EFFECT OF CHLORPROMAZINE ON DEVELOPMENT OF PRIMARY RESPONSES IN THE CORTEX

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The idea has been formulated that primary potentials developing in the cortex on stimulation of afferent nerves might relfect excitation reaching the cortex both by way of specific projections and through the reticular formation. The positive phase of the primary response was determined by impulses reaching levels III and IV of the cortex by way of specific thalamocortical projections. This potential represented discharge by the endings of a thalamic neuron projected to the primary sensory region of the cortex. The negative phase of the primary response was considered to be the result of spread of excitation to the apical dendrites, and developed in consequence of the arrival of impulses from the III and IV cortical layers. The negative phase of the response represents the passage of activity into the cortex [6, 11].

The negative phase of the primary response is thus a truly cortical potential, but it must be assumed that it cannot be influenced by impulses reaching the cortex by way of the nonspecific system [1].

There is, however, much evidence which would indicate that the nonspecific systems of the brain have a different role in the conduction of impulses from visceral and somatic organs.

Tolmasskaya and Dykman [7] found that visceral sensation was more closely linked with the nonspecific than with the somatic systems of the brain. This was demonstrated by recording the general electrographic reactions produced by somatic and visceral stimulation respectively, and from the changes produced in these reactions by the injection of chlorpromazine. Chlorpromazine is known to block the adrenergic substrate of the reticular formation Medium doses of chlorpromazine (1-3 mg/kg) blocked reactions to interoceptive stimulations, but produced no change in reactions to stimulation of somatic receptors.

Some authors have stated that chlorpromazine reduces the negative phase and increases the latent period of the primary response evoked by stimulation of a somatic nerve [3]. On the other hand, several [12] have failed to note any change in the primary potential following administration of chlorpromazine.

An attempt was now made to compare the changes produced by chlorpromazine in the primary responses to stimulation of somatic and visceral nerves respectively.

METHOD

The experiments were carried out on cats, rabbits and hares, under nembutal-chloralose anesthesia (30 and 20 mg/kg respectively). Artificial respiration was employed in some experiments in which the animals were curarized (Flazedil). Single rectangular pulses, 1 msec in length and 1-15 V, were delivered to the central ends of a splanchnic and a sciatic nerve. A cathode-ray oscillograph connected to the second state of an "Alvar" electroencephalograph was used for recording. Responses were recorded only from the contralateral hemisphere.

RESULTS AND DISCUSSION

Figure 1 shows the chlorpromazine-induced changes in the primary response produced in the cortex by stimulation of a sciatic nerve.

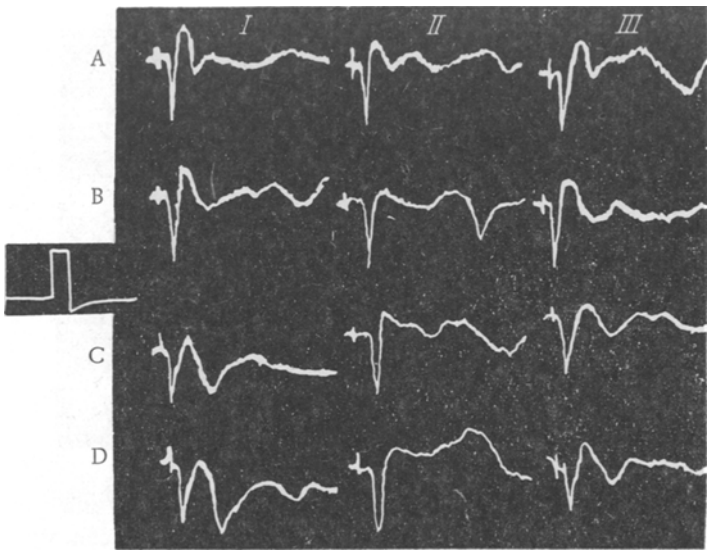

Fig. 1. Changes in primary response in cortex, evoked by stimulation of sciatic nerve, after injection of chlorpromazine. A) Cat; zone I of sensorimotor cortex. D) rabbit; sensorimotor cortex. I) before injection of chlorpromazine. II) 15 min after injection. III) 45 min after injection. Here and in Fig. 2. Amplitude of calibrating pulse 100 μ V, and length 20 msec.

In the cat, a response to sciatic nerve stimulation developed in both zone I and zone II for cutaneomuscular sensation: in zone I the latent period was 8-10 msec, positive phase amplitude 100-150 μV, amplitude of negative phase 100-120 μV, and the lengths of the positive and negative phases were 10-15 msec and 15-20 msec respectively; in zone II latent period was 5-8 msec, amplitude of positive phase 100-150 μV, amplitude of negative phase 80-100 μV, length of positive phase 10-15 msec, and length of negative phase up to 20 msec.

The amplitude of the negative phase was reduced 15 min after intramuscular injection of chlorpromazine (5-10 mg/kg): in zone I to 50-60 μV and in zone II to 20-30 μV; there was also some lengthening of the negative phase in zone II. The positive phase of the primary response remained unchanged. The negative phase of the response had largely regained its original parameters in both zones 20-30 min after the injection of chlorpromazine.

The parameters of the primary response in the sensorimotor cortex of the hare were: latent period 5-10 msec; amplitude of positive phase 100-120 μV; amplitude of negative phase 50-80 μ V; length of positive phase 10-15 msec; length of negative phase up to 30 msec. After chlorpromazine, the negative phase was lengthened slightly and its amplitude was reduced from about the 15th min, but restored again after 30-40 min.

The parameters of the primary response in the sensorimotor cortex to sciatic nerve stimulation were much the same; injection of chlorpromazine produced similar changes in the negative phase of the response.

Chlorpromazine produced much more distinct changes in the primary response to splanchnic nerve stimulation (Fig. 2).

In the cat, the latent period for the primary response in zone I of the sensorimotor cortex was increased by 5-10 msec 15 min after the injection of chlorpromazine, while the negative phase was of increased length but reduced amplitude. In zone II the latent period of the response was increased still more (by 15-20 msec), the amplitude of the negative phase was reduced, and the lengths of the positive and negative phases were increased by 10-15 msec. Smaller doses of chlorpromazine (3-4 mg/kg) produced changes in the response in zone II. The changes in the response began to disappear after 30-40 min in zone I, but might persist for more than an hour in zone II; injection of Phenamine (3 mg/kg), which stimulates the reticular formation and is antagonistic to chlorpromazine, resulted in restoration of the primary response after 10-15 min.

In the hare the latent period of the primary response in the sensorimotor cortex was increased by 20-22 msec 15 min after injection of chlorpromazine, while the amplitude of the negative phase was reduced by 30-50 μV, and both positive and negative phases were lengthened. Phenamine restored a normal response.

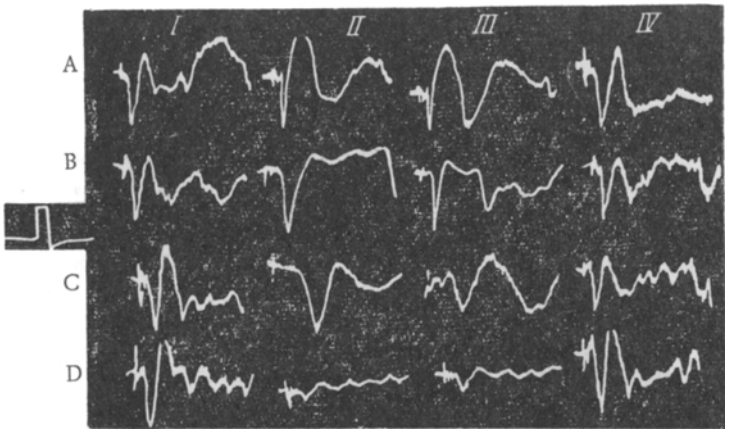

Fig. 2. Changes in primary response in cortex to stimulation of splanchnic nerve after administration of chlorpromazine. A) Cat; zone I of sensorimotor cortex. B) cat; zone II. C) hare; sensorimotor cortex. D) rabbit; premotor cortex. I) before injection of chlorpromazine. II) 15 min after injection. III) 45 min after injection. IV) 10 min after injection of Phenamine.

The primary response from the splanchnic nerve of the rabbit was not recorded in the sensorimotor region, but in the orbital and premotor regions of the cortex [2]; the latent period was 5-10 msec, amplitude of positive phase 100-120 μV, amplitude of negative phase 80-100 μV, and the lengths of the positive and negative phases were respectively 15-20 and up to 30 msec. Even small doses of chlorpromazine (1 mg/kg) produced almost complete blockage of both positive and negative phases of the response to stimulation of a splanchnic nerve after 10-15 min. This blocking of the response by small doses of chlorpromazine might last an hour, but the primary response was rapidly restored by the injection of Phenamine.

The changes produced by chlorpromazine were thus more distinct in the primary responses to electrical stimulation of the visceral nerve than in the responses to somatic nerve stimulation. These changes were clearly evident in all the animal species examined, and they consisted mainly of prolongation of the latent period and reduction of the amplitude and increase in the length of the negative phase. In the rabbit the primary response produced from the visceral nerve was blocked completely by the injection of small doses of chlorpromazine.

The examination of primary responses thus indicated that the conduction of visceral sensation depended more on the nonspecific formations in the brain than the conduction of somatic sensation. The latter is catered for mainly by specific thalamocortical projections. It can be assumed that these differences are connected with the fact that the visceral system is phylogenetically older.

It would appear that the primary response with the short latent period can be linked, in greater or lesser degree, with the brain-stem reticular formation. In the rabbit, the primary response from the visceral nerve was completely suppressed when adrenergic structures in the reticular formation were blocked by chlorpromazine, and was restored when the reticular formation was again rendered excitable with Phenamine. Direct high-frequency electrical stimulation of the reticular formation of the brain-stem in the rabbit resulted in restoration of the primary response, both before and after Phenamine. Electrical stimulation of thalamic nuclei (ventroposterolateral and central median nuclei) did not restore the response completely (only the positive phase on stimulation of the ventroposterolateral nucleus or negative phase on stimulation of the central median nucleus).

The negative phase was more closely connected with nonspecific formations than the positive phase.

The primary response from the visceral curve in the cat differed somewhat in zones I and II of the sensorimotor cortex. Chlorpromazine produced changes in the response in both zones, but the changes in the response to visceral nerve stimulation were greater and more prolonged in zone II, and zone II was more sensitive to chlorpromazine than zone I.

Many have demonstrated functional differences between zones I and II [4, 8, 9]. Zone I is responsible for analysis of the spatial components of sensations, and zone II exercises control over systems concerned with the transmission of afferent signals. It has been established [5] that zone II can influence specific and nonspecific structures in thalamus and brain-stem, by producing selective changes in the functional states of neuronal elements in these structures. Zone I has no such influence. Zone II is responsible for cortical control over the passage of afferent signals in the nonspecific structures of the brain.

The present results indicate that zone II of the sensorimotor cortex is under the influence of the nonspecific structures of the brain to a greater extent than zone I. At any rate, chlorpromazine produced distinct changes in the latent period and negative phase of the primary response in zone II, but similar changes were not observed in zone I. In the cat, different effects were produced by direct electrical stimulation of thalamic nuclei. The response in zone II was improved by stimulation of the central median nucleus, and the response in zone I, by stimulation of the ventroposterolateral nucleus.

This material does not, however, prove that chlorpromazine does not have a direct effect on specific brain structures also, particularly as the question of adrenergic structures in cortex and thalamic nuclei is still not by any means settled [10]. Another possibility, which cannot be excluded is that rabbits are more sensitive to chlorpromazine than the other animals.

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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.