ANALYSIS OF NEUROCHEMICAL MECHANISMS OF CORTICAL ACTIVATION DURING RESPONSES TO PAIN

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Ascending activating influences from the subcortex to the cortex during responses to pain are spread by both axodendritic and axosomatic synapses. Cortical synapses participating in the formation of the pain response utilize both cholinergic and adrenergic mechanisms in their metabolism.

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The discovery of the ascending activating influences of the bulbar reticular formation on the cortex provided a new approach to the study of the central mechanisms of the pain response. The foundations for this approach were laid by the discovery in Anokhin's laboratory of generalized cortical activation occurring in response to nociceptive stimulation and manifested even in animals anesthetized with urethane [1]. As a result of these experiments differences in the nature of ascending activating influences on the cortex became apparent, and certain aspects of the neurophysiological mechanisms of the pain response became amenable to investigation in acute experiments. It was first established that ascending activation of the cortex during nociceptive stimulation was selectively blocked after injection of chlorpromazine [4-9, 13].

The opinion is widely held in the literature that chlorpromazine has a blocking action mainly on adrenergic structures in the rostral portions of the mesencephalic reticular formation [1, 2, 13]. It may therefore be supposed that the subcortical mechanisms forming the pain response are adrenergic in nature. However, the problem of the synaptic organization of the cortex to which the ascending activating influences are directed during the pain response and their chemical nature still remain unexplained.

It has been considered [10] that cortical activation mechanisms in the pain response are cholinergic. However, experiments by Turenko [11], working in Anokhin's laboratory, have shown that cortical activation during nociceptive stimulation is not blocked by local application of cholinolytic substances to the cortex in a concentration which prevents food activation in fasting animals. On the basis of these observations it was decided to carry out special experiments in order to analyze this problem more deeply.

EXPERIMENTAL METHOD

Experiments were carried out on 25 rabbits anesthetized with urethane (1.5-2 g/kg, intraperitoneally). When the animal was anesthetized, its head was fixed in a sterotaxic apparatus and the skull surface exposed.

A hole measuring 0.3 × 0.4 cm was made in the bone above the sensorimotor cortex of one hemisphere, and the dura was removed through it. Two silver ball electrodes were placed on the exposed surface of the cortex and used for recording the EEG and evoked potentials from this area of the brain. The EEG from other parts of the cortex was recorded from the surface of the cranial bones by means of steel needle electrodes.

The reference electrode was placed in the midline on the nasal bones.

Evoked potentials in the sensory cortex of the contralateral hemisphere in response to electrical stimulation of the sciatic nerve with single square pulses (4-8 V, 0.1 msec) through buried bipolar electrodes.

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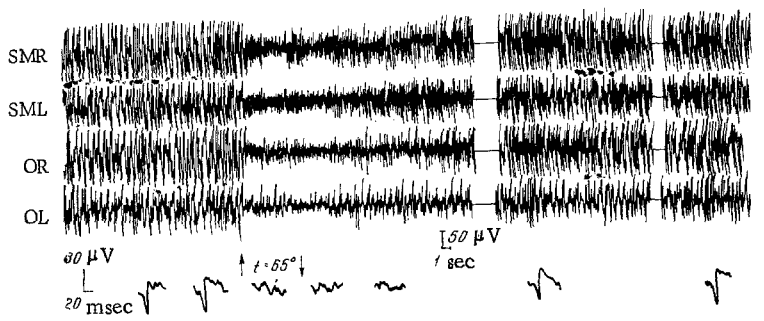

Fig. 1. Changes in EEG and somatosensory evoked potential during immersion of the forelimb of a rabbit anesthetized with urethane in hot water (60°). Beginning and end of nociceptive stimulation marked by arrows. SMR signifies right sensorimotor, SML left sensorimotor, OR right occipital, and OL left occipital region.

The stimuli were generated by a "Physiovar" stimulator with transformer output. Switching on the stimulator was synchronized with the shutter of a camera and the driven sweep of an oscilloscope. Generalized pain activation was obtained by immersing the animal's forelimb in a vessel containing water at 60-65°.

The EEG was recorded on a 10-channel electroencephalograph (Alvar Electronic). Evoked potentials were recorded on a 4-beam "Biophase" CRO made by the same firm, with a transmission band from 0.5 Hz to 10 kHz. The time constant at the input of the amplifier was 0.01 sec.

Neurotropic drugs were applied to the cortex as follows. A drop of solution was applied from the needle of a syringe to the rod of the ball electrode from which it descended to the cortical surface by gravity. In this way the action of the applied substance was localized to the point from which the evoked potential was recorded.

EXPERIMENTAL RESULTS

In the experiments of series I the cortical synapses to which the ascending activating influences are directed during the pain response were studied. Changes in the evoked response produced in somatosensory area 1 to single stimulation of the sciatic nerve were investigated against the background of the pain response. The formation of the primary positive phase of the evoked potential is due to excitation of axosomatic synapses of cortical layer IV. It has been shown in Anokhin's laboratory that the primary negative phase is formed by arrival of ascending excitatory impulses along separate conducting pathways at axodendritic synapses of its superficial plexiform layer [3]. Any change in the initial background of the evoked response during nociceptive stimulation could therefore give definite evidence of the destination of the ascending activating influences during the pain response and the manner of their transmission.

Usually in rabbits under urethane anesthesia, a characteristic evoked response with latent period of 15-20 msec, primary positive phase of 50-60 μV, and primary negative phase of 30-40 μV was recorded in the sensorimotor area of the contralateral hemisphere in response to single stimulation of the sciatic nerve.

After recording of the initial EEG and several initial evoked potentials, one of the animal's forelimbs was immersed in hot water at 60-65°. Recording of the evoked responses continued uninterruptedly during and after the end of nociceptive stimulation. These experiments showed that immediately after immersion of the animal's forelimb in hot water generalized EEG activation developed. This was expressed in these experiments in three forms: a) desynchronization of the EEG, b) the appearance of a regular rhythm of 4-6/sec [12], and c) the appearance of a high-amplitude hypersynchronized rhythm. The amplitude of both phases of the primary response was considerably reduced. While the stimulation continued, the primary negative phase began to be deformed, and ultimately it disappeared completely. Only then did the positive phase of the primary response start to become deformed and then disappear (Fig. 1).

Recovery of the evoked response proceeded in the opposite direction. The positive phase first reappeared, and as the EEG gradually acquired its original slow, high-amplitude character, the negative phase of the primary response appeared. The evoked potential increased in amplitude and reached its initial

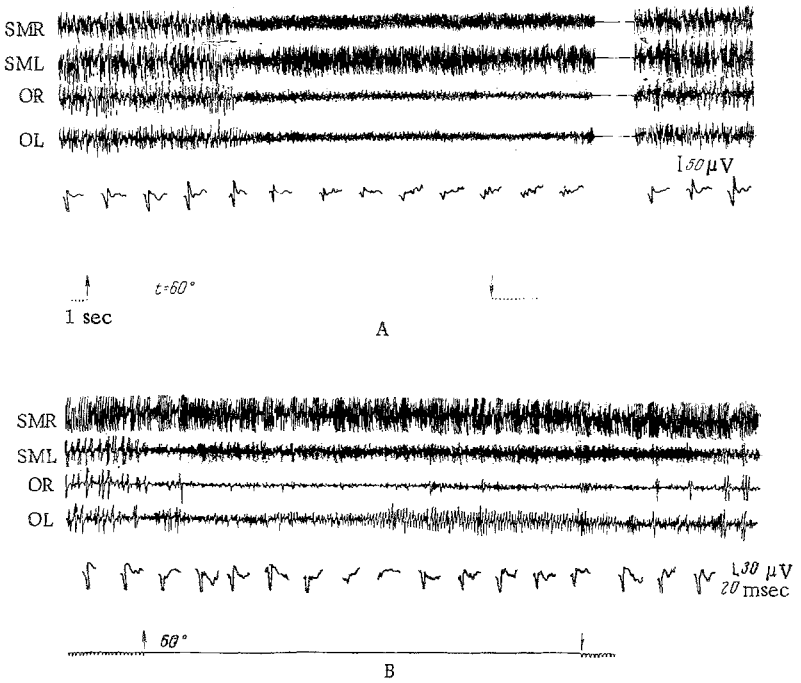

Fig. 2. Effect of nociceptive stimulation against the background of local application of 1% benactyzine solution to the cortex. A) Before application; B) after application of benactyzine to the right sensorimotor area (SMR). Moment of nociceptive stimulation designated by arrows. Legend as in Fig. 1.

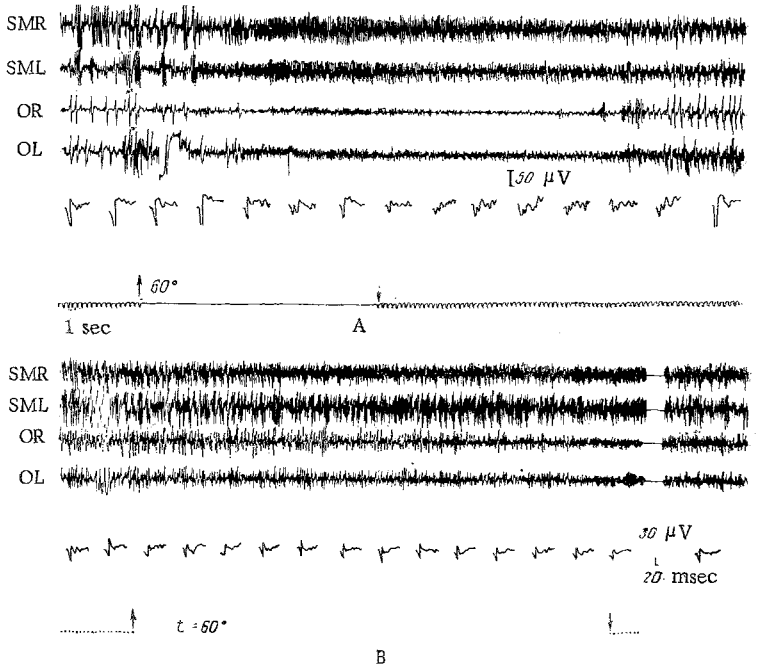

Fig. 3. Effect of nociceptive stimulation against the background of local application of 0.006% chlorpromazine to the right sensorimotor area (A) and after intramuscular injection of chlorpromazine in a dose of 5 mg/kg body weight (B). Legend as in Fig. 1.

value. These observations indicated that ascending activating influences of the cortex during nociceptive stimulation are directed mainly toward the axodendritic synapses of the superficial layers of the cortex, forming the negative phase of the primary response. As the intensity of the pain response increased, they also spread to the axosomatic synapses of cortical layer IV, participating in formation of the positive phase of the primary response of the somatosensory evoked potential.

In the experiments of series II the neurochemical mechanisms of cortical synaptic organization participating in the formation of pain activation were studied. Application of muscarine-like cholinolytic drugs (0.1% atropine and, especially, 0.5-1% benactyzine) to the sensorimotor area in eight experiments itself caused an increase in amplitude of the spontaneous activity and an increase in amplitude of the positive and negative phases of evoked responses recorded at point of application. Against this background, nociceptive stimulation as before caused a generalized EEG desynchronization response. However, this response was less marked at the point of application of the cholinolytics. Nevertheless, just as in the control experiments, nociceptive stimulation blocked the somatosensory evoked responses at this point, although after a longer latent period (Fig. 2). These observations indicated that although cholinergic substances participate in the mechanism of cortical EEG activation during the pain response, involvement of the cortical neurons in the pain response also takes place through other chemical mechanisms.

To analyze the possible participation of adrenergic cortical mechanisms in the genesis of EEG activation during the pain response, chlorpromazine was used. It is usually considered that chlorpromazine, when injected intramuscularly in a mean dose of 5 mg/kg body weight, exerts its blocking action on the adrenergic activating systems of the rabbit's reticular formation. To prove conclusively that chlorpromazine, when applied locally, acts on the cortex in concentrations not below that in which it acts on the subcortical structures when given by the usual intramuscular method, the following calculation was formed. If, for example, to produce a blocking effect on nociceptive stimulation a rabbit weighing 4 kg received 0.8 ml of 2.5% chlorpromazine (20 mg) by intramuscular injection, considering that the total blood volume of the rabbit is about 1/13 of its body weight (in this case 307 g), it can easily be calculated that in these experiments chlorpromazine reached the cortex and subcortex in a concentration not exceeding 0.006%.

These experiments showed that application of chlorpromazine in this concentration to the cortex did not alter the usually observed effects of nociceptive stimulation. Nociceptive stimulation as before produced a response of cortical activation at the point of application of chlorpromazine and blocking of somatosensory evoked responses (Fig. 3A). Only an increase in the latent period of the blocking action of nociceptive stimulation on the somatosensory evoked potentials was observed.

Characteristically, subsequent intramuscular injection of chlorpromazine in a dose of 5 mg/kg usually completely blocked the development of EEG activation and prevented the blocking of the somatosensory evoked potentials (Fig. 3B). When chlorpromazine was applied to the cortex in a higher concentration (0.65%), in 3 of the 8 experiments a block of the effects of nociceptive stimulation was observed at the point of application. Consequently, when applied directly to the cortex in high concentrations, chlorpromazine has a marked blocking action on cortical synapses participating in pain activation.

Meanwhile, the blocking action of chlorpromazine on the subcortical structures concerned with the development of cortical activation during the pain response can be reproduced by a much smaller concentration of the drug than when it acts directly on the cortical synapses. This action of chlorpromazine predominantly on the subcortical structures is evidently the reason for its selective "tranquilizing" action in clinical practice.

In some experiments after intramuscular injections of chlorpromazine, a desynchronizing action of nociceptive stimulation on the EEG was observed without blocking of somatosensory evoked responses. A similar picture was previously observed by Kagramnov [7] in his experiments.

Quantitative differences were thus revealed in the synapses responsible for desynchronization and evoked potentials at the same point of the cortex. The experiments show that both cholinergic and adrenergic substances participate in the mechanism of cortical activation during the pain response.

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