EFFECT OF CARBIDINE ON DEFENSIVE CONDITIONED REFLEXES

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The effect of carbidine on conditioned defensive reflexes during stimulation of the mesencephalic reticular formation was investigated in chronic experiments on rats and rabbits. Carbidine was shown to prevent the inhibition of defensive conditioned reflexes caused by stimulation of the mesencephalic reticular formation. This points to its inhibitory action on these structures. This conclusion was confirmed by experiments conducted on rabbits in which changes in electrical activity were recorded during stimulation of the mesencephalic reticular formation.

KEY WORDS: defensive conditioned reflexes; EEG; reticular formation; carbidine.

One of the most characteristic properties of carbidine is its inhibitory effect on conditioned reflexes and, in particular, on negatively motivated responses. This quality, meanwhile, is to some degree characteristic of all the neuroleptics and it is the experimental equivalent of their antipsychotic action [3]. The reticular formation of the brain stem is known to play an important role in the mechanism of defensive conditioned reflexes. Stimulation of the reticular formation may result both in facilitation of conditioned-reflex responses (to weak stimuli) and, conversely, in their inhibition (with stimulation of higher parameters) [9]. According to an existing concept, schizophrenia is connected with a state of excitation of the central nervous system that is manifested, in particular, as disturbance of ability to concentrate attention [7, 14]. These disturbances are linked with dysfunction of the midbrain or the brain-stem reticular formation [10]. Such patients perform badly in tests requiring the concentration of attention; a close relationship has been demonstrated between the severity of schizophrenia and the degree of disturbance of attention as a manifestation of the state of excitation [7].

Under experimental conditions stimulation of the mesencephalic reticular formation can be used as a model of excitation of this type [9].

It has also been shown that disturbance of defensive conditioned reflexes in rats as a result of stimulation of the mesencephalic reticular formation can be prevented by chlorpromazine [9]. These findings justified an investigation of carbidine, a substance in whose spectrum of therapeutic action antipsychotic properties are particularly pronounced, in this direction.

EXPERIMENTAL METHOD

Experiments were carried out on male rats and rabbits. In series I the performance of conditioned defensive reflexes by rats was studied.

The experiments were carried out in the following order.

1. Defensive conditioned reflexes of climbing onto a rod were produced [5].

2. Electrodes were implanted into the mesencephalic reticular formation [6]. Before the operation the animals were anesthetized with pentobarbital (2.5% solution, dose 51.3 mg/kg, intraperitoneally).

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TABLE 1. Effect of Carbidine and Electrical Stimulation of Reticular Formation on Defensive Conditioned Reflexes

Character of stimulation	Mean time of performance of conditioned reflexes (sec)	Change in time of performance of conditioned reflexes (relative to control)
Control	2,7 (2,4—3,0)	1
Electrical stimulation	13,3 (12,5—14,1)	4,9 (4,5—5,3)
Carbidine	9,1 (8,4—9,2)	3,4 (3,1—3,7)
Carbidine + electrical stimulation	2,8 (2,1—3,5)	1,0 (0,9—2,1)

Legend. Confidence limits shown in parentheses.

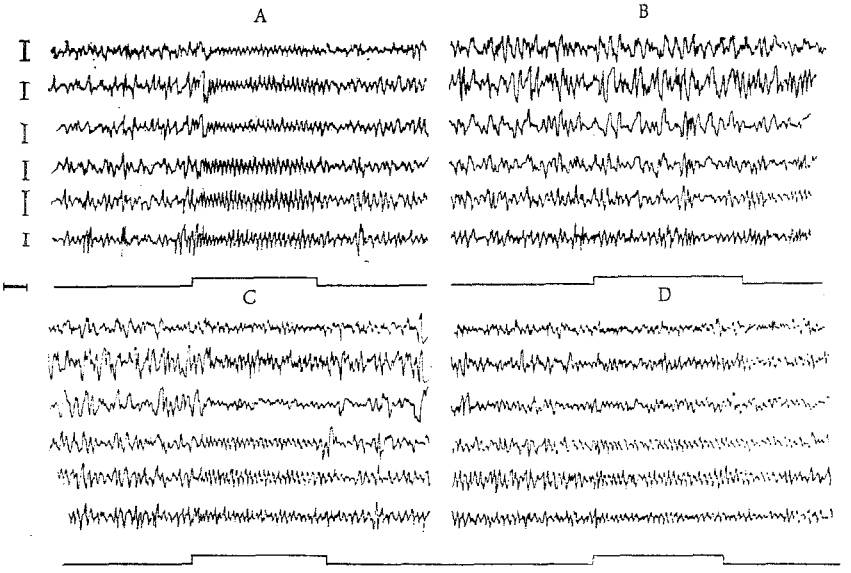

Fig. 1. Effect of carbidine on arousal reaction evoked by electrical stimulation of reticular formation in rabbit with implanted electrodes: A) control, stimulation of mesencephalic reticular formation, intensity 3 V; B) 15 min after injection of carbidine 7 mg/kg, intensity of stimulation 4.25 V; C) 30 min after injection of carbidine, intensity of stimulation 4.5 V; D) 120 min after injection of carbidine, stimulation 3.25 V. From top to bottom: sensory motor, visual, and association areas of cortex, ventrolateral thalamic nucleus, dorsal hippocampus (left, right), marker of stimulation. Calibration: 50 μV and 1 sec.

Monopolar electrodes 0.34 mm in diameter were used; the reference electrode was applied to the animal's ipsilateral ear. After restoration of the conditioned reflexes the magnitude of stimulation (with pulses 2 msec in duration, frequency 100 Hz) at which performance of the conditioned reflexes was disturbed (the animals' behavior under these circumstances was highly characteristic: they turned the head or shook it) was determined as their amplitude. Control provocation of the conditioned reflexes was carried out immediately after stimulation (Table 1).

3. The action of carbidine was tested in doses inducing inhibition of the conditioned reflexes.

4. Performance of the conditioned reflexes was tested during stimulation of the reticular formation and after preliminary (30 min beforehand) injection of the drug.

In the experiments of series II changes in cortical potentials arising during stimulation of the mesencephalic reticular formation were recorded in rabbits. Bipolar electrodes, with an interelectrode distance

of 1 mm, made of nichrome wire 100-125 μ in diameter were used for stimulation [12]. Repetitive stimulation for 5-7 sec with pulses 2 msec in duration and with a frequency of 250 Hz was applied. The threshold voltage was usually 2-4 V. A stimulator with radiofrequency output stage was used. The electrocorticogram was recorded by monopolar silver electrodes inserted epidurally in the region of the sensorimotor, visual, and associative cortex, whereas to record potentials from the dorsal hippocampus and ventrolateral thalamic nucleus bipolar nichrome wire electrodes were used.

In both series of experiments the location of the electrodes was verified histologically [8].

EXPERIMENTAL RESULTS AND DISCUSSION

Series I. 1. As the results showed, a stable conditioned reflex with a latent period of 1-3 sec was formed in most animals after 2 weeks of training.

2. The conditioned reflexes were restored on the third day after the operation, when the latent period of the response was 2.7 (2.4-3.0) sec. The individual sensitivity of the animals to electrical stimulation differed significantly and the amplitude of the pulses inducing inhibition of the conditioned reflexes varied in different animals from 7 to 25 V. Both after injection of carbidine and after electrical stimulation, if no response was present for 15 sec, it did not appear later in the overwhelming majority of animals; this time thus served as the criterion of total inhibition of the reflex.

The selected electrical stimulation evoked marked inhibition of the conditioned reflexes: the mean reaction time increased by 4.9 (4.5-5.3) times, i.e., to 12-14 sec; clearly, therefore, in many cases the conditioned reflexes were completely inhibited (Table 1).

3. Marked inhibition of the conditioned reflexes was produced by carbidine given in a dose of 4 mg/kg by intramuscular injection; the reaction time was increased by 2-3 times (Table 1). In smaller doses carbidine had no clearly defined inhibitory effect.

4. With a combination of electrical stimulation and administration of carbidine no significant inhibition of the conditioned reflexes took place. For instance, after the combined action of carbidine and electrical stimulation a statistically significant inhibition of the response took place in only two of the six animals, but even so the inhibition was less than that produced by the separate action of the electric current or carbidine. On the whole, with a combination of these two factors the performance of the conditioned reflexes was undisturbed. As Table 1 shows, the difference in the reaction time of the control and experimental animals was not significant.

Series II. High-frequency stimulation of the mesencephalic reticular formation potentiates its ascending activating effects and in the present experiments this was expressed as the appearance of low-amplitude (20-30 μV), high-frequency (20-30/sec) rhythms in the anterior cortical zones and also of regular waves with a frequency of 4-6/sec and an amplitude of up to 40-50 μV in the posterior zones of the cortex, the mesencephalic reticular formation, the nonspecific thalamic structures, and the hippocampus; these changes lasted longer than the period of stimulation (Fig. 1).

After administration of carbidine in doses of 2-3 mg/kg this "after-effect" disappeared, but the initial activation reaction was not blocked by carbidine in these doses. In large doses (5-10 mg/kg) carbidine increased the threshold of the activation response by 30-50% compared with the control. This increase, it must be emphasized, was not the result of habituation to the stimulation, for at the end of the experiment definite restoration of the original value of the stimulation threshold was observed.

In some investigations correlation was established between ability to inhibit defensive conditioned reflexes and the effectiveness of phenothiazine derivatives in the treatment of mental diseases [10-12], and the importance of this property in the spectrum of pharmacological activity of neuroleptics will thus be evident.

The results indicate that the ability of carbidine to weaken defensive conditioned reflexes depends on the functional state of the reticular formation and that carbidine depresses the mesencephalic part of this formation.

The therapeutic action of chlorpromazine in schizophrenia is considered to be connected with inhibition of the mesencephalic reticular formation [9]. Since the results of the present experiments indicate that carbidine, in whose action the antipsychotic component is particularly well marked [1, 2], also possesses an inhibitory effect on that same structure, there is reason to suppose that its efficacy in the treatment of schizophrenia depends on its ability to depress functional activity of the reticular formation.

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