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Evidence for a Role of the Ventro-Medial Posterior Hypothalamus in Nociceptive Processes in the Rat

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MILLAN, M. J., R. PRZEWŁOCKI, M. H. MILLAN AND A. HERZ. *Evidence for a role of the ventro-medial posterior hypothalamus in nociceptive processes in the rat.* PHARMACOL BIOCHEM BEHAV **18**(6) 901–907, 1983.—Bilateral, radio-frequency destruction of the ventro-medial posterior hypothalamus (VMPH) resulted, as compared to sham-operated and control rats and evaluated in the tail-flick and vocalization tests, in a significant decrease in basal nociceptive threshold on day 4 post-surgery. By day 12, however, no significant difference between sham and lesioned rats was seen. At this time the antinociception elicited by either acute foot-shock or cold-water-immersion stress was profoundly attenuated. The antinociceptive response to various doses of morphine was not, in contrast, diminished. As established by use of radioimmunoassay, these lesions did not significantly alter hypothalamic levels of β-endorphin, met-enkephalin, dynorphin or α-neo-endorphin. They did, however, produce a pronounced and significant fall in the hypothalamic content of substance P. These data are indicative that the VMPH may, via a mechanism not involving endorphins, be of importance in the determination of basal nociceptive threshold and in the generation of stress-, but not morphine-, evoked antinociception. The relationship of these findings to the interconnections of the VMPH, and to the possible significance of substance P and the pituitary in nociceptive processes, is discussed.

Hypothalamus Substance P Endorphins Morphine Stress Nociception Pituitary

ALTHOUGH it is recognized that the hypothalamus is integrally involved in the regulation of, for example, the endocrine secretion of the pituitary and autonomic functions, its significance in other contexts, such as in the control of nociception, remains unclear. It has, nevertheless, been established that damage to the lateral hypothalamus, through which traverses the median forebrain bundle, results in the gradual development of a hyperalgesia [12] and that destruction of the medio-basal arcuate region, wherein β-endorphin-synthesizing perikaria are localized [3,9], produces a transient hyperalgesia and attenuates the antinociception generated by acute stress [4,31].

The ventro-medial region of the posterior hypothalamus (VMPH) is of particular interest with respect to a possible role in nociceptive processes. Structures therein, the mamillary nuclei (MN), premamillary nuclei (PMN) and posterior hypothalamic nucleus, possess, thus, extensive and reciprocal interconnections with the thalamus, periaqueductal grey and limbic system, tissues involved in the control of nociception and emotion [2, 7, 20, 37]. The activation of peripheral A δ and C fibres, considered the major afferent sources of "nociceptive" information, elicits neuronal excitation in the posterior hypothalamus [8] and the introduction of morphine therein has been reported to result in an antinociception [25,38] (see Discussion). It is, further, rich in substance P, a putative neuro-transmitter or -modulator implicated as involved in the control of nociception in the brain [10, 24, 35]. Indeed, the observation that stimulation in this region elicits a rise in nociceptive threshold (NT) [36] is suggestive of a physiological role in the generation of antinociception.

The above observations suggest that a systematic behavioural examination of the possible role of the VMPH in the control of nociception may be of interest. We have, thus, determined whether this region is of importance in the control of basal NT or for the antinociceptive potency of morphine. In addition, of related interest, many groups have documented the ability of a variety of stressors to induce an antinociception—there being important differences between the stressors as concerns, for example, the role of endorphins in the mediation of this antinociception and the particular neuronal and endocrine mechanisms activated [4, 5, 6, 11, 13, 17, 22, 23, 26, 30, 31, 32, 33, 43, 47, 48, 49]. The present study evaluates, thus, whether the VMPH is of physiological importance in the generation of such "environmentally-evoked" stress-antinociception by use of the models of acute foot-shock and cold water immersion, in each case, of especial pertinence in view of previous indica-

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tions of a significance of other hypothalamic nuclei for the manifestation of these types of stress-evoked antinociception [4,31].

METHOD

Subjects and Operation of Lesions

Male, Sprague-Dawley rats, weighing 180–190 g, were placed, under pentobarbital (40 mg/kg) anaesthesia, in a stereotaxic apparatus. The VMPH was bilaterally destroyed by radiofrequency with the electrode tip located at the following coordinates, derived from the atlas of König and Klippel [19] and relative to the inter-auricular line: frontal, +3.1 mm, vertical +1.2 mm and lateral, ±0.6 mm. The tip was maintained at 55°C for 20 sec for lesions and the unheated electrode lowered to a point 1 mm dorsal to lesion coordinates for sham operations. Control animals were neither anaesthetized nor operated.

In order to preclude the occurence of cross-adaptation between stressors and of cross-tolerance between stress- and morphine-induced antinociception, independent groups of rats were examined as follows. In the first, basal NT was determined on days 4 and 9 post-surgery and foot-shock evoked antinociception on day 12. The second were treated likewise, except that cold-water-swim antinociception was evaluated on day 12. In a third batch, basal NT was measured on day 12 only, and, in a fourth, morphine-evoked antinociception was characterized on day 12.

Analgesiometric Tests

Full details of tests have been published previously [31, 32, 33].

Tail-flick-test. The latency of withdrawal of the tip of the tail from a noxious focused beam of light was determined with a total of 5 consecutive measurements taken. Beam intensity was adjusted and a cut-off imposed as indicated below.

Vocalization test. Rats were introduced into loosely-restraining, aerated, horizontal, Plexiglas cylinders. A moistened, bipolar electrode was applied to the root of the emergent tail and the current required to elicit a scream determined.

Basal nociceptive threshold. Beam intensity was adjusted to give high control latencies of 6–7 seconds (in order to avoid a "base-line" effect), and these read, in every case, prior to vocalization thresholds.

Evaluation of Stress-Induced Antinociception

For foot-shock, rats were placed on a grid and individually exposed to 5 min inescapable, scrambled foot-shock (pulses of 3 mA, 300 msec, 30 per min). This stress is of short duration and identical to that employed in previous studies [31, 32, 33]. It produces only negligible (ca. 2%) weight loss and does not result in any behavioural abnormalities, such as immobility, and rats are easy to handle and not aggressive post-stress. For cold-water-swim, rats were forced to swim in a vertical cylinder of ice-cold water (depth 25 cm and diameter 20 cm) for a period of $2^1/_2$ min and, subsequent to removal, excess water was removed and rats dried as thoroughly as possible.

For each stress, beam intensity was adjusted to give basal latencies of 3–4 sec and a cut-off of 8.0 sec employed. Basal latencies were read directly prior to and at various times post-stress (see Results). In the case of cold-water immersion, prior to stress and immediately after each reading, core temperature was evaluated by insertion of a digital, direct-read thermisto-probe into the anus for a period of 30 sec.

Evaluation of Morphine-Induced Antinociception

Basal tail-flick latencies and vocalization thresholds were determined, then rats injected with either saline or morphine hydrochloride in saline (4.0 ml/kg, SC) and allowed to rest in observations boxes. Tail-flick latencies followed by vocalization thresholds were read at 30, 60 and 90 min (see legend to Fig. 3). Independent groups of rats were employed for each dose: each rat, thus, received only one injection of morphine. Rats injected with 10 mg/kg morphine received naloxone (4.0 ml/kg, 10 mg/kg, IP) at 95 min and vocalization thresholds were re-evaluated 10 min later.

Evaluation of Levels of Peptides and Lesion Position

Since, in all behavioral tests, sham-operated and control animals behaved identically, the latter group were not examined biochemically. Rats were sacrificed, by decapitation, 3 days after completion of testing. Trunk blood was collected and the pituitary dissected into its anterior and neurointermediate lobes. The brain was subdivided to yield the hypothalamus, septum and midbrain. Procedures for the treatment of material and extraction of peptides for radioimmunoassay and properties of the antisera have been detailed previously [15, 16, 27]. Importantly, the antisera for β-endorphin, met-enkephalin, dynorphin and α-neo-endorphin and substance P displayed no mutual cross-reactivity. That to β-endorphin, for example, did not recognize met-enkephalin, dynorphin, α-neo-endorphin or substance P. None of the antisera cross-reacted to a variety of CNS peptides, including α- and γ-endorphin, ACTH, α-MSH and somatostatin. The met-enkephalin antiserum exhibited 14% cross-reactivity to leu-enkephalin and the β-endorphin antiserum recognized β-lipotropin to an equimolar degree. β-Endorphin levels were measured in the hypothalamus of all animals, but in view of limitations of the amount of tissue material available, substance P was measured in rats examined for stress-induced analgesia and those of met-enkephalin, dynorphin and α-neo-endorphin in the other groups.

At sacrifice, the basal hypothalamus was inspected microscopically and, in addition, about 50% of rats were histologically examined by staining of 20 μ thick sections of brain with cresyl violet. Since the block of tissue taken for histology, incorporated the hypothalamus and midbrain, assays could not be performed in these structures in histologically-examined rats.

RESULTS

Evaluation of Lesion Position

The radio-frequency technique allows for the precise and continuous control of electrode tip temperature such that lesions highly reproducible in characteristics may be achieved and the present lesions were highly consistent in shape, size and position. They resulted in an elimination of the nucleus mamillaris (MN) pars medialis and the nucleus premamillaris (PMN) pars dorsalis (Fig. 1). Rostrally, they invaded the caudal aspect of the arcuate nucleus and the pars dorsalis of the nucleus dorsomedialis. Caudally, they destroyed the nucleus supramamillaris and damaged the MN pars posterior. Laterally, the PMN pars ventralis was sub-

TABLE 1

HYPOTHALAMIC CONCENTRATIONS (fmole/mg)

	ir-β-EP	ir-ME	ir-DYN	ir-α-NE	ir-substance P
Sham	13.17 ± 1.44 (12)	1097.24 ± 87.93 (19)	18.31 ± 0.91 (19)	27.94 ± 1.16 (19)	614.93 ± 56.14 (12)
Lesion	12.87 ± 0.92 (8)	1129.34 ± 91.16 (11)	17.32 ± 1.58 (11)	26.87 ± 1.07 (11)	331.46 ± 29.13 (8)

The influence of bilateral radiofrequency destruction of the ventro-medial posterior hypothalamus upon the concentrations of various peptides therein.

Abbreviations: Immunoreactive (ir), β-endorphin (β-EP), met-enkephalin (ME), dynorphin (DYN) and α-neo-endorphin (α-NE).

Mean ± S.E.M. is indicated: n is given in parentheses. Significance of sham vs. lesion differences indicated.

*$p<0.001$. (Students two-tailed t-test).

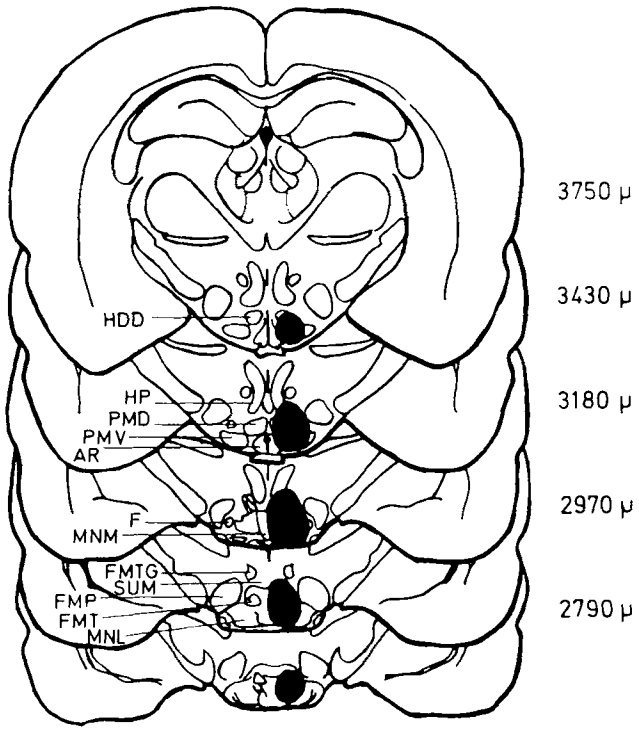

FIG. 1. Schematic frontal sections through the brain of a rat: a typical lesion is indicated by the shaded area on the right and locations of structures on the left. Adjacent figures indicate anterior-posterior coordinates according to the atlas of König and Klippel. Abbreviations: AR (nucleus arcuatus), F (fornix), FMP (fasciculus medialis prosencephali), FMT (fasciculus mamillothalamicus), FMTG (fasciculus mamillotegmentalis), HDD (nucleus dorsomedialis, pars dorsalis), HP (nucleus posterior), MNL (nucleus mamillaris medialis, pars lateralis), MNM (nucleus mamillaris medialis, pars medialis), PMD (nucleus premamillaris pars dorsalis), PMV (nucleus premamillaris, pars ventralis), SUM (nucleus supramamillaris).

stantially damaged as was the MN pars lateralis and the fornix which marked the lateral extent of lesions such that the fascicularis medialis prosencephali was, in general, untouched. Dorsally, the lesions incorporated the ventral aspect of the posterior nucleus and the encroached upon the medial part of the supramamillary decussation. The lesions, at their centre, also interrupted the mamillothalamic and mamillotegmental tracts, the two major efferent pathways of the MN.

Influence of Lesions upon Levels of Peptides

As shown in Table 1, destruction of the VMPH did not significantly alter hypothalamic concentrations of immunoreactive-(ir-) β-endorphin. Hypothalamic weight was reduced by a mean of 8% and the total content of ir-β-endorphin therein was also not significantly depressed (not shown). This indication of the survival of β-endorphin-containing perikarya was confirmed by the observation that, in its major projection targets, the septum and midbrain, there was, similarly, no significant change in levels of ir-β-endorphin (not shown). This stability of levels of ir-β-endorphin is consistent with immunohistochemical findings that β-endorphin-containing fibres originating from somata in the arcuate nucleus project rostrally and/or dorsally to innervate these structures, rather than caudally through the VMPH [3,9]. We also observed that concentrations of ir-β-endorphin in the plasma, anterior and neurointermediate lobes were not significantly modified by these lesions (not shown).

The lesions did not, further, produce a significant change in hypothalamic concentrations of ir-dynorphin and ir-α-neo-endorphin. Likewise, in the neurointermediate lobe, which derives these peptides from the hypothalamus, there was no significant change in their levels and anterior lobe pools were also unaffected (not shown). The lesions did not modify hypothalamic levels of ir-met-enkephalin. It may, thus, be concluded that these lesions of the VMPH did not directly disrupt networks of any of these endorphins. In contrast, however, lesioned animals manifested a pronounced depression in hypothalamic levels of ir-substance P (Table 1).

Influence of Lesions on Nociceptive Processes

Basal nociceptive threshold. In comparison to sham and

TABLE 2

	Tail-Flick Latency (sec)			Vocalization Threshold (μAMPs)		
	day 4	day 9	day 12	day 4	day 9	day 12
Control	7.35 ± 0.23	6.46 ± 0.13	6.68 ± 0.17	505 ± 15	458 ± 19	428 ± 21
Sham	7.91 ± 0.29	6.89 ± 0.12	6.42 ± 0.13	489 ± 19	445 ± 12	434 ± 15
Lesion	5.58 ± 0.11†	6.91 ± 0.12	6.54 ± 0.12	378 ± 20†	409 ± 13*	418 ± 14

The influence of bilateral radiofrequency destruction of the ventro-medial posterior hypothalamus upon basal nociceptive thresholds as evaluated in the tail-flick and vocalization tests at various times post-surgery.

Days 4 and 9: control (n=12), sham (n=12) and lesion (n=16).

Day 12: control (n=10), sham (n=14) and lesion (n=15).

Mean ± S.E.M. shown. Significance of lesion vs. sham differences indicated.

*$p<0.05$, †$p<0.005$. (Students two-tailed t-test).

control rats, VMPH-lesioned rats displayed a significant hyperalgesia in both the tail-flick and vocalization tests on day 4 post-surgery (Table 2). This difference proved, however, transient with lesioned rats showing no difference in tail-flick latencies and only a slight decrease in vocalization thresholds on day 9. The data from each test were subjected to a rigorous analysis of variance (ANOVA) (University of Pittsburgh, programme SPSS-20). For the tail-flick test, a pronounced lesion effect was seen, $F(2)=38.7$, $p\leq0.001$, in addition to a strong lesion-time interaction, $F(2)=32.5$, $p\leq0.001$, but no effect of time alone, $F(1)=1.3$, $p>0.05$. Similarly, in the vocalization test, there was a clear lesion effect, $F(2)=9.4$, $p\leq0.005$, and a lesion-time interaction, $F(2,)=12.3$, $p\leq0.001$: in this test, the influence of time was also significant, $F(1)=4.7$, $p\leq0.05$. These lesion-induced changes were only, however, transient since, on day 12, there was no difference between the basal NT of sham, control and lesioned animals which had not been previously tested on days 4 and 9. This observation demonstrates that the disappearance of the hyperalgesia was a genuine phenomenon rather than reflecting some type of adaptation to the procedure of testing between days 4 and 9 post-lesioning.

Stress-induced antinociception. As depicted in Fig. 2, VMPH-lesioned animals, in contrast to sham and control rats, exhibited a dramatic attenuation in the intensity and duration of the antinociception elicited by foot-shock stress 12 days post-surgery showing only a slight rise in tail-flick latencies which subsided within 20 min post-stress. An ANOVA demonstrated that the factors of both groups, $F(2)=233.3$, $p\leq0.001$, and time, $F(4)=114.2$, $p<0.001$, exerted a significant influence. Further, there was a significant group-time interaction, $F(8)=15.6$, $p\leq0.001$. A comparable reduction of the antinociceptive response to cold-water stress was seen in lesioned animals. ANOVA showed a significant effect of both lesions, $F(2)=310.9$, $p\leq0.001$, and time, $F(3)=694.9$, $p\leq0.001$, and a significant group-time interaction, $F(6)=53.7$, $p\leq0.001$. Lesioned rats did not differ as concerns the suppressive impact of this immersion upon core temperature at any time-point post-stress. The peak fall in temperature was for, respectively, control, sham and lesioned rats, to core temperatures of 28.91±0.11, 29.02±0.09 and 29.09±0.12°C.

Morphine-induced antinociception. As seen in Fig. 3, on

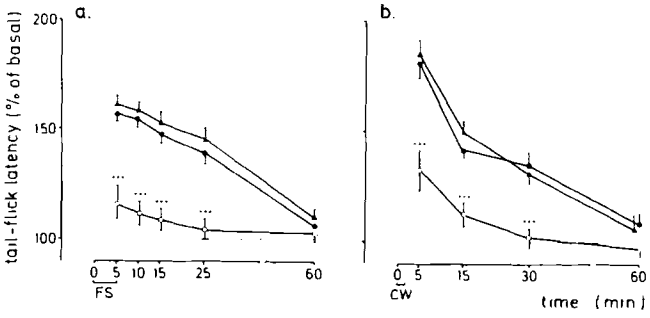

FIG. 2. The influence of bilateral radiofrequency destruction of the ventro-medial posterior hypothalamus upon stress-induced antinociception, as evaluated in the tail-flick test, on 12 days post-surgery. (a) 5 min foot-shock. Control (n=12), sham (n=12), lesion (n=16). Basal latencies: control 3.75±0.12, sham 4.14±0.19 and lesion 3.98±0.13 sec: no significant differences. (b) 2 min cold-water-immersion. Control (n=10), sham (n=11), lesion (n=15). Basal latencies: control 3.94±0.17, sham 4.03±0.11 and lesion 3.89±0.12 sec: no significant differences. Control=▲, sham=● and lesion=□. Mean±S.E.M. indicated. Significance of lesions vs. sham differences indicated. ***$p<0.001$. (Students two-tailed t-test).

day 12 post-surgery, morphine elicited a dose-dependent antinociception in sham animals (control animals responded similarly to a dose of 5 mg/kg morphine, not shown). In the tail-flick test, at neither 30, 60 (Fig. 3) nor 90 (not shown) min post-injection did VMPH-lesioned rats differ significantly from sham animals. The ED_{50}'s (i.e., doses required for half-maximal antinociception) at 60 min, for, respectively, sham and lesioned rats were 1.75 and 1.85 mg/kg. ANOVA showed that there was no significant lesion effect, $F(1)=0.2$, $p\geq0.05$, and no significant lesion-dose interaction, $F(3)=0.1$, $p\geq0.05$. The factor of dose was significant, $F(3)=27.6$, $p\leq0.001$.

As in the tail-flick test, in the vocalization test, no attenuation in the antinociceptive efficacy of morphine was

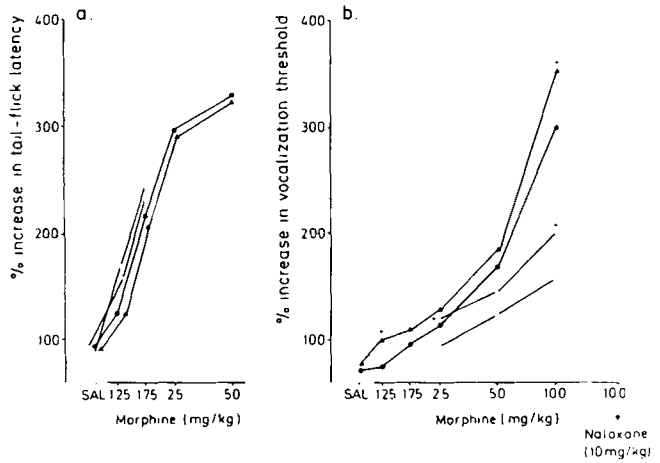

FIG. 3. The influence of bilateral radiofrequency destruction of the ventro-medial posterior hypothalamus upon the antinociception elicited by morphine as evaluated in the (a) tail-flick test and (b) vocalization test, 12 days post-surgery. Sham, 30 min=○, sham, 60 min=●, lesion, 30 min=△, lesion, 60 min=▲. Sham, 90 min + naloxone (■); lesion, 90 min + naloxone (□). Means indicated (S.E.M.'s omitted for clarity). N=4–5 per point. In the tail-flick test, rats with 2.5 and 5.0 mg/kg had approached cut-off latencies at 30 min so were not tested at 60 min to prevent tissue damage. For doses of 1.25 and 1.75 mg/kg, vocalization thresholds were not read at 30 min since these are only threshold analgesic doses in this test. Basal tail-flick latencies: control, 3.65±0.12, sham 3.71±0.09 and lesion, 3.73±0.11 sec: no significant differences. Basal vocalization thresholds: control 417, sham 424 and lesion 412 μAmp: no significant differences. Significance of lesion vs. sham differences indicated. *$p<0.05$. (Students two-tailed t-test).

detected (Fig. 3, 90 min values, not shown). In fact, a slight enhancement was apparent and at 30 min in particular, the dose-response curve was shifted to the left in lesioned rats. At 60 min, ED_{50}'s for, respectively, sham and lesioned animals were 7.1 and 5.9 mg/kg. ANOVA revealed, in addition, to a significant time, $F(2)=54.7$, $p\leq0.001$, and dose effect, $F(4)=78.3$, $p\leq0.001$, a significant influence of lesions, $F(1)=30.9$, $p\leq0.001$. A 2-way interactions ANOVA, further, revealed a significant group-dose interaction, $F(4)=7.8$, $p\leq0.01$. These analyses confirm the existence of a potentiation by VMPH lesions of the antinociceptive potency of morphine in this test. Further, the absence of a group-time interaction demonstrates that, although enhancing the intensity, the lesions did not alter the time-course of antinociception, $F(1)=0.01$, $p\geq0.9$.

In addition to the above studies, a number of (experimentally-naive) rats were examined at a longer time period post-surgery with the tail-flick test to check for possible time-dependent changes. In fact, at 4 weeks post-operation, the pattern of data was similar to that obtained at 12 days with lesioned rats displaying basal nociceptive thresholds not significantly different from sham animals, and an abolition of foot-shock-, but no attenuation of morphine-, evoked antinociception (not shown).

DISCUSSION

The present study demonstrates that bilateral destruction of the VMPH results in the development of a transient hyperalgesia and a substantial attenuation of stress-, but not morphine-, evoked antinociception. These data are evidential of a role of the VMPH in the modulation of nociception and the fact that this region is reciprocally interconnected with, for example, the periaqueductal and central grey, amygdala and midbrain tegmental area, structures involved in the processing and control of nociception, constitutes a clear anatomical basis for such a role [2, 7, 20, 37]. Further direct support for a role of the VMPH in the mediation of antinociception is constituted by the fact that electrical stimulation of the MN has been found to elicit an analgesia and posterior hypothalamic stimulation to inhibit noxious stimulus-evoked firing of neurones in the dorsal horn of the spinal cord [36,46].

The present finding of a transient hyperalgesia on day 4 post-surgery which did, however, eventually disappear (Table 2 and Results), is in line with previous observations of the influence of destruction of the PMN alone upon basal nociceptive threshold [12,44]. It is suggested that the VMPH plays a role in the determination of basal nociceptive threshold but that, in analogy to many CNS structures, for example, the arcuate nucleus and nucleus raphe magnus [31,39], this is non-essential and compensation for its elimination may occur. While introduction of opiates into the posterior hypothalamus results in an antinociception [25,38], the interpretation that this structure is an important mediator of the antinociceptive actions of opiates is questionable since the proximity of the ventricle facilitates diffusion to more caudal regions, such as the mesencephalic peri-aqueductal tissue, which are major sites for the induction of antinociception by opiates [51]. Our finding that the antinociceptive efficacy of parenterally administered morphine is not moderated in VMPH-lesioned rats (Fig. 3) demonstrates that the VMPH is not necessary for a full antinociceptive action of systemically applied morphine, although a minor significance of receptors therein, masked by systemic injections, cannot be discounted. In contrast to morphine, the present lesions greatly attenuated the rise in NT evoked by acute stress (Fig. 2), indicative that the integrity of the VMPH is critical for the manifestation of these forms of stress-induced antinociception. (This effect was selective in that stress-induced hyperthermia was found not to be affected by VMPH lesions (not shown)). A role of the VMPH in the control of the antinociceptive response to stress is of interest in light of its interconnections with limbic structures [2, 7, 20, 37] and evidence that the MN is of significance in the control of other behaviours with a prominent emotional dimension, for example, avoidance reactions, aggression, and responses to novelty [1, 18, 20, 41].

Although there is compelling evidence for a participation of endorphins in certain forms of stress-elicited antinociception, they are not exclusive mediators of the particular types employed in the present study and the present data provide a clear illustration of differences in the neural mechanisms requisite for the appearance of these types of stress- as compared to morphine-antinociception [4, 5, 6, 11, 13, 17, 22, 23, 26, 30, 31, 32, 33, 43, 47, 48, 49]. This distinction between stress- and morphine-elicited antinociception does not, further, appear to reflect temporal differences between them as concerns the rate of development of the effect of the lesions since at both 12 days and 4 weeks post-surgery a selective attenuation of stress- but not morphine-evoked antinociception was observed (Fig. 2 and Results). It is, however, necessary to qualify this assertion of differences between the antinociceptive effects of stress and morphine in

pointing out that various types of stress-induced antinociception differ as concerns their underlying neural substrates and the participation of endorphins therein [4, 5, 6, 11, 13, 17, 22, 23, 26, 30, 31, 32, 33, 43, 47, 48, 49]. Indeed, endorphins appear to be comparatively minor contributors to the present types of stress-induced antinociception [4, 5, 30, 31, 32, 33] and the significance of the VMPH in other types of stress-evoked antinociception which show greater communalities with the antinociceptive actions of morphine would be of interest to determine.

Concerning possible neurochemical mechanisms of the role of the VMPH, the endorphins are, nevertheless, of especial pertinence. Destruction of the VMPH did not, in fact, modify levels of either ir-β-endorphin, -met-enkephalin, -α-neo-endorphin or -dynorphin in either the hypothalamus, various other tissues of brain, the pituitary or plasma. These data, in agreement with immunocytochemical studies of the localization of the perikaryal sources of these peptides in the hypothalamus [3, 9, 42, 50] are indicative that a disruption of endorphinergic networks is very unlikely to underlie the effects of VMPH destruction. Indeed the present antagonism of these models of stress-induced antinociception is far greater than that effected by either naloxone or destruction of β-endorphin somata of the arcuate nucleus [4, 5, 30, 31, 32, 33]. The pronounced lesion-induced depression in hypothalamic levels of ir-substance P is, in contrast, consistent with the presence of a dense population of substance P-containing somata in the PMN and supramamillary nucleus [24]. Indeed, CNS pools of substance P are strongly implicated as modulators of nociception and although their actions are complex, intracerebral injections of low amounts dose-dependently induces an antinociception [10,35] such that the possibility that the effects of VMPH elimination relate to a depletion of substance P deserves further evaluation. However, the significance of other putative neurotransmitters and -modulators localized in the VMPH also remains to be determined.

A final aspect of the role of the VMPH in nociception concerns its relationship with the pituitary. The ablation of this is not, in general, accompanied by persistent alterations in nociceptive threshold but results in a blockade of certain (although not all) form of stress-induced antinociception, including both those employed in the present study [5, 6, 14, 30, 33, 45, 49]. Hypophysectomy does not, in contrast, attenuate the antinociception elicited by systemic morphine but results in a potentiation of this, primarily reflecting a disturbance of adrenal function [14]. The effects of VMPH lesions and hypophysectomy upon nociception are, evidently, very similar. The actions of VMPH lesions could, thus, reflect a disruption of pituitary secretion and the VMPH is rich in peptides and transmitters (including substance P) which are potent regulators of pituitary function and projects strongly to both the median eminence and to hypothalamic nuclei central to pituitary regulation [18, 28, 37]. Alternatively, the present data raise the possibility that hypophysectomy interferes with the operation of the VMPH. This is a possibility of clinical relevance since a further parallel is represented by the fact that both hypophysectomy and stereotactic posterior hypothalamotomy are therapeutically employed for the alleviation of intractable pain. Indeed, there is evidence that the efficacy of alcohol-effected pituitary destruction might not reflect a disruption of pituitary secretion but partially an indirect necrosis of the basal, possibly posterior, hypothalamus [21, 29, 34, 40].

In conclusion, although the mechanisms involved remain to be clarified, the present data provide evidence that the VMPH plays a role in the control of basal nociceptive threshold and is of major importance for the expression of certain types of stress- but not morphine-induced antinociception.

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