animals before morphine; following its intrathecal injection the magnitude of the tremor activity was much enhanced.

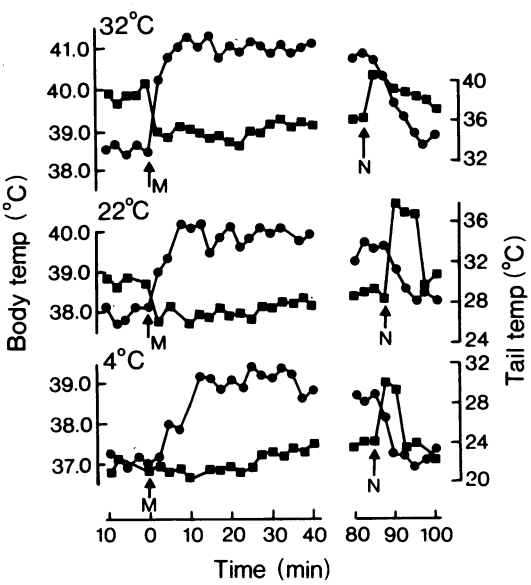

Figure 2 The rectal (●) and tail (■) temperature of a single rat is plotted as a function of time after the intrathecal injection of morphine sulphate (45 μg) at the first arrow (M) whilst the animal is in a hot (32°C), thermoneutral (22°C) or cold (4°C) environment. At the second arrow (N), the animal received an intraperitoneal injection of naloxone hydrochloride (2 mg/kg).

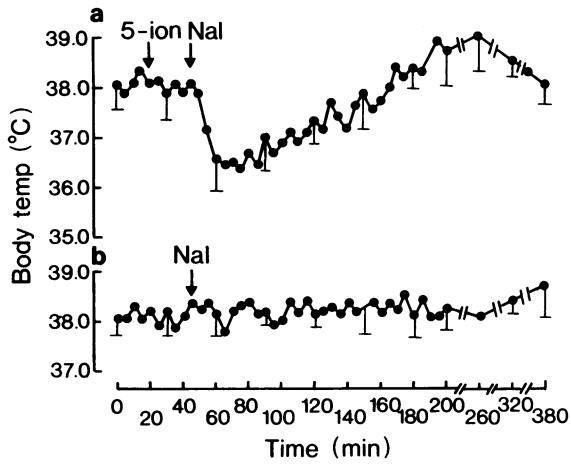

Figure 3 (a) Mean colonic temperature is plotted for 5 animals which had previously been rendered tolerant to the hyperthermic effects of systemically administered morphine. Vertical lines show s.e. mean. At the first arrow, a control intrathecal injection of vehicle (5-ion) was given, while at the second arrow, 10 μg of naloxone hydrochloride (Nal) was similarly injected. (b) The effect of an injection of naloxone (10 μg) on the colonic temperature of 4 control animals.

Table 1 Effects of intrathecally and systemically administered naloxone on the hyperthermia produced by systemically administered morphine

		Deviation from baseline temp. (°C)	
Group	n*	*Post morphine†*	*Post naloxone‡ or vehicle*
Morphine + intrathecal vehicle	4	1.63 ± 0.42	1.78 ± 0.57**
Morphine + intrathecal naloxone (5 μg)	6	1.41 ± 0.34	0.63 ± 0.38§**
Morphine + intrathecal naloxone (50 μg)	4	1.72 ± 0.51	0.56 ± 0.24§**
Morphine + systemic naloxone (2 mg/kg)	4	1.58 ± 0.42	0.17 ± 0.32§

* Size of group; † Value is mean with s.e. mean, measured 45 min after the injection of systemic morphine (20 mg/kg); ‡ Value is mean with s.e. mean, measured 20 min after the injection of either naloxone or vehicle (about 65 min after the injection of morphine).
§$P < 0.05$ as compared to postmorphine effect; ** $P < 0.05$ as compared to zero.

To demonstrate that the vasoconstriction associated with the hyperthermia was not simply the result of a direct effect on peripheral vasomotor tone, 3 rats received intrathecal morphine (45 μg) whilst in an ambient temperature of 22°C. After reaching a stable level of hyperthermia (+1.8° ± 0.4°C) a heat lamp was focussed on the body. Care was taken to prevent any direct heating of the tail. Within 30–45 s, before any detectable change in core temperature, tail temperatures were observed to rise 6–10° suggesting that morphine did not produce an obligatory vasoconstriction.

Antagonism of the narcotic effects on temperature by intrathecal naloxone in tolerant and non-tolerant rats

If morphine administered systemically is in fact producing its thermoregulatory effects by a direct action on spinal function, then a local antagonism of this action by the intrathecal injection of naloxone should predictably antagonize the effects of systemically administered morphine. These experiments, the results of which are summarized in Table 1, show that morphine injected intraperitoneally yielded a significant increase in colonic temperature which reached maximum within 45 min after the injection and remained stable for about 3 hours. Vehicle administered intrathecally 45 min after the morphine had no effect on the developed hyperthermia whereas, a similar injection of naloxone (5 μg) administered at this time produced approximately a 60% reduction in the magnitude of the temperature response. As indicated in Table 1 this reduction, though statistically significant, did not reach pre-morphine levels. In four animals, ten times this dose of naloxone (50 μg) failed to produce any greater reduction. Full reversal of the hyperthermic effects of systemic morphine could, however, be achieved by the administration of naloxone (2 mg/kg) systemically.

As hypothermia has been reported following the precipitated withdrawal of morphine from tolerant rats (Martin, Wikler, Eades & Pescor, 1963) and as we have observed precipitated withdrawal following intrathecal naloxone (Yaksh, Kohl & Rudy, 1977) we examined the effects of naloxone in the spinal cord on body temperature of rats chronically treated with and tolerant to morphine. Five rats were injected twice daily for 7 days (06 h 00 min and 18 h 00 min) with morphine (20 mg/kg i.p.). While on the first day, these injections produced a mild hyperthermia (+1.34 ± 0.56°C; mean ± s.e. mean), by the 7th day, such injections produced no change in the animal's baseline temperature (0.36 ± 0.43°C). At 12 h 00 min on the 7th day, rats were placed in the restraining cages and following the establishment of a baseline record, received an intrathecal injection of naloxone (10 μg total dose). Figure 3 shows the rapid fall in body temperature produced in the 5 animals following injection of the antagonist. Tail temperatures, measured in two animals indicated that the injection of naloxone produced a marked vasodilatation (6 and 7.5°C rise in tail temperature) while the recovery to the pre-naloxone levels was associated with a fall in tail temperature during the period of recovery. As in the experiments shown in Figure 2, as body temperature approached the pre-naloxone levels in these tolerant animals, tail temperature fell indicating an active vasoconstriction.

In view of the attenuation of the hyperthermic effects of morphine, we sought to examine whether naloxone alone in the range of doses employed here had any effects on body temperature. Systemic injections of naloxone 2 mg/kg in 5 rats had no systemic effect on temperature for a period of up to 4 h after injection (mean ± s.e. mean of maximum temperature change observed during 4 h = +0.35 ± 0.42°C). Similarly, the injection of naloxone (10 μg) intrathecally had no effect on body temperature as shown in Figure 3.

Discussion

That the action of the morphine injected into the spinal subarachnoid space is limited to this region and does not gain access in significant quantities to supraspinal structures has been examined in detail elsewhere (Yaksh & Rudy, 1976b; 1977a,b). Injections of radiolabelled morphine failed to appear in brain during the period after the intrathecal injection. Distribution of label along the cord following an intrathecal injection in fact revealed that the maximum spread of label did not exceed a distance of approximately 4 cm from the catheter tip. More importantly, the time course of the hyperthermic effect was too rapid to be coincidental with the diffusion of a compound which, due to its low lipophilicity, passes the blood brain barrier slowly. Similarly, examination of the dose-response curves for intrathecal morphine indicates that 45 μg produced about a 2°C rise in body temperature. Injections of that amount of morphine systemically (i.e. about 0.15 mg/kg for a 350 g rat) have consistently failed to produce any reliable change in colonic temperature.

The observed hyperthermia was a specific effect of morphine on opiate receptors. The effect was dose-dependent and treatment with indomethacin failed to have any influence upon the effect of the narcotic; this probably excludes the prostaglandins as having an intermediary role in the hyperthermia produced by intrathecal morphine.

Intrathecally administered naloxone reduced the hyperthermic effects of systemically administered morphine, thus supporting the view that the thermogenic effects are mediated in part by an action on the spinal cord. However, even high doses of intrathecal naloxone failed to antagonize completely the hyperthermia produced by systemic morphine. The fact that a subsequent systemic injection of

naloxone could in fact produce such a complete reversal suggests that a portion of the hyperthermia produced by systemically administered morphine might be mediated by a pharmacological action of the narcotic on brain regions not directly accessible to the intrathecally injected naloxone. A likely alternative site of action would be the anterior hypothalamus (see Introduction for references). Similarly, Yaksh & Rudy (1977b) observed that the analgesia produced by high doses of systemic morphine was not antagonized completely by intrathecal naloxone. Such results suggest that alternative brain sites may also subserve the analgesic action of morphine and are in accord with the observation that opiates can exert their analgesic effect by an action on several supraspinal structures (Jacquet & Lajtha, 1974; Sharpe, Garnet & Cicero, 1974; Pert & Yaksh, 1974; Yaksh, Yeung & Rudy, 1976; Takagi, Doi & Akaike, 1976).

We suggest that the common factor in these analgesic and thermogenic effects of intrathecal morphine is the modulation of sensory transmission. Just as the perception of and response to pain is not organized at the spinal level, the change in the thermoregulatory set point observed here does not indicate that the centre for thermoregulation is at the spinal level. An animal's thermoregulatory response is in part dictated by input from the peripheral thermal environment. Thus, cooling of the skin evokes predictable and co-ordinated efforts to gain heat. The same behavioural effects could be achieved if a systematic alteration in the thermal information received by supraspinal regulatory centres through the spinal sensory system, were achieved. We believe that the results of the present experiments and the known action of morphine in the spinal cord (see below) is consistent with such a possibility.

Considerable physiological and anatomical evidence exists to support the proposed existence of an endogenous, opiate-sensitive, modulatory system located within the spinal cord. Physiologically, it has been demonstrated that morphine administered into the spinal animal can in fact reduce the discharge of neurones located in lamina 5 of the dorsal horn (Iwata & Sakai, 1971; Besson, Wyon-Maillard, Benoist, Conseiller & Hamann, 1973; Kitahata, Kosaka, Taub, Bonikos & Hoffert, 1974; Le Bars, Menetrey, Conseiller & Besson, 1975), as well as selectively antagonize activity in the ventrolateral tract of the spinal cord evoked by peripheral stimulation (Grossman & Jurna, 1974; Jurna & Grossman, 1976). This spinal tract carries thermal information (Wünneberg & Brück, 1970). Patients in which ventrolateral cordotomies have been performed commonly report a loss of temperature sensation (White & Sweet, 1969). With regard to the locus of narcotic action, recent autoradiographic studies have demonstrated that stereospecific narcotic binding occurs with the substantia gelatinosa of the spinal cord (LaMotte, Pert & Snyder, 1976; Atweh & Kuhar, 1977). Significantly, this complex, polyneuronal region has been suggested as a probable locus for a physiological system mediating the passage of sensory information (Wall, 1973; Melzack & Wall, 1965). Direct evidence linking the pharmacological action of morphine in the substantia gelatinosa to these effects on activity in lamina 5 of the dorsal horn has recently been presented by Duggan, Hall & Headley (1976). They showed that morphine, applied by iontophoresis into the substantia gelatinosa produced an antagonism of the evoked activity recorded in the underlying lamina 5 cells.

Therefore it is likely that intrathecally administered narcotics act upon a modulatory system located within the dorsal horn, presumably in the regions of the stereospecific binding within the substantia gelatinosa, to modulate the passage of sensory information. The opiate-sensitive system may be primarily associated with the input of small fibre systems such as are thought to transmit thermal and nociceptive information (Bessou & Perl, 1969; Price & Wagman, 1970). Our results may be due to an action on these systems.

The present results do not subtract from the apparent importance of rostral diencephalic elements in regulating body temperature. However, significant thermoregulatory effects may be initiated by drugs acting on neural systems in the spinal cord. Whether such systems play a natural role in thermoregulation remains to be considered. The possibility that drugs may produce their effects on thermoregulation by an action at the spinal level, clearly precludes any simplistic interpretation limited to the hypothalamus.

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