PHARMACOLOGY AND TOXICOLOGY

Effect of Semax and ACTH(5-10) on Electrical Activity of Central Neurons

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 125, No. 3, 304-306, March, 1998
Original article submitted August 28, 1996

Experiments on cats with the use of microelectrode technique and microionophoresis show that semax and ACTH(5-10) modulate spontaneous activity of approximately 60% cortical neurons, which probably accounts for their effect on general integrative function of the cortex. Neurons of the medial vestibular nucleus are highly sensitive to microionophoretic applications of these peptides (59-69% cells). It is assumed that the direct effect of semax and ACTH(5-10) to a great extent determines their efficiency in motion sickness.

Key Words: *peptides; neuronal activity; brain cortex; medial vestibular nucleus*

Original Russian-manufactured nootropic drug semax [ACTH(4-7)-Pro-Gly-Pro], is a synthetic analog of ACTH(4-10) possessing prolonged activity compared with its prototype [1,3,4,6,13]. We previously showed that semax and ACTH(5-10) exhibit pronounced antiamnestic and vestibuloprotective activities [9]. The aim of the present study was to elucidate the neuronal mechanism of anti-motion sickness and antiamnestic effects of semax. To this end, two brain areas were chosen: the primary somatosensory cortex and the medial vestibular nucleus (MVN), a central component of vestibular reflexes [5,8,11].

MATERIALS AND METHODS

Experiments were carried out on 7 curarized male cats (3-4 kg). The animals were artificially ventilated, and body temperature was maintained using a heating pad. Preliminary surgical manipulations were performed under Nembutal narcosis (35 mg/kg, intraperitoneally). Multichannel glass microelectrodes for extracellular recording of electrical activity of individual neurons in the primary somatosensory cortex and MVN (8-10 h after Nembutal injection) and microionophoresis [7] were stereotactically positioned in the studied structures under visual control according to the Stereotaxic Atlas coordinates [16]. Semax and ACTH(5-10) (Serva) were applied microionophoretically (+10-50 nA current strength). Lateral inclinations were used as adequate stimuli [12]. All MVN neurons selected for pharmacological testing responded to this stimulation. Spontaneous neuronal activity was analyzed during the experiment; in some cases, neuronal activity evoked by electrocutaneous stimulation of the hindlimb (20-40 V, 0.5 msec) was assessed. The experimental procedure was described in details elsewhere [7,10,11].

RESULTS

A total of 38 neurons in the primary somatosensory cortex was studied. These neurons were characterized by spontaneous electrical activity and clearly responded to electrocutaneous stimulation. Most of these neurons had abundant afferentation: we ob-

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0007-4888/98/0003-0268$20.00

served changes in neuronal activity in response to some additional stimuli (light flashes, sound, and adequate stimulation of the vestibular apparatus).

Semax and ACTH(5-10) had similar effects on spontaneous activity of cortical neurons. In particular, reaction to microionophoretic application of semax and ACTH(5-10) was noted in 63 and 58% neurons, respectively. The proportion between activating and depressive reaction was practically the same for semax (29 and 34%) and ACTH(5-10) 29%, Table 1). Reactions of individual neurons to semax and ACTH(5-10) were usually codirected. We found only 3 cells, which were resistant to ACTH(5-10), but responded to semax (the amplitude of action potential increased in two and decreased in one neuron).

The effects of test peptides on spontaneous activity of MVN neurons were different. ACTH(5-10) and semax applied to individual MVN cells predominantly inhibited their spontaneous activity (41 and 48% neurons, respectively, Table 1). Excitatory effects were 2.2-2.3-fold less frequent (21 and 18% neurons for semax and ACTH(5-10), respectively). One third of vestibular neurons were insensitive to these peptides (31-41%, Table 1). Reactions of individual neurons to semax and ACTH(5-10) were usually codirected, except for 2 neurons that were insensitive to ACTH(5-10), but responded to semax (inhibitory reaction). This phenomenon and the fact that the number of neurons sensitive to semax surpassed that of ACTH(5-10)-sensitive cells by 10% suggest that semax is a more potent agent.

Our findings are consistent with published data. For instance, it was shown that hippocampal and hypothalamic neurons of alert rabbits are very sensitive to microionophoretic applications of ACTH [2]. In brainstem sections from intact and delabyrinted guinea pigs, ACTH(4-10) suppressed spontaneous activity of MVN neurons. It was demonstrated that nootropics with different chemical structure (piracetam, oxiracetam, nooglutil, etc.) strongly modulate electrical activity of cerebral neurons in dogs and cats.

Thus, our findings suggest that the majority of cortical neurons (60%) are sensitive to semax and ACTH (5-10). This may account for their effect on general integrative function of the brain. The efficiency of these peptides in motion disease is largely determined by their direct influence on MVN neurons.

TABLE 1. Effect of Microionophoretic Applications of Semax and ACTH(5-10) on Spontaneous Activity of Central Neurons

Brain area, effect	Semax	ACTH(5-10)
Primary somatosensory cortex		
total	35 (100)	31 (100)
excitation	12 (34)	9 (29)
inhibition	10 (29)	9 (29)
abset	13 (37)	13 (42)
MVN		
total	29 (100)	27 (100)
excitation	6 (21)	5 (18)
inhibition	14 (48)	11 (41)
absent	9 (31)	11 (41)

Note. Percentage is shown in parentheses.

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