ELECTROMYOGRAPHIC STUDIES OF EFFECTS OF CHLORPROMAZINE ON NOCICEPTIVELY AND PROPRIOCEPTIVELY INDUCED REFLEX PATTERN OF RABBIT'S HINDLIMB

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Numerous reports including Courvoisier et al. (1) have been made of the pharmacological studies on chlorpromazine. The action of chlorpromazine on the central nervous system has been studied in reference to electroencephalography and evoked potentials from the brain of animal. Although the action mechanism of the drug has been well explained, much seems still left unclarified. The most conspicuous characteristics of the drug so far reported is a tranquilizing effect which, on the animal experimental basis, has been confirmed by Das et al. (2), Hendley et al. (3), and Preston (4). However, the locus of the action in the central nervous system does not seem to have been agreed upon. Evoked potentials from brain or spinal cord have been regarded to be a favorable medium through which the action of a drug on the central nervous system is to be investigated. This application seems very significant in studying chlorpromazine. It is, however, not without a drawback in that the test animal must be previously anesthetized with the central depressant, as was regarded by Takeuchi (5). Since chlorpromazine has been suggested by many investigators to have a comparatively weak suppressive action to the central nervous system, it does not appear reasonable to study the drug using an anesthetized animal. It must be admitted that in animal experiments it is not always safe to define that an apparent recovery from anesthesia is a proof of return to a normal function of central nervous system.

Accordingly it seems necessary to use unanesthetized animals in order to accurately study the central action mechanism of a drug. Thus the author took up as indicator Electromyogram (EMG) evoked by adequate stimuli in unanesthetized rabbits in an attempt to clarify the central action mechanism of chlorpromazine.

METHODS

Rabbits weighing 2 to 3 kg were used in these experiments, whose central nervous system had been left intact and midbrain and spinal. Midbrain and spinal rabbits were prepared under non-anesthesia by transection of nervous system at the posterior edge of thalamus and between Th12 and L1 respectively. These rabbits had their skin cut open at fossa poplitea; peroneal nerve and tibial nerve were exposed and the latter resected. In
all cases, ipsilateral transection was made on Achilles tendon. Animals were put on experiment 2 to 3 hours after the transection of their central nervous system.

Rabbits were fixed on supine position on the special designed metal instrument (Fig. 1). In the experiment of nociceptive reflex, electric stimulation was given to the central end of the ipsilateral, cut tibial nerve to induce twitch of the tibialis anterior muscle. In the experiment of proprioceptive reflex, a certain amount of stretch was given to the tibialis anterior muscle by bending the ankle joint dorsally. In order to study the action of the drug on the neuromuscular junction, the peroneal nerve was resected; and the resected peripheral end was electrically stimulated. The strength of electrical stimuli was always kept constant with the low frequency of 1.5 c/sec and high frequency of 30 c/sec. The lead 0.7 electrode was the coaxial needle type. An insulated copper wire of 0.1 mm was sealed as active electrode in a 1/3 hypodermal needle. The tip of the wire was left exposed. The electrode was inserted into the tibialis anterior muscle. Action potential of the muscle was observed by C-R coupled cathode-ray oscillograph, and recorded by magnetic oscillograph.

In this paper, “after discharge” and “delayed discharge” are being used as well as “evoked discharge.” This nomenclature is not based upon original mechanism; what follows evoked discharge is designated as after discharge, still later development as delayed discharge. The author studied the effect of chlorpromazine on these discharges by intravenous administration of the drug in all cases.

RESULTS

I. Effect of Chlorpromazaine on the Nociceptively Induced Reflex Discharge

1) Spinal rabbit
   a) EMG of reflexly induced twitch in spinal rabbit

   Application of electrical stimulation of 1.5 c/sec to the spinal rabbit’s tibial nerve resulted in the development of spike discharges, latency 9 msec, and voltage 0.5 to 1.5 mV in the tibialis anterior muscle. The discharge was mostly polyphasic with ca. 18 msec (15 to 23 msec) duration. Subsequent to the discharge thus evoked, a spike discharge with shorter duration and smaller voltage, i.e., 10 to 100 μV delayed discharge was often observed and was developed with more increased frequency after increased summation of stimuli. Application of the stimuli of 30 c/sec was followed by the development of after discharge between evoked discharges in parallel to summation of stimuli. This after discharge being observed considerably long after discontinuance of stimulation, became difficult to distinguish from evoked discharge (Fig. 2, A). Evoked discharge of the muscle above obtained, was
observed only in the muscle which was ruled by polysynaptic reflex discharge of the ventral root reported by Lloyd (6, 7). After discharge is considered to develop through the reverberating circuit of the spinal cord. Delayed discharge is understood to originate from proprioceptive reflex arc (Morita et al. (8)).

b) Effect of chlorpromazine on the reflex pattern in spinal rabbit

A small dosage of chlorpromazine, 0.2 to 1 mg/kg administered depressed all the above mentioned discharges. The depression was slightly in evoked discharge and after discharge, and pretty highly in delayed discharge (Fig. 2, B). By a dosage of 2 to 5 mg/kg administered delayed discharge was disappeared and after discharge markedly depressed (Fig. 2, C). A further increase in the dosage was followed by a disappearance of after discharge and a marked depression of evoked discharge. A less than 20 mg/kg dosage did not show a disappearance of this evoked discharge. Sometimes a considerably large dosage administration, as much as 20 mg/kg, was followed by a slight depression. In spinal rabbits, increased stimuli given after the depression or disappearance of the discharge by chlorpromazine resulted in the development of the same pattern of discharge as shown in the pre-administration stage.

2) Midbrain rabbit

a) EMG of reflexly induced twitch in midbrain rabbit

If the tibial nerve was stimulated there appeared in the tibialis anterior muscle a similar discharge to that evoked in spinal rabbits. A high frequency stimulation of 30 c/sec, was followed by the development of after discharge. It was characteristic in midbrain rabbits, that the after discharge appeared at a low frequency stimulation of 1.5 c/sec and the delayed discharge took a form of grouping discharge unlike spinal rabbits (Fig. 3, A). The after discharge on a low frequency stimulation had latency of about 28 msec (23 to 36 msec) with a duration of about 30 msec, sometimes reaching over 100 msec. This after discharge was
sometimes difficult to distinguish from evoked discharge. It was found therefore, that the
discharge form in midbrain rabbit was different from spinal rabbit.

\section*{b) Effect of chlorpromazine on the reflex pattern in midbrain rabbit}

Chlorpromazine depressed delayed discharge at a
dosage of 0.2 to 1 mg/kg, and disappeared it at 2 to
5 mg/kg. It depressed evoked discharge and after
discharge under low frequency stimulation at 0.2 to
0.5 mg/kg, and highly depressed after discharge under
high frequency stimulation. At 0.5 to 1 mg/kg the
depression of after discharge obtained by low frequency
stimulation became intensive, at 2 to 5 mg/kg, as was
the case with delayed discharge, after discharge dis-
appeared altogether, demonstrating a high depression
of evoked discharge (Fig. 3, B, C). Sometimes a higher
depression of evoked discharge required a more amount
of chlorpromazine. Occasionally this evoked discharge
disappeared following the administration of 5 mg kg
of the drug.

The discharges of midbrain rabbits did not reappear
after being given a stronger stimulus after they were
depressed, except for evoked discharge (Fig. 3, D). Midbrain rabbits and spinal rabbits were, therefore,
different in the susceptibility to chlorpromazine. The
former required, in general, a less amount than the
latter for a higher depression of reflex discharges.

Of 6 cases, however, one case showed an increase
in reflex discharge at a low frequency stimulation following the administration of 0.5 mg/kg
of the drug. But, ever in this case more than 2 mg/kg administration depressed all dis-
charges. In midbrain rabbits, sometimes the development of spontaneous discharges related
to contracture of extremities was observed following the administration of 0.2 to 0.5 mg/kg
of chlorpromazine. These discharges, however, disappeared following the administration of
2 to 5 mg/kg of the drug. After intravenous administration of 5 mg/kg of the drug abolished
or highly depressed all discharges, increased stimuli were given occasionally resulting in the
development of spontaneous discharge related with walking movement.

\section*{3) Intact rabbit}

a) EMG of reflexly induced twitch in intact rabbit

Stimulation on the tibial nerve of an intact rabbit resulted in the development of evoked
discharge in the tibialis anterior muscle, as was the case with a spinal rabbit. Under low
frequency stimulation, this discharge was generally followed by after and delayed discharges
like in a midbrain rabbit. But these after and delayed discharges were mostly difficult to distinguish to each other as in a midbrain rabbit. Under high frequency stimulation, after discharge developed as well as in the other experiments.

b) Effect of chlorpromazine on reflex pattern in intact rabbit

Chlorpromazine showed the same effects to these discharges as was the case with a midbrain rabbit. Namely, it slightly depressed evoked discharge, and markedly depressed after and delayed discharges at a dosage of 0.2 to 0.5 mg/kg. At 2 to 5 mg/kg it markedly depressed evoked discharge, and abolished after and delayed discharges. On increased stimuli, only evoked discharge re-appeared. In the midbrain rabbit experimentation, after discharge appearing under low frequency stimulation had somewhat higher susceptibility than delayed discharge, but these discharges in an intact rabbit showed the same depressive reaction to chlorpromazine.

In an intact rabbit, as midbrain rabbit, the small amount of chlorpromazine administered, sometimes resulted in an increase of all discharges under low frequency stimulation. The amount required was 0.2 mg/kg. These increased discharges were depressed at 0.5 mg/kg. Such a facilitatory effect of the small amount of the drug on discharge under low frequency stimulation has not been observed in the experimental case under high frequency stimulation.

Spontaneous discharge related with tremor sometimes developed in an intact rabbit. This discharge disappeared at a dosage of 0.2 to 0.5 mg/kg being more sensitive to chlorpromazine than after and delayed discharge.

II. Effect of Chlorpromazine on Neuromuscular Junction of the Tibialis Anterior Muscle

To examine the influence on the neuromuscular junction of the tibialis anterior muscle, the electrical stimulation was given to the peripheral end of the cut peroneal nerve. The twitch of tibialis anterior muscle occurred responding to the indirect stimulation to the muscle. In these cases, it was found that the discharge developed in the muscle was 1- to 3-phasic spike discharges.

Following the administration of 20 mg/kg of chlorpromazine which dosage was markedly depressive on the evoked discharge of nociceptive reflex, the drug showed no effect. Thus it was clarified that the effect of chlorpromazine to reflex discharge was of a central nature.

III. Effect of Chlorpromazine on the Proprioceptively Induced Reflex Discharge

1) Spinal rabbit

a) Proprioceptively induced EMG in spinal rabbit

The application of a certain amount of stretch to the tibialis anterior muscle resulted in the development of various sized spike discharges at 10 to 30 c/sec frequency, with 80 to 100 µV and 10 to 30 µV (Fig. 4, A). It is understood that larger ones of these discharges (hereafter to be abbreviated as G I b discharge) is of Golgi's tendon organ origin, and smaller ones (hereafter to be abbreviated as G I a discharge) originates from muscle spindle (Morita et al. (9)).
b) Effect of chlorpromazine on proprioceptive reflex pattern in spinal rabbit

Chlorpromazine did little affect G Ia discharge and mostly depressed G Ib. Namely, chlorpromazine gave no effect to these discharges at a dosage of 0.2 to 0.5 mg/kg. At a dosage of 5 mg/kg it developed a depression of G Ib discharge with a decrease in number and voltage; at 10 to 20 mg/kg it showed a clear disappearance (Fig. 4, B). The dosage, however, little affected G Ia discharge. In some cases, both G Ia and G Ib discharges showed an increase in number and voltage at a dosage of 0.5 to 2 mg/kg. Even in such cases, an increased dose administration was followed by depression and virtually disappearance of G Ib discharge; G Ia discharge which had acquired the pre-administration stage following the administration of 5 mg/kg, showed no further depression at an increased dosage of less than 20 mg/kg. The application of more stretch after the disappearance of G Ib discharge by chlorpromazine resulted in the re-appearance of this discharge.

2) Intact rabbit

a) Proprioceptively induced EMG in intact rabbit

The application of stretch to the tibialis anterior muscle of an intact rabbit was followed by the appearance of spike discharges with larger voltage (300 to 400 μV) than a spinal rabbit. These discharges consisted of two grouping discharges with a varying latency (Fig. 5, A). Hereafter grouping discharge with shorter latency is to be called E discharge, while that with longer latency D discharge.

These discharges in intact rabbit are different from proprioceptively induced reflex discharge in spinal rabbit. They are understood to have their voltage and number increased following parenteral administration of procaine (2 c.c. of 2 per cent Ringer’s solution) around the tibialis anterior muscle tendon to paralyse Golgi’s tendon organ (Morita et al. (8)). It may be considered that this phenomenon is due to an inhibitory influence of the impulse arising from Golgi’s tendon organ on motoneurone. Thus it is expected that a drug which intensively affects the reflex arc originating from this receptor, influences on grouping discharges of an intact rabbit differently according to the presence or absence of procaine administered. Takeuchi (5) verified this finding with barbiturate and myanesin. In the present experiment with intact rabbits, two experimental groups were made, one, the animal was pre-administered around the tibialis anterior muscle tendon with 2 c.c. of 2 per cent procaine Ringer’s solution in order to remove the peripheral inhibitory mechanism, and the other, without such pre-treatment.
h) Effect of chlorpromazine on proprioceptive reflex pattern in intact rabbit

Unlike barbiturate and myanesin in Takuchi’s report (5), chlorpromazine showed the same manner in the effect on E and D discharge, whether procaine was administered around the tendon or not. Chlorpromazine at a dosage of 0.2 to 2 mg/kg depressed these discharges and abolished them at 3 to 5 mg/kg. This depressive action was markedly observed in D discharge, and in some cases D discharge disappeared prior E discharge. After the disappearance of these discharges even an increased stretch did not result in re-appearance. In the experiment of proprioceptively induced reflex in intact rabbit, it was specific from nociceptive reflex experimentation that about a half of the animals tested showed no reaction following the administration of the drug at a dosage of 0.5 mg/kg or showed a temporary increase in E and D discharge (Fig. 5, B). The increase of discharge by chlorpromazine was marked in D discharge showing a prolonged duration of development. But such a case showed a depressed discharge leading to its complete disappearance after being administered with an

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FIG. 5. Effect of chlorpromazine on reflex discharges from the tibialis anterior muscle during stretch of the ankle joint in intact rabbit.
A, Control; B, after intravenous injection of 0.5 mg/kg chlorpromazine; C, after 1 mg/kg of chlorpromazine; D, after 3 mg/kg of chlorpromazine. Time scale, 60 c/sec.

FIG. 6. Effect of chlorpromazine on inhibition of spontaneous discharges from the tibialis anterior muscle by stretch of the ankle joint in intact rabbit.
A, Control; B, after intravenous injection of 0.5 mg/kg chlorpromazine. Time scale, 60 c/sec.
increased dosage of the drug (Fig. 5, C, D). In the experiment of proprioceptively induced reflex discharge, 2- or 3-phasic spontaneous discharge was frequently observed. This discharge was depressed when stretch was given to the tibialis anterior muscle (Fig. 6, A). A small amount (0.5 mg/kg) of chlorpromazine was able to diminish the stretch effect which was depressive to this spontaneous discharge (Fig. 6, B).

3) Midbrain rabbit

a) Proprioceptively induced EMG in midbrain rabbit

Stretch given to the tibialis anterior muscle of midbrain rabbit resulted in the development of grouping discharge. The discharge was less than an intact rabbit in voltage, and was apparently similar to G Ia discharge of a spinal rabbit. The discharge in midbrain rabbit was so low in voltage that it was generally less recognizable than a spinal or intact rabbit. But the voltage and number of this discharge generally increased as in the case of an intact rabbit, following the injection of 2 c.c. of 2 per cent procaine Ringer's solution into the tendon. So the experiment in midbrain rabbit was performed with 2 c.c. of 2 per cent procaine injection into the tendon.

b) Effect of chlorpromazine on proprioceptive reflex pattern in midbrain rabbit

Chlorpromazine showed a depressive effect to the discharge of a midbrain rabbit. The discharge disappeared at a dosage of 0.2 to 0.5 mg/kg of chlorpromazine. After the disappearance, increased stretch did not result in a re-appearance. It is interesting that the discharge of a midbrain rabbit despite its similarity to G Ia discharge of a spinal rabbit showed another susceptibility to chlorpromazine. As to this finding Granit and Kaada (10) reported that the brain stem reticular formation gave a facilitatory influence on proprioceptive reflex arc. This report seems more acceptable than the interpretation that midbrain rabbit's discharge is developed by activity of a different reflex arc from that of spinal rabbit in explaining the above obtained result. Also it seems reasonable to consider that chlorpromazine acts on brain stem reticular formation to cause disappearance of midbrain rabbit's discharge since the reflex arc in midbrain rabbit which originates from the muscle spindle, receives a facilitatory influence of brain stem reticular formation.

One case of the experiment of midbrain rabbit's proprioceptive reflex was performed simultaneously with the nociceptive reflex experiment. Here an increased nociceptively induced reflex discharge by a small dosage of chlorpromazine above mentioned was observed when this proprioceptively induced reflex discharge was disappearing.

IV. Gross Behavior Changes

Experiments have been so far made of effects of chlorpromazine on various reflex discharges of the tibialis anterior muscle. Another approach was made by a comparative study of the changes of perception, motion, and reflex appearing following an intravenous administration of chlorpromazine, in an attempt to examine the relation between the changes of these muscle discharges and rabbit behavior. The most conspicuous characteristic observed
in rabbit following an administration of chlorpromazine at a small dosage was animal's apparent indifference to its surroundings. After the drug was administered at a dosage of 0.2 to 0.5 mg/kg the animal's spontaneous movements were lessened, its gait became unsteady, its response to tactile stimulation disappeared, and its muscle tension on the extremities was reduced.

However, under this condition normal reactions were observed to develop to nociceptive stimuli; righting reflex showed no changes. A decrease in muscle tension was more marked in the anterior extremity than the posterior extremity. This inhibitory phenomenon augmented as the dose of chlorpromazine increased. As the dosage increased to 2 to 5 mg/kg, muscle tension on the neck as well as on the extremities decreased; reaction to nociceptive stimuli was interfered with (Fig. 7, A). At 10 mg/kg the inhibition was stronger; all the symptomatic manifestations described above were almost abolished with the exception for righting reflex. But a further increase in the amount of chlorpromazine as much as 15 to 20 mg/kg was followed by a pose of increasing muscle tension in the extremities and neck (Fig. 7, B). This gross behavior test performed for intact rabbits as well as for midbrain rabbits resulted in the development of similar reactions to chlorpromazine.

DISCUSSION

Since the depressive effect of chlorpromazine on central nervous system was introduced, effects of this drug on EEG have been studied by many investigators including Das et al. (2), and Hagihara and Murayama (11). As a common result of these experiments there has developed a high voltage slow wave. This wave is of the same type as what develops following barbiturate anesthesia (Toman and Davis (12)) or destruction of brain stem reticular formation (Lindsley et al. (13)). So at first chlorpromazine was considered to act on brain stem reticular formation (Luhman and Hanrahan (14)). Longo et al. (15) and De Maar and Martin (16) evidenced that EEG arousal response which developed via brain stem reticular formation was depressed with a considerably small amount of chlorpromazine. In the present experiment, a study was made of effects on midbrain rabbit's after discharge as well as proprioceptive reflex discharge considered to be connected with the activity of, or via reticular
formation (Takagi et al. (17)), revealing that these discharges were relatively less resistant to chlorpromazine. It is therefore considered that chlorpromazine affects certainly brain stem reticular formation. Next to brain stem reticular formation the thalamocortical reverberating system as the site of action of chlorpromazine was taken into consideration. Das et al. (18) maintained that chlorpromazine showed an intensive action on the system in reference to the action on EEG of *cereau isolé* of cat. The action of chlorpromazine on the thalamocortical reverberating system was comparatively slight. And it was almost the same on brain stem reticular formation. In this respect, the action of chlorpromazine does not seem to concentrate upon the ascending activating system which has been so far accepted as extralemniscal pathway (Moruzzi and Magoun (19), and French et al. (20)) and also upon the thalamocortical reverberating system (Morison and Dempsey (21)). But on the effect of chlorpromazine Killam and Killam (22) referred the limbic system. Preston (4) made clear that EEG of amygdaloid nuclear complex which is part of the limbic system was more affected by a small dosage of chlorpromazine than other aspects. Since then great emphasis has been laid on the interpretation that the drug acts primarily on the limbic system.

The author's study on chlorpromazine centering around various reflexly induced muscle discharges has led to conclude that chlorpromazine shows, so far as nociceptively induced reflex discharge is concerned, the strongest action on intact and midbrain rabbit's after discharge under stimuli of high frequency and the stronger action on intact and midbrain rabbit's delayed discharge and after discharge under stimuli of low frequency. It is also revealed that evoked discharge and spinal rabbit's after discharge show a weak susceptibility. It is now obvious that regarding proprioceptively induced reflex discharge, the drug shows a strong action on midbrain rabbit's discharge, demonstrating the next strong action on E and D discharge and that G Ib discharge disappears only after a considerably massive dosage. Another fact obtained is that G Ia discharge within dosages adopted has been little affected.

The author's result features that the after discharge of nociceptively induced reflex has shown the strongest susceptibility in intact rabbits, then in midbrain rabbits followed by spinal rabbits in order. This proves that chlorpromazine show a strong action on a higher centre. This specific efficacy for a higher centre is well evidenced by proprioceptively induced reflex discharge. It is understood that spinal rabbit's discharges are not so affected as intact rabbit's discharges. This specific efficacy has been further confirmed by the fact that the drug acts on the discharge which is related with tremor. Because, in this case, tremor is considered referable to tremor at intension which may accompany mental excitation, chlorpromazine is assumed to act intensively on the centre related with such mental phenomenon.

The site of action of chlorpromazine, disclosed by Preston (4) and Killam and Killam (22), i.e., limbic system was indispensable for emotional expression (Papez (23), Kaada (24), Mac Lean (25), and Gloor (26, 27)). These authors support to conclude that the drug acts most effectively on a higher centre in the central nervous system which is related with mental activities. The present experiment failed to locate the exact site of action, because
it was aimed at reflex discharge. But Takagi and Takaori (28) demonstrated that chlorpromazine acted on Chang's second component (29) at a small dosage. This encourages the author not to maintain an absolute denial of the action of chlorpromazine in the cerebral cortex.

So far discussion has been made in this paper of central depressive action of chlorpromazine. On the other hand, the drug has been noted for its excitatory action on the central nervous system. Das et al. (18) reported that the drug administered at a small dosage resulted in the development of spike and wave in cerveau isolé of cat. Baker et al. (30) reported that the administration of chlorpromazine was followed by the appearance of spike in the striatum and pallidum. Preston (4) stated that a massive administration of chlorpromazine led to the appearance of spike and convulsion. In the author's experiment, the walking movement and the pose of increasing muscle tone were occasionally observed; probably because of a small dosage administration the convulsion described by Preston (4) was not observed. This drug may, therefore, possess a central excitatory action as well as a central inhibitory action. But its action mechanism has not been fully explained.

On the central excitatory action of chlorpromazine Preston (4) took up two aspects, i.e., the direct stimulation on the organization of central nervous system and the release phenomenon of central nervous system from inhibition. The author's experiment on intact rabbit's proprioceptive reflex revealed that chlorpromazine at a small dosage depressed the inhibition of spontaneous discharge due to stretch. This fact indicates that chlorpromazine paralyses the inhibitory area of higher centre against spontaneous discharge.

On the basis of the drug's action on the inhibitory area of the central nervous system, the drug is considered to possess a secondary facilitatory effect, which seems referable to a temporary increase in various reflexly induced muscle discharges. In the experiment on spinal rabbit's proprioceptive reflex it was found that G Ia discharge might be subject to facilitatory influence by chlorpromazine, and that no further depression was observed after an increased dosage of the drug resulted in the recovery of the pre-administration stage.

From the above description it is strongly suggestive that the drug's facilitatory phenomenon is ascribable to a release from inhibition. Takagi and Takaori (28) observed in reference to the evoked discharge led off the ventral root that chlorpromazine depressed polysynaptic reflex discharge (Lloyd (6, 7)), more markedly in intact cats than in spinal, cats. They maintained that the depressive action of the drug was due to the excitement of the inhibitory area. This maintenance is corresponding to the author's finding in the nociceptive reflex experimentation. Therefore it is supported to assume that the drug's direct excitatory action on the central nervous system and the subsequently developing inhibitory effect may be reasonably anticipated to occur.

Thus, it seems safe to assume that chlorpromazine possesses two actions, i.e. direct depression and stimulation, on the central nervous system and that these two actions are carried out indirectly as well. Since the drug acts on the regulatorily functioning area upon the motor as well as mental system, the drug is considered to act intensively on a higher centre
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of the nervous system. This interpretation is supported by the present experimental result where a small dosage of the drug administered showed a decrease in spontaneous activity and in response to tactile stimulation.

SUMMARY

Electromyographical studies was made of effects of chlorpromazine on nociceptively and proprioceptively induced reflex discharges in spinal, midbrain and intact rabbit, and the following results were obtained.

1. A small dosage administration of chlorpromazine resulted in mostly depressive action on nociceptively induced reflex discharge, with a temporary increase developing in a few cases. The action of the drug was the most marked on intact and midbrain rabbit’s after discharge under stimuli of high frequency, followed in degree by its delayed discharge, and after discharge under stimuli of low frequency in order. Evoked discharge, and spinal rabbit’s after discharge were not easily affected.

2. Chlorpromazine showed a very strong action on intact rabbit’s tremor.

3. Chlorpromazine showed the strong inhibitory action on midbrain rabbit’s proprioceptively induced reflex discharge; E and D discharge in intact rabbit showed a high susceptibility to the drug. G Ib discharge disappeared only with a considerably large dosage; G Ia discharge was little affected.

4. So far as proprioceptive reflex is concerned, in some cases G Ia, G Ib, E and D discharges showed a transient facilitation following a small dosage administration of chlorpromazine.

5. Gross behavior changes in rabbit were observed after chlorpromazine administration, i.e. apparent indifference to its surroundings, lessened spontaneous movement and also hyporesponsibility to tactile stimulation. Gross amount of the drug produced the increasing muscle tension.

6. It was discussed that chlorpromazine might have both direct and indirect excitatory, as well as inhibitory action on the central nervous system and that especially the drug might exert a strong action on a higher centre of the nervous system.

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REFERENCES

1) COURVOISIER, S., FOURNEL, J., DUCROT, R., KOLSKY, M. AND KOETSCHET, P.: Arch. int. Pharmacodyn. 92, 305 (1933)
4) PRESTON, J.B.: J. Pharmacol. 118, 100 (1956)
5) TAKEUCHI, Y.: Folia pharmacol. japon. 53, 177 (1957)
6) LLOYD, D.P.C.: J. Neurophysiol. 6, 11 (1943)
7) LLOYD, D.P.C.: Ibid. 6, 293 (1943)
9) MORITA, M., YASUHARA, M., TAKEUCHI, Y., KIMURA, T. AND ITO, C.: Ibid. 52, 104§ (1956)
10) GRANIT, R. AND KAADA, B.R.: Acta physiol. scand. 27, 130 (1952)
26) GLOOR, P.: Ibid. 7, 223 (1955)
27) GLOOR, P.: Ibid. 7, 242 (1955)