INFLUENCE OF DRUGS ON EVOKED POTENTIALS IN THE CAT CEREBELLM: II. EFFECTS OF MORPHINE HYDROCHLORIDE (1)

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Abstract—Effects of morphine hydrochloride on the cerebellum were examined in cats. Morphine (2.0 mg/kg, i.v.) decreased the potentials by superficial radial nerve (SR), nucleus reticularis lateralis (LRN), or nucleus olivaris inferior (ION) stimulation on the cerebellar cortices. These effects were antagonized by naloxone hydrochloride (0.4 mg/kg, i.v.). In the LRN or ION, morphine decreased the potentials evoked by SR stimulation. In the LRN or ION-lesioned cat, morphine decreased the potentials evoked by SR stimulation on the cerebellar cortices. This opiate decreased the potentials evoked by tooth pulp stimulation on the vermis, and this effect was also antagonized by naloxone. Morphine slightly decreased the potentials evoked by SSA-I stimulation on the cerebellar cortices. Furthermore, the potentials evoked by SR stimulation on the SSA-I were slightly decreased by morphine. These results may suggest that the cerebellum plays an important role in not only the motor system, but also the sensation of pain.

The functions of the cerebrum and periphery are significantly influenced by the cerebellum and this area of the brain plays an important role in the modulation of physiological function not only as a regulator of motor system function, but also as a coordinator of the autonomic system (1, 2). With regard to pharmacological effects of morphine, Fujita et al. (3) reported that this opiate inhibited the protopathic afferent system. Satoh and Takagi (4) and Oliveras et al. (5) demonstrated that morphine inhibits the pain-afferent pathways in the spinal cord due to excitation of the descending inhibitory system from the nucleus reticularis gigantocellularis of the medulla oblongata and the periaqueductal gray matter to the spinal cord. LeBars et al. (6) showed that morphine depressed the lamina V cells activities in the dorsal horn of the spinal cat. Shima et al. (7) suggested that the inhibition of pain-afferent pathways containing the nucleus centralis lateralis influences the analgesic mechanism of morphine. Jurna et al. (8) reported that morphine increased the primary evoked potentials in the somatosensory area. Thus, while there are numerous reports on the action of morphine, few attempts have been made to study the effects of morphine on the evoked potentials in the cerebellum. We have reported previously that CNS depressants and stimulants affected the cerebellar afferent pathways, probably in an indirect manner (9), and that morphine depressed the potentials evoked in the cerebellar cortex by the superficial radial nerve (SR) (10).

In our present studies, in order to study the minute action of morphine on cerebellar afferent pathways, we examined the effects of morphine on evoked potentials in cerebellar cortices produced by the electrical stimulation.
of the somatosensory area I (SSA-I), the nucleus reticularis lateralis (LRN), the nucleus olivaris inferior (ION), the tooth pulp, or SR. Furthermore, experiments of the electrical lesion of unilateral LRN and ION or the recording of the potentials evoked by SR stimulation in the LRN or ION were carried out in order to determine the effects of morphine on the pathways from the periphery to the cerebellar cortex. The effects of morphine on the evoked potentials produced by SR stimulation in SSA-I were also investigated in this study.

Materials and Methods
Forty-nine adult cats (2.3–4.0 kg) of either sex were fixed on a stereotaxic instrument (Todai Nohken type) following anesthesia with ether and a tracheal cannula was inserted. The femoral vein was cannulated for injection of drugs. The somatosensory area I (SSA-I) of the cerebral cortex was exposed by removing the skull and dura, and a bipolar stainless steel stimulating electrode, 0.6 mm in diameter and with a tip separation of 0.5 mm, was placed on SSA-I. The stimulation was applied with a single rectangular pulse (0.1 Hz, 20–30 V, 0.5 msec). The superficial radial nerve (SR) of the forelimb was dissected and cut at its peripheral end. The central part of the nerve end was placed on the bipolar stimulating electrode (platinum wires) with a 2 mm polar separation and was stimulated with a single rectangular pulse (0.1 Hz, 30 V, 0.5 msec). The superficial radial nerve of the forelimb was dissected and cut at its peripheral end. The central part of the nerve end was placed on the bipolar stimulating electrode (platinum wires) with a 2 mm polar separation and was stimulated with a single rectangular pulse (0.1 Hz, 30 V, 0.5 msec). The superficial radial nerve of the forelimb was dissected and cut at its peripheral end. The central part of the nerve end was placed on the bipolar stimulating electrode (platinum wires) with a 2 mm polar separation and was stimulated with a single rectangular pulse (0.1 Hz, 30 V, 0.5 msec). The superficial radial nerve was stimulated with a single rectangular pulse (0.1 Hz, 30 V, 0.5 msec). The experimental arrangements for stimulation and recording are shown in Fig. 1. After the recovery from ether, the cats were artificially respired (25 revolution per minute) and immobilized with gallamine triethiodide (5–10 mg/kg, i.v.). End-tidal CO₂ was maintained at 4.0–4.5%. Body temperature, monitored by a rectal probe, was maintained at 37–38°C with a heating pad. Arterial blood pressure, ECG, Hb and O₂ saturation were recorded throughout the experiments. At termination of the experiment, 0.3 mA direct current was passed for 10 sec through the electrodes from which evoked potentials had been recorded. The cerebellum was removed and fixed in 10% formalin and then sectioned serially at 50 μm to histologically
verify the area of the electrode insertion. In above experiments, a stimulator (Model ME 6022, MEC) was used to stimulate the SR, LRN, ION, SSA-I and tooth pulp. The evoked potentials were averaged by a signal processor (Model 7T07, San-ei Instrument Co., Ltd.) via a dual beam oscilloscope (Model 331, San-ei Instrument Co., Ltd.), and these recordings were made on an X-Y recorder (Model WX 442, Watanabe). The amplitude of the evoked potentials were measured from baseline to the peak of a negative or positive wave. The time from the stimuli to the peak of the negative or positive component was termed as the peak time. The drugs used were morphine hydrochloride (Sankyo) and naloxone hydrochloride (Endo Laboratories). Drugs for injection were dissolved in 0.9% saline.

The statistical significance of the data obtained was assessed using the two-tailed Student's t-test.

Results

1. The evoked potentials on the cerebellar cortices: Electrical stimulation of the SR evoked potentials consisting of negative and positive components and which respectively had a peak times of 22.5±3.4 msec and 46.5±7.9 msec on the vermis (Fig. 2), 24.6±3.3 msec and 48.3±7.5 msec on the contralateral crus I, and 22.5±4.0 msec and 46.5±8.6 msec on the ipsilateral crus I. The effects of 2.0 mg/kg morphine, i.v., were investigated with regard to the amplitude of the evoked potentials. This dose of morphine hydrochloride decreased the cerebellar cortex potentials evoked by the stimulation of SR by 50%, as shown in our previous studies (14). At 30 min, this opiate significantly decreased the amplitude of both negative and positive components by 40–49% on each cerebellar cortex (Table 1). Recovery was seen at 150–180 min after. Blood pressure was only slightly depressed by drug infusion, and there occured rapid recovery (<3 min) to the pre-drug level on removal of the drug. This inhibition by morphine was antagonized by naloxone hydrochloride (0.4 mg/kg, i.v.)
treatment 35 min after the administration of morphine.

The evoked potentials consisting of negative and positive components, which had respective peak times of 7.2±1.0 msec and 28.0±2.3 msec on the vermis, 7.6±1.2 msec and 32.6±7.1 msec on the contralateral crus I, and 7.9±1.3 msec and 29.3±2.0 msec on the ipsilateral crus I were also produced by SSA-I stimulation. As shown in Table 1, morphine did not produce a significant depression of the potentials evoked by SSA-I stimulation on each cerebellar cortex.

As shown in Table 2, the evoked potentials produced by LRN stimulation possessed a negative component alone and had a peak time of 6.0±1.3 msec on the vermis, 6.4±1.3 msec on the contralateral crus I and 6.4±2.1 msec on the ipsilateral crus I. At 30 min, morphine decreased significantly the amplitude of these evoked potentials by 39–58% on each of the cerebellar cortices. Particularly, this action on the ipsilateral crus I was remarkable. Recovery was seen after 120–150 min. These effects were antagonized by naloxone.

The evoked potentials produced by ION stimulation also possessed a negative

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**Table 1.** Effects of morphine hydrochloride (2.0 mg/kg, i.v.) on the evoked potentials produced by SR or SSA-I stimulation on the cat cerebellar cortices

| Recording sites | Components | SR | SSA-I |
|-----------------|------------|----|-------|
|                 |            | Control | Morphine | Decrease (%) | Control | Morphine | Decrease (%) |
| Vermis          | N          | 114±13  | 64±6  | 44  | 87±11  | 78±9  | 10        |
|                 | P          | 116±11  | 63±5  | 46  | 55±15  | 43±7  | 22        |
| Contralateral   | N          | 94±16   | 48±8  | 49  | 101±6  | 87±14 | 14        |
| Crus I          | P          | 58±7    | 32±10 | 45  | 70±8   | 69±12 | 3         |
| Ipsilateral     | N          | 71±13   | 39±14 | 45  | 63±13  | 59±9  | 6         |
| Crus I          | P          | 53±8    | 32±10 | 40  | 29±10  | 24±7  | 17        |

Each value is shown as the mean±S.E.M. of 5 animals before and 15 min after administration of the drug. *P<0.05, **P<0.01: significant difference vs. the control value. SR: superficial radial nerve, SSA-I: somatosensory area I, N: negative, P: positive.

**Table 2.** Effects of morphine hydrochloride (2.0 mg/kg, i.v.) on the evoked potentials produced by LRN or ION stimulation on the cat cerebellar cortices

| Recording sites | Component | LRN | ION |
|-----------------|-----------|-----|-----|
|                 | Amplitude (μV) | Decrease (%) | Amplitude (μV) | Decrease (%) |
|                 | Control | Morphine |          | Control | Morphine |          |
| Vermis          | N       | 70±11   | 43±9*    | 39     | 78±9    | 55±10*   | 29       |
| Contralateral   | N       | 38±8    | 19±4**   | 51     | 34±11   | 26±3*    | 24       |
| Crus I          | N       | 33±7    | 14±3**   | 58     | 55±8    | 34±4**   | 38       |

Each value is shown as the mean±S.E.M. of 5 animals before and 30 min after administration of the drug. *P<0.05, **P<0.01: significant difference vs. the control value. LRN: nucleus reticularis lateralis, ION: nucleus olivaris inferior, N: negative.
component alone, and here the peak time was $5.9 \pm 0.9$ msec on the vermis, $5.8 \pm 1.3$ msec on the contralateral crus I and $5.8 \pm 1.3$ msec on the ipsilateral crus I. Morphine significantly decreased the amplitude of the cerebellar potentials evoked by ION stimulation by 24–38% at 30 min. The decreasing action on the ipsilateral crus I was particularly marked (Table 2). Recovery was seen 120–150 min. These effects of morphine were antagonized by naloxone.

The evoked potentials produced by tooth pulp stimulation consisted of both negative and positive components, their peak times being $18.9 \pm 4.3$ msec and $56.3 \pm 8.8$ msec, respectively, on the vermis. At 15 min, morphine decreased significantly the amplitude of both negative and positive components by 42–44% on the vermis (Table 3). Recovery was seen 150–180 min later. These effects were antagonized by naloxone.

2. The evoked potentials on the SSA-I: SR stimulation-evoked potentials consisted of negative and positive components which had peak times of $10.6 \pm 1.8$ msec and $47.3 \pm 11.4$ msec, respectively, on the SSA-I. Though morphine did not alter the amplitude of the negative component, this drug maximally decreased that of the positive component by 27% at 15 min (Table 4). Recovery was seen at 180 min.

3. The evoked potentials on the LRN and ION: The evoked potentials produced by SR stimulation possessed both negative and positive components which had respective peak times of $14.8 \pm 2.7$ msec and $59.3 \pm 3.2$ msec on the LRN and $7.3 \pm 1.0$ msec and $36.3 \pm 4.6$ msec on the ION (Fig. 3). Morphine produced significant decreases in the amplitude of both components on the LRN and ION in 30 min. The effects disappeared 150–180 min later. The decreasing action of this opiate on the positive component in the LRN was stronger than that in the ION (Table 5). Naloxone antagonized these effects of morphine.

Table 3. Effects of morphine hydrochloride (2.0 mg/kg, i.v.) on the evoked potentials produced by tooth pulp stimulation on the cat cerebellar cortex (vermis)

| Recording site | Components | Amplitude (µV) | Decrease (%) |
|----------------|------------|---------------|--------------|
| Vermis         | N          | 53±5          | 42           |
|                | P          | 87±7          | 44           |

Each value is shown as the mean±S.E.M. of 5 animals before and 15 min after administration of the drug. *P<0.05, **P<0.01: significant difference vs. the control value. N: negative, P: positive.

Table 4. Effects of morphine hydrochloride (2.0 mg/kg, i.v.) on the evoked potentials produced by superficial radial nerve stimulation on the cat SSA-I

| Recording site | Components | Amplitude (µV) | Ratio (%) |
|----------------|------------|---------------|-----------|
| SSA-I          | N          | 101±15        | +12       |
|                | P          | 83±9          | −27       |

Each value is shown as the mean±S.E.M. of 5 animals before and 15 min after administration of the drug. *P<0.05: significant difference vs. the control value. SSA-I: somatosensory area I, N: negative, P: positive, +: increase, −: decrease.
Table 5. Effects of morphine hydrochloride (2.0 mg/kg, i.v.) on the evoked potentials produced by stimulation of the superficial radial nerve on the LRN or ION.

| Recording sites | Components | Amplitude (μV) | Decrease (%) |
|-----------------|------------|---------------|--------------|
|                 | Control    | Morphine      |              |
| LRN             | N          | 98±11         | 73±10*       | 26            |
|                 | P          | 72±9          | 41±8*        | 43            |
| ION             | N          | 114±9         | 89±12*       | 22            |
|                 | P          | 106±6         | 76±8*        | 28            |

Each value is shown as the mean±S.E.M. of 5 animals before and 30 min after administration of the drug. *P<0.05: significant difference vs. the control value. LRN: nucleus reticularis lateralis. ION: nucleus olivaris inferior. N: negative, P: positive.

4. Evoked potentials on the cerebellar cortex in the ION- or LRN-lesioned cat:
The electrical stimulation of SR evoked potentials in the cerebellar cortices of the ION- or LRN-lesioned cat that consisted of negative and positive components whose respective peak times were 24.6±3.7 msec and 48.4±6.1 msec on the vermis, 25.1±4.3 msec and 49.4±7.9 msec on the contralateral crus I, and 23.8±4.1 msec and 45.9±8.9 msec on the ipsilateral crus I. Morphine decreased at 30 min the amplitude of these evoked potentials by 20–40% on all of the cerebellar cortices. The decreasing action of morphine in the ION or LRN-lesioned cat were not stronger than those in the intact cat (compare Table 6 with Table 1).

Discussion

We, at first, examined the time course of the evoked potentials with saline (0.5 ml/kg, i.v.). We found that the amplitude of the evoked potentials showed changes within 10% with regard to the stability of physiological functions during experiments. Effects of morphine on the cerebellar afferent pathways are summarized in Table 7. Morphine hydrochloride (2.0 mg/kg, i.v.) decreased by 40–49% the amplitude of both negative and positive components of the potentials evoked in the cerebellum by superficial radial nerve (SR) stimulation at each recording site (Table 1), and it depressed by 27% the amplitude of only the positive component of the potentials evoked by SR stimulation on the somatosensory area I (SSA-I) (Table 4). Thus, it was considered that morphine not only influenced the inputs from the periphery to the cerebral cortex, but also might decrease inputs to the...
Table 6. Effects of morphine hydrochloride (2.0 mg/kg, i.v.) on the potentials evoked in the cerebellar cortices by superficial radial nerve stimulation in the nucleus olivaris inferior- and the nucleus reticularis lateralis-lesioned cat

| Recording sites | Componennts | ION | Lesioned sites | LRN |
|-----------------|-------------|-----|----------------|-----|
|                 |             | Amplitude (μV) | Decrease (%) | Amplitude (μV) | Decrease (%) |
|                 |             | Control | Morphine | | Control | Morphine | |
| Vermis          | N           | 179±13  | 107±11*  | 40  | 126±18  | 86±7*  | 32  |
|                 | P           | 83±10   | 51±8*  | 39  | 118±11  | 76±6*  | 36  |
| Contralateral   | N           | 157±12  | 98±6*  | 38  | 118±11  | 75±9*  | 36  |
| Crus I          | P           | 53±13   | 39±9  | 26  | 56±14   | 41±10  | 27  |
| Ipsilateral     | N           | 107±13  | 68±4** | 38  | 64±10   | 48±5*  | 25  |
| Crus I          | P           | 48±10   | 38±10 | 21  | 49±9    | 39±7  | 20  |

Each value is shown as the mean±S.E.M. of 5 animals before and 30 min after administration of the drug. *P<0.05, **P<0.01; significant difference vs. the control value. ION: nucleus olivaris inferior, LRN: nucleus reticularis lateralis, N: negative, P: positive.

Table 7. Summary of the effects of morphine hydrochloride (2.0 mg/kg, i.v.)

1. Intact cat

| Stimulating sites | Recording sites | Lesioned sites |
|-------------------|-----------------|----------------|
| SR                | Contralateral N  |                   |
| SSA-I             | Crus I P        | N N  |
| LRN               |                 | N P  |
| ION               |                 |     |

2. ION- or LRN-lesioned cat

| Lesioned sites | Stimulating sites | Contralateral Crus I | Recording sites |
|---------------|-------------------|----------------------|-----------------|
| ION           | SR                |                       |                 |
| LRN           | SR                |                       |                 |

↓↓↓, marked inhibition (40% depression); ↓, moderate inhibition (20–40% depression); ↓, slight inhibition (10–20% depression); →, no effect. SR: superficial radial nerve, SSA-I: somatosensory area I, LRN: nucleus reticularis lateralis, ION: nucleus olivaris inferior, N: negative, P: positive.
cerebellar cortex. Pertaining to the projections from the SR to the cerebellum, the following pathways have been reported: the pathways projecting to the cerebellar cortex via the nucleus reticularis lateralis (spino-reticulo-cerebellar tract: SRCT) or the nucleus olivaris inferior (spino-olivo-cerebellar paths: SOCPs) and the pathways directly projecting from the forelimb to the cerebellar cortex (cuneocerebellar tract: CCT or rostral spino cerebellar tract: RSCT) (15, 16). Concerning the effects of morphine on the pathways from SR via the precerebellar nuclei (LRN or ION) to the cerebellar cortices, morphine decreased by 22-43% the amplitude of the potentials evoked by SR stimulation in the LRN and ION (Table 5), and decreased the amplitude by LRN or ION stimulation on the cerebellar cortices by about 24-58% (Table 2). However, in the LRN- or ION-lesioned cat, morphine-induced decreasing actions of the potentials evoked by SR stimulation on the cerebellar cortex were little different from those in the unlesioned cats (Tables 1 and 6). Thus, it was suggested that morphine has an inhibitory effect on the pathways which project directly to the cerebellum (CCT or RSCT), rather than SRCT or SOCPs. With regard to projections from the cerebral cortex to the cerebellum, many pathways such as those via the nucleus pontis, nucleus reticularis lateralis or nucleus reticularis tegmenti pontis have been reported (17-20). Morphine only slightly decreased the potentials evoked by SSA-I stimulation on the cerebellar cortices (Table 1). Thus, morphine may hardly influence pathways from SSA-I to the cerebellum.

Concerning the analgesic mechanism of morphine, many workers have found that the descending inhibitory mechanisms from the periaqueductal gray matter, the nucleus reticularis gigantocellularis and nucleus raphe of the medulla oblongata are effective sites of morphine analgesia (4, 5, 21, 22). Yaksh (23) reported that a local spinal application of morphine produced analgesia in the subarachnoid space in chronic animals, suggesting direct inhibitory action to the spinal cord. Furthermore, the higher threshold group III fibers from the muscle and skin to the cerebellum would in part be carrying nociceptive information (24–26). In our present work, it was considered that morphine-induced decreasing actions of the potentials evoked by SR stimulation on the cerebellar cortex were due to the facilitation of the descending inhibitory system or to inhibition of the spinal cord. However, as morphine decreased potentials evoked the precerebellar nuclei stimulation on the cerebellar cortex, this opiate may affect the pathways from the precerebellar nuclei to the cerebellar cortex. On the other hand, morphine decreased the evoked potentials by the painful stimulus of tooth pulp stimulation on the vermis of the cerebellar cortex by 42-44% (Table 3). We also reported that pentazocine (2.0 mg/kg, i.v.), as an analgesic agent, decreased the potentials evoked by SR stimulation on the cerebellar cortices (10). These indicate that the cerebellum may modify the analgesic mechanism of morphine.

In conclusion, morphine-induced depression of the input from the periphery to the cerebellum may suggest that the cerebellum may play an important role in not only the motor system, but also in the sensation of pain.

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