THE EFFECT OF ATRAXIN (MEPROBAMATE) ON THE SPINAL CORD IN CATS

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Many clinical experiments on meprobamate (Atraxin, Daiichiseiyaku) have been done in the last few years which have demonstrated that this compound has tranquilizing and anticonvulsive effects (1, 2 and 3). The minute process of the effect on the central nervous system, however, is still uncertain. Therefore, it might be of value to investigate the effect on this system with a more direct method. For this purpose the reflex discharges of the cats spinal cord following the intravenous application of Atraxin were recorded and analyzed to show how this compound effects the synaptic transmission and also to show what kinds of spinal neurones are sensitive to this compound.

METHODS

Cats were anesthetized with ether, and the spinal cord was cut at the level between Th 10 and Th 11 segments. The anesthesia was discontinued during the experiment. By removing the posterior arches of vertebrae between L 4 and S 1 the spinal cord was exposed. The left L 7 and S 1 ventral roots were cut at about 2 cm away from the spinal cord and mounted on recording electrodes made of platinum wire for the purpose of recording the reflex discharges. An indifferent electrode made of platinum foil was attached to the exposed muscle close to the spinal cord. The flexor side of the left femur was opened and sural, semitendinosus and biceps nerves were mounted on the stimulating electrodes respectively. The two operated areas were converted into troughs by elevating the skin edges and they were filled with liquid paraffin. Nerves were stimulated with a square pulse current of 0.1 msec. duration. The polysynaptic discharges were picked up from L 7 or S 1 ventral root by stimulating the sural nerve. The monosynaptic discharges were picked up from L 7 ventral root by stimulating the biceps and semitendinosus nerves. These discharges were amplified and displayed on the cathode ray oscilloscope.

The vena saphena magna or poplitea of left leg was exposed and a small polyethylene tube was inserted in this vein for the injection of a necessary amount of Atraxin.

RESULTS

1) The effect on polysynaptic reflex

By the application of small doses of Atraxin (less than 0.1 mg/kg) no change was

observed in polysynaptic discharges. When 0.5 mg/kg was given, usually a slight augmentation appeared a few minutes after injection, although no change was observed in some cases. Fig. 1 shows the polysynaptic discharges after applying 2 mg/kg of Atraxin. The discharge was markedly augmented and several sharp peaks appeared on it. The effect started immediately after the injection and reached maximum about five minutes later. Usually it continued for about 20 to 30 minutes and gradually returned to the normal. By the injection of 10 mg/kg the reflex remained as was seen when 2 mg/kg of Atraxin was applied, or the degree of the augmentation decreased. Following the injection of 30 mg/kg, augmentation disappeared and slight depression was recognized. Following the injection of 50 mg/kg, strong depression appeared immediately and in some cases the reflex disappeared for several minutes (see Fig. 2). In extreme cases the respiration was ceased simultaneously. At the respiratory cessation, artificial respiration was applied until recovery and reflex reappeared, but usually it remained at about 1/3 of the control.

Fig. 1. Augmentation of the polysynaptic reflex discharge following the intravenous application of Atraxin (2 mg/kg). A, Control; B-G, 1, 3, 5, 10, 20, and 30 min. after application. Time signal, 2 msec.

Fig. 2. Depression of the polysynaptic reflex discharge following the intravenous application of Atraxin (50 mg/kg). A, Control; B-H, 1/3, 2/3, 1, 2, 3, 5 and 15 min. after application. Time signal, 2 msec.

Fig. 3. The effect of Atraxin on the monosynaptic reflex discharge. Series A, showing a slight depression induced by Atraxin (20 mg/kg): 1, Control; 2-4, 2, 5 and 10 min. after intravenous injection. Series B, showing a strong depression after applying Atraxin (50 mg/kg): 1, Control; 2, 10 sec. after application; from 2 to 10, each photograph was taken with 10 sec intervals. Time signal, 1 msec. The height of time signal indicates 0.1 mV.

2) The effect on monosynaptic reflex

Following the application of Atraxin (less than 10 mg/kg) usually monosynaptic discharges did not show any difference from the control. In a few cases the monosynaptic discharges were depressed slightly, but it was difficult to define this as an effect of the Atraxin because of the height of the monosynaptic reflex which changes at random in the range of 5 to 10% without applying Atraxin. By the application of 20 to 30 mg/kg monosynaptic discharges were apparently depressed. As shown in Fig. 3, the maximum decreasing of the spike height was about 20% of the control and it took about 10 minutes after application of Atraxin. The effect continued for more than a half hour. Following the application of 50 mg/kg the monosynaptic reflex was strongly depressed and immediately became about 1/10 of the control, or in some cases the reflex was almost ceased for several minutes. In the latter cases, the degree of depression seems to be dependent upon respiratory disturbances. The effect of this dosage continued for a long time and sometimes almost no recovery was observed.

DISCUSSION

The compounds which act on the spinal reflex have special characteristics in their effect. For instance, Myanessin depresses the polysynaptic activities without serious impairment of the monosynaptic reflex (4, 5). A certain amount of curare produces the appearances of an increase in monosynaptic potentials. This is accompanied by an increase in polysynaptic potentials. In other instances, and rather

uniformly with higher doses, both of mono- and polysynaptic reflexes are depressed (6). Thus, Myanesin has a selective blocking action on interneurons, and curare has a mixture of stimulating and depressant action on spinal neurons.

The present experiment showed that Atraxin of small doses augmented the polysynaptic discharges and did not give much effect on monosynaptic firing. The higher doses of Atraxin, however, depressed both mono- and polysynaptic reflexes. From these results, it can be said that spinal interneurons are more sensitive to this drug than the neurons involved in the monosynaptic pathway. The higher dosage of Atraxin loses its selective effect and might possibly lower the activities of these two kinds of synapses and even the other component in the spinal cord.

The process of tranquilizing and anticonvulsive effects of Atraxin might be due to the augmentation of inhibitory interneuron activities when small doses of this drug are applied, and due to nonselective depressing effect on both synaptic activities when higher doses are applied.

SUMMARY

The effect of Atraxin on the spinal reflex was observed in the decerebrated non-anesthetized cat, and following results were obtained.

1) Polysynaptic reflex is augmented when 2 mg/kg of Atraxin is applied intravenously and at over 20 mg/kg the reflex is inhibited.

2) Atraxin has practically no effect on the monosynaptic reflex when the applied dosage is under 20 mg/kg, and at over 30 mg/kg the reflex is depressed.

3) Spinal interneurons are more sensitive to Atraxin than motoneurons.

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