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## BRIEF COMMUNICATION

# Intraventricular Administration of MSH Induces Hyperalgesia in Rats

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SANDMAN, C. A. AND A. J. KASTIN. *Intraventricular administration of MSH induces hyperalgesia in rats.* PEPTIDES 2(2) 231-233, 1981.—In a completely crossed, double blind designed study, six rats received intraventricular injections of 0.1, 1.0 and 10  $\mu\text{g}$  of  $\alpha$ -MSH and a placebo. The rats were tested for response to painful thermal stimuli with the tail-flick test. All of the doses of  $\alpha$ -MSH produced hyperalgesia during the first 20 min of testing. Only the 1.0  $\mu\text{g}$  dose of  $\alpha$ -MSH produced hyperalgesia throughout the 80 min course of the experiment. This study, coupled with previous reports that MSH/ACTH fragments may attenuate morphine-induced analgesia, suggest that MSH can have opposite actions from those of the endorphins. It is possible that  $\alpha$ -MSH and related peptides may be endogenous anti-opiates.

MSH    Hyperalgesia    Tail-flick test

THERE are striking anatomical and neurophysiological relationships between melanocyte stimulating hormone (MSH) and  $\beta$ -endorphin. Both of these peptides have been localized in the same cells of the arcuate nucleus [17,23], both are stored and released by the intermediate lobe of the pituitary [4], and both peptides are contained in a larger precursor molecule [14]. It may be argued that these shared relationships suggest that the peptides subserve redundant functions and indeed there is scattered support for such a speculation [8, 12, 16, 18]. However, there is also support for the possibility that these two peptides (including the 4-10 fragment shared by MSH and ACTH) have reciprocal functions. For instance, these molecules can have opposing actions on cyclic AMP; MSH/ACTH and their fragments increase cyclic AMP in the brain [6,9], whereas  $\beta$ -endorphin decreases it *in vitro* in neuroblastoma cells [15]. Differences in learning [22], social behavior [2,22], and electrical activity of the brain [22] further suggest a reciprocal relationship between these substances. Among the most direct evidence of a modulating relationship between these peptides is the attenuation of opioid-induced analgesia by MSH/ACTH compounds [14]. Recently, Szekely *et al.* [23] reported that  $\alpha$ -MSH administered concomitantly with morphine also reduces tolerance and dependence on morphine.

There are many reports that  $\beta$ -endorphin produces

analgesia when injected centrally [6,25]. Two recent reports [1, 3, 4] suggested that hyperalgesia resulted from central administration of ACTH. Bertolini *et al.* [3] proposed that ACTH may be an endogenous anti-endorphin. Since major behavioral differences have been related to small changes in the structure of MSH/ACTH fragments [21], the current study was designed to investigate the hyperalgesic influence of  $\alpha$ -MSH.

### METHOD

#### Subjects

Nine Sprague-Dawley, male, ninety day old rats served as subjects. Histological confirmation of placement of the cannulae indicated that six rats reliably received intraventricular administration of the peptide.

#### Surgery

At least a week before testing, ventricular cannulae were implanted into the left ventricle of the rats. Stereotaxic coordinates were 1 mm posterior to bregma, 1.5 mm lateral of the midline, and 4.1 mm below the skull surface. The cannulae were secured with dental acrylic and stainless steel hooks. The cannulae were constructed from 22 ga stainless steel hypodermic tubing beveled at the tips. A 26 ga needle of

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a microsyringe was extended 1 mm below the cannulae for injections of the  $\alpha$ -MSH. Histological verification of the cannulae placement was done by observation of marker dyes injected into the ventricle before sacrifice.

#### Apparatus

Response to thermal stimulation was measured with the tail-flick test of D'Amour and Smith [8]. The apparatus consisted of an adjustable heat source directed to the rat's tail. A solid state timer was initiated automatically when the heat was applied. The timer and the heat were terminated when the tail was withdrawn from the source of heat. The latency of response, to tenths of a second, provided a measure of pain sensitivity.

#### Procedure

Immediately before testing, each rat was administered an intraventricular injection of 0.1, 1.0 or 10  $\mu$ g of  $\alpha$ -MSH or the vehicle solution. The vials containing the peptides were coded so that the experimenter was unaware of the solutions administered. The completely crossed design ensured that every animal received every treatment. At least one week elapsed between treatments to control for the possible lingering effects of the peptides. The heat source was calibrated so that the mean latencies were between 3.5 and 4.5 sec during the pretreatment phase. Tail-flick latencies were measured for each animal in each session before treatment, and the proper calibrations were performed. The measures confirmed that there was no long-term influence of MSH on the tail-flick test. The criterion of 6 consecutive latencies within 1 sec was established during the pretreatment period in order to obtain reliable measures. The mean of the 6 consecutive trials was established as the zero point and all results after treatment with the solutions were calculated as a percentage of change from baseline measurement. Latencies were measured every 2-3 min throughout the entire session. The data were summarized into 10 min intervals by averaging all of the latencies within each 10 min epoch.

#### RESULTS

As illustrated in Fig. 1, during the first 10 min all of the doses of  $\alpha$ -MSH resulted in an increase in sensitivity compared to the saline solution. The major effect of the peptides was observed only with the 1.0  $\mu$ g dosage. This dosage produced an effect which persisted during the entire course of the testing period (80 min),  $F(7,28)=5.49$ ,  $p<0.01$ . Although the early testing periods differentiated the other two doses of  $\alpha$ -MSH from the saline solution, after 20 minutes the effect of the low and high doses of the peptides were indistinguishable from that of the saline injection. Thus, the dose-response relationship of the peptides for hyperalgesia is quadratic,  $F(1,5)=10.35$ ,  $p<0.03$ .

#### DISCUSSION

The results of this study indicated that intraventricular injections of  $\alpha$ -MSH produced hyperalgesia in a dose-

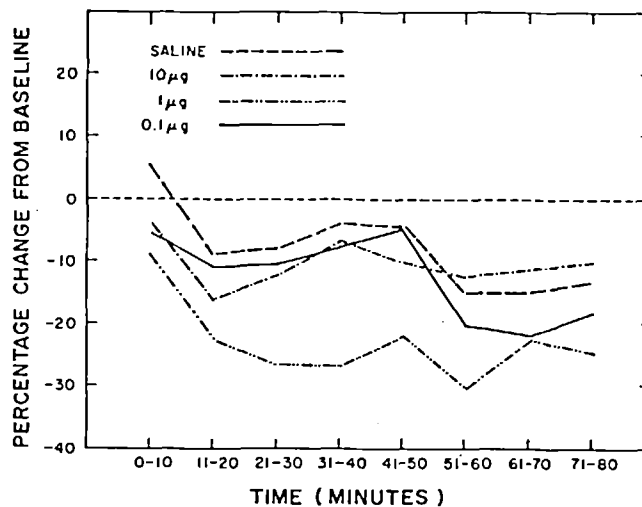


FIG. 1. Changes in latency of response to thermal stimulation after intraventricular injections of  $\alpha$ -MSH or vehicle.

dependent manner. Although all doses of  $\alpha$ -MSH produced hyperalgesia during the first 20 min, only the 1.0  $\mu$ g dose produced long-lasting effects. The reason for this dose response is unknown, although quadratic functions often describe drug/peptide-behavior relationships [21]. In related studies using much higher doses of ACTH 1-24 (20-50  $\mu$ g/rat), linear relations with hyperalgesia were reported with the highest dose producing the greatest effect [3]. Direct comparisons are tenuous since the ACTH 1-24 molecule produces different behavioral effects than  $\alpha$ -MSH [21]. Indeed, there is evidence that an analog of ACTH 4-9 (ORG 2766) injected directly into the midbrain central gray produced significant analgesia [24]. This effect was only apparent for the largest dose (30  $\mu$ g) injected and was not observed when injected into the lateral ventricles. Further, the current study provides dose characteristics only at the lower end of the dosage curve. It is conceivable that with larger pharmacological doses, linear relationships between hyperalgesia and dose of peptide may exist.

Perhaps the potent influence of ACTH 1-24 in the study of Bertolini *et al.* [3] was a function of its steroidogenic properties. For instance, Holaday *et al.* [11] have reported that morphine-induced analgesia can be attenuated in adrenalectomized rats by treatment with dexamethasone. Thus, ACTH 1-24 may have a dual or additive influence; one effect may be due solely to the peptide and a second effect may be related to the stimulation of corticosterone by ACTH 1-24. In the current study, hyperalgesia was produced by  $\alpha$ -MSH, the actions of which are not mediated by secretion of corticosterone. Our results suggest that  $\alpha$ -MSH, like ACTH [4] and perhaps MIF-1 [12], may represent endogenous antiopiates.

#### REFERENCES

1. Amir, S. and Z. Amit. The pituitary gland mediates acute and chronic pain responsiveness in stressed and nonstressed rats. *Life Sci.* 24: 439-448, 1979.
2. Beckwith, B. E., R. R. O'Quinn, M. S. Petro, A. J. Kastin and C. A. Sandman. The effect of neonatal injections of  $\alpha$ -MSH on the open field behavior of juvenile and adult rats. *Physiol. Psychol.* 5: 295-299, 1977.

3. Bertolini, A., R. Poggioli and W. Ferrari. ACTH-induced hyperalgesia in rats. *Experientia* 35: 1216-1217, 1979.
4. Bertolini, A., R. Poggioli and W. Ferrari. Possible physiological role of ACTH-peptide in nociception. In: *Neural Peptides and Neuronal Communication*, edited by E. Costa and M. Trabucchi. New York: Raven Press, 1980, pp. 291-304.
5. Bloom, R., E. Battenber, J. Rossier, N. Ling, J. Leppaluoto, T. M. Vargo and R. Guillemin. Endorphins are located in the intermediate and anterior lobes of the pituitary gland, not in the neurohypophysis. *Life Sci.* 20: 43-48, 1977.
6. Bloom, F., D. Segal, N. Ling and R. Guillemin. Endorphins: Profound behavioral effects effects in rats suggest new etiological factors in mental illness. *Science* 194: 630-632, 1976.
7. Christensen, C. W., C. T. Hartston, A. J. Kastin, R. M. Koszrzewa and M. A. Spirtes. Investigations on  $\alpha$ -MSH and MIF-I effects on cyclic AMP levels in rat brain. *Pharmac. Biochem. Behav.* 5: 117-120, 1976.
8. D'Amour, F. E. and D. L. Smith. A method for determining loss of pain sensation. *J. Pharmac. exp. Ther.* 72: 74-79, 1941.
9. DeWied, D., B. Bohus, J. M. van Ree and I. Urban. Behavioral and electrophysiological effects of peptides related to lipotropin ( $\beta$ -LPH). *J. Pharmac. exp. Ther.* 104: 570-580, 1978.
10. Gispen, W. H., M. E. Reith, P. Schotman, V. M. Weignant, H. Zwiers and D. DeWied. CNS and ACTH-like peptides: Neurochemical response and interaction with opiates. In: *Neuropeptide Influences on the Brain and Behavior*, edited by L. H. Miller, C. A. Sandman and A. J. Kastin. New York: Raven Press, 1977, pp. 61-80.
11. Holaday, J. W., P. Law, H. H. Loh and C. H. Li. Adrenal steroids indirectly modulate morphine and  $\beta$ -endorphin effects. *J. Pharmac. exp. Ther.* 208: 176-183, 1979.
12. Kastin, A. J., R. D. Olson, R. H. Ehrensing, M. C. Berzas, A. V. Schally and D. H. Coy. MIF-I's differential actions as an opiate antagonist. *Pharmac. Biochem. Behav.* 11: 721-723, 1979.
13. Kastin, A. J., E. L. Scollan, M. G. King, A. V. Schally and D. H. Coy. Enkephalin and a potent analog facilitate maze performance after intraperitoneal administration in rats. *Pharmac. Biochem. Behav.* 5: 691-695, 1976.
14. Krivoy, W. A., D. C. Kroeger and E. Zimmerman. Neuropeptides: Influence of acute and chronic effects of opiates. *Psychoneuroendocrinology* 21: 43-51, 1977.
15. Law, P. Y., T. D. Nicksic and H. H. Loh. Enkephalin inhibition of adenylate cyclase activity in neuroblastoma N18T62 cells: Effect of sulfatide incorporation. In: *Neural peptide and Neuronal Communication*, edited by E. Costa and M. Trabucchi. New York: Raven Press, 1980, pp. 291-304.
16. Mains, R. E., B. A. Eipper and N. Ling. Common precursor to corticotropins and endorphins. *Proc. natn. Acad. Sci. U.S.A.* 74: 3014-3018, 1977.
17. O'Donohue, T. L., R. L. Meller and D. M. Jacobowitz. Identification characterization and stereotaxic mapping of intraneuronal  $\alpha$ -melanocyte stimulating hormone-like immunoreactive peptide in discrete regions of the rat brain. *Brain Res.* 175: 1-23, 1979.
18. Olson, G. A., R. D. Olson, A. J. Kastin and D. H. Coy. Endogenous opiates: Through 1978. *Neurosci. Biobehav. Rev.* 3: 285-299, 1979.
19. Panskepp, J., H. Herman, R. Correr, P. Bishop and J. P. Scott. The biology of social attachments: Opiates alleviate separation distress. *Biol. Psychiat.* 13: 607-618, 1978.
20. Rigter, H. Attenuation of amnesia in rats by systemically administered enkephalins. *Science* 200: 83-85, 1978.
21. Sandman, C. A., B. E. Beckwith and A. J. Kastin. Are learning and attention related to the sequence of amino acids in ACTH/MSH peptides? *Peptides* 1: 277-280, 1980.
22. Sandman, C. A., A. J. Kastin and A. V. Schally. Neuropeptide influences on the central nervous system: A psychobiological perspective. In: *Neuroendocrine Regulation and Altered Behavior*, edited by P. D. Hrdina and R. L. Singhal. London: Croom Helm, 1981, pp. 5-26.
23. Szekely, J., E. Miglecz, Z. Dunai-Kovacs, I. Tarnawa, A. Z. Ronai, L. Graf and S. Bajusz. Attenuation of morphine tolerance and dependence by  $\alpha$ -melanocyte stimulating hormone. *Life Sci.* 24: 1931-1938, 1979.
24. Walker, J. M., G. Berntson, C. A. Sandman, A. H. Kastin and H. Akil. Induction of analgesia by central administration of ORG 2766, an analog of ACTH 4-9. *Eur. J. Pharmac.* 69: 71-79, 1981.
25. Walker, J. M., C. A. Sandman, R. McGurra, D. H. Coy and A. J. Kastin. Endorphin analogs with potent and long lasting analgesic effects. *Pharmac. Biochem. Behav.* 7: 543-548, 1977.
26. Watson, S. and H. Akil.  $\alpha$ -MSH in rat brain: Occurrence within and outside of  $\beta$ -endorphin neurons. *Brain Res.* 192: 217, 1980.