EFFECT OF TRIFLUOPERAZINE AND CHLORPROMAZINE ON HIPPOCAMPAL ELECTRICAL ACTIVITY

G. N. Krolevets

UDC 615.214.22:547:869].015.4:
612.825.266.014.423

Responses in the hippocampus to stimulation of the sciatic nerve (somatic response) or of the ipsilateral (local response) and contraleteral hippocampus (transcommissural response) were studied in acute experiments on unanesthetized, curarized rabbits. Chlorpromazine and trifluoperazine were found to cause marked changes in the local and transcommissural responses. The somatic response was less severely affected by these drugs.

The limbic system, in which the synaptic transmission is of particular interest to neuropharmacologists, plays an imporant role in the integration of psychological and emotional activity. For this reason it was decided to study the effect of chlorpromazine and trifluoperazine on the hippocampus, the central structure of the limbic system.

EXPERIMENTAL METHOD

Acute experiments were carried out on unanesthetized, curarized rabbits. Several types of hippocampal evoked responses were studied: local, transcommissural, and somatic. A detailed account of the methods used to obtain each of these responses and of their characteristics was given previously [1].

Trifluoperazine and chlorpromazine were injected intravenously in doses of between 1 and 5 mg /kg.

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments showed that the changes in the hippocampal evoked responses produced by the action of trifluoperazine differed in degree (Fig. 1A, 2; 1B, 2; 1C, 2). The amplitude of the negative and positive components of the local response (Fig. 1B, 2) was increased by 40-100% of its initial level. Trifluoperazine also caused marked changes in the transcommissural hippocampal response (Fig. 1C, 2), and the amplitude of its positive and negative components was increased by more than 100% of the initial level. These changes in the local and transcommissural responses appeared 5-10 min after injection of trifluoperazine and lasted for 40-50 min. Potentials evoked by sciatic nerve stimulation (Fig. 1A, 2) showed only slight changes: their latent period was not increased but remained at 17-22 msec, and the amplitudes in most experiments (two-thirds of the total number) likewise was unchanged. In those experiments in which trifluoperazine had a marked synchronizing effect (one-third of the total number), the amplitude of the somatic response was increased by not more than 20-30%. Chlorpromazine also increased the amplitude of the local and transcommissural hippocampal responses. During the period of maximum effect (between 20 and 60 min the amplitude of the local response was increased by 80-100%, and that of the transcommissural response by 100% or more compared with its initial level on account of both components. By contrast with the above experiments, the amplitude of the potentials evoked by sciatic nerve stimulation showed only a very slight increase.

Laboratory of Pharmacology of the Nervous System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 74, No. 9, pp. 57-60, September, 1972. Original article submitted November 30, 1971.

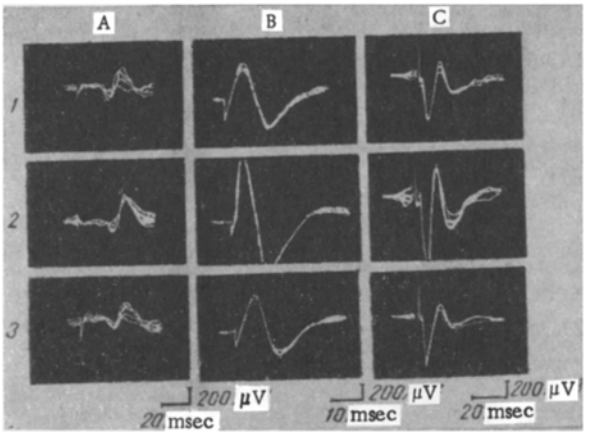

Fig. 1

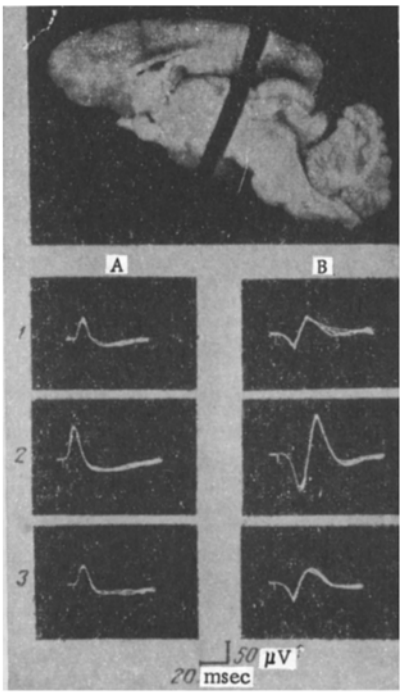

Fig. 2

Fig. 1. Effect of trifluoperazine (3 mg/kg) on somatic (A), local (B), and transcommissural (C) hippocampal evoked responses in rabbits with an intact brain: 1) before injection; 2) 15 min after, and 3) 180 min after intravenous injection of trifluoperazine.

Fig. 2. Different types of hippocampal responses in rabbits with premesencephalic transection before (1) and 30 min (2) and 180 min (3) after intravenous injection of trifluoperazine (3 mg/kg): A) local; B) transcommissural hippocampal responses. Level of section of the brain is shown above.

The local and transcommissural responses are known to be associated with synaptic excitation of dendrites of the pyramidal cells [3, 4]. The local response arises during direct stimulation of the hippocampus, and the transcommissural response during activation of neurons of the contralateral hippocampus by endings of commissural fibers. A marked change in these responses after injection of trifluoperazine and chlorpromazine thus reflects the effect of these drugs on these particular types of monosynaptic transmission within the hippocampus on one side and also between symmetrical points of the hippocampus on opposite sides.

This effect was not due to the well-known inhibitory effect of phenothiazine derivatives on the reticular formation or on its collaterals from the specific system [6]. This was shown by the results of experiments with premesencephalic transection of the brain stem, which showed that the ability of these two neuroleptics to modify the local and transcommissural responses was still preserved under conditions ruling out any possible influence of the mesencephalic reticular formation on higher levels of the brain (Fig. 2A, 2; 2B, 2). Since the local and transcommissural responses are entirely formed in the hippocampus these results suggest that the neuroleptics had a direct effect on the hippocampus which was independent of the reticular formation.

So far as the increase in amplitude of the local and transcommissural responses under the influence of trifluoperazine and chlorpromazine is concerned, it may have been due to blocking of the basket cells of the hippocampus, which are inhibitory in function [5], by the neuroleptics. The absence of inhibitory influences from the basket cells leads to liberation of the pyramidal neurons whose dendrites generate the response, with a corresponding increase in the amplitude of the evoked responses. However, the possibility likewise cannot be ruled out that other mechanisms may play a role in the changes in the local and transcommissural responses: a change in the modulating effect of the entorrhinal and limbic cortex or a change in the inhibitory function of the amygdala.

The very slight nature of the changes in the somatic response under the influence of the neuroleptics is also interesting. The positive component of this response is, of course, the postsynaptic potential, which arises in the apical dendrites of the pyramidal neurons under the influence of impulses arriving along afferent fibers; the negative component is generated in the basal dendrites of the same neurons [2]. The differences found in the degree of change in these three types of hippocampal responses suggest that the synapses concerned with the conduction of the different types of excitation in the hippocampus are heterogeneous in their chemical sensitivity. Although the somatic responses changed only slightly as a result of the action of the neuroleptics, they are considerably modified by the action of general anesthetics which, on the other hand, have little effect on the local and transcommissural responses. [1]. The pathways of spread of afferent impulses over the hippocampus are evidently under strong ascending influence from the reticular formation. General anesthetics are known to have a stronger action than neuroleptics on the reticular formation. Systems generating the local and transcommissural responses are known to be independent to a large extent of the reticular formation.

The results of these experiments suggest that the neuroleptics studied have a less marked effect on the pathways of afferent impulses to the hippocampus and on their spread over the hippocampus than on systems concerned with the connection of symmetrical zones of the hippocampus on opposite sides of the brain and with the spread of impulses within a circumscribed zone of the hippocampus on the same side. The effect of neuroleptics on the local and transcommissural responses is primary and is not due to their blocking effect on the mesencephalic reticular formation.

LITERATURE CITED

1. G. N. Krolevets, Byull. Éksperim. Biol. i Med., No. 12, 47 (1969).
2. F. N. Serkov and G. F. Makul'kin, in: Electrophysiology of the Central Nervous System. Proceedings of the 5th All-Union Conference [in Russian], Tbilisi (1966), p. 274.
3. P. Andersen, Acta Physiol. Scand., 47, 63 (1959).
4. P. Andersen, Acta Physiol. Scand., 48, 178 (1960).
5. P. Andersen, in: Modern Trends in Neuromorphology, Vol. 5, Budapest (1965).
6. A. I. Hanse, J. Physiol. (London), 145, 41 (1959).