EFFECT OF SMALL DOSES OF SCOPOLAMINE AND CHLORPROMAZINE ON THE ELECTRICAL ACTIVITY OF THE CORTEX, THE RETICULAR FORMATION, AND CERTAIN PARTS OF THE HYPOTHALAMUS OF RABBITS DURING THE DEFENSIVE (AVOIDANCE) CONDITIONED REFLEX

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It is considered by many physiologists that the performance of defensive reactions is associated with the excitation of the adrenergic structures of the reticular formation of the mesencephalon [1, 2, 4, etc.], and food reactions with activation of the cholinergic structures of the subcortex [5, 7, 8, etc.]. Less attention has been paid to the study of the point of application in the central nervous system of the action of cholinolytic and adrenolytic substances influencing animals' behavior. Some authors [4, 7] consider that the region of action is the reticular formation of the mesencephalon, others [5, 8, 10, 16] locate it in the hypothalamus.

The object of the present investigation was to study the dynamics of the changes in conditioned-reflex defensive activity of the cortex, the reticular formation of the mesencephalon, and the medial and lateral portions of the hypothalamus following administration of small doses of scopolamine and chlorpromazine. Attention was concentrated on the changes in the EEG in the form of synchronized waves with a frequency of 8-10 per sec, waves which were shown by L. G. Voronin and B. I. Kotlyar to arise in response to a conditioned stimulus and to exhibit a constant association with the conditioned reflex at all its stages; during consolidation of the food reflex, this synchronized rhythm is concentrated in the lateral portion of the hypothalamus and in the case of the defensive reflex—in the ventro-medial structures of the hypothalamus.

EXPERIMENTAL METHOD

Experiments were carried out on rabbits in a soundproof chamber. The potentials were recorded from the animals able to move freely (by B. I. Kotlyar's method [6]). The recordings were made on a 16-channel electroencephalograph made at the "Biofizpribor" factory, with leads from the optico-auditory cortex, the reticular formation of the mesencephalon, and the ventro-medial and lateral nuclei of the hypothalamus. A conditioned defensive reflex to a sound or a light was formed by means of the avoidance method [5]. Scopolamine was injected intramuscularly immediately before the experiment in a dose of 0.1-0.2 mg/kg, and chlorpromazine in a dose of 1-2 mg/kg. Injection of physiological saline was used as the control.

EXPERIMENTAL RESULTS AND DISCUSSION

After consolidation of the conditioned defensive reflex, in response to the signal all the rabbits gave a burst of synchronized waves with a frequency of 8-9.5 per sec in the medial portions of the hypothalamus, the optico-auditory region of the cortex, and the reticular formation of the mesencephalon (Fig. 1A). Immediately after injection of scopolamine, the electrical activity and the conditioned-reflex activity showed no appreciable change.

*O.B. D'yachkova also took part in the work.

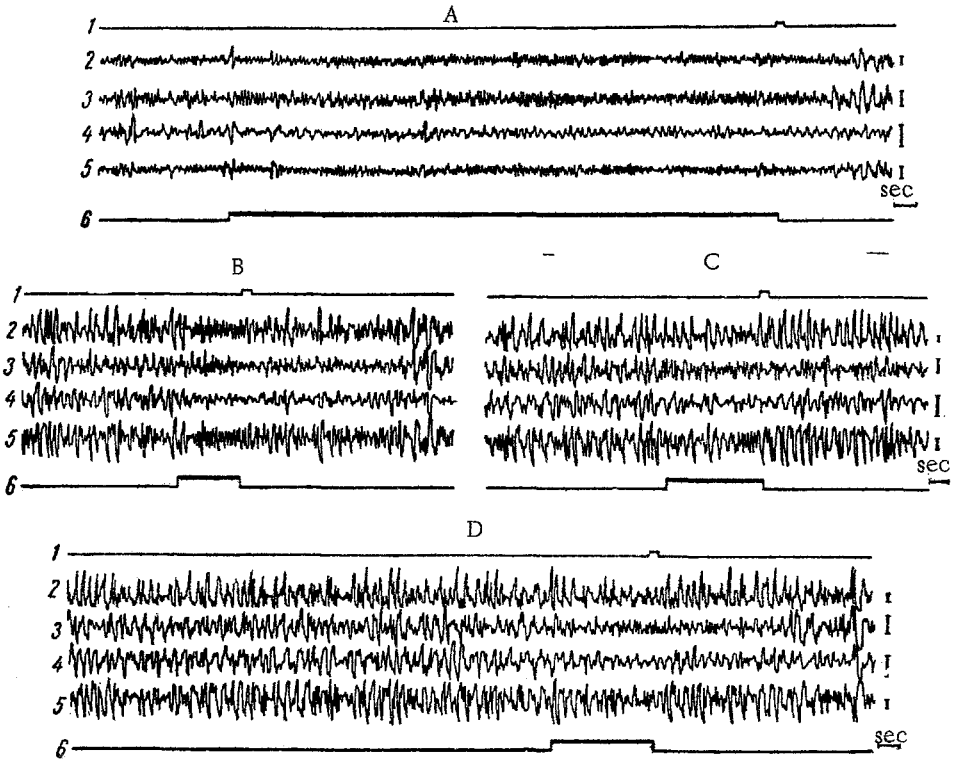

Fig. 1. Effect of scopolamine on electrical activity during conditioned stimulation. A) Changes in electrical activity in response to a conditioned stimulus before injection of scopolamine; B) 20-30 min after injection; C) 30-40 min after; D) 40-50 min after; 1) marker of pressure by animal on pedal; 2) optic cortex; 3) ventro-medial nucleus of hypothalamus; 4) lateral nucleus of hypothalamus; 5) reticular formation of mesencephalon; 6) marker of action of conditioned stimulus. Explanation in text.

Between 10 and 15 min after injection of scopolamine, slow waves (2-3 per sec), characteristic of the state of sleep, appeared in all the tested leads in the intervals between the signals. The signal stimulus also evoked a conditioned-reflex movement on the EEG—an arousal reaction with a frequency of 3-6 waves per second, followed by a synchronized rhythm with a frequency of 8-10 per sec, in the same leads as before the injection of scopolamine. After the signal had been turned off, the slow waves reappeared immediately. From 20 to 30 min after the injection of scopolamine the conditioned stimulus did not evoke an arousal reaction on the EEG, but just at the same time as the behavioral conditioned-reflex reaction a burst of synchronized waves with a frequency of 8-9.5 per sec appeared in the cortex, the medial hypothalamus, and the reticular formation, followed by slow waves (Fig. 1B).

During the next 20-30 min of the action of scopolamine, the burst of synchronized waves in response to the conditioned stimulus appeared sooner in the medial portion of the hypothalmaus and later in the cortex and the reticular formation (Fig. 1C). Later still, the synchronized waves in response to the signal appeared only in the hypothalamus and were absent in the cerebral cortex and the reticular formation (Fig. 1D). In these circumstances a conditioned defensive reaction was observed in response to practically any external acoustic stimulus. After this stage a gradual restoration of the normal electrical activity was observed, passing through all the stages described above, although in the opposite order.

Hence, scopolamine caused depression of the arousal reaction, but did not exclude the appearance of a rhythm with a frequency of 8-9.5 per sec in the structures of the medial hypothalamus and the performance of a conditioned defensive reflex.

From 10 to 15 min after the injection of chlorpromazine slow waves appeared in the intervals between the conditioned stimuli on the EEG. The conditioned stimulus gave rise to the usual picture of a burst of synchronized waves with a frequency of 8-9.5 per sec. A further 15-20 min after injection of the preparation the latent period of the

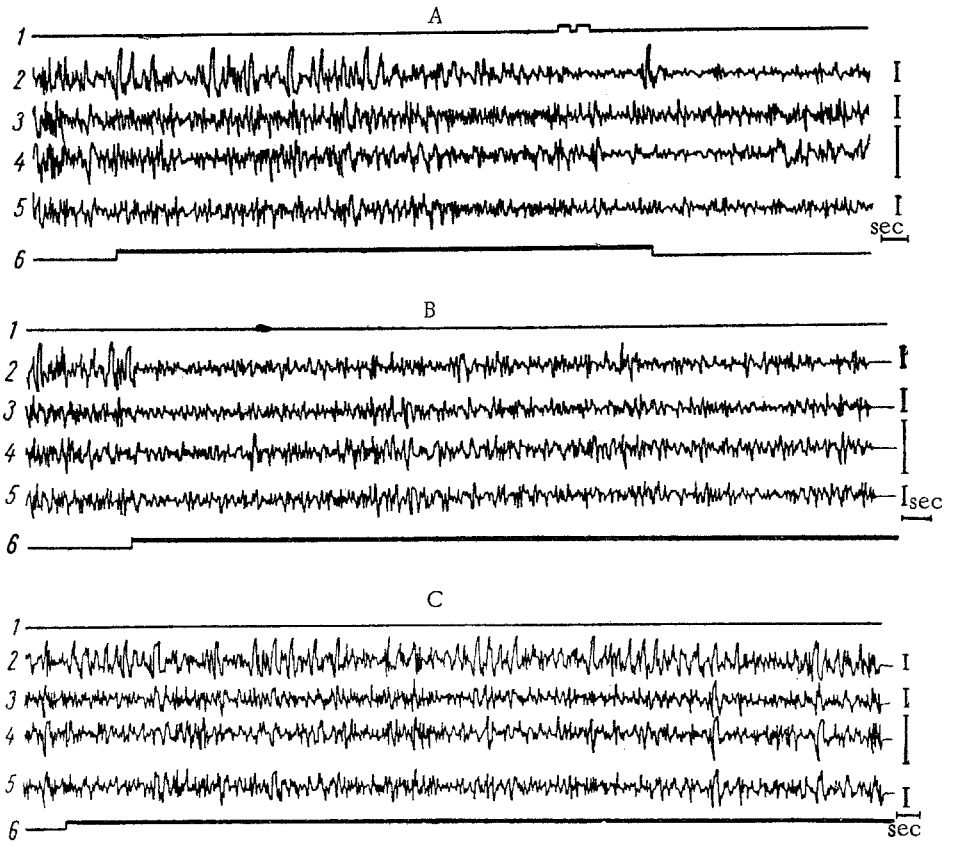

Fig. 2. Effect of chlorpromazine on electrical activity during conditioned stimulation. A) 20-30 min after injection of chlorpromazine; B) 30-40 min after; C) 40-50 min after. Legend as in Fig. 1. Explanation in text.

reflex was lengthened and a rhythm of 8-9.5 per sec appeared on the EEG, initially in the structures of the medial hypothalamus and later in the cortex and mesencephalic reticular formation. Later still a burst of synchronized waves with a frequency of 8-9.5 per sec in response to the conditioned stimulus was recorded only in the medial hypothalamic leads, and it was absent in the cerebral cortex (Fig. 2A). The conditioned defensive reaction persisted. From 30 to 40 min after the administration of chlorpromazine the conditioned-reflex component of the defensive reflex disappeared, and no rhythm of 8-9.5 per sec was present on the EEG, although the arousal reaction persisted throughout the time of action of the conditioned stimulus (Fig. 2B).

The animal's motor reaction, in the form of pressing on a pedal, was preserved but only in response to a direct nociceptive stimulus, and in these circumstances the threshold of the unconditioned pain reflex was considerably raised. The arousal reaction on the EEG was subsequently observed only at the moment of switching the signal on, and later this effect also disappeared. Hence, no changes were observed in the EEG on presentation of the conditioned or any other indifferent stimulus (Fig. 2C). As a rule the unconditioned reflex was absent at this period. After this, the normal electrical activity and the conditioned-reflex defensive activity were gradually restored. First to return was the arousal reaction and the animal's unconditioned pain reaction. Next, the conditioned-reflex component was restored, with the appearance of a burst of synchronized waves with a frequency of 8-10 per sec, at first in the medial leads of the hypothalamus and later in the cortex and the mesencephalic reticular formation.

Hence chlorpromazine, unlike scopolamine, at first caused disappearance of the conditioned defensive reflex. At the same time absence of the rhythm of 8-10 waves per sec was observed in the medial portions of the hypothalamus, and this was followed by depression of the arousal reaction and of the unconditioned reflex.

Following injection of scopolamine into the rabbits the conditioned defensive reaction did not disappear, whereas chlorpromazine blocked both the conditioned and the unconditioned component of this reflex. Characteristically,

after the action of the cholinolytic, not only the synchronized activity (8-10 per sec) in the cortex, the mesencephalic reticular formation, and the lateral nucleus of the hypothalamus disappeared, but also the electroencephalographic arousal reaction to the external stimulus and in the intervals between signals. Other authors have obtained similar results [12, 15]. Evidently the disappearance of the arousal reaction is evidence of a lowering of the tonus of the cerebral cortex of the "waking level" [9, 14], as a result of the blocking of the cholinergic component of the mesencephalic reticular formation. However, as these experiments demonstrate, this partial blocking of the nonspecific activating system is insufficient to inhibit the defensive reaction. The probable reason for this is that scopolamine does not block the excitation of the ventro-medial nucleus of the hypothalamus, the functioning of which is associated with the manifestation of the animal's defensive reactions [5, 8, 13, 17]. Since this particular structure in the hypothalamus is not blocked by scopolamine, it may be supposed that it does not belong to the cholinergic system.

Unlike scopolamine, chlorpromazine at first caused depression of the conditioned defensive reaction with disappearance of the synchronized activity (8-10 waves per sec) in all the structures tested, including the ventro-medial nucleus of the hypothalamus, although the arousal reaction on the EEG still continued. Evidently chlorpromazine, because of its adrenolytic properties, causes a primary blocking of the subcortical morphological substratum of the defensive reaction, as demonstrated by the disappearance of the rhythm of 8-10 per sec in the ventro-medial nucleus of the hypothalamus, and then lowers the "waking level" (the tonus of the cerebral cortex), blocking the mesencephalic reticular formation and, at the same time, the unconditioned pain reaction. Since the ventro-medial nucleus of the hypothalamus is not blocked by scopolamine, and in these circumstances the animals's defensive reaction is preserved, while during the action of chlorpromazine it disappears along with the synchronized activity (8-10 waves per sec) in the ventro-medial nucleus of the hypothalamus, it may be supposed that the defensive reflex is associated with the functioning of this particular structure in the hypothalamus, which is adrenergic in its chemical structure [11].

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