ANTAGONISTIC EFFECT OF 5-HYDROXYTRYPTOPHAN AND NEUROLEPTICS ON HIPPOCAMPAL EVOKED POTENTIALS

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Responses arising in the hippocampus to stimulation of the sciatic nerve (somatic response) or of the ipsilateral hippocampus (local response) and contralateral hippocampus (transcommissural response) were studied in acute experiments on unanesthetized curarized rabbits. 5-Hydroxytrypotophan was found to produce long inhibition of the local and transcommissural responses whereas the change which it produced in the somatic response was negligible. Depression of the hippocampal responses could be prevented by preliminary administration of chlorpromazine and trifluoperazine. After administration of 5-hydroxytryptophan, chlorpromazine and trifluoperazine abolished the depression of the local and transcommissural responses.

The antiserotonin activity of the phenothiazine derivatives has so far been investigated mainly on peripheral organs. The important role of serotonin in brain activity necessitates the detailed study of this problem at the level of the central nervous system. Since serotonin does not pass readily through the blood-brain barrier, its precursor 5-hydroxytryptophan has been used, for this substance undergoes decarboxylation and thereby raises the serotonin level in the brain.

The object of the present investigation was to study the effects of neuroleptics and 5-hydroxytryptophan on hippocampal evoked potentials.

EXPERIMENTAL METHOD

Acute experiments were performed on unanesthetized curarized rabbits. Several types of hippocampal evoked responses – local, transcommissural, and somatic – were studied.

A full account of the method and of each of the responses studied was given in the previous paper [1]. The neuroleptics used were chlorpromazine and trifluoperazine, which were injected intravenously in doses of 1-5 mg/kg, while 5-hydroxytryptophan was injected intravenously at the rate of 1.67 mg/kg per minute to avoid lowering the arterial pressure. At this rate of infusion 5-hydroxytryptophan induced EEG activation which began at a strictly definite time (22.25 ± 1.61 min), corresponding to the results of administration of 5-hydroxytryptophan in a dose of 37.15 ± 2.68 mg/kg [2].

EXPERIMENTAL RESULTS AND DISCUSSION

Chlorpromazine and trifluoperazine caused a marked increase in amplitude of the local and transcommissural responses by 100-200% of their initial level (Fig. 1B; Fig. 2C, 2). Potentials evoked by sciatic nerve stimulation (Fig. 1A, 2) were completely or almost completely unchanged by the action of these drugs. These changes affected mainly the positive wave of the somatic response, which was increased by not more

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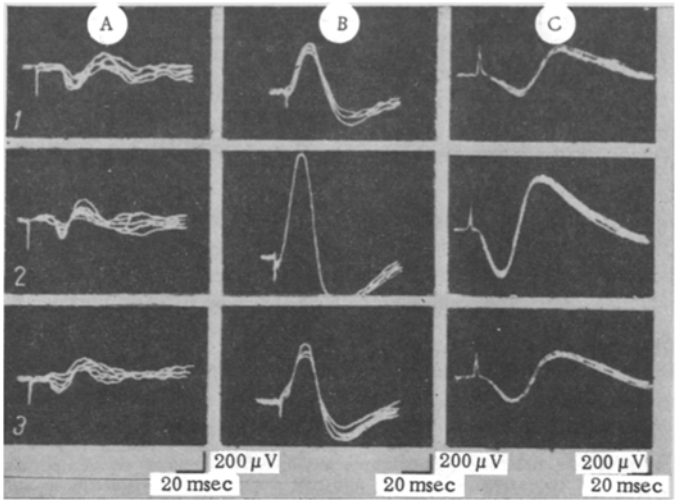

Fig. 1. Effect of chlorpromazine on somatic (A), local (B), and transcommissural (C) hippocampal evoked responses of a rabbit before (1) and 15 (2) and 180 min (3) after intravenous injection of chlorpromazine (5 mg/kg).

than 20-30% of its initial level, and they were observed only in those experiments in which the synchronizing effect of the drugs on the hippocampal electrical activity was well marked.

Parallel recording of evoked responses and global activity of the hippocampus showed that the phasic changes in the EEG after administration of 5-hydroxytryptophan [2] corresponded strictly to phases of the change in the hippocampal responses. During the synchronization phase, which developed at the 9th-10th min of intravenous injection of 5-hydroxytryptophan the amplitudes of the local and transcommissural responses were increased by 30-40% whereas the somatic response remained unchanged. During the period of activation the local and transcommissural hippocampal responses (Fig. 2B, 2 and Fig. 2C, 2) were sharply reduced in amplitude or even disappeared completely, in some experiments the inhibition of the transcommissural response commencing rather earlier (i.e., after a smaller dose of 5-hydroxytryptophan) than inhibition of the local response. By contrast with the two responses mentioned, the somatic response was never completely inhibited, even at the maximum of action of the drug in most experiments its amplitude remained unchanged (Fig. 2A, 1 and 2). In individual experiments it was reduced, but by not more than 30%, and 20-30 min later, when the local and transcommissural responses were still sharply inhibited, the somatic response had returned to its initial level. Restoration of the local and transcommissural responses occurred only after 2-3 h, when the normal EEG was restored. These results thus show that the local and transcommissural responses were changed by a much greater degree than the somatic response by the action of 5-hydroxytryptophan.

A study of the effect of 5-hydroxytryptophan and the neuroleptics on hippocampal electrical activity showed that if chlorpromazine was injected in a dose of 5 mg/kg at the maximum of action of 5-hydroxytryptophan (the 30th min of infusion) the sharp low-amplitude (not more than 40-50 μV) potentials with a frequency of up to 30/sec, characteristic of the activation reaction induced by 5-hydroxytryptophan in the hippocampus [2, 3] disappeared and were replaced by a curve with a dominant slow (2-3/sec), high-amplitude (250-300 μV) rhythm. The amplitude of the local and transcommissural responses was restored to its initial level, and then rose sharply by 200-300% over its initial level (Figs. 2B, 3 and 2C, 3). In those experiments in which a slight decrease in amplitude of the somatic response was observed at the maximum of action of 5-hydroxytryptophan chlorpromazine restored it to the initial normal level, while in the other experiments the somatic response was unchanged. The antagonistic effect of chlorpromazine with respect to changes in the hippocampal responses and spontaneous hippocampal electrical activity was detectable not only when the drug was given after, but also when it was given before the 5-hydroxytryptophan. If 5-hydroxytryptophan was given in a period of synchronization of the EEG and an increase in the local and transcommissural responses induced by chlorpromazine (5 mg/kg), neither spontaneous electrical activity nor hippocampal responses were changed. Despite the continued infusion of 5-hydroxytryptophan, the slow low-amplitude activity remained dominant and depression of the hippocampal responses did not take place.

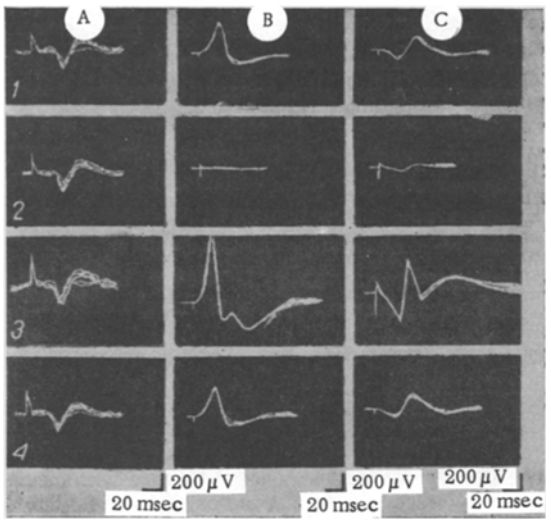

Fig. 2. Abolition by chlorpromazine of changes in hippocampal responses induced by 5-hydroxytryptophan: A) somatic; B) local; C) transcommissural hippocampal responses. 1) Before injection, 2) 30 min after infusion of 5-hydroxytryptophan (total dose 51 mg/kg), 3) 20 min, 4) 180 min after intravenous injection of chlorpromazine (5 mg/kg).

Closely similar patterns were observed in the study of the action of trifluoperazine on the effects of 5-hydroxytryptophan described above. If trifluoperazine was injected during the development of 5-hydroxytryptophan activation, it abolished the activation, as it also did the depression of the hippocampal responses (local and transcommissural). The somatic response, which was unchanged or only slightly inhibited by 5-hydroxytryptophan, was restored to its initial values after administration of trifluoperazine. In the intensity of its effect trifluoperazine was slightly lower than chlorpromazine. To abolish the developing effect of 5-hydroxytryptophan a dose of 7 mg/kg trifluoperazine was necessary, whereas chlorpromazine abolished this effect in a dose of 5 mg/kg. Trifluoperazine also prevented the development of the effects of 5-hydroxytryptophan (injection of 5-hydroxytryptophan after trifluoperazine), but whereas chlorpromazine in a dose of 5 mg/kg completely prevented the effect of 5-hydroxytryptophan, trifluoperazine, even in a dose of 7 mg/kg, merely delayed the onset of the changes described (from 20-25 min to 1-1.5 h).

Definite antagonism was thus revealed between 5-hydroxytryptophan and the phenothiazine derivatives chlorpromazine and trifluoperazine in their effect on the local and transcommissural responses. The intensity of this effect of trifluoperazine is somewhat lower than that of chlorpromazine.

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