IN INVOLVEMENT OF THE CHOLINERGIC MECHANISM IN DEPRESSION OF THE CAUDATE SPINDLE

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Abstract—Involvement of the cholinergic and catecholaminergic mechanisms in the caudate spindle recorded from the anterior and posterior sigmoid gyri was examined in cats. Physostigmine (0.01 to 0.1 mg/kg i.v.) abolished the appearance of the caudate spindle. These inhibitory effects were antagonized by the administration of atropine (0.25 to 1 mg/kg i.v.). The caudate spindle was inhibited by high frequency stimulation of the mesencephalic reticular formation: This inhibitory effect was antagonized by atropine. On the other hand, L-DOPA (25 to 50 mg/kg, i.v.), L-DOPA+MAO inhibitor and methamphetamine (0.5 to 5 mg/kg i.v.) did not influence the caudate spindle. These results suggest an involvement of cholinergic mechanism in depression of the caudate spindle.

Electrical stimulation of the caudate nucleus elicits a spindle burst (caudate spindle) in the cortex, thalamus and caudate nucleus (1, 2). For estimation of properties of neuroleptics or other related compounds, the effects of such drugs on the caudate spindle have been observed (3, 4, 5). Stille and Sayers (4) and Stille (5) reported that cataleptogenic neuroleptics, blocking the dopaminergic neuron, enhanced the caudate spindle. On the other hand, Ishikawa et al. (3) reported that the caudate spindle was inhibited by neuroleptics.

Yamamoto et al. (unpublished data) observed that electrical stimulation of the dorsal raphe nucleus caused a complete suppression of the caudate spindle and that this suppression seemed to involve a serotonergic mechanism. On the other hand, Buchwald et al. (1) reported that electrical stimulation of the reticular formation caused a complete suppression of the caudate spindle, but the mechanism involved was unknown. In the present investigation, the influence of cholinergic and catecholaminergic mechanism on the caudate spindle was examined.

MATERIALS AND METHODS

Preparation of animals: Experiments were carried out on 25 mature cats of both sexes weighing 2-4 kg. Tracheotomy was done with the animals under ether anesthesia. The animals were immobilized with gallamine triethiodide and positive artificial respiration was maintained at 24/min. The drugs used were physostigmine, atropine sulfate, L-DOPA, pheniprazine and methamphetamine, dissolved in 0.9% saline solution and given i.v. through a cannula which had been fixed in the femoral vein. All wound edges and pressure points

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were locally anesthetized with 5% procaine solution administered periodically during the course of the experiment. Systemic blood pressure (femoral artery), electrocardiogram, and rectal temperature were continuously monitored.

**Electroencephalographic studies:** Spontaneous EEG: Screw electrodes for recording the cortical EEG were placed on the surface of the anterior sigmoid gyrus (GSA) and posterior sigmoid gyrus (GSP) and were fixed into the skull at the level of the GSA and GSP; EEG was recorded bipolarily.

Caudate Spindle: A bipolar concentric steel stimulating electrode with a tip separation of 0.2–0.5 mm and a diameter of 0.5 mm was inserted into the head of the caudate nucleus (A: 15.0, L: 4.0, V: +8.0 to +3.0) according to the atlas of Snider and Niemer (6) and caudate spindles were recorded from the ipsilateral GSA and GSP by stimulation of the caudate nucleus with a single rectangular wave pulse (0.2 Hz, 3 msec, 2–5 V) for 1 min. The spindle wave was classified into four grades (3–0) according to the amplitude and duration; score 3 being the highest and 0 the lowest. The effects of drugs were estimated by total scores of 12 spindle waves observed in every recording session.

Effect of Mesencephalic Reticular Formation on Caudate Spindle:—A bipolar concentric steel electrode as described above for the caudate nucleus, was inserted into the mesencephalic reticular formation (A: 3.5, L: 2.5, V: +1.0 to −1.0) and the effect of stimulation of the mesencephalic reticular formation with rectangular wave pulses (100 Hz, 1 msec, 1–2 V) for 10 sec on the caudate spindle was observed. The effect of the drugs was estimated by the duration of the inhibition of the caudate spindle induced by electrical stimulation of the mesencephalic reticular formation.

**Localization of Electrodes:** At the end of each experiment, the animals were perfused with 10% formol saline via the left cardiac ventricle. Serial frozen sections were cut parallel to the electrode tracks and stained with cresyl violet and luxol fast blue. The positions of the tips of the stimulation electrodes were checked histologically.

**RESULTS**

**Effects of drugs on caudate spindle**

The caudate spindle was abolished 5 min after the administration of physostigmine (0.01 to 0.1 mg/kg). All spindle waves showed a score of 0, and had the smallest degree of amplitude and duration. Atropine (0.25 to 1 mg/kg) was administered 30 min after treatment with physostigmine. The inhibitory effects by physostigmine were antagonized by atropine 10–30 min after the drug injection. All spindle waves recovered to the state of pre-injection, and had a score of 3 (Fig. 1). The caudate spindle was increased in both amplitude and duration 30 min after the administration of single doses of atropine (0.25 to 1 mg/kg) (Fig. 2). L-DOPA (25 to 50 mg/kg) had no influence on the caudate spindle. Even in animals pretreated with pheniprazine, a monoamine oxidase inhibitor, 30 min before administration of L-DOPA, L-DOPA (25 to 50 mg/kg) showed no influence on the caudate spindle (Fig. 3). The caudate spindle was not influenced by the administration of methamphetamine (0.5 to 5 mg/kg).
The caudate spindle was inhibited by high frequency stimulation (100 Hz, 1 msec) of the mesencephalic reticular formation. This inhibitory effect was completely antagonized 10-30 min after the injection of atropine (0.25 to 1 mg/kg) (Fig. 4).

Effects of mesencephalic reticular formation on caudate spindle

The caudate spindle was inhibited by high frequency stimulation (100 Hz, 1 msec) of the mesencephalic reticular formation. This inhibitory effect was completely antagonized 10-30 min after the injection of atropine (0.25 to 1 mg/kg) (Fig. 4).
FIG. 3. Effect of L-DOPA on caudate spindle in an immobilized cat pretreated with pheniprazine. A. Control: All spindle waves showed a score of 3. B. The cat was pretreated with pheniprazine (3 mg/kg i.v.) 30 min before the injection of L-DOPA (25 mg/kg i.v.). The caudate spindle was not changed by pheniprazine 30 min after the drug injection. C. At 30 min after the administration of pheniprazine, L-DOPA (25 mg/kg i.v.) was injected. The caudate spindle was not influenced by L-DOPA 30 min after the injection. The caudate nucleus was stimulated electrically (3 V, 3 msec, 0.2 Hz) at the point indicated by a dot.

FIG. 4. Effect of stimulation of the mesencephalic reticular formation on the caudate spindle and the effect of atropine on this response in an immobilized cat. A. The caudate spindle was inhibited by stimulation of the mesencephalic reticular formation (4 V, 1 msec, 100 Hz) as indicated by the horizontal line. B. This inhibitory effect was antagonized completely by atropine 30 min after the drug injection. MRF=mesencephalic reticular formation, The caudate nucleus was stimulated (3 V, 3 msec, 0.2 Hz) at the point indicated by a dot.

DISCUSSION

The caudate spindle recorded from the cerebral cortex reflects not only the function of the neostriatum but also that of the thalamocortical system (7). It is considered that the ascending reticular activating system is involved in the mechanism eliciting the caudate spindle and drugs depressing the EEG arousal response enhance the caudate spindle. For example, neuroleptics which depress the ascending reticular activating system, are known to enhance the caudate spindle (4, 5).

In the present study, the caudate spindle was abolished by physostigmine and this
inhibitory effect induced by physostigmine was antagonized by the injection of atropine. Single doses of atropine also enhanced the caudate spindle. On the other hand, in animals non-pretreated and pretreated with pheniprazine, a monoamine oxidase inhibitor, L-DOPA showed no influence on the caudate spindle. Methamphetamine also had no influence on the caudate spindle. These results suggested that the cholinergic mechanism was closely related to the inhibition of the caudate spindle.

Buchwald et al. (1) reported that electrical stimulation of the brain stem activating system caused a suppression of the caudate spindle. In the present study, the caudate spindle was inhibited by stimulation of the mesencephalic reticular formation and this inhibitory effect was blocked by atropine. These results indicate that this inhibitory effect on the caudate spindle, by stimulation of the mesencephalic reticular formation, seems to partly involve a cholinergic mechanism. On the other hand, Yamamoto et al. (unpublished data) observed that the caudate spindle was inhibited by high frequency stimulation of the dorsal raphe nucleus where many serotonergic fibers have their cell bodies (8). The inhibitory effect was completely antagonized by a serotonergic mechanism. It may be further postulated that the enhancement (4, 5) or attenuation (3) of the caudate spindle by neuroleptics may also reflect an involvement of the cholinergic or serotonergic systems.

REFERENCES