CERTAIN DATA REGARDING THE EFFECT OF AMINAZINE ON THE COMPLEX CONDITIONED REFLEX ACTIVITY OF ANIMALS WHEN DIRECTLY INJECTED INTO VARIOUS DIVISIONS OF THE BRAIN

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It has been established that the mechanism by which aminazine effects conditioned reflex activity is over-complex. The theory has been advanced in many works that aminazine primarily acts on the subcortical structures, particularly on the reticular formation of the brain stem [1, 2, 9 and others]. Along with this, weighty proof is presented in the literature that its primary activity is on the cerebral cortex [5, 6 and others]. The majority of investigators studied the effect of aminazine on the central nervous system by means of its subcutaneous, intramuscular or intravenous injection into the organism.

In our previous experiments [3, 7, 8], performed on dogs, we determined the action of various doses of aminazine, injected subcutaneously, on complex motor-conditioned reflex activity. In order to further analyze the obtained data, we considered it of interest to employ a permanent canula for the purpose of directly injecting aminazine into various divisions of the brain.

At present, a number of investigators have injected therapeutic materials into the brains of animals via a permanent canula: Haley and Weinberg [9], Lishak, Endrusti and Vintse and others. Since 1960 it has been used in the I. P. Pavlov Division of Physiology.

EXPERIMENTAL METHOD

Under intraperitoneal nembutal narcosis, an incision was made along the midline of the animal's head (cat), the soft tissues were moved to the side, and the point at which the canula was to be inserted was located on the surface of the bone with the aid of a stereotaxic apparatus, following the atlas of Jasper and Aimon-Marsan. Using a dental drill, apertures were made in the bone at these points, the dura mater was pierced with a needle, and two canulas, set in a small plexiglas plate which was flattened at the lower portion, were simultaneously inserted into the aperture to the necessary depth. Each canula was a hollow stainless steel tube, with a mandrel inserted inside it. The top of both canulas were closed by a common, curved, plexiglas cap (Fig. 1). The plate, together with the tubes, was fixed to the bone with cement. The wound was sutured in such a way that the cap projected above the skin freely (Fig. 2). The pharmacological substances were injected into the brain by the use of two other needles, with lengths and widths corresponding to the mandrels inserted in the canulas. The animals with the transfixed canulas (one or two) were kept under our observation for many months without signs of unrest or disruption of the motor-conditioned reflexes developed in them earlier.

The investigations were carried out on 9 cats, in whom motor alimentary conditioned reflexes had been developed earlier according to the method of situational conditioned reflexes (P. S. Kupalov). The experiments were set up in a small room (6 m^2), in which the floor had been divided into 6 squares. In different places within the room there were sound-and light-conditioning stimuli, a mat and a feed box. As a non-conditioning stimulus we used a piece of dried meat (2-3 grams). Positive conditioned reflexes were developed to a metronome, the light of a 150 watt lamp, and a tone with a pitch of 600 hertz. The differentiating stimuli were the light of a 25 watt lamp and a tone with a pitch of 200 hertz. The conditioned reflex activity that was developed included the following: the animals, led into the experimental room, immediately went to the mat and stood or sat on it. When the positive conditioning stimuli were switched on, they ran to the feed box, ate the meat and again returned to the mat; when the inhibitory stimuli were switched on, they remained on the mat.

EXPERIMENTAL RESULTS

Two canulas were simultaneously put into place, one of which was inserted into the subcortex (into the reticular formation, mid-brain, caudate nucleus, internal geniculate body, anterior colliculi), and the other into the cortex (usually into the posterior division of the sigmoid convolution). At 4-6 days after the operation the animals were started on the experiment, and by the 7-10 day, when the strength of the conditioned reflexes developed earlier had been confirmed with certainty, they were administered the therapeutic substances. We used the standard form of aminazine, produced in ampules in the form of a 2.5% solution. On the day the aminazine was introduced the animals were put through the experiment before the injection, immediately after the injection, and then every 30 minutes over the course of the first 2 hours, or sometimes even longer. The intervals between injections depended on the dose of the preparation administered earlier, and on the state of the conditioned reflex activity. Before proceeding to the injection of the therapeutic substances into various formations of the brain, control investigations were performed involving the injection of varying amounts of physiological saline into these same formations. After all the series of investigations were carried out, the animals were sacrificed and the brains subjected to histological study.

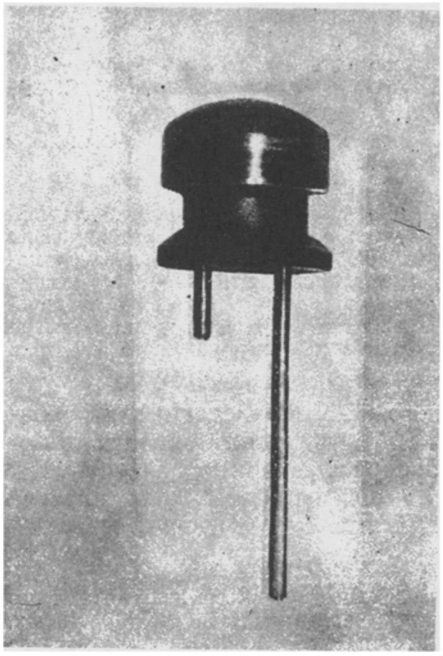

Fig. 1. Canula.

The basic problem was to detect clear changes in the motor alimentary conditioned reflexes developed earlier, caused by the injection of aminazine into the subcortex, into the cortex, and subcutaneously, in minimal doses (see table). We also had to discern whether both the general behavior of the animals and the developed motor conditioned reflexes depended on the different methods of injecting the aminazine.

It is apparent from the table presented that the minimal doses used for the various methods of its injection into the animal organism were different. Thus, with injection into the cerebral cortex (0.47-0.63 mg/kg) they were significantly higher than in the subcortex (0.03-0.16 mg/kg), but several times smaller than the minimal doses used for the subcutaneous injection (1.25-3.57 mg/kg). Hence, the cerebral cortex and subcortex have a different threshold of sensitivity to aminazine. With injection of aminazine into the subcortex, into the cortex and subcutaneously, a clear difference was seen in the speed with which its action was manifested. Thus, with injection of aminazine into the subcortex, the effect occurred immediately after its introduction; in the cortex, there was a somewhat longer latent period (1-10 minutes), and subcutaneously it was seen after 15-30 minutes or more.

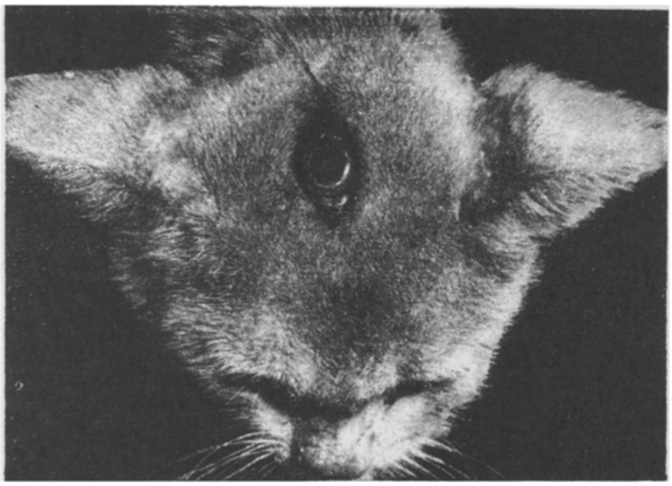

Fig. 2. Head of a cat with affixed canula.

Of the subcortical structures, the reticular formation possessed a particularly high sensitivity to aminazine. Hence, with injection of the substance into the rostral portion of the recticular formation in the mid-brain, clear changes in the conditioned reflex activity were observed at a dose of 0.03 mg/kg, while other subcortical structures required significantly greater doses (0.13-0.16 mg/kg).

In addition, with injection of aminazine into the reticular formation, changes in the conditioned reflex activity occurred within several seconds, while with application of this substance to the other subcortical structures, they began at later intervals.

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Basically, it is essential to note the uniform character of the changes occurring in the behavior of the animals with the different methods of injecting aminazine into the organism. They began with the animals' legs giving way, their walk developed a rocking character, the speed of the motor reactions decreased, a general flaccidity and somnolence appeared, and pain sensitivity decreased or completely disappeared (with retention of cutaneous and tactile sensation), etc. Changes in the conditioned reflex motor activity were manifested by an increase in the latent periods of the conditioned reflexes, release from the inhibitory effects of the differentiating stimuli, instability of the reflexes, and an intensification of the succeeding inhibition.

Minimal Doses of Aminazine Causing Changes in Motor Alimentary Conditioned Reflexes

Animal No.	Minimal doses of aminazine (in mg/kg), injected:		
	into the subcortex	into the cortex	subcutaneously
7	0.13	–	–
9	0.07	–	–
10	0.12	–	–
1	0.11	–	2.66
3	0.16	–	1.67
5	0.03	–	1.25
11	0.09	–	3.57
4	0.13	0.63	1.50
6	0.06	0.47	2.91

With injection of aminazine into the subcortex, we noted a decided strengthening of the first alimentary reaction (with initiation of the conditioned signal, the animals did not head directly for the feed box, but rather to the source of the conditioned stimulus, and only after a certain amount of time did they run up to the feed box); in addition, the majority of animals became very affectionate, continuously purring. With direct injection of aminazine into the subcortex and cortex, we repeatedly observed a fan-like spreading of the toes in the animals. It is interesting that, with the different methods of injecting the aminazine into the organism, we observed clearly manifested, individual sensitivity of the animals to this substance.

Thus, the investigations carried out show that with injection of aminazine into the subcortical structures, changes in the behavior of the animals occur as a result of considerably smaller doses, and occur considerably earlier, than with intracortical or subcutaneous injection. In addition, the injection of aminazine into the subcortical structures causes a number of peculiarities in the behavior of the animals, although, on the whole, there is a great deal of similarity in the character of the changes occurring with the different methods of injecting. Our experiments with direct application of aminazine to different portions of the brain corroborate the widespread belief in a particularly high sensitivity of the reticular formation to this preparation.

SUMMARY

Investigations were staged on cats by using the method of situational conditioned reflexes (P. S. Kupalov). Chronic canula was used to administer aminazine directly into various portions of the brain. With aminazine administered into the subcortical structures changes in the animal's behavior occurred much earlier that with the intracortical or subcutaneous injection. When aminazine is administered subcortically changes occur with lower doses than in intracortical or subcutaneous administration. With subcortical administration a number of peculiarities are observed with the animals' behavior, although as a whole there is a considerable similarity in the nature of changes occurring with various routes of aminazine administration. Experiments with direct administration of aminazine into various portions of the brain confirm the widespread opinion on high sensitivity of reticular formation to this preparation.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.