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ROLE OF 5-HYDROXYTRYPTAMINE IN MORPHINE-, PETHIDINE-, AND METHADONE-INDUCED HYPOTHERMIA IN RATS AT LOW AMBIENT AND ROOM TEMPERATURE

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1 The effect of morphine (10 or 20 mg/kg s.c.), pethidine (25 or 50 mg/kg s.c.) or methadone (4 or 8 mg/kg s.c.) on the body temperature of nontreated and *p*-chlorophenylalanine-pretreated rats was studied at room (21 ± 0.2°C) or low ambient (12 ± 0.2°C) temperature.

2 Neither pethidine nor smaller doses of morphine and methadone altered the mean rectal temperature of rats kept at room temperature but larger doses of morphine and methadone produced significant hypothermia.

3 All narcotic analgesics at doses used in the present investigation produced significant hypothermia in rats maintained in a low ambient temperature. The hypothermia was prevented by naloxone (1 mg/kg s.c.).

4 The administration of *p*-chlorophenylalanine (PCPA, 320 mg/kg i.p.) 48 h before the narcotic injection prevented the fall in body temperature both at room and low ambient temperature.

5 The administration of narcotic analgesics at doses, which when administered by themselves did not alter the body temperature of rats, produced significant hyperthermia in rats pretreated with PCPA.

6 When rats pretreated with PCPA were given 5-hydroxytryptophan (75 mg/kg s.c.) 30 min before narcotic administration, the usual response to narcotics was restored.

7 It appears that pethidine and methadone as well as morphine have both hyperthermic and hypothermic actions in rats and that 5-hydroxytryptamine may be involved in the narcotic-induced hypothermia not only at room temperature but also at low ambient temperature.

Introduction

The involvement of 5-hydroxytryptamine (5-HT) in the morphine-induced hypothermia of rats at room temperature has already been documented (Oka & Nozaki, 1970; Haubrich & Blake, 1971; Oka, Nozaki & Hosoya, 1972; Samanin, Kon & Garattini, 1972). There have also been several reports which suggest the participation of 5-HT in the decrease in locomotor activity of rats induced not only by morphine (Oka & Nozaki, 1970; Eidelberg & Schwartz, 1970; Buxbaum, Yarbrough & Carter, 1973; Oka & Hosoya, 1976a), but also by pethidine or methadone (Oka & Hosoya, 1976b). Thus, it is of interest to investigate the role of 5-HT in the hypothermia induced by the administration of pethidine or methadone to rats. In initial experiments it was found that neither pethidine nor a small dose of morphine or methadone produced hypothermia in rats at room temperature; however, significant hypothermia was produced at a lower ambient temperature. Therefore, the present experiments were performed both at room temperature and at a low ambient temperature.

Methods

Male Wistar rats weighing between 170 and 250 g were used in the present study. Body temperature was measured as described previously (Oka *et al.*, 1972), with a thermistor probe inserted through the anus for a distance of 6 cm and taped to the base of the tail. Animals were placed in individual cages and could move relatively freely during the experiment. The interior of the experimental chamber was maintained at either 12 ± 0.2°C or 21 ± 0.2°C with $50 \pm 2\%$ relative humidity. Rectal temperatures were continuously recorded on Hokushin E36N1 P313 recorders. All experiments were begun at 10 h 00 min.

Morphine hydrochloride was bought from Sankyo Company (Tokyo, Japan), pethidine hydrochloride from Tanabe Seiyaku Co. (Osaka, Japan), and DL-*p*-chlorophenylalanine (PCPA) and 5-hydroxy-DL-tryptophan (5-HTP) from Nakarai Chemicals (Kyoto, Japan). Naloxone hydrochloride was a gift from Sankyo Co. Methadone hydrochloride was kindly supplied by Nippon Roche Research Center (Kamakura, Japan).

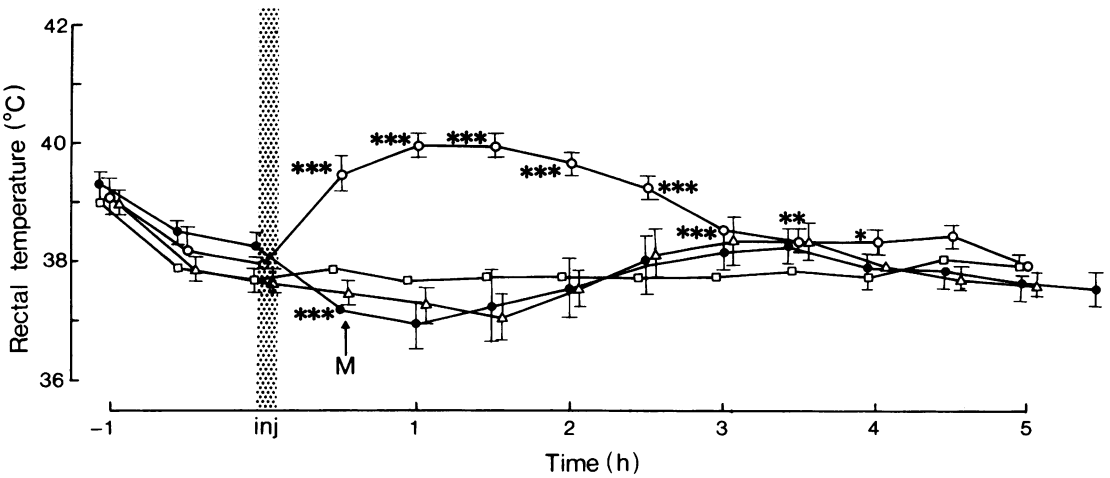

Figure 1 The effect of morphine on the mean rectal temperature of rats pretreated with *p*-chlorophenylalanine (PCPA); ambient temperature 21°C. Measurements of body temperature were begun immediately after the thermistor probe was inserted into the rectum. Saline (5 ml/kg), morphine (10 mg/kg) or 5-hydroxytryptophan (5-HTP, 75 mg/kg) was administered (at stippled bar) subcutaneously 1 h after inserting the thermistor probe, except for one group in which morphine (M) was given (indicated by arrow) 30 min after 5-HTP administration to PCPA pretreated rats. PCPA (320 mg/kg) was injected 48 h before stippled bar. Symbols and vertical bars represent means with s.e. mean. (□) saline, $n=6$; (△) morphine, $n=6$; (○) PCPA + morphine, $n=6$; (●) PCPA + 5-HTP + morphine, $n=6$.
*, $P<0.05$; **, $P<0.02$; ***, $P<0.01$ when compared with values of a group that had received saline.

All drugs except PCPA were dissolved in sterile 0.9% NaCl solution (saline) and were administered subcutaneously or intraperitoneally in volumes of 5 ml/kg. All drug dosages are expressed in terms of their salts. PCPA was adminsitered as a very fine saline suspension.

All data were statistically analyzed by Student's *t* test.

Results

After the thermistor probes had been inserted and the rats placed in the experimental chamber, a period of 1 h elapsed before their body temperatures stabilized between 37.5 and 38.5°C. Thereafter, their body temperatures remained constant over the next 5 h both at room and at low ambient temperatures (Figures 1 and 2). Accordingly, test substances were administered 1 h after insertion of the thermistor probe.

Effects of narcotic analgesics on the body temperature of rats at room temperature and its modification by pretreatment with p-*chlorophenylalanine and 5-hydroxytryptophan*

Effects of narcotic analgesics on body temperature of rats placed at a room temperature of 21 ± 0.2°C with 50 ± 2% relative humidity are illustrated in Figure 1 and Tables 1, 2 and 3.

The subcutaneous administration of morphine (10 mg/kg), pethidine (25 or 50 mg/kg) or methadone (4 mg/kg) alone had almost no effect on the mean rectal temperature of rats. In contrast, methadone (8 mg/kg) produced a significant fall in the body temperature (Table 3). Morphine (20 mg/kg), on the other hand, induced a hypothermic response followed by a hyperthermic response in rats (Table 1). Pretreatment of rats with PCPA (320 mg/kg, i.p.) 48 h before narcotic administration not only blocked the hypothermic response to morphine (20 mg/kg) but converted it to a significant hyperthermic response (Table 1). Pretreatment with PCPA did not block the hypothermic response to methadone (8 mg/kg) at 1 h but blocked it at 2 h and the animals exhibited a significant hyperthermic response at 3 h after methadone injection (Table 3). The administration of morphine (10 mg/kg), pethidine (25 or 50 mg/kg) or methadone (4 mg/kg) to PCPA pretreated rats produced prominent hyperthermia (Figure 1 and Tables 2 and 3). When rats pretreated with PCPA were given 5-hydroxytryptophan (5-HTP) (75 mg/kg, s.c.) 30 min before morphine administration, a typical hyperthermic response to morphine in PCPA-pretreated rats was no longer seen (Figure 1). Although 5-HTP alone produced a marked fall in the body temperature of rats pretreated with PCPA

Table 1 The effect of morphine on the mean rectal temperature of rats and its modification by *p*-chlorophenylalanine (PCPA); ambient temperature 21°C

Treatment	n	*0 h*	*1 h*	*2 h*	*3 h*	*4 h*
Saline	6	37.7 ±0.2	37.7 ±0.1	37.8 ±0.1	37.8 ±0.1	37.8 ±0.1
Morphine	6	37.7 ±0.3	36.5 ±0.5 †	35.3 ±1.0 †	36.4 ±0.8	38.7 ±0.2 ††
PCPA	6	38.0 ±0.2	38.1 ±0.2	38.2 ±0.3	38.3 ±0.3	38.1 ±0.2
PCPA + morphine	6	38.1 ±0.2	38.9 ±0.5 *** †	39.6 ±0.3 *** †††	38.8 ±0.2 ** †††	38.3 ±0.2 †

Either saline (5 ml/kg) or morphine (20 mg/kg) was administered subcutaneously at 0 h. PCPA (320 mg/kg) was injected intraperitoneally 48 h before 0 h. The body temperature measurements were begun one hour before 0 h. Values before 0 h of each treatment are omitted here since they were essentially the same as data depicted in Figure 1. Data of a group which had received saline are those depicted in Figure 1, but are included here for ease of comparison. Values are the mean with s.e. mean. n = number of animals tested.
†, $P<0.05$; ††, $P<0.02$; †††, $P<0.01$ when compared with values of a group which had received saline. **, $P<0.02$; ***, $P<0.01$ comparing PCPA + morphine with morphine alone.

Table 2 The effect of pethidine on the mean rectal temperature of rats and its modification by *p*-chlorophenylalanine (PCPA); ambient temperature 21°C

Treatment	n	*0 h*	*1 h*	*2 h*	*3 h*	*4 h*
Saline	6	37.7 ±0.2	37.7 ±0.1	37.8 ±0.1	37.8 ±0.1	37.8 ±0.1
Pethidine (25 mg/kg)	6	37.7 ±0.2	37.4 ±0.3	37.7 ±0.2	37.7 ±0.2	37.5 ±0.2
Pethidine (50 mg/kg)	6	37.7 ±0.3	37.6 ±0.4	37.2 ±0.3	37.3 ±0.3	37.7 ±0.2
PCPA + pethidine (25 mg/kg)	6	38.2 ±0.4	39.0 ±0.5 ** ††	38.8 ±0.3 ** †	38.4 ±0.2 *	38.2 ±0.3
PCPA + pethidine (50 mg/kg)	6	38.0 ±0.2	39.0 ±0.3 *** †††	38.1 ±0.3 *	37.7 ±0.2	37.8 ±0.2
PCPA + 5-HTP	6	38.3 ±0.2	36.6 ±0.3 †††	37.1 ±0.2 ††	37.4 ±0.3	37.5 ±0.2
PCPA + 5-HTP + pethidine (25 mg/kg)	6	38.2 ±0.2	35.8 ±0.3 †††	35.8 ±0.2 °°° †††	36.2 ±0.4 ° †††	36.8 ±0.4 ††

Either pethidine or 5-hydroxytryptophan (5-HTP, 75 mg/kg) was administered subcutaneously at 0 h except in the experiment, listed at the foot of the table, in which pethidine was injected at 0.5 h (i.e., 30 min after 5-HTP). PCPA (320 mg/kg) was injected intraperitoneally 48 h before 0 h. Values of a group that had received saline are those depicted in Figure 1. Values are the mean with s.e. mean. n = number of animals tested.
†, $P<0.05$; ††, $P<0.02$; †††, $P<0.01$ when compared with values of a group that had received saline. *, $P<0.05$; **, $P<0.02$; ***, $P<0.01$ comparing PCPA + narcotic with corresponding narcotic alone. °, $P<0.05$; °°°, $P<0.01$ comparing PCPA + 5-HTP + pethidine with PCPA + 5-HTP.

Table 3 The effect of methadone on the mean rectal temperature of rats and its modification by *p*-chlorophenylalanine (PCPA); ambient temperature 21°C

Treatment	n	*0 h*	*1 h*	*2 h*	*3 h*
Saline	6	37.7 ±0.2	37.7 ±0.1	37.8 ±0.1	37.8 ±0.1
Methadone (4 mg/kg)	6	37.8 ±0.2	36.7 ±0.8	38.0 ±0.3	38.1 ±0.2
Methadone (8 mg/kg)	6	37.8 ±0.1	††† 35.1 ±0.2	††† 34.4 ±0.8	37.0 ±0.5
PCPA + methadone (4 mg/kg)	6	38.1 ±0.3	††† 39.2 ±0.2 **	†† 38.8 ±0.3	38.1 ±0.3
PCPA + methadone (8 mg/kg)	7	38.1 ±0.1	††† 35.8 ±0.4	37.8 ±0.5 ***	† 38.3 ±0.1 *
PCPA + 5-HTP + methadone (4 mg/kg)	6	38.2 ±0.3	††† 35.9 ±0.3	††† 35.8 ±0.4 °°	37.1 ±0.4

Either methadone or 5-hydroxytryptophan (5-HTP, 75 mg/kg) was administered subcutaneously at 0 h except in the experiment, listed at the foot of the table, in which methadone was injected at 0.5 h (i.e., 30 min after 5-HTP). PCPA (320 mg/kg) was injected intraperitoneally 48 h before 0 h. Values of a group that received saline are those depicted in Figure 1. Values are the mean with s.e. mean. n = number of animals tested.
†, $P<0.05$; ††, $P<0.02$; †††, $P<0.01$ when compared with values of a group that had received saline. *, $P<0.05$; **, $P<0.02$; ***, $P<0.01$ comparing PCPA + narcotic with corresponding narcotic alone. °°, $P<0.02$ comparing PCPA + 5-HTP + methadone with PCPA + 5-HTP.

Table 4 The effect of morphine on the mean rectal temperature of rats and its modification by *p*-chlorophenylalanine (PCPA); ambient temperature 12°C

Treatment	n	*0 h*	*0.5 h*	*1 h*	*2 h*	*3 h*
Saline	6	38.0 ±0.1	*38.2* ±0.1	38.0 ±0.2	37.9 ±0.3	38.1 ±0.2
Morphine	6	37.9 ±0.2	††† 37.2 ±0.3	36.8 ±0.5	36.5 ±0.8	37.9 ±0.4
PCPA	6	38.2 ±0.2	38.0 ±0.2	38.1 ±0.2	38.3 ±0.1	38.1 ±0.1
PCPA + morphine	7	38.1 ±0.2	38.0 ±0.2	38.4 ±0.5 *	† 38.7 ±0.2 **	38.5 ±0.2

Morphine (10 mg/kg) was administered subcutaneously at 0 h. PCPA (320 mg/kg) was injected intraperitoneally 48 h before 0 h. Values of a group that had received saline are those depicted in Figure 2. Values are the mean with s.e. mean. h = number of animals tested.
†, $P<0.05$; †††, $P<0.01$ when compared with values of a group received saline. *, $P<0.05$; **, $P<0.02$ comparing PCPA + morphine with morphine alone.

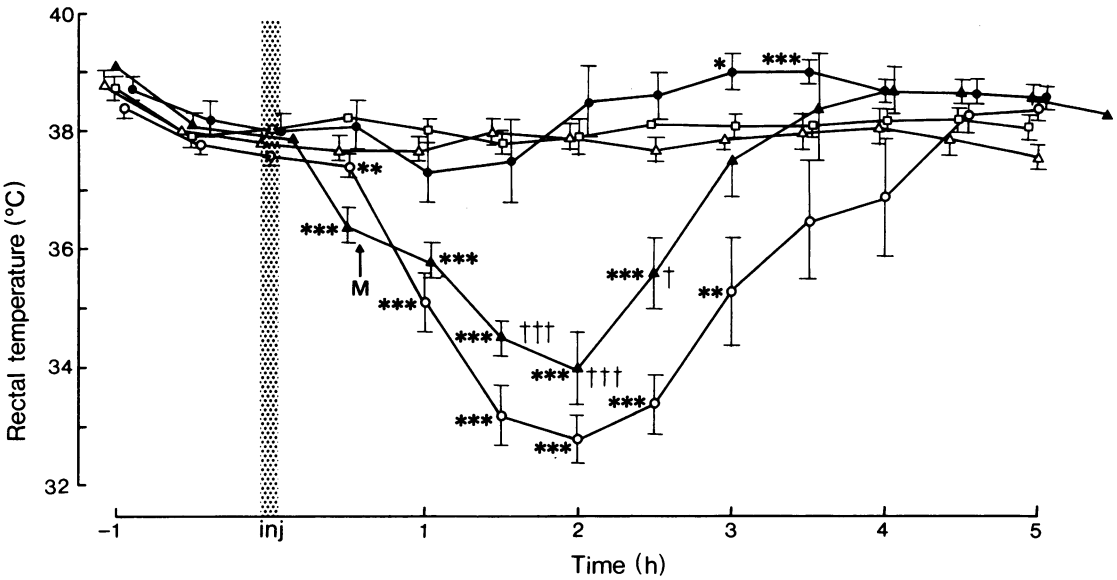

Figure 2 The effect of morphine on the mean rectal temperature of rats and its modification by *p*-chlorophenylalanine (PCPA), 5-hydroxytryptophan (5-HTP) and naloxone at 12°C. Acute administration of drugs or saline at stippled bar. One group of rats ($n=6$) received saline (5 ml/kg, s.c., □). Another group ($n=6$) received morphine (20 mg/kg s.c., ○). A third group ($n=8$) was pretreated with PCPA (320 mg/kg i.p.) 48 h before morphine administration (●). A fourth group ($n=6$) was pretreated with PCPA 48 h before 5-HTP (75 mg/kg, s.c.) administration (at stippled bar) and then received morphine (M, at arrow) 30 min after 5-HTP administration (▲). A fifth group ($n=6$) was pretreated with naloxone (1 mg/kg s.c.) immediately before morphine administration (△). Symbols and vertical bars represent means with s.e. mean.
*, $P<0.05$; **, $P<0.02$; ***, $P<0.01$ when compared with values of a group received saline. †, $P<0.05$; †††, $P<0.01$ comparing PCPA + 5-HTP + morphine with PCPA + 5-HTP.

(Table 2), body temperatures of a group that had received PCPA, 5-HTP and morphine were not significantly different from animals that had received PCPA and 5-HTP. On the other hand, the body temperatures of a group given PCPA, 5-HTP and pethidine or methadone were significantly lower than those injected with PCPA and 5-HTP (Tables 2 and 3).

Effects of narcotic analgesics on the body temperature of rats at low ambient temperature and its modification by pretreatment with p-chlorophenylalanine and 5-hydroxytryptophan

Values of the mean rectal temperature of control (saline-treated) rats kept at a low ambient temperature (12°C) were essentially the same as those kept at room temperature throughout the experimental period (Figures 1 and 2). Data of PCPA pretreated rats exposed to a low environmental temperature were also not significantly different from those kept at room temperature (Tables 1 and 4). Effects of narcotic analgesics on body temperature of rats maintained at a low ambient temperature, however, were clearly different from those kept at room temperature. All narcotics produced a significant fall in body temperature of rats maintained in an ambient temperature of 12 ± 0.2°C with $50\pm2\%$ relative humidity (Figure 2 and Tables 4, 5 and 6). Pretreatment of rats with naloxone (1 mg/kg, s.c.), a specific narcotic antagonist, immediately before narcotic administration prevented the morphine-induced hypothermia (Figure 2) and greatly reduced the hypothermic effects of pethidine and methadone (Tables 5 and 6). The intraperitoneal administration of 320 mg/kg of PCPA 48 h before the narcotic injection not only reduced the hypothermic response to narcotics (Figure 2 and Tables 4, 5 and 6), but the animals exhibited significant hyperthermic response to morphine or to a lower dose of methadone (Figure 2 and Table 6). When rats pretreated with PCPA were given 5-HTP 30 min before administration of morphine, a typical hypothermic response to morphine was restored (Figure 2). The administration of 5-HTP alone to PCPA pretreated rats produced a fall in body temperature (Table 5). However, the body tem-

peratures of a group which had received PCPA, 5-HTP and either morphine, pethidine or methadone were significantly lower than those which received PCPA and 5-HTP (Figure 2 and Tables 5 and 6).

Discussion

The results of the present investigation suggest that narcotic analgesics such as morphine, pethidine and methadone are likely to have both stimulant and depressant actions on the body temperature of rats and that 5-HT may be involved in the narcotic-induced hypothermia not only at room temperature but also at low ambient temperature.

The involvement of 5-HT in narcotic-induced hypothermia is suggested by the fact that the usual marked hypothermic response of rats to narcotic analgesics is inhibited by the pretreatment of the animals with PCPA, which depletes 5-HT stores (Koe & Weissman, 1966). Additionally, the administration of 5-HTP, a 5-HT precursor, to the animals pretreated with PCPA restored the typical hypothermic response to narcotic analgesics. Moreover, hypothermia can be

Table 5 The effect of pethidine on the mean rectal temperature of rats and its modification by naloxone or *p*-chlorophenylalanine (PCPA); ambient temperature 12°C

Treatment	n	*0 h*	*1 h*	*2 h*	*3 h*	*4 h*	*5 h*
Saline	6	38.0 ±0.1	38.0 ±0.2	37.9 ±0.3	38.1 ±0.2	38.2 ±0.2	38.1 ±0.2
Pethidine (25 mg/kg)	5	38.0 ±0.2	††† 35.7 ±0.3	† 36.7 ±0.5	37.4 ±0.4	37.7 ±0.1	37.9 ±0.3
Pethidine (50 mg/kg)	6	37.5 ±0.3	††† 34.4 ±0.7	††† 33.6 ±0.9	††† 34.8 ±0.8	†† 36.0 ±0.7	36.9 ±0.6
Naloxone	6	38.4 ±0.1	38.1 ±0.1	38.2 ±0.1	38.1 ±0.2	38.3 ±0.2	38.3 ±0.1
Naloxone + pethidine (50 mg/kg)	6	37.9 ±0.2	††† 36.8 ±0.3 XX	††† 36.3 ±0.3 X	††† 36.1 ±0.2	†† 37.2 ±0.3	†† 37.3 ±0.2
PCPA + pethidine (25 mg/kg)	6	38.1 ±0.1	37.8 ±0.3 ***	37.7 ±0.3	37.8 ±0.2	37.9 ±0.2	38.0 ±0.1
PCPA + pethidine (50 mg/kg)	5	38.4 ±0.2	††† 36.1 ±0.4 *	††† 35.9 ±0.3	††† 36.3 ±0.3	37.7 ±0.3	38.4 ±0.2
PCPA + 5-HTP	5	37.9 ±0.2	††† 36.2 ±0.4	† 36.8 ±0.5	37.6 ±0.3	38.1 ±0.1	37.9 ±0.1
PCPA + 5-HTP + pethidine (25 mg/kg)	5	37.9 ±0.1	††† 35.9 ±0.3	††† 35.5 ±0.4 °	††† 36.2 ±0.3 °°	††† 37.2 ±0.2 °°°	37.5 ±0.4

Pethidine, naloxone (1 mg/kg) or 5-hydroxytryptophan (5-HTP, 75 mg/kg) was injected subcutaneously at 0 h except in the experiment, listed at the foot of the table, in which pethidine was injected at 0.5 h (i.e., 30 min after 5-HTP). PCPA (320 mg/kg) was administered intraperitoneally 48 h before 0 h. Values of a group that had received saline are those depicted in Figure 1. Values are the mean with s.e. mean. *n* = number of animals tested.

†, $P<0.05$; ††, $P<0.02$; †††, $P<0.01$ when compared with values of a group that received saline. X, $P<0.05$; XX, $P<0.02$ comparing naloxone + pethidine with pethidine. *, $P<0.05$; ***, $P<0.01$ comparing PCPA + narcotic with corresponding narcotic alone. °, $P<0.05$; °°, $P<0.02$; °°°, $P<0.01$ comparing PCPA + 5-HTP + pethidine with PCPA + 5-HTP.

shown in rats after intraventricular (Feldberg & Lotti, 1967) or intracisternal (Bruinvels, 1970) administration of 5-HT. Finally, it has been reported that morphine accelerates the turnover rate of 5-HT in rat brain (Yarbrough, Buxbaum & Sanders-Bush, 1973; Goodlet & Sugrue, 1974; Sawa & Oka, 1976), pethidine inhibits the uptake mechanism of 5-HT-containing neurones (Carlsson & Lindqvist, 1969), and methadone inhibits the uptake of [^{3}H]-5-HT by synaptosomes (Ciofalo, 1974).

On the other hand, 5-hydroxytryptamine does not appear to play an important role in the maintenance of body temperature in rats kept both at room and at a low ambient temperature since the administration of PCPA alone had no effect on the body temperature at these environmental temperatures.

A small dose of morphine has been reported to produce hyperthermia in the rat (Hermann, 1942; Cox, Ary, Chesarek & Lomax, 1976), and, even with a large dose of morphine, a prominent hyperthermia can be produced in morphine-tolerant rats (Gunne, 1960; Oka *et al.*, 1972). Thus, morphine may have both hyperthermic and hypothermic effects in rats. Moreover, small, moderate or large doses of morphine produce, respectively, an elevation of, no significant change in or a fall in body temperature of rats. Thus, the apparent lack of effect of moderately large doses of morphine may be due to the simultaneous activation of hyperthermic and hypothermic responses of equal magnitude. If this hypothesis were correct, the hyperthermia induced by the administration of morphine to PCPA pretreated rats may result from the suppresssion of the hypothermic response to morphine. Although a hyperthermic action of

Table 6 The effect of methadone on the mean rectal temperature of rats and its modification by naloxone or *p*-chlorophenylalanine (PCPA); ambient temperature 12°C

Treatment	n	*0 h*	*0.5 h*	*1 h*	*1.5 h*	*2.5 h*	*5 h*
Saline	6	38.0 ±0.1	38.2 ±0.1	38.0 ±0.2	37.8 ±0.2	38.1 ±0.1	38.1 ±0.2
Methadone (4 mg/kg)	5	37.9 ±0.2	††† 35.8 ±0.2	††† 34.7 ±0.7	35.6 ±1.2	37.5 ±0.3	38.3 ±0.1
Methadone (8 mg/kg)	7	37.7 ±0.1	††† 35.1 ±0.2	††† 32.5 ±0.3	††† 31.6 ±0.6	††† 34.8 ±0.7	37.7 ±0.2
Naloxone + methadone (8 mg/kg)	6	37.9 ±0.2	††† 37.3 ±0.1 XXX	††† 37.1 ±0.2 XXX	37.3 ±0.2 XXX	37.9 ±0.2 XXX	37.8 ±0.2
PCPA + metahdone (4 mg/kg)	6	38.1 ±0.3	z 38.1 ±0.3 ***	†† 38.6 ±0.5 ***	39.0 ±0.3 **	38.6 ±0.3 *	38.5 ±0.1
PCPA + methadone (8 mg/kg)	6	38.2 ±0.2	††† 36.2 ±0.1 ***	††† 33.5 ±0.5	††† 32.3 ±1.5	36.3 ±1.1	38.5 ±0.3 *
PCPA + 5-HTP + methadone (4 mg/kg)	6	38.0 ±0.3	††† 36.9 ±0.1	††† 34.3 ±0.5 °°	††† 33.0 ±0.6 °°°	††† 32.9 ±0.5 °°°	37.4 ±0.4

Methadone, naloxone (1 mg/kg) or 5-hydroxytryptophan (5-HTP, 75 mg/kg) was injected subcutaneously at 0 h except in the experiment, listed at the foot of the table, in which methadone was injected at 0.5 h (i.e., 30 min after 5-HTP). PCPA (320 mg/kg) was administered intraperitoneally 48 h before 0 h. Values of a group that had received saline are those depicted in Figure 1. Values are the mean with s.e. mean. *n* = number of animals tested.

††, $P<0.02$; †††, $P<0.01$ when compared with values of a group that had received saline. XXX, $P<0.01$ comparing naloxone + methadone with methadone alone. *, $P<0.05$; **, $P<0.02$; ***, $P<0.01$ comparing PCPA + narcotic with corresponding narcotic alone. °°, $P<0.02$; °°°, $P<0.01$ comparing PCPA + 5-HTP + methadone with PCPA + 5-HTP.

pethidine or methadone on the body temperature of rats has not been reported previously, it is concluded from the results of the present investigation that both pethidine and methadone, as well as morphine, may have biphasic effects on the body temperature of rats since both of these narcotic analgesics also produce hyperthermia in PCPA pretreated rats.

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