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Morphine-Induced Tail Erection: Site of Action[1,2]

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LEE, H. K., C. Y. CHAI, M. J. WAYNER, C. H. HSU AND P. M. CHUNG. *Morphine-induced tail erection: site of action.* PHARMAC. BIOCHEM. BEHAV. 8(1) 69–73, 1978. – Acute ablation techniques were used to localize morphine-induced tail erection (MITE) within the central nervous system of mice. Morphine produced no elevation of tails in mice whose spinal cord had been transected at the lower thoracic or lumbar levels. Decortication and high-level precollicular decerebration did not prevent MITE while morphine caused no tail response at all in low-level inferior collicular decerebrate mice. Lesions in various portions of the mesencephalon revealed that the degree of MITE was closely related to the size of the lesions of the central gray matter. The larger the lesion, the smaller the degree of tail elevation. MITE could not be elicited in mice when the mesencephalic central gray matter had been completely destroyed. Results indicate that morphine acts on the mesencephalic central gray matter producing tail erection and the pathway responsible for the reaction descends from the midbrain downward to the spinal cord.

Tail erection Morphine Spinal transection Decortication Decerebration Mesencephalic central gray matter

MORPHINE elicits a unique dose-dependent tail erection in mice [5] and the response has been used for biological detection of morphine and other narcotic analgesics [10]. Little is known regarding the site of action of this reaction. Previous results [1] indicated that morphine-induced tail erection (MITE) was abolished by bilateral section of the muscles causing extension to the tail; however, section of the spinal cord, decortication, division of the anal sphincter and perineal floor, or ablation of the pelvic splanchnic nerves did not suppress the appearance of MITE. It was thereby concluded that MITE was produced mainly by the action of the sacro-coccygeus dorsalis muscle and required an intact lumbo-sacral cord with a peripheral nervous outflow. Results of preliminary experiments revealed, however, that MITE was abolished by spinal transection. In addition, MITE could not be elicited in spinal transected mice. Therefore, the present study was conducted to find the central locus responsible for MITE using surgical ablation techniques. Results indicate that the degree of MITE is closely related to the extent of destruction of the mesencephalic central gray matter.

METHOD

Male albino mice, weighing 20–25 g, were used. They were placed in individual cages for observation. The ambient temperature was kept at 25°C. To minimize effects of noise the experimental room was kept relatively quiet. Morphine HCl (Chinese Pharmacopeia Standard, supplied by the Bureau of Narcotic Drugs, R.O.C.), 100 mg/kg, was administered subcutaneously to elicit tail erection [5]. The volume of drug administration was 0.1 ml/20 g. As mentioned in a previous article [5], two latencies were measured; one, from when the morphine was administered to when the tail was elevated to at least 45° to the horizontal; second, from when the morphine was administered to when the tail was elevated to at least 90° to the horizontal. Duration of tail erection was defined as the total time the tail was elevated at least 45°. All times were measured by means of stop watches. The total test session was 60 min following the first latency or 120 min following the morphine administration in cases where there was no tail response at all.

The influence of spinal cord, cerebral cortex, diencephalon and mesencephalon on MITE was studied in animals using acute brain tissue ablation techniques. The surgical operations were performed under ether anesthesia. Morphine was usually administered 2 hr after the surgery. Mice were divided into 5 groups of at least 6 animals each.

(A) Spinal cord transection at the lower thoracic or lumbar segments.

(B) Decortication: the cerebral cortices were removed according to a previously described technique [6].

(C) High-level decerebration: a precollicular transection

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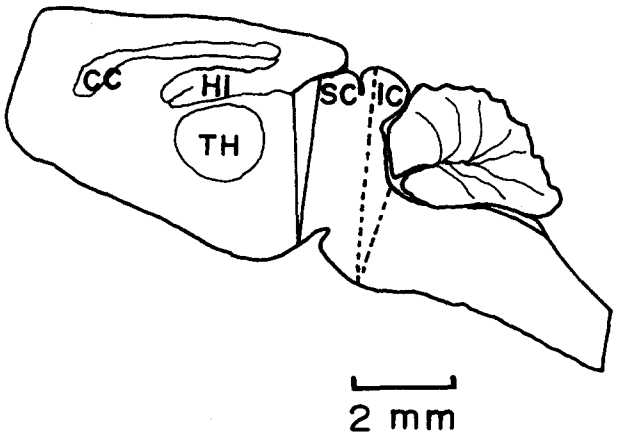

FIG. 1. Schematic drawing of a midsagittal section of the brain of mouse to illustrate the high (solid line) and low (broken line) levels of decerebration. Abbreviations: CC = corpus callosum; HI = hippocampus; IC = inferior colliculus; SC = superior colliculus; TH = thalamus.

was performed (Fig. 1, solid line). Brain tissues rostral to the section were removed.

(D) Low-level decerebration: brain stem was sectioned at the inferior collicular level (Fig. 1, broken line). Brain tissues rostral to the section were removed.

(E) Mesencephalic lesioning: part of the mesencephalic tissue was removed by gentle suction with a small glass pipette.

Sham operations were performed to serve as controls. At the end of each experiment, autopsies were carried out. Only data from animals with satisfactory lesions were included in the results. Mesencephalic lesions produced by pipette extirpation were confirmed histologically as described previously [6].

RESULTS

Effects of Spinal Transection

Table 1 summarizes the effects of spinal transection on MITE. The number of mice which responded with a tail elevation to at least 45° or 90°, the median and range of the latencies, and the duration of tail elevation are presented. Similar to a previous study [5], all normal control mice treated with morphine 100 mg/kg SC, displayed tail elevation of at least 90° with a median latency of 9.5 min and a duration of 60 min. In another group of 6 normal mice put on ether anesthesia as soon as MITE was elicited, the tail response was abolished while the animals were unconscious. However, when ether was discontinued the tail gradually elevated again to an angle of at least 90° within 5–20 min. As shown in Table 1, two groups of sham operated mice, either at the lower thoracic or lumbar level, reacted to morphine administration very similarly to those of the controls. On the other hand, no tail elevation was observed with the same dose of morphine after the spinal cord had been transected at lower thoracic (T10–12) or lumbar (L2–4) segments. In another two groups of mice, MITE was elicited first. Likewise, spinal transection at T10–12 or L2–4 abolished MITE in these animals. Tail elevation was still not present 2 hr following surgery. The animals only became excited and increased motor activities following morphine administration. From these results, it is concluded that the spinal cord is essential for MITE. More experiments, therefore, were performed to determine whether or not the spinal cord is the sole site of action.

Effects of Decortication

As shown in Table 2, decortication did not prevent MITE. All 8 decorticate animals tested showed tail erection of at least 90° and had a duration of tail erection of 60 min. Compared to MITE observed in sham operated group, the only difference was the latency of the reaction. In

TABLE 1

EFFECTS OF SPINAL TRANSECTION ON TAIL ERECTION INDUCED BY MORPHINE (100 MG/KG SC) IN MICE

Animals	No. of mice responded (≥45°) No. tested	Latency: median and range (min)	No. of mice responded (≥90°) No. tested	Latency: median and range (min)	Duration: median and range (min)
Normal controls	6/6	6.5(3.1– 8.2)	6/6	9.5(6.0–10.5)	60
Lower thoracic transection					
1. Sham operation	6/6	7.8(2.5– 9.0)	6/6	9.9(6.5–14.5)	60
2. Transection followed by morphine	0/9	–	0/9	–	–
3. Morphine followed by transection	0/9	–	0/9	–	–
Lumbar transection					
1. Sham operation	6/6	6.0(4.2–11.5)	6/6	8.9(6.5–17.5)	60
2. Transection followed by morphine	0/6	–	0/6	–	–
3. Morphine followed by transection	0/6	–	0/6	–	–

TABLE 2

EFFECTS OF DECORTICATION AND DECEREBRATION ON TAIL ERECTION INDUCED BY MORPHINE (100 MG/KG SC)

Animals	No. of mice responded (≥45°) No. tested	Latency: median and range (min)	No. of mice responded (≥90°) No. tested	Latency: median and range (min)	Duration: median and range (min)
Decortication					
1. Sham operation	6/6	8.2(6.5–12.0)	6/6	11.0(8.3–16.1)	60
2. Decortication	8/8	26.3(20.1–34.2)	8/8	42.5(23.5–55.8)	60
Decerebration					
1. Sham operation	6/6	8.5(6.8–11.1)	6/6	10.9(8.3–17.2)	60
2. High-level decerebration	6/6	13.4(5.7–23.2)	6/6	17.8(14.3–30.5)	60
3. Low-level decerebration	0/6	–	0/6	–	–

TABLE 3

EFFECTS OF MESENCEPHALIC LESIONING ON TAIL ERECTION INDUCED BY MORPHINE (100 MG/KG SC)

Animals	No. of mice responded (≥45°) No. tested	Latency: median and range (min)	No. of mice responded (≥90°) No. tested	Latency: median and range (min)	Duration: median and range (min)
Sham operation	6/6	7.0(5.5–12.1)	6/6	10.1(8.3–16.3)	60
Lesion not involved central gray matter	15/15	10.0(6.5–20.0)	15/15	15.2(7.8–26.5)	60
Lesion partly destroyed central gray matter	9/9	18.1(14.5–30.0)	0/9	–	60
Lesion completely destroyed central gray matter	0/9	–	0/9	–	–

decorticate animals the latencies 26.3 and 42.5 min for responses greater than 45° and 90° respectively were substantially longer than those of the sham operated group. Furthermore, decorticate animals usually became excited and convulsed intermittently after morphine treatment.

Effects of Decerebration

MITE was elicited in all 6 high-level decerebrate mice (Table 2). The characteristics of the reaction were similar to those of the sham operated group, except the latencies were slightly prolonged. In contrast, low-level decerebration did prevent MITE. None of the 6 low-level decerebrate animals tested showed any sign of tail elevation. No excitation or convulsions were observed following morphine administration in both decerebrate groups. The results indicate that the brain tissues inbetween the high and low decerebrate levels are critical for morphine producing tail erection. This was confirmed by the results of the mesencephalic lesion experiment.

Effects of Mesencephalic Lesions

Morphine was administered to 33 mice in which midbrain lesions had been made. The results are summarized in Table 3. These mice were divided into 3 groups according to the differences in response to morphine: the first group (non central gray lesions, 15 animals) whose response was similar to the sham operated ones (Table 3, 6 animals) and displayed tail elevation of at least 90°; the second group (partly destroyed central gray lesions, 9 animals) which displayed tail elevation of at least 45° but never reached 90°; the third group (completely destroyed central gray lesion, 9 animals) which showed no tail elevation of at least 45°. The lesion animals which responded to morphine treatment had slightly longer latencies than those of the sham operated mice; however, the duration of the tail erection remained the same, i.e., 60 min. Histological examination revealed that the mesencephalic lesions of the first group of mice were confined only to the superior and inferior colliculi and hardly invaded the central gray matter. A typical example is shown in Fig. 2A. For the second group of mice, the mesencephalic lesions were larger than those of the first group and usually destroyed about 40–70% of the central gray matter. Figure 2B illustrates one of the typical examples. The mesencephalic lesions of the third group of mice were the largest and had destroyed the whole central gray matter. Six of the nine animals in this group had lesions similar to that shown in Fig. 2C. The central gray matter was completely removed but the

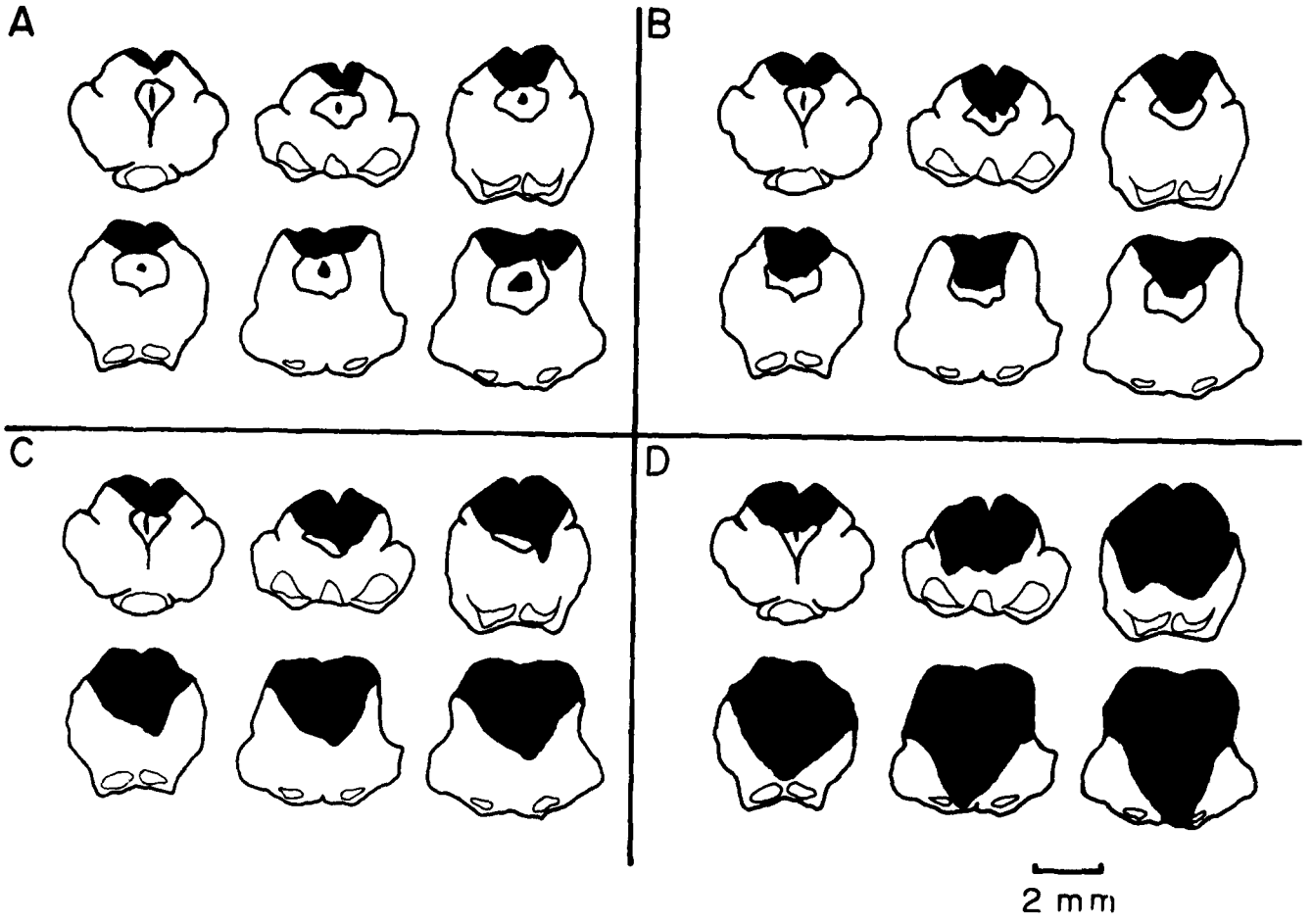

FIG. 2. Cross-sectional reconstruction of mesencephalic lesions. Ablated tissue is indicated by solid dark areas. A: Lesion did not involve central gray matter. B: Lesion partly destroyed central gray matter. C: Lesion completely destroyed central gray matter but with little damage of the tegmentum. D: Lesion completely destroyed central gray matter and with massive damage of the tegmentum.

mesencephalic tegmentum was damaged slightly. On the other hand, the lesions of the other 3 mice were even larger and destroyed substantially the mesencephalic tegmentum (Fig. 2D). Therefore, the degree of MITE is closely related to the damage to the central gray matter but not to the other areas of the mesencephalon.

DISCUSSION

Results of the present study indicate that the mesencephalic central gray matter is the principal site in the central nervous system responsible for MITE in mice. First, MITE can not be induced in low-level decebrate mice where the mesencephalon as well as the rostral brain tissues have been removed; however, MITE can be elicited in high-level decerebrate mice where the mesencephalon is intact. Second, removal of superior and inferior colliculi had little if any effect on MITE. The reduction in MITE is dependent upon the amount of mesencephalic destruction. The larger the lesion of the central gray, the smaller the degree of tail elevation. MITE was abolished in mice where the mesencephalic central gray matter had been completely removed.

Transection of the spinal cord at the lower thoracic or lumbar levels abolished MITE. Likewise, morphine could not induce tail elevation in mice where the spinal cord had been transected either at the lower thoracic or lumbar level. In view of the fact that the mesencephalic central gray matter is essential for MITE, the results of the spinal transection experiments strongly indicate that the descending pathway responsible for MITE runs from the mesencephalon downward to the spinal cord. Some discrepancies exist between the results of the present study and a previous investigation [1] in which it was reported that following transection at various levels at the lower thoracic and lumbar segment, morphine administration (100 mg/kg SC) excited the animal and caused a moderate stiffening and curling of the tail. Only 3 mice were used for spinal cord experiments and there were no appropriate sham operated controls. In contrast, in the present study 42 mice were used including the sham operated animals. In addition, not only was MITE abolished by spinal transection but also inversely, spinal transection always prevented MITE.

Findings of the present investigation support the importance of the mesencephalic central gray in the pharmacological action of morphine which is in agreement with several recent reports [3, 4, 7, 8]. Opiate receptor sites have been found in a high concentration in the periaque-

ductal gray matter [4]. It has also been demonstrated with microinjection techniques that the analgesic action of morphine appears to be concentrated in sites surrounding the third ventricle, cerebral aqueduct, and fourth ventricle [2, 9, 11]. In addition, focal electrical stimulation of the mesencephalic central gray matter reduces responsiveness to noxious stimuli [7,8]. Some evidence indicates that morphine and electrical stimulation produce analgesia by a common mechanism [7,8].

Consequently, further investigation of the role of the mesencephalic gray in MITE will utilize electrical stimulation and intracerebral injection techniques.

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