MULTIPLICATION OF THE LATE SLOW COMPONENT OF THE EVOKED POTENTIAL TO LIGHT DURING CHLORPROMAZINE ADMINISTRATION

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In experiments on unanesthetized rabbits with electrodes permanently implanted into various brain formations the effect of chlorpromazine was studied on the phenomenon of multiplication of the late slow component of the evoked potential to flashes of light applied at a frequency of 1 Hz, some of which were given simultaneously with electric shocks to the hind limb. Chlorpromazine was found to reduce the multiplication of the slow component to flashes applied without electric shocks and to facilitate the reduplication of this component to flashes applied along with the nociceptive stimulation. In the discussion of the results a role of adrenergic structures is postulated in the formation of the defensive action acceptor, one of the most important and crucial mechanisms of the functional system.

KEY WORDS: evoked potential; convergence; cortical-subcortical reverberation of excitation; chlorpromazine.

According to data obtained in the late P. K. Anokhin's laboratory, an indicator of a mismatching response between the action acceptor of a functional system of defensive character and the action of reciprocal afferentation indicating nociceptive reinforcement is reduplication of the late slow negative-positive component of the evoked potential (EP) in various brain formations in response to flashes applied as the conditioned stimulus evoking the defensive response. The phenomenon of reduplication of the late response is manifested no less clearly if a combined stimulus consisting of nine flashes is used, in which the 4th, 5th and 7th flashes are applied simultaneously with an electric shock to the limb. Nociceptive stimulation increases the amplitude of the primary response of the EP to light but inhibits its late slow component. As a result of the repeated use of this model, light becomes a signal of pain, and in response to flashes if applied without nociceptive reinforcement (first-third and, in particular, 7th-9th) reduplication or multiplication of the slow wave arises.

Special analysis showed that the phenomenon of repetition of the slow wave is the EEG-reflection of cortico-subcortical reverberation of excitation [5-7]. This reverberation appears during the orienting-investigative response that arises should mismatching occur between the results predicted by the action acceptor, in the form of a pain response, and the reciprocal afferentation in the absence of nociceptive stimulation not in agreement with that result [5].

One of the factors potentiating the mismatching response and facilitating the phenomenon of multiplication of the slow component is emotional stress, which depends on the strength of the reinforcing electric shock.

The object of this investigation was to study the effect of chlorpromazine, abolishing the EEG stress response by blocking adrenergic structures of the reticular formation of the brain stem and hypothalamus [1-4], on the process of multiplication of the late component.

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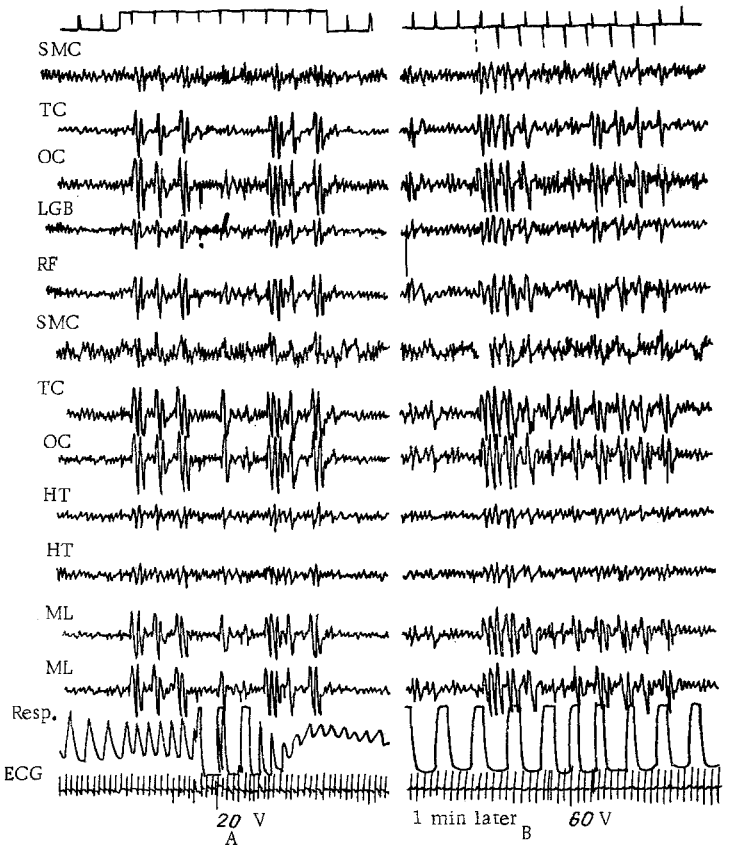

Fig. 1. Changes in respiration, cardiac activity, and EP to photic stimulation 1 min after injection of chlorpromazine. A) Before injection of chlorpromazine (background); increased respiration rate and multiplication of slow component to flashes; breath holding and inhibition of slow component in response to flash applied simultaneously with electric shock to limb. B) 1 min after injection of chlorpromazine: in response to flash applied simultaneously with electric shock, respiration rate is very slightly increased and multiplication of slow component of EP appears. SMC) Sensomotor cortex; TC) temporal cortex; OC) occipital cortex; LGB) lateral geniculate body; RF) recticular formation; HT) posterior hypothalamus; ML) medial lemniscus; Resp) respiration. Artefact on respiration and ECG marks electric shock. Top line: upward strokes show time marker, in sec; downward strokes show flashes, one per second.

EXPERIMENTAL METHOD

Chronic experiments were carried out on 12 unanesthetized rabbits with implanted electrodes for recording electrical activity of the sensomotor, temporal, and visual areas of the cortex, the lateral geniculate body, the poterior hypothalamus, the reticular formation of the brain stem, and the medial lemniscus. The reference electrode was inserted into the bones over the frontal sinus. Global electrical activity was recorded by a monopolar technique on a 50-channel "Alvar" electroencephalograph on which the ECG and respiration also were recorded. Flashes with a frequency of 1 Hz were applied in series of 9. Concurrently with the 4th, 5th and 6th flashes, a painful electric shock (10-15 V, 1 msec) was applied to the skin of the hind limb, inhibiting the late negative-positive wave of the EP to light.

Rabbits in which the slow component of the EP to light was wide and was consistently generalized over the various brain formations were chosen for the experiments. The effect of chlorpromazine was studied against the background of multiplication of the slow component of the EP appearing before and after nociceptive stimulation. A 1% solution of chlorpromazine was injected intravenously in a dose of 1 mg/kg body weight.

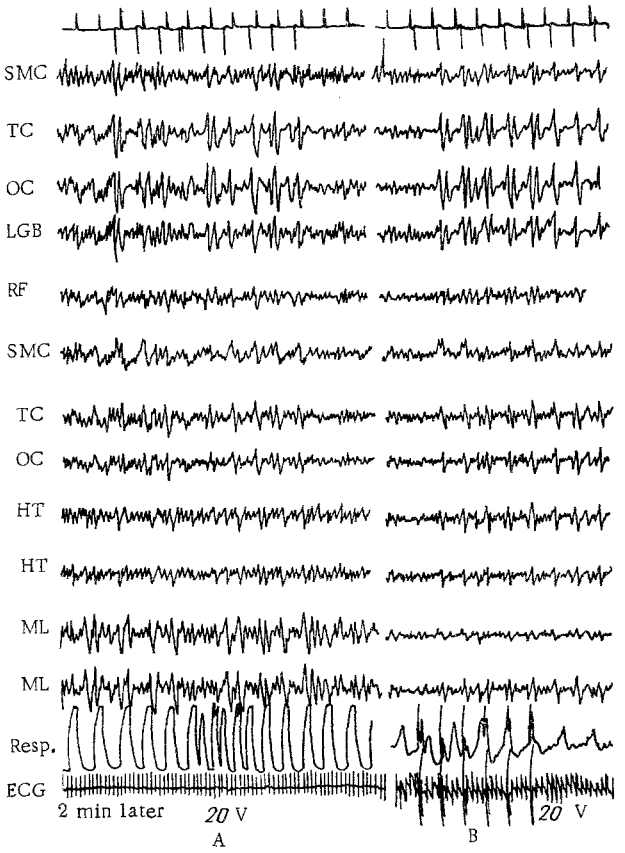

Fig. 2. Multiplication of slow components of EP independently of stereotype. A) During EEG disactivation, slow component of EP to flashes becomes unstable. Multiplication of slow component during convergence of photic and electrodermal stimulation may be confined to structures of one hemisphere. B) Multiplication of slow component arising also when photic stimulation begins with application of flash simultaneously with electric shock. Legend as in Fig. 1.

EXPERIMENTAL RESULTS

In the course of blocking of the adrenergic structures of the CNS by chlorpromazine a definite sequence and certain special features were noted in the changes taking place in the autonomic components, behavioral responses, and brain electrical activity. As early as 1 sec after the injection of chlorpromazine, respiration became slower and the heart rate faster. Respiration became quiet, uniform, and deep, was unchanged in response to flashes, and increased only very slightly in frequency during nociceptive stumulation (Fig. 1B). The rabbit remained almost motionless, its head resting on the bench. During nociceptive stimulation the animal did not exhibit restlessness, but shook the stimulated limb. Disactivation of the potentials soon appeared in various brain formations. Against this background potentiation of the phenomenon of multiplication of the late slow component of the EP to light was found: in response to flashes, preceding the nociceptive stimulation, the EP had three slow waves instead of two (Fig. 1B). During simultaneous application of the flash and electric shock, the slow wave of the EP remained in most rabbits, although in a reduced form.

Disactivation of spontaneous activity developed rapidly, and 2-3 min after the injection of chlorpromazine it was represented by slow high-amplitude potentials. At this time the EP to photic stimulation was either deformed or absent.

Stable disactivation of the EEG continued for 8-10 min and then began to alternate with periods of brief activation. In this stage of the action of chlorpromazine the late slow wave was restored and the phenomenon of multiplication of the EP in response to photic stimulation became less stable and frequently absent. Meanwhile multiplication of the late response appeared to flashes applied together with nociceptive

stimulation. It was recorded consistently for 15-18 min after the injection of chlorpromazine. The multiplication phenomenon could be generalized in all structures recorded from both hemispheres (Fig. 1B) or it could be localized to one hemisphere (Fig. 2A).

Since electrodermal stimulation was always applied in conjunction with the 4th, 5th and 6th flashes it was natural to suggest that the multipication of the slow wave arising at this point was connected with reproduction of a stereotype. As a result of blockade of the adrenergic structures, when the flash was applied simultaneously with the electric shock a response of mismatching appeared between the model of nociceptive excitation programed in the action acceptor and the absence of reciprocal afferentation indicating pain reinforcement. To shed light on this problem control tests were carried out in which nociceptive stimulation was applied simultaneously with flashes differing in their position in the series. These tests showed that multiplication of the slow component in response to nociceptive stimulation arises independently of whether this stimulation was combined with the first or subsequent flashes (Fig. 2B). These experiments showed that blockade of the adrenergic structures of the brain by chlorpromazine did not completely abolish the conduction of noiceptive excitation. This was shown by the admittedly slight increase in the respiration rate, shaking of the stimulated limb and, more especially, by multiplication of the slow component of the EP to light when applied simultaneously with the painful electric shock.

On the basis of these data a dual nature and two genetically linked components of nociceptive excitation can be postulated. One component is not blocked by chlorpromazine and spreads along the thalamic relay pathways (the spino-thalamic tract) as far as the cerebral cortex. The second component, with more dispersed conduction pathways, is connected with the adrenergic structures of the reticular formation of the brain stem and hypothalamus, which are blocked by chlorpromazine. On account of this component the emotional background of nociceptive excitation and the EEG stress response, generalized among various brain formations, is formed. Simultaneous application of the flash and nociceptive stimulation at a time when the generalized emotional component was blocked by chlorpromazine evoked an EEG response of mismatching, and this was manifested by multiplication of the late slow component of the EP to light. If the emotional component of nociceptive stimulation was signalled by stimulation of a different modality on the basis of their temporary connection, the administration of chlorpromazine abolished the EP multiplication phenomenon to this warning stimulus, i.e., to light. Relationships of this sort after administration of chlorpromazine are revealed during conditioned and unconditioned defensive excitation. In response to a conditioned defensive stimulus the spontaneous activity of the brain potentials is unchanged, whereas an EEG activation response arises to the electric shock reinforcement.

LITERATURE CITED

1. V. G. Agafonov, Zh. Nevropat. i Psikhiat., No. 2, 94 (1956).
2. P. K. Anokhin, The Biology and Neurophysiology of the Conditioned Reflex [in Russian], Moscow (1968).
3. M. N. Bantsekina, "Analysis of the slow regular rhythm of brain potentials of the rabbit (stress rhythm)," Author's Abstract of Candidate's Dissertation, Moscow (1962).
4. A. I. Shumilina, Zh. Nevropat. i Psikhiat., No. 2, 116 (1956).
5. A. I. Shumilina, in: The Integrative Activity of the Nervous System under Normal and Pathological Conditions [in Russian], Moscow (1968), p. 276.
6. S. H. Bartley and G. H. Bishop, Am. J. Physiol., 103, 139 (1933).
7. G. H. Bishop and J. O'Leary, Am. J. Physiol., 117, 292 (1936).