THE EFFECT OF ANALGESICS ON THE SPINAL REFLEX ACTIVITY OF THE CAT*

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During recent years the electrical phenomena associated with spinal reflex functions have been recorded by means of electrodes placed on the ventral and dorsal roots or on the dorsal cord.

The physiological significance of these electrical phenomena has been determined to a certain extent by neurophysiologists.

More recently, Magoun and his associates (1, 2, 3) found that the reticular formation of the brain stem has descending inhibitory and facilitatory influences upon the spinal reflex activity.

The electrophysiological study of the effect of morphine on the spinal reflex has been reported by Wikler (4), but its effect on the reticular formation of the brain stem remains to be investigated.

The precise analysis concerning the sites of action of analgesics on the various afferent pathways of pain has been performed by Fujita et al. (5, 6) in our laboratory. The effects of these drugs on the spinal reflexes, however, are not yet sufficiently settled.

The purpose of the present investigation is to obtain further information regarding the effect of some analgesics and related drugs on the reflex activity of the spinal cord, and to trace the relationship between their effect and the function of reticular formation of the brain stem.

METHODS

The experiments were carried out on 89 cats of which some were made thalamic, midbrain, high spinal and low spinal by transection under ether anesthesia. The spinal cord was exposed by bilateral laminectomy at the appropriate segmental levels under ether, after which artificial respiration was instituted and anesthetic discontinued. d-Tubocurarine chloride (0.3mg/kg) or dimethyl-tubocurarine iodide (0.1mg/kg) was used to keep the animal quiet.

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The cat was suspended by special clamps (Otani-Araki’s instrument) attached to the spinous processes and iliac crests.

The peripheral parts of the sciatic and splanchnic nerves were electrically stimulated. The spinal cord was covered with warm paraffin oil at all times. The monopolar Ag-AgCl electrode was placed on the ventral root (Th9 and S1 or L1), dorsal root or dorsal funicule at the suitable level and the indifferent electrode on the adjacent spinous process, 1-2 cm away. In order to prevent antidromic impulses, the ventral roots, from which are recorded the potentials, were cut approximately 1.5 cm away from the cord.

Unilateral electrolytic lesion was made in the inhibitory or facilitatory region of the reticular formation of the brain stem described by Magoun, using a Johnson’s stereotaxic instrument.

The following were the coordinates relative to stereotaxic instrument zero [Hen-neman et al. (15)].

**Inhibitory region:**
- Posterior: 8 to 12 mm
- Lateral: 0 to 2 mm
- Vertical: -5 to -8 mm

**Facilitatory region:**
- Anterior: 12 mm to posterior 6 mm
- Lateral: 4 to 5 mm
- Vertical: -1 to 5 mm

The extent of the electrolytic lesion was subsequently determined from serial sections of the brain stained by Nissl’s method.

All potentials were photographically recorded by means of an R-C coupled amplifier and a cathode-ray oscilloscope. All the drugs were injected intravenously.

**RESULTS**

**A. Effect of drugs on the reflex discharges evoked by the sciatic afferent stimulation**

1) Preliminary study

As it has been reported by Bernhard et al. (7, 8) and McCawley (9) that the spinal reflex activity is influenced by d-tubocurarine, this problem was preliminarily investigated.

The reflex discharges recorded from a S1 ventral root of an intact cat were illustrated in Fig. 1A. The first spike in this recording represents impulses traversing the monosynaptic arcs, the irregular discharges which follow represent the responses mediated through the polysynaptic arcs [Renshaw (10) and Lloyd (11)].

Sometimes the polysynaptic reflex discharges were followed by other irregular reflex discharges which have a very long latency (about 25 msec) (Fig. 2A).

Although the pathway and the nature of these third reflex discharges have not reported as yet, these discharges may be related to the supraspinal structures since they do not appear in high and low spinal cats. We are studying more precisely the nature of these reflex discharges.
Single injection of d-tubocurarine chloride (0.3mg/kg) or dimethyl-tubocurarine iodide (0.1mg/kg), used in the present experiments, caused no notable changes in both the monosynaptic and polysynaptic reflex discharges in the intact cats as well as in the low spinal cats.

2) Morphine hydrochloride

The effect of morphine on the spinal reflex of the intact (not spinal) cat was first studied. The administration of morphine (7mg/kg) depressed, or completely suppressed, the polysynaptic discharges, having a weaker depression of the monosynaptic spike (Fig. 1B). This depressive action continued for about 10-30 minutes.

The third reflex discharges mentioned above were also depressed, following an injection of the same dose of morphine (Fig. 2B). In some cases, after the injection of morphine, a transient increase of the polysynaptic discharges was observed before suppressive action appeared.

The slow potentials recorded from the dorsal root and dorsal funicule were also suppressed by morphine (Fig. 3 and 4).

In low spinal cats which were prepared by transecting at Th1-Th2 or L2-L4 spinal levels, no inhibitory action of morphine was observed, even at twice the dose of morphine (Fig. 5).
FIG. 3. Effect of morphine on potential recorded from L7 dorsal root following single sciatic stimulation. 
A: before, B: five minutes after injection of morphine (7mg/kg). 
Time scale: 60c/s.

FIG. 4. Effect of morphine on potential recorded from L7 dorsal funicule following single sciatic stimulation. 
A: before, B: five minutes after injection of morphine (7mg/kg). 
Time scale: 60c/s.

FIG. 5. Effect of morphine on reflex discharges recorded from S1 ventral root following single sciatic stimulation in low spinal cat, transected at L5-L3 spinal levels. 
A: before, B: five minutes after injection of morphine (7mg/kg). 
Time scale: 60c/s.

FIG. 6. Effect of morphine on reflex discharges set up by single sciatic stimulation in a cat of which inhibitory region of reticular formation of brain stem was electrolytically destroyed. 
A: before, B: two minutes after injection of morphine (7mg/kg), C: ten minutes after injection. 
Time scale: 700c/s.
In high spinal cats transected between C₂ and C₆ levels, it was recognized that the polysynaptic discharges were markedly depressed, while the monosynaptic ones were partially depressed after the injection of morphine (7mg/kg). The duration of the inhibitory action of morphine in spinal cats was for 5-10 minutes.

In midbrain and thalamic cats, the inhibitory action of morphine was approximately the same as that of intact cats.

The above facts show that the inhibitory action induced by morphine is not due to the direct suppressive action of the segmental reflex, but to the indirect action from the higher levels. To further elucidate the site of the origin of the influences from the higher levels, the destruction of the inhibitory or facilitatory region of reticular formation of the brain stem was performed electrolytically, using the Johnson's stereotaxic instrument.

After the destruction of the ipsilateral inhibitory region, both the monosynaptic and polysynaptic reflex discharges were found to be facilitated by the administration of morphine (7mg/kg), but no sign of inhibition was observed even at twice the dose (Fig. 6). The duration of facilitation was for 10 minutes.

In these experiments, the extent of the electrolytic lesion was determined histologically. The lesion was located at the ventromedial part of the Formatio reticularis and involved both the Nucleus ruber and Nucleus pontis partially. However, the Nucleus oculomotorius was intact (Fig. 7). It was recognized that the principal part of the

**FIG. 7.** A cross-section of brain stem to show destruction of the ventromedial part of the Formatio reticularis (Nissl stain). The brain stem is sectioned through the Nucleus oculomotorius and the Nuclei pontis.

**FIG. 8.** Effect of morphine on reflex discharges set up by single sciatic stimulation in a cat of which facilitatory region of brain stem was electrolytically destroyed.
A: before, B: three minutes after injection of morphine, C: ten minutes after injection.
Time scale: 60c/s.
electrolytic lesion corresponds to the inhibitory region described by Magoun.

On the contrary, after the ipsilateral facilitatory lesion, it resulted in a complete diminution of the polysynaptic discharges and a partial decrease of the monosynaptic ones after the injection of the same dose of morphine (Fig. 8). This inhibitory effect persisted over one hour and no facilitation was observed.

The rostral end of the lesion was located at the rostral level of the nuclei of the H. habenula, while the caudal end was situated at the frontal level of the Nucleus Deiters. The lateral parts of the Formatio reticularis and the Corpus quadrigeminum anticum were destroyed, but the Nucleus ruber was intact. Although the extent of the electrolytic lesion in this experiment was larger than planned and we could not determine the location of facilitatory region exactly, it is conceivable that this lesion involved the facilitatory region described by Magoun (Fig. 9).

3) *Dolantin (Demerol)*

Similar experiments injecting dolantin (13mg/kg) showed essentially the same results as morphine.

4) *The combination of morphine and adrenaline or ephedrine*

One of the authors, Yanai (12), has reported that the potentiative effect between morphine and adrenaline is observed in the suppression of tail flick responses of mice by the modified method of D'Amour and Smith's technique (13). The electrophysiological method, therefore, was applied to the analysis of these interesting phenomena.

When a subeffective dose (4mg/kg) of morphine was administered ten minutes after an injection of adrenaline (5μg/kg), the reflex discharges were depressed similarly to the injection of effective dose of morphine. Single injection of adrenaline (5μg/kg) had no effect on those reflex discharges. These potentiative effects were observed only in intact cats and recognized neither in thalamic cats, nor in spinal cats, nor in some cats of which the inhibitory region of the brain stem was electrolytically destroyed.

The administration of morphine before the injection of adrenaline, inverting the order of injection, also caused the same results as above.

The potentiative action between morphine (4mg/kg) and ephedrine (5mg/kg) also was observed in the same manner as the combination of morphine and adrenaline.
5) Ohton (3-dimethylamino-1,1-di-2 thienyl-buta-1-en hydrochloride)

An injection of ohton (10mg/kg) suppressed initially the polysynaptic reflex discharges and finally the monosynaptic ones in low spinal cats as well as in intact cats.

6) Evipan sodium and amytal sodium

Evipan sodium (30mg/kg) completely depressed both the monosynaptic and polysynaptic reflex discharges in low spinal cats as well as in intact cats.

Amytal sodium (30mg/kg) caused the same results as evipan sodium.

7) Salicylamide and myanesin

The spinal depressant action of salicylamide, reported by one of the authors, Matsumura (14), was studied electrophysiologically and compared with that of myanesin.

The administration of salicylamide (30mg/kg) markedly suppressed the polysynaptic reflex discharges without any remarkable effect on the monosynaptic discharges. These effects were substantially similar to those of myanesin (30mg/kg).

B. Effect of drugs on the reflex discharges evoked by splanchnic afferent stimulation

In order to study the effect of analgesics on other types of the spinal reflexes, a reflex pathway, which had connections with the splanchnic afferent fibers, was employed. The reflex discharges were led off from the Th9 ventral root, while stimulating the ipsilateral splanchnic nerve. The reflex discharges obtained by the present experimental method had no monosynaptic spike (Fig. 10 A). The effects of analgesics on this splanchnic reflex were tested.

1) d-Tubocurarine chloride

d-Tubocurarine did not cause any notable changes of these potentials at the dose (0.3-0.5mg/kg) used in the present experiments.

2) Morphine hydrochloride

In intact cats, morphine (7mg/kg) produced a suppression or diminution of these discharges (Fig. 10). The suppressive action of morphine was observed only temporarily in spinal cats (Th1-Th4) (Fig. 11).

3) Dolantin

Dolantin (13mg/kg) had the same effect as did morphine.

4) The combination of morphine and adrenaline

The administration of a subeffective dose (4mg/kg) of morphine, prior to an injection of adrenaline (5μg/kg), showed no potentiative effect in either intact or spinal cats.

5) Ohton

Ohton caused the suppression of the splanchnic reflex discharges in spinal cats as well as in intact cats.

6) Evipan sodium

In both the intact and spinal cats it was recognized that evipan sodium (30 mg/kg) produced the complete suppression of the reflex discharges (Fig. 12).

7) Myanesin

Myanesin (30 mg/kg) resulted in a transient suppression of the reflex discharges.
Atropine sulfate and methantheline bromide (Banthine)

Atropine (5mg/kg) produced a little decrease of potentials in spinal cats. After administration of methantheline (1mg/kg), no change was observed in splanchnic reflex discharges.

DISCUSSION

Hitherto, the effect of drugs on the spinal reflex has been investigated by means of the spinal animal. The work of Magoun and his associates (1, 2), however, showed that the spinal reflex activity was influenced by the function of the reticular formation of the brain stem. From this viewpoint, not only spinal animals but intact ones should be used for the analysis of the effect of drugs on the spinal reflex.

The investigation by Wikler (4) was mainly directed at the effect of analgesics on the high spinal animal. He reported that a small dose (5mg/kg) of morphine enhanced the monosynaptic spike and depressed the polysynaptic reflex discharges which were recorded from the ventral root following sciatic stimulation.

In our experiments, however, no enhancement of this sort was observed after the administration of morphine (5mg/kg). The cause of this discrepancy between Wikler and the present authors remains to be investigated.

A larger dose (7mg/kg) of morphine caused a marked decrease of the polysynaptic reflex discharges and a little decrease of the monosynaptic ones in high spinal cats. Both decreases persisted for several minutes. A more prolonged depression is observed in intact, thalamic and midbrain cats following administration of the same dose of morphine. In low spinal cats, however, no potential changes were observed even after an injection of twice the dose (14mg/kg) of morphine.

Morphine also depresses both the potentials recorded from dorsal root and dorsal funicule in high spinal cats.

After destruction of the ipsilateral inhibitory region of the brain stem, morphine causes a marked enhancement both in the monosynaptic and polysynaptic discharges. The stimulant action of morphine on the facilitatory region gives a key to interpret the fact that a transient facilitation by morphine is observed in some intact cats.

On the other hand, following the ipsilateral facilitatory lesion, morphine depressed completely the polysynaptic reflex discharges and partially the monosynaptic discharges for a long time. Therefore, it seems that morphine has stimulant actions on both the inhibitory and facilitatory regions of the reticular formation of the brain stem, but its inhibitory effect is so great that the facilitatory one is covered by inhibition in intact cats.

From the results obtained above, it may be suggested that the effect of morphine on the spinal reflex is chiefly based upon a descending inhibitory action mediated through the reticular formation of the brain stem. In high spinal cats which showed a short depression by morphine, however, the reticular formation of the cervical cord seems to play some part in the manifestation of inhibitory effects of morphine.
Through the present experiments, it is confirmed that the balance between inhibitory and facilitatory activities of the brain stem plays an important role in controlling the spinal reflex activity, especially the polysynaptic reflex activity which is caused by sciatic afferent stimulation.

The mechanism of action of dolantin on those reflexes is essentially the same as that of morphine.

The sympathomimetic amines, such as adrenaline or ephedrine, can potentiate the effect of morphine on the spinal reflex to sciatic afferent stimulation. These results in the cats are in agreement with the report of Yanai (12) in the mice. This potentiative effect can be demonstrated only in intact cats, but neither in thalamic, nor in midbrain, nor in spinal cats. This phenomenon, therefore, seems to be mediated through the cerebral cortex. There is no evidence to suppose that sympathomimetic amines may owe their potentiative properties to their pressor ability.

Ohton and barbiturates initially suppress the polysynaptic reflex discharges and finally the monosynaptic ones in both the intact and low spinal cats. The results obtained here, concerning barbiturates, confirm the study of Wikler (4).

Salicylamide markedly suppressed the polysynaptic discharges without any remarkable effect on the monosynaptic ones in low spinal cats as well as in intact cats. These effects are similar to those of myanesin reported by Henneman et al. (15), Kaada (16), and Taverner (17).

By recording from the ventral root of Th_9 or Th_10 after stimulation of ipsilateral splanchnic nerve, the irregular reflex discharges which have a long latency (about 25 msec) are observed. There is no monosynaptic spike in this recording. Downman (18) has studied the feature of reflex discharges into intercostal nerves evoked by splanchnic afferent stimulation. He reported that the monosynaptic spike is absent in these reflex discharges. It seems, therefore, that there is no monosynaptic reflex arc in the pathway of the splanchnic reflex. The splanchnic reflex obtained here, may represent the combined activity of the viscero-somatic reflex and viscero-visceral reflex.

Morphine or dolantin decreases the amplitude of these reflex discharges in intact cats, while these drugs produce a transient depression of those in low spinal cats. Therefore, it is supposed that the principal inhibitory action of morphine and dolantin on this reflex is due to a descending suppression mediated through the higher level, but the direct inhibitory action on the spinal interneurons plays some part in their action.

No potentiative action between morphine and adrenaline is observed in the splanchnic reflex.

Ohton or barbiturates decrease the splanchnic reflex discharges in both low spinal and intact cats. It may be concluded that these drugs have a direct inhibitory action on the interneurons at all the spinal levels.
Myanesin depresses transiently the splanchnic reflex discharges in low spinal cats as well as in intact cats. It seems that the effect of myanesin on the interneurons of thoracal cord is less potent than on those of lumbar or sacral cord.

Bernhard and his associates (7, 8) reported that a larger dose of \( d \)-tubocurarine (1mg/kg) increased the amplitude of the monosynaptic reflex, having no effect on the polysynaptic reflex which was caused by an afferent sciatic stimulation. On the other hand, McCawley (9) reported that \( a \) tubocurarine produced a suppression of both polysynaptic and monosynaptic reflex discharges at a large dose.

Under the conditions adopted here, a small dose (0.3mg/kg) of \( d \)-tubocurarine alters neither the monosynaptic spike nor the polysynaptic reflex discharges which were caused by either sciatic or splanchnic stimulation.

SUMMARY

1. The effect of morphine and related drugs on the spinal reflex discharges, evoked by sciatic or splanchnic afferent stimulation, was investigated using intact, thalamic, midbrain, high spinal and low spinal cats.

2. Morphine depressed both the polysynaptic and monosynaptic discharges caused by sciatic stimulation in all preparations except the low spinal preparation. These actions might be due to a descending inhibitory action, mediated through the higher levels, mainly the reticular formation of the brain stem and partially cervical reticular structure.

Morphine also decreased the reflex discharges produced by splanchnic afferent stimulation in intact cats; while the depressive action in low spinal cats was transient. These actions might be mainly based upon the descending inhibitory action mediated through the higher levels, and partially upon the direct inhibitory action on the interneurons at the segmental levels which are connected with the splanchnic nerves.

3. Dolantin depressed both the sciatic and splanchnic reflexes by the similar mode of action with morphine.

4. The potentiative effect between morphine and adrenaline or ephedrine was observed in the suppression of the sciatic reflex.

This potentiation seems to be mediated through the cerebral cortex.

No potentiation was observed in the splanchnic reflex.

5. Ohton (aminobutene) and barbiturates depressed both the sciatic and splanchnic reflex discharges in low spinal cats as well as in intact cats.

6. Myanesin and salicylamide markedly suppressed the polysynaptic reflex discharges, without any remarkable effect on the monosynaptic ones evoked by sciatic stimulation.

Myanesin produced the transient suppression of the splanchnic reflex discharges.

7. Atropine slightly suppressed the splanchnic reflex discharges. Methantheline (Banthine) did not suppress them.
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