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α-Melanocyte-Stimulating Hormone (MSH) and [Nle^4,D-Phe^7]-α-MSH: Effects on Core Temperature in Rats

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RAIBLE, L. H. AND D. KNICKERBOCKER. *α-Melanocyte-stimulating hormone (MSH) and [Nle^4,D-Phe^7]-α-MSH: Effects on core temperature in rats.* PHARMACOL BIOCHEM BEHAV 44(3) 533-538, 1993.—The thermoregulatory effects of α-melanocyte stimulating hormone (MSH), its potent analog, [Nle^4,D-Phe^7]-α-MSH (NDP-MSH), and the 1-7, 4-10, and 7-13 amino acid fragments of NDP-MSH were examined by administering these substances to the anterior hypothalamic-preoptic area (AHPOA) of rats. In Experiments 1a (MSH) and 1b (NDP-MSH), animals received 0, 0.5, 1, 5, 10, or 50 pM peptide in 0.5 μl sterile saline (n = 6/group), with core rectal temperatures being recorded 0, 10, 20, 30, 40, 50, and 60 min after injection. In Experiment 2, subjects received 5 pM NDP-MSH$_{1-7}$, NDP-MSH$_{4-10}$, NDP-MSH$_{7-13}$, NDP-MSH, or the vehicle, 0.5 μl sterile saline, in a counterbalanced fashion (n = 13). Results indicated a significant effect of dose for both MSH, $F(5, 30) = 2.81$, $p = 0.03$, and NDP-MSH, $F(5, 30) = 4.98$, $p = 0.002$. A Newman-Keul's analysis indicated that mean temperatures for all groups receiving MSH or NDP-MSH were significantly greater than for the group that received saline ($p < 0.05$). An analysis of the data from Experiment 2 indicated a significant effect of substance, $F(4, 48) = 17.31$, $p < 0.001$. Mean temperature of animals receiving NDP-MSH, the 4-10, or the 7-13 fragments, did not differ from each other but were significantly greater than mean temperatures for animals receiving sterile saline or the 1-7 fragment of NDP-MSH ($p < 0.05$).

α-Melanocyte-stimulating hormone [Nle^4,D-Phe^7]-α-MSH Hyperthermia Preoptic area Anterior hypothalamus Rat

SEVERAL decades of research have indicated that many of the peptides derived from proopiomelanocortin (POMC) exert important behavioral and physiological effects in a range of species. Adrenocorticotropic hormone (ACTH) influences grooming, metabolic rate, and locomotion (1,33). Both met- and leu-enkephalin increase cardiovascular reactivity (28) and can influence somatostatin release (22), and ACTH, β-endorphin, and the enkephalins have been found to exert thermoregulatory actions (3,7,8,21,33).

Although not as thoroughly studied as many of the POMC peptides, α-melanocyte-stimulating hormone (MSH) also shows promise as a peptide important to CNS functions in mammals. In the rat, MSH may play a role in sexual receptivity and false pregnancy (24,25,32,36). Research also suggests that, like ACTH, MSH can act in the CNS to influence learning and memory (2,14,29). Finally, Lipton and coworkers (11,15,23) found that MSH plays a role in thermoregulation and the immune response in the rabbit. Of particular interest is the finding that (Nle^4,DPhe^7]-MSH (NDP-MSH), an analog of great potency in frog and lizard skin assays (30), is also a potent antipyretic in the rabbit (16).

The few early experiments examining the effects of MSH on temperature in the rat (5,37,38) yielded inconsistent findings. However, the use of peripheral routes of MSH administration and other differences in testing procedures may account for the discrepant results of these early studies. The use of site-specific injections may produce more conclusive information about the effects of MSH on temperature in the rat, as suggested by the recent findings of Resch and Simpson (26), who noted that injections of MSH to the anterior hypothalamus-preoptic area (AHPOA) increased colonic temperature in female Sprague-Dawley rats. Because the brain region most clearly involved in the regulation of body temperature is the AHPOA (6,20,31), the present experiments also utilized this target site to examine the thermoregulatory effects of MSH, NDP-MSH, and the beginning, middle, and terminal fragments of NDP-MSH.

GENERAL METHODS

SUBJECTS

Subjects were male and female Long-Evans rats bred at Kalamazoo College (from stock purchased from Charles River Laboratories, Portage, MI). Animals were housed individu-

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ally in wiremesh cages on a reversed 12 L : 12 D cycle (lights off at 9:00 a.m.), with food and water available ad lib. Animals were approximately 120 days old at the time of surgery. Subjects were housed and tested in a temperature-controlled room (20 ± 1.2°C).

APPARATUS AND PROCEDURE

Ten minutes prior to IP administration of sodium pentobarbital anesthesia (65 mg/cc/kg), animals received an IP injection of atropine sulfate (4 mg/0.4 cc/kg). All guide cannulae were constructed from 23-ga stainless steel syringe needles. Pilot studies indicated that unilateral implants near the anterior border of the preoptic area could be obtained by using the following coordinates—A-P, 0.2 mm; M-L, 0.6 mm; D-V, −8.1 mm—with the incisor bar set at 0 mm. After unilateral cannulae implantation, subjects received bilateral ovariectomies. Accuracy of placements was initially assessed by determining pyrogenic response to 100 pM prostaglandin E2 (PGE2) (7). Animals that failed to show a pyrogenic response to PGE2 were not tested for responsiveness to MSH and were not used in the present studies.

To reduce temperature increases due to handling (4,9) animals were habituated to the testing procedure by conducting sham tests (no injections actually given). When animals consistently exhibited temperature changes of less than 0.3°C, they were considered habituated to the testing procedure. Testing was initiated 2–3 weeks after surgery and occurred 4–8 h after light offset. Core temperatures (6 cm) were taken using a lubricated Yellow Springs Instruments (YSI) 401 rectal probe and a YSI Telethermometer (Yellow Springs Instruments, Yellow Springs, OH). A washer fixed with dental acrylic to the probe at the appropriate depth allowed insertion to a consistent and accurate depth. Animals were allowed relatively free movement during temperature tests, with gentle pressure ensuring that probe depth was maintained during movement. Injections were administered via a Sage Instruments syringe pump at a rate of 1 μl/min. Animals were allowed free movement during the injection procedure. At least 24 h separated all tests.

All animals were sacrificed by sodium pentobarbital overdose and their brains removed and sectioned on a cryostat. Histological analysis indicated that of the six subjects that failed to respond to PGE2 only one had a placement within the AHPOA. This placement was the most posterior of all placements observed. One subject in Experiment 2 was found to have a placement outside of the AHPOA and her data were discarded. The remainder (30 for Experiment 1, 13 for Experiment 3) were found to have placements within the borders of the AHPOA.

Analyses were conducted on the difference scores, which were calculated by subtracting the core temperature immediately after injection from temperatures taken later.

EXPERIMENT 1

The research of Lipton on the thermoregulatory effects of MSH in the rabbit indicates that, depending upon dose, MSH can produce antipyretic and hypothermic effects. For example, 350 ng MSH (approximately 175 pM) administered into the POA reduces fever while higher doses (e.g., approximately 750 pM) induce hypothermia (10). NDP-MSH is even more potent in producing these effects in the rabbit (16). Recently, Resch and Simpson (26) reported that doses of MSH as low as 10 pg (approximately 5 fM) raise colinic temperature in the rat. Experiments 1a and 1b were designed to examine the dose and temporal parameters of MSH and NDP-MSH administration on temperature in the rat.

METHOD

Thirty animals that had exhibited a pyrogenic response to PGE2 were randomly divided into five groups. Subjects received either 0, 0.5, 1, 5, 10, or 50 pM MSH (Experiment 1a) or NDP-MSH (Experiment 1b), with core temperatures being taken 0, 10, 20, 30, 40, 50, and 60 min after injection. The same subjects were used in both experiments, with subjects being randomly assigned to new groups for Experiment 1b. MSH and NDP-MSH were purchased from Peninsula Laboratories (Belmont, CA).

RESULTS

An examination of Fig. 1 suggests that both MSH and NDP-MSH elevate body temperature. This effect was seen within 10 min of injection for all doses, although it appears most pronounced for the 1-pM dose. Indeed, an examination of the maximum temperature change for each dose of MSH and NDP-MSH reveals that the middle range of doses was the most effective in inducing hyperthermia (see Fig. 2). The hyperthermic effects of MSH and NDP-MSH appear to stabilize by 20–30 min after injection and lasted throughout the 60-min testing period. There does not appear to be a large difference in the hyperthermic effects produced by MSH and NDP-MSH, although the lower doses of NDP-MSH appear somewhat more effective than those of MSH.

An analysis of variance (ANOVA) performed on the data indicated a significant effect of dose [$F(5, 30) = 2.81$, $p = 0.03$ (MSH); $F(5, 30) = 4.98$, $p = 0.002$ (NDP-MSH)], with the control group showing a significantly lower temperature change than all other groups. In animals receiving NDP-MSH, those receiving the 1-pM dose exhibited a significantly greater mean temperature than did other groups receiving NDP-MSH.

EXPERIMENT 2

The contrasting effects of MSH on temperature in the rat and rabbit may reflect species differences in the active sequences of MSH or in the response to the active sequences of MSH. Lipton and coworkers (10,27) suggested that, in the rabbit the 11-13 amino acids in MSH are the most essential for the thermoregulatory action. Further, although the 4-10 sequence failed to alter temperature in the rabbit NDP-MSH, with modifications at sites 4 and 7, was 10 times more potent in its antipyretic activity than was MSH (18). It is interesting to note that in the rat $ACTH_{4\text{-}10}$ ($MSH_{4\text{-}10}$) did not alter grooming behavior but that replacement of L-Phe at position 7 with D-Phe did increase grooming behavior (13). Thus, structural modifications can clearly alter the activity of the 4-10 segment. To further examine the importance of various fragments of the NDP-MSH molecule in the hyperthermia observed in the rat, the present experiment examined the effects of the beginning, middle, and end sequences of the NDP-MSH molecule on core temperature.

METHOD

Fourteen subjects that had responded to PGE2 and were not used for the previous experiment were utilized. Subjects were administered 5 pM NDP-MSH, NDP-$MSH_{1\text{-}7}$, NDP-$MSH_{4\text{-}10}$, NDP-$MSH_{7\text{-}13}$, or the vehicle, 0.5 μl sterile saline. NDP-MSH and its fragments were supplied by Dr. Tomi Saw-

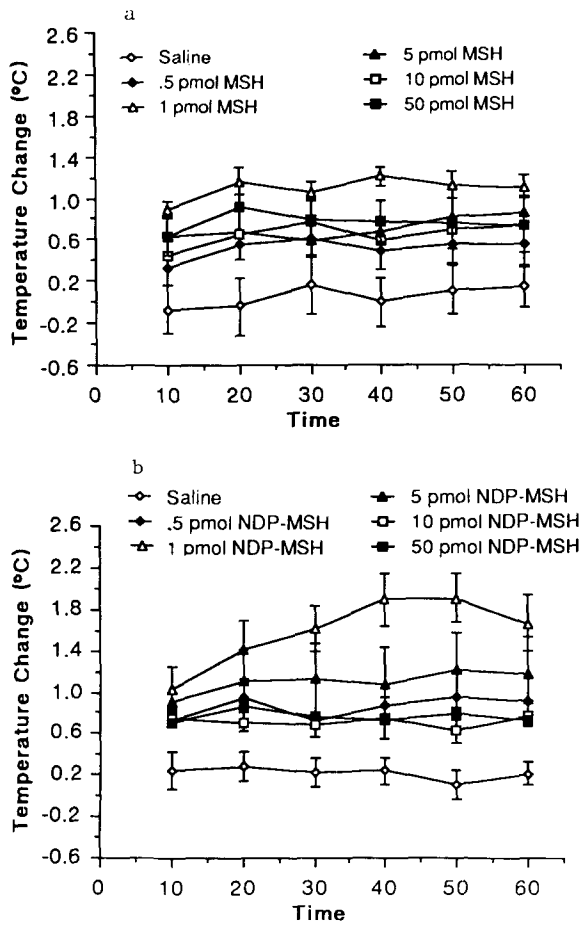

FIG. 1. a and b. Mean core temperature change after anterior hypothalamic-preoptic area administration of varying doses of α-melanocyte-stimulating hormone (MSH) and [Nle^4,D-Phe^7]-MSH (NDP-MSH). Subjects received 0.5 μl sterile saline or 0.5, 1, 5, 10, or 50 pM MSH (top) or NDP-MSH (bottom) in 0.5 μl sterile saline. Core temperatures (6-cm depth) were taken 0, 10, 20, 30, 40, 50, and 60 min after injection. Scores represent the differences between temperatures at time 0 and temperatures at each of the additional times. For both MSH and NDP-MSH, the mean temperatures for the control group were significantly lower than those for all other doses ($p < 0.05$). The mean for the 1-pM NDP-MSH group was significantly greater than that for other groups ($p < 0.05$).

yer of The Upjohn Co. (Kalamazoo, MI). Temperatures were taken 0 and 30 min after injection. One subject was later eliminated when it appeared that the implant site was not within the AHPOA.

RESULTS

An examination of the data suggests that NDP-MSH and its 4-10 and 7-13 fragments elevated body temperature while saline and the 1-7 fragment of NDP-MSH did not (see Fig. 3).

An ANOVA revealed a significant effect of fragment, $F(4, 48) = 17.31$, $p < 0.001$. A Newman-Keul's analysis revealed that the mean temperatures after administration of NDP-MSH and the 4-10 and 7-13 fragments did not differ from each other but were significantly greater ($p < 0.05$) than mean temperatures after administration of saline and the 1-7 fragment. Mean temperatures after administration of saline and the 1-7 fragment were also not significantly different.

GENERAL DISCUSSION

The results of Experiment 1 suggested that MSH and NDP-MSH increased core temperature in the rat. This contrasts with the antipyretic and hypothermic effects of MSH and NDP-MSH observed in the rabbit (16,18,23). However, it is consistent with findings that in the rat hyperthermia is produced by MSH (26) and by ACTH and $ACTH_{1-24}$ [(9,17), but see (34,35)], which contain MSH as their first 13 amino acids. It should be noted that in the rabbit MSH and ACTH also produce similar effects, with ACTH inducing hypothermia (19). Thus, within species the actions of MSH and ACTH are similar. Indeed, the thermoregulatory effects of ACTH may be the result of ACTH being cleaved to MSH.

The results of Experiment 1 also indicated that MSH and NDP-MSH acted within 10 min to elevate temperatures, with the 1- and 5-pM doses being more effective that the lower and higher doses. Further, the hyperthermic effects of MSH and NDP-MSH persisted throughout the 60-min test period. The time course findings of the present experiment resemble those of Colbern and Twombly (9), who found that ICV administration of 3 μg $ACTH_{1-24}$ increased core temperature in rats within 10 min. However, in their study core temperatures returned to baseline in approximately 1 h. The more rapid return to baseline temperatures seen in their study may reflect differences in the peptides used and/or differences in the route of administration. That low doses of NDP-MSH appear to produce somewhat greater hyperthermia than low doses of MSH is consistent with evidence indicating increased potency of NDP-MSH due to resistance to degradation by brain enzymes.

Experiment 2 indicates that both the 4-10 and the 7-13 fragments of NDP-MSH increase core temperature in the rat. Lipton and coworkers, utilizing MSH, found the 4-10 fragment to be inactive and the 7-13 fragment active in the rabbit (10,18,26). Indeed, it appears that the 11-13 fragment of MSH is most essential for the antipyretic action of MSH in the rabbit (27). Thus, the finding that $NDP\text{-}MSH_{4-10}$ is active in the rat appears to be in contrast to findings in the rabbit. However, this is not necessarily the case. Research indicates that while $ACTH(MSH)_{4-10}$ does not effect grooming in the rat, D-Phe^7-$ACTH(MSH)_{4-10}$ does (13). Recall that in the rabbit NDP-MSH, which contains the D-Phe^7 modification as well as a Nle^4 modification, is 10 times more potent in reducing fever than is MSH (8). Clearly, modifications outside the 11-13 amino acid sequence can alter thermoregulatory potency of the molecule in the rabbit. In view of these findings, it seems likely that $NDP\text{-}MSH_{4-10}$ would exert antipyretic effects in the rabbit, even though MSH_{4-10} does not. Thus, although the thermoregulatory effects observed in rats and rabbits differ, there may be consistency in the structural aspects of the molecule that produce the thermoregulatory effects in both species. Certainly, the C-terminal end of these molecules appears to be the most crucial for thermoregulatory action, regardless of species.

The temperature-increasing effects of MSH observed in these studies are of general interest in light of the known effects of both ACTH and MSH on grooming behavior and of ACTH on temperature. Colbern and Twombly (9) found that in the rat temperature increases produced by $ACTH_{1-24}$ were accompanied by increases in head and body grooming, responses that can serve to decrease body temperature. However, the effects of $ACTH_{1-24}$ on both grooming and tempera-

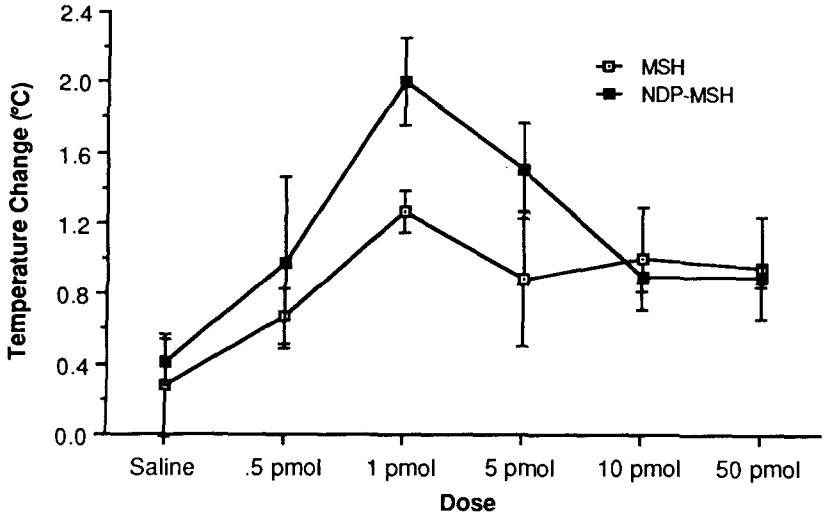

FIG. 2. Maximum core temperature change as a function of dose. Subjects received 0.5 μl sterile saline or 0.5, 1, 5, 10, or 50 pM αmelanocyte-stimulating hormone (MSH) or [Nle^4,D-Phe^7]-MSH (NDP-MSH) in 0.5 μl sterile saline. Core temperatures (6-cm depth) were taken 0, 10, 20, 30, 40, 50, and 60 min after injection. Scores represent the maximum temperature change seen for each peptide at each dose.

ture could be disrupted by SC injections of saline (9), which could explain why others (33,34) sometimes failed to note ACTH-induced increases in core temperature. Work in our laboratory also indicated that stressors could diminish the effects of MSH administration. Indeed, such findings led us to incorporate fairly lengthy habituation procedures in the present experiments. It should be noted that we did not observe unusual levels of grooming behavior, although it is possible that the testing procedures of both experiments would interfere with the display of grooming behavior.

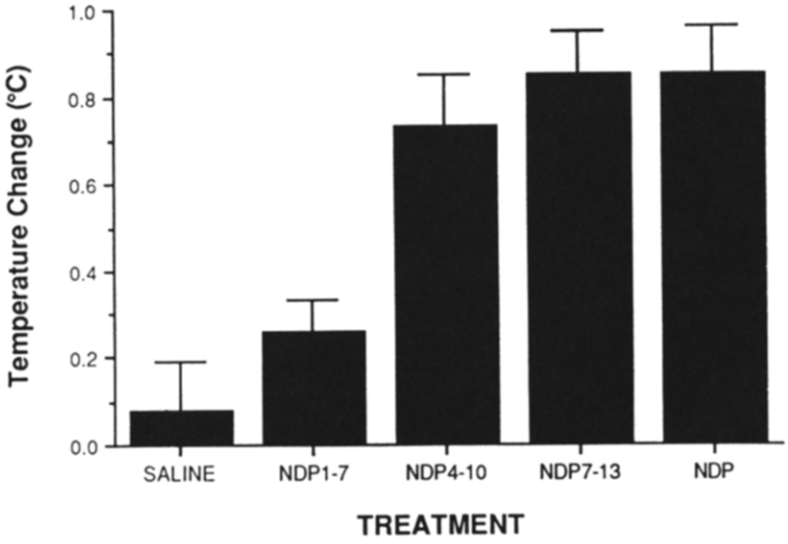

FIG. 3. Mean core temperature changes after anterior hypothalamic-preoptic area administration of [Nle^4,D-Phe^7]-MSH (NDP-MSH) and its fragments. Subjects received 0.5 μl sterile saline or 5 pM NDP-MSH, NDP-MSH1-7, NDP-MSH4-10, or NDP-MSH7-13 in 0.5 μl sterile saline. Core temperatures (6-cm depth) were taken 30 min after injection. Scores represent the difference between core temperature at the time of injection and 30 min after injection. The mean temperatures for groups receiving the 4-10 and the 7-13 fragments did not differ from each other but were significantly greater than the mean temperatures for groups receiving saline and the 1-7 fragment ($p < 0.05$).

It is also interesting to note that Colbern and Twombly (9) found that naloxone, an opiate antagonist, blocked the action of $ACTH_{1-24}$ on grooming behavior. The effects of naloxone on temperature were less clear, perhaps because the naloxone was administered via SC injection, which itself could interfere with ACTH-induced increases in temperature and grooming (9). Because opiate antagonists have been found to block ACTH-induced grooming (9,12), and may also block ACTH-induced increases in core temperature (9), it would be interesting to determine if naloxone and other opiate antagonists would block MSH-induced increases in temperature. Such studies would undoubtedly add to our understanding of the thermoregulatory response and could help determine the underlying cause of the species differences observed in the thermoregulatory action of MSH in rats and rabbits.

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