Dettmar, P. W., Lynn, A. G., Tulloch, I. F. (1981) Br. J. Pharmacol. 74: 843–844P

Doxey, J. C., Everitt, J., Metcalf, G. (1978) Eur. J. Pharmacol. 51: 1–10

Doxey, J. C., Roach, A. G., Smith, C. F. C. (1983) Br. J. Pharmacol. 78: 489–505

Drew, G. M. (1976) Eur. J. Pharmacol. 36: 313–320

Drew, G. M., Gower, A. J., Marriott, A. S. (1979) Br. J. Pharmacol. 67: 133–141

Handley, S. L., Brown, J. (1982) Neuropharmacology 21: 507–510

Michel, A. D., Nahorski, S. R., Whiting, R. L. (1981) Br. J. Pharmacol. 74: 485–486P

Paciorek, P. M., Shepperson, N. B. (1983) Ibid. 79: 12–14

Rhodes, K. F., Waterfall, J. F. (1978) J. Pharm. Pharmacol. 30: 516–517

Witkin, L. B., Spitaletta, P., Plummer, A. J. (1959) J. Pharmacol. Exp. Ther. 126: 330–333

J. Pharm. Pharmacol. 1984, 36: 481–483
Communicated December 6, 1983

Is the hypothermic effect of α-methyldopa mediated by opioid peptides?

J. M. A. SITSEN*, F. P. NIJKAMP, *Rudolf Magnus Institute for Pharmacology, Medical Faculty, State University of Utrecht, Vondellaan 6, 3521 GD Utrecht, The Netherlands*

At an ambient temperature of 21 °C α-methyldopa (25–200 mg kg^{-1}) induces a dose-dependent decrease in body temperature in rats. A relationship between adrenergic and opioid neuronal systems has been reported. Therefore, in this study the hypothesis that α-methyldopa produces hypothermia through release of endogenous opioid peptides has been investigated using the opiate antagonist naltrexone. The hypothermic effect of α-methyldopa is potentiated by naltrexone pointing to antagonism of an hyperthermic acting opioid system. However, at an ambient temperature of 6 °C, pretreatment with naltrexone did not significantly alter the hypothermic effect of α-methyldopa. Although the hypothesis proved not to be correct, it is concluded that depending on ambient temperature opioid peptides are involved in the determination of the ultimate effect of α-methyldopa on body temperature in rats.

Several neuronal systems are involved in the maintenance of constant body temperature in mammals. Both classical neurotransmitters such as noradrenaline, 5-hydroxytryptamine, dopamine and histamine and neuropeptides such as endorphins, substance P, cholecystokinin, bombesin and somatostatin have been studied from this aspect. The centrally acting adrenergic agonists α-methyldopa (Nijkamp et al 1975) and clonidine (Laverty & Taylor 1969; Zacny 1982) have been shown to lower body temperature in rats. The opioid peptide β-endorphin, after intracerebroventricular administration, also causes changes in body temperature in rats, high doses resulting in hypothermia and low doses in hyperthermia (Tseng et al 1979). Evidence is accumulating for a relationship between adrenergic and opioid systems. The fall in blood pressure observed after administration of α-methyldopa and its active metabolite α-methylnoradrenaline is prevented by pretreatment with the opiate antagonist naloxone (Petty & de Jong 1982) and the α-agonist clonidine causes analgesia in rats (Paalzow & Paalzow 1976; Fielding et al 1978) and alleviates opiate withdrawal symptoms in morphine-treated animals (Fielding et al 1978). Furthermore, adrenergic agonists such as α-methylnoradrenaline cause release of opioid peptides from the pituitary of the rat both in-vivo and in-vitro (Pettibone & Mueller 1982). For these reasons we investigated a possible interaction between α-adrenergic and endorphin systems involved in the regulation of body temperature in the rat by using the centrally acting α-agonist α-methyldopa and the opiate antagonist naltrexone.

Methods

Male Wistar rats (Wu-Cpb, Central Breeding Laboratories TNO, Zeist, The Netherlands), 225–275 g, were maintained at an ambient temperature of 22 °C. During the experiments the rats were individually housed in a quiet room at an ambient temperature of 21·0 ± 0·5 °C or 6·0 ± 0·5 °C. After an adaptive period of 30 min, core temperature was measured with a precalibrated rectal probe inserted 6 cm beyond the anus (Tele-Thermometer, Yellow Springs Instruments Co., Yellow Springs, Ohio, USA). Drugs were administered between 10.30 and 11.00 am and at hourly intervals core temperature was measured for 6 h post administration. Drugs used were: naltrexone hydrochloride (Endo Laboratories Inc., Garden City, New York, USA), α-methyldopa (Merck Sharp and Dohme, Haarlem, The Netherlands) and morphine sulphate (O.P.G., Utrecht, The Netherlands). For naltrexone and morphine solutions, 0·9% NaCl (saline) was used as vehicle, α-methyldopa was dissolved in distilled water in the appropriate concentration. Naltrexone or saline was administered subcutaneously (0·1 ml/100 g) 15 min before α-methyldopa or morphine (or vehicle), that was injected intraperitoneally. To provide evidence for an opiate antagonist action of naltrexone experiments were also carried out in which naltrexone was administered

* Correspondence.

subcutaneously followed by morphine intraperitoneally. One way analysis of variance and a Student-Newman-Keuls procedure were used for statistical analysis of results.

Results

As shown in Fig. 1, α-methyldopa (25 to 200 mg kg^{-1} i.p.) caused a dose-dependent decrease in body temperature, maximum responses being reached later with higher doses. Administration of naltrexone (1 and 10 mg kg^{-1} s.c.) as a single drug did not result in changes in body temperature significantly different from controls, either at 21 °C or at 6 °C ambient temperature, the exception being the 1 h post administration reading in the high dose naltrexone group at low ambient temperature (−0·8 ± 0·1 vs −0·2 ± 0·1 °C for naltrexone-treated and control rats respectively; $P <$ 0·01).

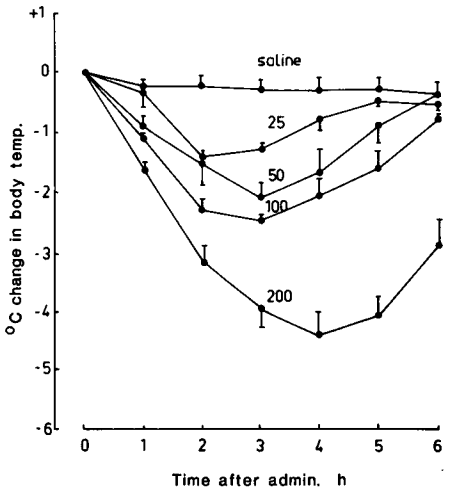

FIG. 1. Mean changes in body temperature from pre-injection values in groups of rats (n = 5) after intraperitoneal administration of saline and different doses of α-methyldopa (25 = 25 mg kg^{-1} etc.). Ambient temperature 21 ± 0·5 °C. Mean baseline temperatures in the groups were in the range of 37·7–37·9 °C (without statistically significant differences).

The subcutaneous administration of saline followed by morphine (10 mg kg^{-1} i.p.) in an ambient temperature of 21 °C resulted in a rise of body temperature, the change being maximally +1·5 ± 0·2 °C at 2 h post administration and gradually returning to base-line values (n = 8, $P <$ 0·01 vs saline). A higher dose of morphine (20 mg kg^{-1} i.p.) resulted in a decrease of body temperature and death from respiratory depression in four of eight rats. The maximal changes was −2·4 ± 0·6 °C, reached at 2 h post administration ($P <$ 0·01 vs saline). These morphine-induced effects on body temperature and respiration were abolished by pretreatment with naltrexone (both 1 and 10 mg kg^{-1} s.c.).

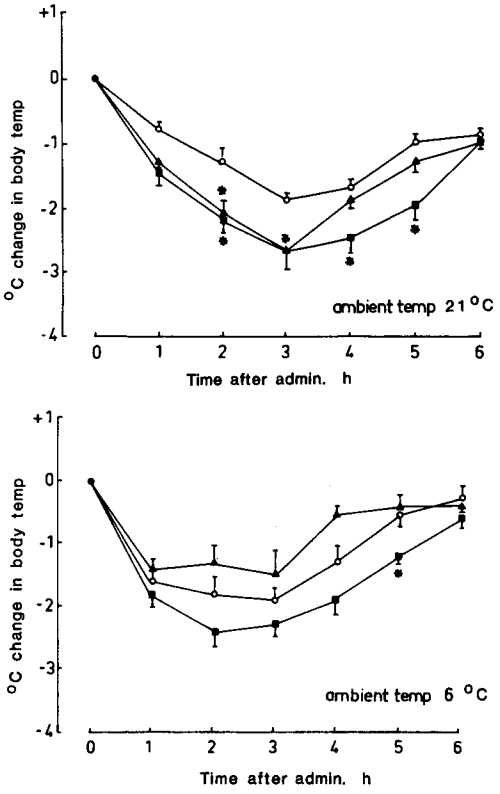

FIG. 2. Mean changes in body temperature from pre-injection values in groups of rats (n = 5) after subcutaneous administration of saline (○——○) or naltrexone 1(▲——▲) and 10(■——■) mg kg^{-1} followed after 15 min by intraperitoneal administration of α-methyldopa (50 mg kg^{-1}). Ambient temperature 21 ± 0·5 °C (upper) or 6 ± 0·5 °C (lower). Mean baseline temperatures in the groups were in the range of 37·6–37·9 °C (without statistically significant differences).

An intermediate α-methyldopa dose (50 mg kg^{-1} i.p.) was chosen to study the effect of naltrexone on α-methyldopa-induced hypothermia. At an ambient temperature of 21 °C, naltrexone, both 1 and 10 mg kg^{-1}, potentiated the hypothermic effect of α-methyldopa to a similar extent, the effect lasting longer with the higher dose of naltrexone (Fig. 2, upper panel). At an ambient temperature of 6 °C, the results are more complex (Fig. 2, lower panel). Neither dose of naltrexone (with the exception of the highest dose at 5 h after administration) caused changes in body temperature significantly different from controls receiving saline vehicle (s.c.) and also α-methyldopa (50 mg kg^{-1} i.p.). Differences between the high and the low dose were, however, statistically significant, the body temperatures in the rats receiving low dose naltrexone being higher than in those receiving the high dose. When α-methyldopa was used in a dose of 200 mg kg^{-1}, no interaction with naltrexone (1 and 10 mg kg^{-1}) was elicited, either at 21 °C or at 6 °C (results not shown).

Discussion

Our results indicate that at an ambient temperature of 21 °C the hypothermic effect of a moderate dose of α-methyldopa is potentiated by the opiate antagonist naltrexone. Apparently, the hypothermic effect of α-methyldopa under these circumstances is not brought about by the release of an endogenous hypothermic opioid peptide, a mechanism that has been suggested to be involved in the hypotensive effect of α-methyldopa (Petty & de Jong 1982). Presumably, the hyperthermic action of an opioid system that counteracts the decrease in body temperature caused by α-methyldopa is antagonized, resulting in a further lowering of body temperature. After the high dose of α-methyldopa (200 mg kg^{-1}), resulting in a much greater hypothermic effect, this action is not elicited, possibly because the hyperthermic opioid system involved cannot effectively antagonize the ensuing enormous decrease in body temperature.

At an ambient temperature of 6 °C the situation is complex. A high dose of naltrexone disturbed the rats' ability to acclimatize to the change in ambient temperature in the first hour of the experiment (Thornhill et al 1980). This effect cannot explain our findings, since it is too small and only present in the first hour. Interestingly, the results obtained with low dose α-methyldopa (50 mg kg^{-1}) both at 21 °C and 6 °C are identical, the maximum effect being −1·9 °C and this was observed at the same time (3 h) after administration. Pretreatment with either low (1 mg kg^{-1}) or high (10 mg kg^{-1}) doses of naltrexone at an ambient temperature of 6 °C caused no effects that were significantly different from controls, with the exception of the 5 h measurement in the high dose naltrexone group. But between the two naltrexone treatments there was a significant difference in body temperature, the higher dose of naltrexone causing a lower temperature than the low dose. Although in this respect no firm conclusions can be drawn, these data may indicate that, at the low temperature, different opioid systems are involved, one hypo- and the other hyperthermic, being differently susceptible to the opiate antagonist naltrexone. It is of interest that both morphine (Van Ree et al 1976) and β-endorphin (Tseng et al 1979) cause hypo- and hyperthermic effects depending on dose and exact site of administration, as also shown by our present results. The low dose of morphine caused hyperthermia and the high dose hypothermia (and respiratory depression). Prior treatment with 1 or 10 mg kg^{-1} naltrexone abolished these effects, indicating that these actions of morphine are due to opiate receptor stimulation and that the naltrexone doses used are effective in opiate receptor antagonism. At the ambient temperature of 6 °C the high dose α-methyldopa resulted in slightly lower body temperatures than the low dose, whilst pretreatment with naltrexone did not significantly affect these results. Thus, the results obtained at 21 °C are confirmed.

In conclusion, although the hypothesis that the hypothermic effct of α-methyldopa is brought about by the release of endogenous opioid peptides proved not to be correct, it has been shown that under certain circumstances opioid peptide systems are involved in the determination of the ultimate effect of α-methyldopa on body temperature in rats.

REFERENCES

Fielding, S., Wilker, J., Hynes, H., Szewczak, M., Novick, Jr., W. J., Lal, H. (1978) J. Pharmacol. Exp. Ther. 207: 899–905

Laverty, R., Taylor, K. M. (1969) Br. J. Pharmacol. 35: 254–264

Nijkamp, F. P., Ezer, J. P., de Jong, W. (1975) Eur. J. Pharmacol. 31: 243–249

Paalzow, G., Paalzow, L. (1976) Naunyn Schmiedeberg's Arch. Pharmacol. 292: 119–126

Pettibone, D. J., Mueller, G. P. (1982) J. Pharmacol. Exp. Ther. 222: 103–108

Petty, M. A., de Jong, W. (1982) Clin. Sci. 63: 293S–295S

Thornhill, J. A., Cooper, K. E., Veale, W. L. (1980) J. Pharm. Pharmacol. 32: 427–430

Tseng, L. F., Ostwald, T. J., Loh, H. H., Li, C. H. (1979) Psychopharmacology 64: 215–218

Van Ree, J. M., Spaapen-Kok, W. B., de Wied, D. (1976) Neuroendocrinology 22: 318–324

Zacny, E. (1982) J. Pharm. Pharmacol. 34: 455–456