THE EFFECT OF CAFFEINE ON THE SPINAL REFLEXES IN WARM-BLOODED ANIMALS

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One of the greatest achievements of Russian physiology has been its research on the effect of caffeine on the cortical processes. However, despite the numerous works of Pavlov's school, and the extensive research and experience in the therapeutic use of caffeine, the mechanism of its action on reflex activity cannot be considered adequately understood. There are several indications that the physiological action of caffeine approximates that of strychnine [3]. Certain authors attribute the increase in reflex activity induced by caffeine to its anticholinesterase action [4].

The purpose of our work was to study the mechanism of caffeine's action on simple and easily investigated spinal reflexes.

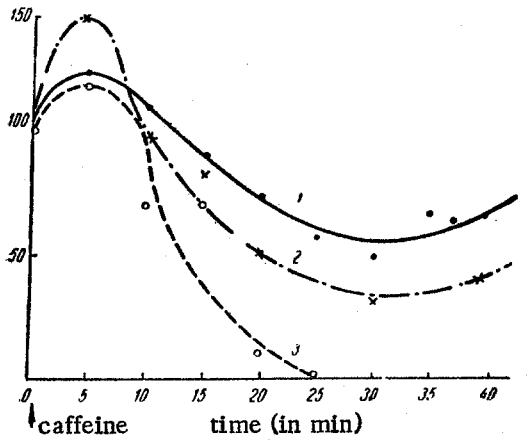

Fig. 1. Changes in the reflex responses: 1) of gastrochemius muscle; 2) of anterior tibialis muscle – after intravenous injection of caffeine in a dose of 10 mg/kg; 3) changes in the reciprocal inhibition (induced by stimulating the ipsilateral deep peroneal nerve) of the reflex contractions of the gastrocnemius muscle. The ordinate axis shows the change in the amplitude of the muscle's action currents (in percent).

Experimental Methods

The experiments were performed on spinal cats. Laminectomy was performed in the region of the sacrolumbar thickening, and the meninges were carefully removed. An electrode was buried in the exposed popliteal nerve of each extremity. A tiny (30μ) glass-insulated electrode was inserted into the motor nucleus of the experimental muscle (anterior tibialis). A silver disk embedded in the muscles of thespine was used as the second electrode. Stimulation of the nerves and direct stimulation of the motor nucleus cells was effected with single breaking induction shocks. Needle electrodes were stuck into the muscle, and the action currents of the latter were led off through an amplifier to a cathode oscillograph.

In our investigation of the extensor reflexes, reflex contractions of the gastrocnemius muscle were induced by stimulating the corresponding posterior root, and inhibition of these contractions was induced by stimulating the ipsilateral deep peroneal nerve.

A Helmholtz pendulum was used to provide a definite sequence of stimulation for the afferent nerves and the cells of the motor nucleus, as well as to synchronize

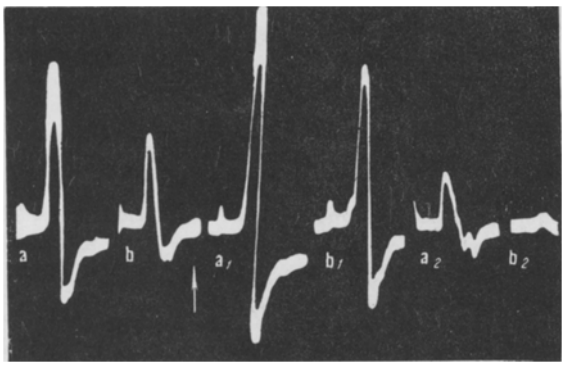

Fig. 2. Electromyogram illustrating the changes in the reflex excitability and reciprocal inhibition of the anterior tibialis muscle after the intravenous injection of caffeine (↑). a, a_1, a_2) Action currents recorded during reflex contraction of anterior tibialis muscle; b, b_1, b_2) action currents of the same muscle during cross inhibition; a, b) before caffeine injection; a_1, b_1) 5 min after injection of caffeine in a dose of 2.5 mg/kg; a_2, b_2) 30 min after caffeine injection.

the stimulations with the simultaneous sweep of the oscillograph ray. During the experiment, the animal was kept in a humid, heated chamber. To prevent drying, vaseline oil was poured over the cord. After the experiment, the spinal cord section containing the electrode was resected, fixed, and processed. The tip of the stimulating electrode was located by making laminary sections.

Caffeine (coffeinum purum) was injected intravenously in doses of 1-10 mg per 1 kg of animal weight.

Experimental Results

The curves shown in Fig. 1 illustrate the typical changes in reflex excitability. Caffeine caused biphasic changes in the reflex responses: there was a brief initial increase, lasting 5-10 min, which was then succeeded by a longer period of depression. This occurred in the reflex arcs of both the flexor (anterior tibialis) and extensor (gastrocnemius) muscles.

The same graph shows the changes in inhibition of the reflex contractions of the gastrocnemius muscle induced by the intravenous injection of caffeine. During the initial period of caffeine's effect, characterized by intensified reflex responses, the inhibition decreased, then grew progressively stronger as the reflex responses diminished in value.

The same pattern was also observed in relation to inhibition of the flexor reflexes. As the electromyogram in Fig. 2 shows, three minutes after the intravenous injection of 1 ml of a 0.5% caffeine solution per 2 kg of cat's weight, the reflex contraction of the tibialis became clearly intensified, while the inhibition induced by stimulation of the contralateral peroneal nerve weakened considerably. The reflex was inhibited 50% before the caffeine injection and 32% after the injection. Thirty-eight minutes after the caffeine injection, the depressive stage of the drug's effect was clearly apparent; the value of the reflex response dropped to half the original. At this time, stimulation of the contralateral peroneal nerve caused total inhibition of the reflex.

Analyzing the experimental data regarding the changes in inhibition caused by the action of caffeine, one is struck by the fact that the weakening of inhibition always coincided with the phase of intensified reflexes, while intensified inhibition was observed during the depressive stage of caffeine's effect. This implies that caffeine does not specifically affect the inhibition processes, and that the changes observed in inhibition are contingent upon the changes in reflex excitability. In this connection, one should mention that P. M. Nikiforovskii [2], in his study of caffeine's effect on the excitation and inhibition processes in the cerebral cortex, concluded that "caffeine, which acts on the excitation processes, evidently does not affect the inhibition processes." As our own observations have shown, however, in contrast to its prolonged and stable effect on the cerebral cortex, caffeine's stimulating effect on the spinal reflexes is of very brief duration.

The effect of caffeine on the spinal reflexes is similar to that of strychnine. P. G. Kostyuk [1] observed an increase in the inhibition threshold of the reflexes due to the action of strychnine, as well as intensification of both polysynaptic and monosynaptic reactions.

In the next group of experiments, we examined the effect of caffeine on the excitability of the cells of the motor nucleus of the anterior tibialis muscle. A microelectrode was inserted into the grey matter of the spinal cord from the dorsal aspect until stimulation of the contralateral popliteal nerve ceased to inhibit the response to direct stimulation. When an electrode is buried in the zone of the motor cells, the inhibition of the response to direct stimulation which is effected by stimulating the contralateral popliteal nerve, usually changes abruptly into reinforcement. The electrode's position was considered satisfactory when direct stimulation by a single breaking induction shock induced a strictly local contraction of the anterior tibialis muscle.

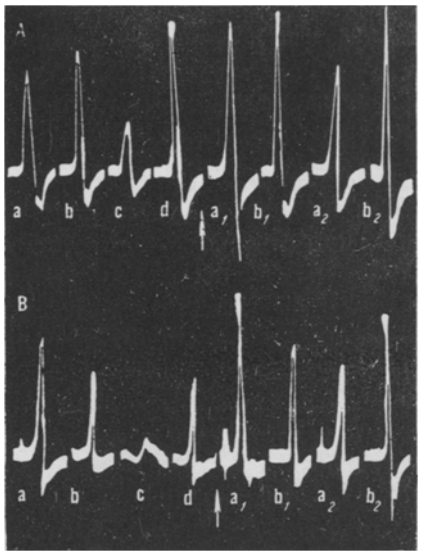

Fig. 3. Changes in reflex excitability and excitability of motor cells after intravenous injection of caffeine: a) action current recorded during reflex contraction of muscle; b) the same, during contraction induced by stimulating cells of motor nucleus of the same muscle; c) action current recorded during reflex contraction of muscle on a background of preceding stimulation of contralateral popliteal nerve; d) the same, during direct stimulation of motor nucleus cells; a_1) reflex response; b_1) response to direct stimulation 5 min after caffeine injection; a_2, b_2) 30 min after injection of caffeine in a dose of 2.5 mg/kg; A, B) electromyograms recorded in different experiments.

We simultaneously recorded the action currents which developed during the reflex contractions of the same muscle induced by stimulation of the ipsilateral popliteal nerve.

Figure 3 shows electromyograms illustrating the results of two typical experiments. It is evident from this figure that stimulation of the contralateral popliteal nerve induced strong inhibition of the reflex contraction of the muscle and reinforced the response of the same muscle to direct stimulation by the microelectrode of the cells of its motor nucleus. Five minutes after the intravenous injection of caffeine, both the reflex response and the response to direct stimulation of the motor nucleus cells became intensified. The increase in reflex excitability, however, was not lasting; as soon as 15-20 min after the injection, the muscle's reflex reaction became considerably weaker, while the response to direct stimulation of the cells of the muscle's motor nucleus remained intensified. In a few experiments, the increase in the excitability of the motor cells lasted an hour or more after the caffeine injection, and was combined with marked depression of the reflex responses of the same muscle.

Histological investigation showed that the tip of the stimulating electrode was located, in the two sample experiments, in the region of the motor nucleus of the anterior tibialis muscle.

On the basis of the data presented, one can conclude that the depression of reflex activity which occurs during the second phase of caffein's effect is due not to reduced excitability of the motor cells, but to either change in the conditions of the synaptic transmission of excitation or functional changes developing in the intercalary neurons of the experimental reflex, arc.

SUMMARY

The effect of the intravenous injection of caffeine upon flexor and extensor reflexes and reciprocal inhibition was studied on spinal cats. The change of the motor cell excitability was investigated by their direct stimulation with the aid of microelectrodes inserted into the gray matter of the spinal cord. Caffeine provokes biphasic changes in the reflex responses, i.e., the initial brief intensification of the reflexes is replaced by their more prolonged depression. Reciprocal inhibition decreases at the phase of reflex intensification, and increases during the depressive action of caffeine. Caffeine raises the motor cell excitability in the spinal cord, which increase remains manifest during the depression of the reflex responses. This leads to the conclusion that the reflex activity depression during the second phase of caffeine action is caused not be reduced excitability of the motor cells, but by the latered condition of the synaptic transmission of excitation, or by the functional changes developing in the intercalary neurons.

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