Effects of Chlorpromazine on Spinal Reflex

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Many investigations on the tranquilizing effect of chlorpromazine have been reported in various papers and its depressant action on spinal reflex is described by some authors (3, 9). Beside this action, however, it is also well known that chlorpromazine has an action of lowering the blood pressure. Judging from the dosage used in these researches and the period of experiments, the possibility that the depression of spinal reflex may be secondarily caused by the lowering of blood pressure can not be neglected.

Eccles performed the "close arterial injection" in order to localize the action of drgus around the synaptic elements of spinal cord (5). If we adopt this method, it is likely that the secondary action followed with the lowering of blood pressure can be excluded. So, this method was used in the present paper, and the primary depressant action of chlorpromazine on the spinal reflex will be described.

METHOD

All the experiments were carried out on cats weighing from 2.4 to 4.3 kg. The spinal cord was sectioned at the height of L_1 under ether anaesthesia, and after a day of this operation it was exposed from L_3 to S_1 under nembutal narcosis. The stimulating electrodes were placed on the proximal side of preliminarily cut dorsal root and the recording electrodes were placed also on the proximal side of ventral root of appropriate spinal segment. At the distal pole of the recording electrode the ventral root was totally depolarized by KCl. The reflex discharges were recorded by a.c. amplifier (time constant : 200 msec.) and the cathod ray oscilloscope. Chlorpromazine was administred by means of intravenous injection or close arterial injection(5). The dosages were ranged in 5 to 20 mg/kg in the former and in 0.2 to 1.0 mg/kg in the latter.

In order to observe the action of chloromazine to the peripheral nerve fibre, the stimulating electrode were placed on the proximal, and the recording ones were placed on the distal side of ventral root, and the action potentials were recorded. In these experiments, the nerve trunk between stimulating and recording electrode was enveloped by the wool wetted with Ringer solution containing 1×10^{-5} g/ml chlorpromazine.

RESULTS

As shown in Figs. 1 and 2, the main changes of reflex discharges in the spinal cord caused by the intravenous injection of chlorpromazine are the decrease in height of mono- or polysynaptic discharge. Generally speaking, the polysynaptic reflex discharge has a tendency to be affected more markedly than the monosynaptic; e.g. when the 10 mg/kg of chlorpromazine was injected intravenously, the

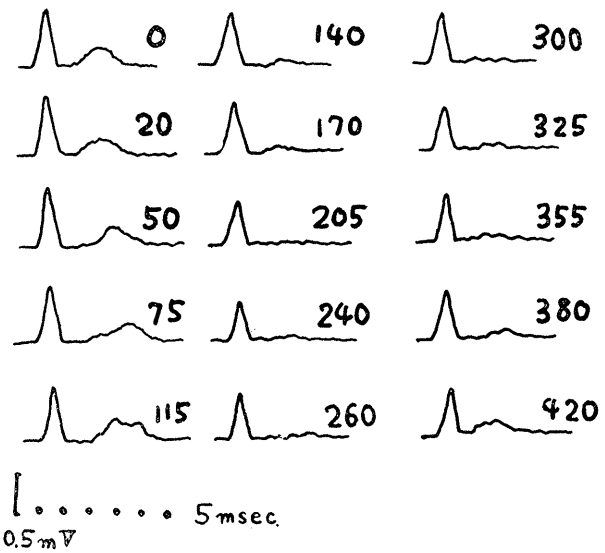

Fig. 1. Changes of reflex discharges after the interavenous injection of chlorpromazine. Numbers show time in seconds after the injection.

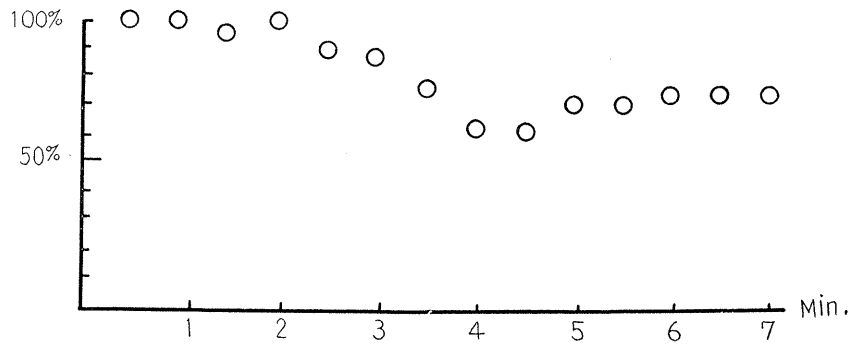

Fig. 2. Diagram showing the changes of monosynaptic reflex after the intravenous injection. Ordinate : amplitude of monosynaptic discharge (control value shows 100%). Abscissa : time in minutes after the injection.

polysynaptic reflex discharge could not be obtained after five minutes of this proce-

dure, but the monosynaptic one were elicitable though its amplitude was diminished to 50–70% of control value. These depressed state continued from 40 minutes to two hours in most cases, and however strong the intensity of stimulation, may be, the polysynaptic discharges were hardly recognized. Moreover, in the recovery from the effect of the drug, the time regaining the control value was shorter in the monosynatic reflex discharge than the polysynaptic.

Changes in the spinal reflex discharges caused by close arterial injection of 0.5

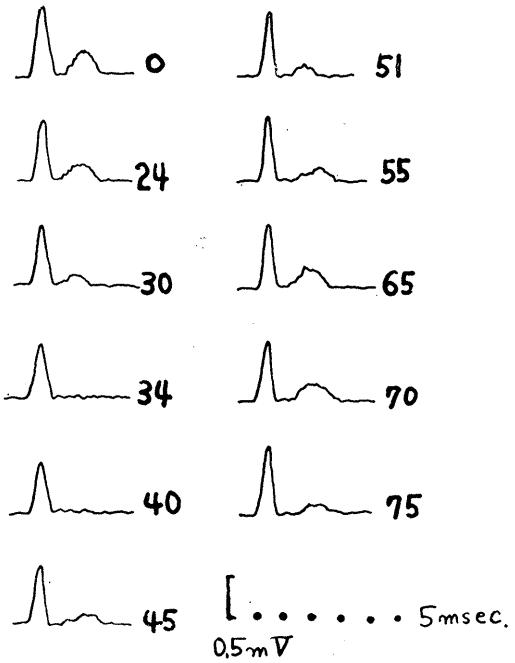

Fig. 3. Changes of reflex discharges by the close arterial injection. Numbers show time in seconds after the injection.

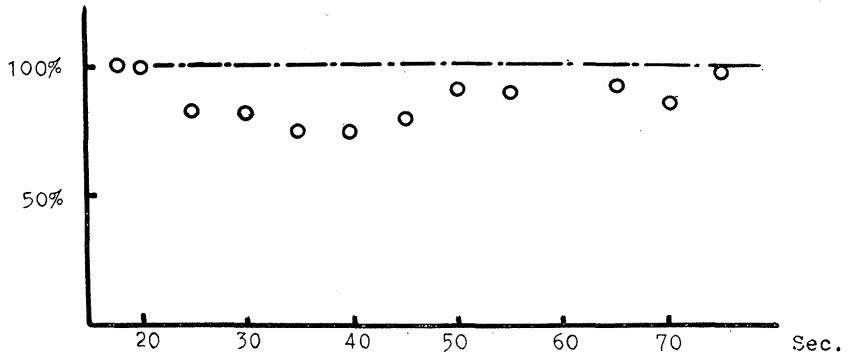

Fig. 4. Diagram showing the changes of monosynaptic reflex after the close arterial injection. Ordinate and abscissa are same as Fig. 2.

mg/kg chlorpromazine are shown in Figs. 3 and 4. The general features resemble to the results obtained by the intravenous injection method. But it must be noted that the time required for appearing these changes differs from the latter case: i. e. as shown in Fig. 3, the decrease of amplitude occured at 25 seconds and became most evidently at 35–40 seconds after the injection. The recovering process in this case is also interesting: i.e. the time required for complete recovery is much shorter than that of intravenous injection. In the present experiment this time was 75 seconds in average.

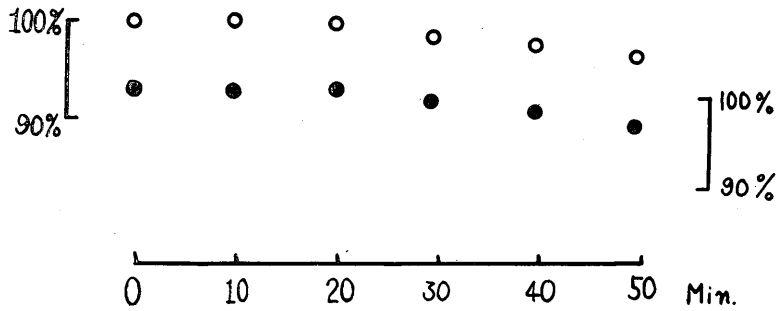

Fig. 5. Diagram showing the changes of action potential of the nerve fibre treated with chlorpromazine.
Open circle: non-treated (for the control).
Solid circle: treated with the drug.
Note that the height of action potential is scarcely affected by this treatment.

Fig. 5 shows the result of experiments performed for the purpose of observing the action of chlorpromazine on nerve fibre. Contrary to the experimental data on spinal reflex discharge, any remarkable change in the amplitude of action potential could not be observed. With the lapse of time, the height of action potential decreased in small degree, but this change may be due to the drying of the preparation, and it was negligible small compared with that of the synaptic reflex discharge.

DISCUSSION

Huidobro (7) studied the effects of chlorpromazine on the neuromuscular junction and on the other synapses, and discussed that the drug does not block the synaptic transmission. However, the results obtained in the present experiments do not agree with him, and the objective opinions to his data have been reported by some authors (5, 9, 8). *Preston* pointed out that chlorpromazine decreases the height of both mono- and polysynaptic reflex discharge, and the changes of response in sensory pathway in the spinal cord were also reported by him. Furthermore, it was ascertained in the present experiment that the polysynaptic reflex was abolished more easily than monosynaptic one by the administration of chlorpromazine, and that the

drug in such a small dosage used here exerts no effect on the peripheral nerve fibre for an hour or more. From these facts, it is likely that the drug affects synaptic structure primarily, and that the number of the synaptic element in reflex pathway is one of the determing factors for the effectivity of chlorpromazine.

It is also mentioned that the influence of chlorpromazine to blood pressure becomes manifest within 1.5 or 5 minutes after the intravenous injection and continues for over half an hour (1, 4, 6). This time covers sufficiently the one during which the changes in spinal reflex discharge were observed in the present experiment, therefore, as already noted, the results obtained here might be a secondary effect produced by the lowering of blood pressure. But by the close arterial injection, it was shown that these changes occur within a few second at least, and the depressed state of spinal function recovers completely within a few minutes. These findings demonstrate that chlorpromazine acts primarily upon the reflex function of spinal cord.

Lastly, it must be considered whether chorpromazine can pass through blood-brain barrier or not. If the membrane-permeability of nerve cell depends only upon the size of molecule, results reported here and that of other workers are difficult to explain because the fact that gamma-amino-butyric acid with its molecular size smaller than chlorpromazine does not pass this barrier is recognized by some physiologists (2). But in the present stage of our knowledge this thesis cannot be discussed fully, I think, and it is desirable to be treated elsewhere.

SUMMARY

1. Action of chlorpromazine on the spinal reflex of cat was studied by injecting the drug intravenously or close arterially.
2. It was concluded that the depression of spinal reflex caused by the chlorpromazine is primarily effected by the reduced activity of synaptic element and is not the secondary effect of lowered blood pressure.

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