Effect of the Adrenocorticotropic Hormone Fragments and Atriopeptides on the Development of Toxic Brain Edema

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 122, No. 11, pp. 521-523, November, 1996
Original article submitted September 20, 1995

A fragment of adrenocorticotropic hormone and its analog Semax exhibit pronounced antiedematous activity in rats and cause dehydration of the arbitrarily intact hemisphere. By contrast, atriopeptides protect the hemisphere, but exhibit no antiedematous activity. These peptides may be involved in the pathogenesis of toxic brain edema.

Key Words: *brain edema; adrenocorticotropic hormone fragments and their analogs*

So far, some problems associated with prevention and therapy of brain edema (BE) remain unsolved [6,10]. In this connection, the search for new drugs with antiedematous activity seems relevant.

Considerable attention has been focused on regulatory peptides: atrial natriuretic factor (ANF), a set of atriopeptides with natriuretic, diuretic, vasodilatory, hypotensive, neuroendocrine, and neuromodulatory activities [1,5,10]. It was shown that ANF_{99-126} facilitates water transport across the blood-brain barrier, while its receptors on brain capillary endothelium participate in the regulation of the permeability of the blood-brain barrier [12,13]. These findings imply that atriopeptides can be used as antiedematous agents.

Adrenocorticotropic hormone (ACTH) exhibits antiedematous activity in humans and animals [4,10]. Moreover, ORG-2766, a synthetic analog of $ACTH_{4-10}$, promotes functional recovery of rat brain after injury [15]. Consequently, it can be suggested that other analogs of ACTH fragments such as $ACTH_{5-10}$ and $ACTH_{4-7}$-Pro-Gly-Pro (Semax), a Russian-manufactured analog of $ACTH_{4-10}$, may exhibit antiedematous activity. This suggestion is tested in the present study.

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MATERIALS AND METHODS

A rat model of nicotine-induced BE [14] was employed in this study. Male Wistar rats weighing 150-190 g were used. After trepanation over the temporoparietal lobe, the animals were injected with nicotine (40 μg/kg, intraperitoneally) 1 h before sacrifice. The effects of the following substances on nicotine-induced BE were examined: rat atriopeptides $ANF\text{-}II_{103-125}$, $\alpha\text{-}ANF_{99-126}$, and $ANF\text{-}IV_{102-126}$ (Cardiology Research Center, Russian Academy of Medical Sciences, a generous gift of Prof. Zh. D. Bespalova), $ACTH_{5-10}$ (Serva), and Semax (Research Institute of Tissue, Blood, and Hormonal Preparations). The substances were injected 1 h prior to nicotine.

Physical parameters (humidity and density) of the nervous tissue during the development of BE were generally evaluated only in the affected hemisphere, whereas contralateral (intact) hemisphere served as the control [6,10]. However, this arbitrarily intact hemisphere may be involved in the process. Therefore, in the present study the humidity and density of the brain tissue were determined in both hemispheres [8].

RESULTS

There were no statistically significant differences between intact and control animals in terms of water

0007-4888/96/0011-1102$15.00

content and density of the brain tissue (Table 1). The edematous factor (nicotine) increased the water content and reduced the density of both hemispheres, implying the development of BE.

Semax and $ACTH_{5-10}$ exhibited antiedematous activity only in high doses: 100 and 1000 mg/kg (Table 1) and restored the studied parameters almost to the original level in both hemispheres. However, a marked asymmetry ($p<0.05$), i.e., specific redistribution of water, developed in BE against the background of the above-mentioned doses of regulatory peptides. Dehydration was higher in the right (arbitrarily intact) hemisphere. This was also observed after administration of low doses of regulatory peptides.

This phenomenon may be associated with unequal influence of the studied neurotropic peptides on the functional activity of brain hemispheres, i.e., pharmacological asymmetry, which has been demonstrated not only for humans, but also for animals, including rats [7].

The N-terminal ACTH fragments exhibit no corticotropic activity [5,9]. Consequently, the anti-

TABLE 1. Effect of ACTH Fragments and Atriopeptides on the Development of Toxic (Nicotine-Induced) BE ($M\pm m$, $n=10$)

Experimental conditions	Hemisphere	Total water content, %	Brain tissue density, g/cm³
Intact rats	Left	78.331±0.138	1.0423±0.0003
	Right	78.315±0.094	1.0425±0.0003
Toxic (nicotine-induced) BE (control)	Left	79.724±0.216**	1.0378±0.0003**
	Right	79.266±0.252**	1.0385±0.0002**
Substances against the background of nicotine, μg/kg:			
$ACTH_{5-10}$:			
10	Left	80.263±0.349	1.0380±0.0003
	Right	78.541±0.088*	1.0414±0.0003*
50	Left	78.577±0.242*	1.0399±0.0005
	Right	76.977±0.069	1.0422±0.0004*
100	Left	78.725±0.281*	1.0403±0.0004*
	Right	77.287±0.205*	1.0424±0.0002*
Semax:			
1	Left	79.154±0.269	1.0390±0.0005
	Right	78.322±0.105*	1.0417±0.0003*
10	Left	79.101±0.481	1.0392±0.0006
	Right	77.765±0.401*	1.0411±0.0006*
100	Left	79.450±0.258	1.0386±0.0005
	Right	77.295±0.115*	1.0418±0.0003*
1000	Left	78.467±0.123*	1.0417±0.0003*
	Right	77.706±0.161*	1.0416±0.0002*
rat $ANF\text{-}II_{103-125}$:			
0.1	Left	79.995±0.202	1.0384±0.0002
	Right	78.418±0.092*	1.0406±0.0003*
0.2	Left	80.144±0.177	1.0381±0.0003
	Right	78.978±0.160*	1.0406±0.0003*
0.4	Left	80.028±0.067	1.0379±0.0002
	Right	78.911±0.089*	1.0402±0.0005*
rat $\alpha\text{-}ANF_{99-126}$			
0.2	Left	80.025±0.264	1.0379±0.0002
	Right	79.585±0.067	1.0384±0.0001
rat $ANF\text{-}IV_{102-126}$			
0.1	Left	79.193±0.350	1.0411±0.0005*
	Right	78.163±0.192*	1.0420±0.0003*

Note. $p<0.001$: *compared with the control, **compared with intact animals.

edematous activity of these fragments is realized predominantly by central mechanisms, specifically, via modulation of choline- and monoaminergic processes in the central nervous system [2,3,9,11]. Moreover, the involvement of the regulatory peptides in the pathogenesis of BE cannot be ruled out.

Rat atriopeptides (ANF-$II_{103-125}$, α-ANF_{99-126}, and ANF-$IV_{102-126}$) exhibited no appreciable antiedematous activity (Table 1). However, they protected arbitrarily intact brain hemisphere, which implies their involvement in the pathogenesis of BE.

Thus, $ACTH_{5-10}$ and Semax exhibit pronounced antiedematous activity and dehydrate an arbitrarily intact brain hemisphere. Atriopeptides possess no antiedematous properties and protect the arbitrarily intact hemisphere.

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