Effect of Spreading Depression on the Activity of Sensory Neurons in the Trigeminal Complex

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 126, No. 12, pp. 640-642, December, 1998
Original article submitted March 12, 1998

Spreading cortical depression in cerebral hemispheres increases 1.5-2-fold the background discharge frequency of sensory neurons in the trigeminal complex and intensifies their response to electrical stimulation of the superior sagittal sinus 1.5-fold. Inactivation of antinociceptive cerebral systems markedly decreases activation of sensory neurons of the trigeminal complex by spreading cortical depression.

Key Words: *spreading depression; neuronal activity; trigeminal complex; dura matter vessels; antinociceptive systems*

The pathogenesis of headache during migraine is a subject of extensive research and vigorous discussion [2,3, 8,10]. Neuronal disturbances are supposed to provoke changes in vascular tone leading to a headache seizure. From the viewpoint of trigeminovascular theory, headache is caused by activation and sensitization of the trigeminal afferent fibers that innervate meningeal vessels [5]. Nociceptive information from the dura mater vessels travels via the trigeminal nerve to the sensory nuclei of the trigeminal complex in the brain [4]. Spreading cortical depression (SCD) is a possible mechanism underlying the release of vasoactive neuropeptides from the sensory fibers of trigeminal nerve [7]. At present, the effect of SCD on meningeal microcirculation and its relation to the migraine aura are known in detail [6]. However, the effect of SCD on the activity of sensory neurons in the trigeminal complex and the role of antinociceptive systems in the realization of this influence are unknown. Our aim was to study the effect of SCD on the activity of sensory neurons in the trigeminal complex.

MATERIALS AND METHODS

The study was carried out on 37 non-narcotized immobilized random-bred male rats weighing 150-220 g. Stimulation of the superior sagittal sinus (SSS) was performed with the help of ball-type bipolar silver electrodes through which a train of 3-5 pulses (amplitude 0.1-10 mA, duration 300-500 μsec, intervals 50-100 μsec) was delivered.

SCD was induced by application of 5 μl KCl (1 mM) to the cerebral cortex with the help of a MSh-10M microsyringe via a perforation made in the dura mater. The orifice 2 mm in diameter was located 6.5 mm caudally to the bregma and 1.5 mm laterally to the left of the midline. KCl saline was carefully removed with a cotton tampon 30 sec after application.

Inactivation of the nucleus raphes in the medulla oblongata was attained by microinjection of lidocaine (15 μg in 2 μl). The position of the injecting needle was controlled with the help of cerebral histological sections.

The neurons that responded to electrical stimulation of SSS were found in the rostral portion of caudate nucleus and in the caudal portion of the interpolar nucleus. The neural spike activity was recorded with extracellular glass microelectrodes (diameter 1-5 μm) filled with 2 M KCl. The microelectrode resistance was 3-5 MΩ. Spike signals were fed into the amplifier of an EPM electrophysiological complex (Institute of Experimental Medicine) and then to a computer.

The results were statistically analyzed using Wilcoxon-Mann-Whitney's test.

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0007-4888/98/0012-1210$20.00

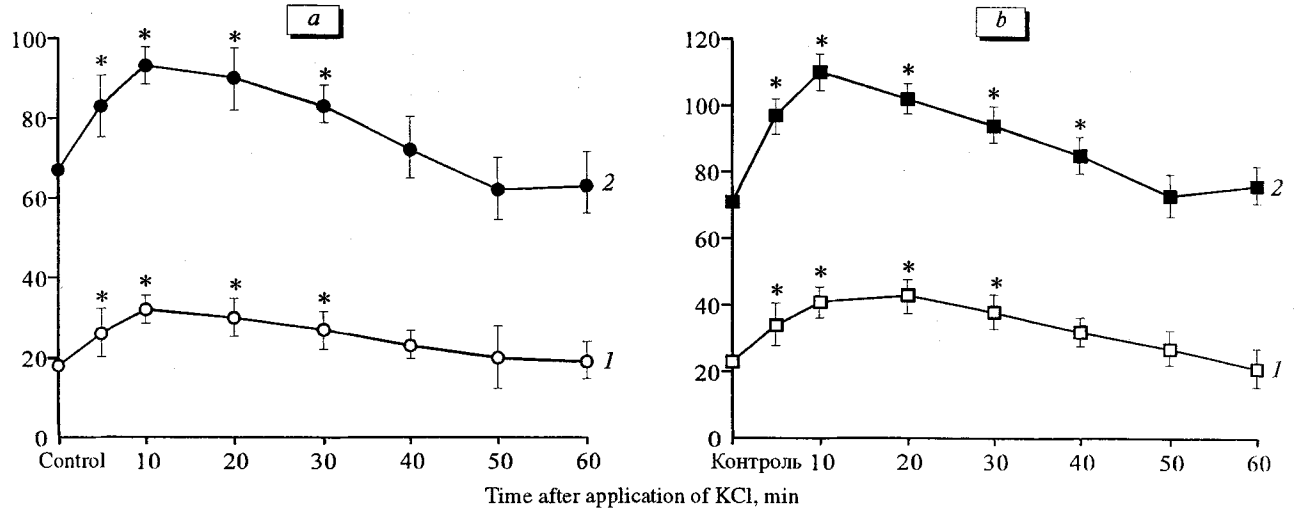

Fig. 1. Effect of spreading depression on ongoing discharge rate (*1*) and discharge (*2*) rate of sensory neurons in the trigeminal complex. The depression was evoked by stimulation of the superior sagittal sinus with intact (*a*) and lidocaine-inhibited main nucleus raphes (*b*). Ordinates: mean discharge rate, imp/sec. *$p<0.05$ in comparison with control.

RESULTS

We studied the effect of SCD on the ongoing and evoked (induced by electrical stimulation of SSS) activity of 21 sensory neurons in the trigeminal complex. Three to five minutes after application of KCl (1 mM) to the cerebral cortex, the frequency of the ongoing neuronal activity increased from 18±5 to 32±5 imp/sec, while the SSS-evoked response increased 1.5-fold. The maximum effect of SCD was observed 5-10 min after application of KCl, which intensified the spike activity from 67±7 to 93±8 imp/sec (Fig. 1, *a*). The SCD-induced increase in neuronal activity restored 1 h after application of KCl (1 μM).

Ongoing activity in sensory neurons in the trigeminal complex of medulla oblongata and their response to tactile and noxious stimulation increased significantly 5-10 min after microinjection of lidocaine into the main nucleus raphes. While the ongoing discharge rate in control rats was 17±3 imp/sec, injection of lidocaine into the main nucleus raphes enhanced it to 23±5 imp/sec. Functional inhibition of nuclei raphes was accompanied by an increase in the rate of discharge evoked by electrical stimulation of SSS from 58±6 to 71±6 imp/sec.

The ongoing discharge rate under SCD and uninhibited nucleus raphes was 32±6 imp/sec, while the corresponding value under functional block of nucleus raphes was 41±4 imp/sec. Electrical stimulation of SSS against the background SCD and functional block of nuclei raphes increased the discharge rate from 93±8 to 110±7 imp/sec (Fig. 1, *b*).

These data suggest that SCD activates sensory neurons in the trigeminal complex and enhances their sensitivity to noxious stimulation of the dura mater vessels and to tactile stimulation of cutaneous receptive fields. It is probable that SCD is a mechanism responsible for the sensitization of trigeminal afferent fibers. In addition, hyperactivity of the trigeminal complex neurons may result from functional insufficiency of the cerebral antinociceptive systems and main nucleus raphes in particular. More pronounced activation of the trigeminal complex sensory neurons by SCD against the background of functional block of the main nucleus raphes attests to the key role of antinociceptive structures in pathogenesis of migraine. However, the postulated existence of "migraine generator" in the brain stem [9] indicates that the relationships between various structures in the brain stem may be more intricate in reality.

There is evidence that SCD underlies the migraine aura because the spreading of changes in cerebral circulation in patients with migraine has the same temporal parameters as SCD [6]. However, it is currently believed that migraines with and without aura have similar pathophysiological mechanism [1]. Changes in the cerebral circulation under migraine of both types are similar, but aura is observed only under ischemia [1]. Therefore, SCD may be a factor that activates the trigeminovascular system with and without concomitant aura.

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