PHARMACOLOGY AND TOXICOLOGY

Vestibuloprotective and Antiamnestic Properties of Adrenocorticotropic Hormone Fragments and Their Analogs

V. V. Yasnetsov, V. M. Popov, N. M. Kiseleva, A. A. Kamenskii, and V. N. Nezavibat'ko

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It is established that low-intensity electromagnetic waves of superhigh frequency and motion sickness induce in rats a retrograde amnesia revealed in the passive avoidance test. Fragments of adrenocorticotropic hormone (ACTH) (4-10) and (5-10), ORG-2766 [ACTH (4-9) analog], and a domestic ACTH (4-10) analog, ACTH (4-7)-Pro-Gly-Pro (semax), in doses of 0.05-0.1 mg/kg significantly weaken the anamnestic effect of both extreme factors. Semax and ORG-2766 also possess a marked anti-motion sickness activity.

Key Words: *ACTH fragments; analogs; amnesia; motion sickness*

It is known that various fragments of the adrenocorticotropic hormone (ACTH) molecule (1-24, 4-10, 5-10, 4-7, etc.) and a series of their synthetic analogs possessing prolonged activity, including an original domestic analog of ACTH (4-10), ACTH (4-7)-Pro-Gly-Pro (semax), exert a pronounced effect upon learning and memory in human beings and animals [1-3,7,8,10]. Moreover, the ACTH (4-10) fragment can affect certain properties of vestibular function, especially in the event of its disturbance, and inhibit spontaneous activity of vestibular neurons [13,14]. Motion sickness is known to affect memory [6,9]. It has been shown [4,5] that electromagnetic radiation (EMR) of superhigh frequency (SHF) and low intensity induces a retrograde amnesia in rats. In the present investigation we attempted to check the ability of ACTH fragments and semax to prevent the amnestic effect of nonthermal SHF EMR and to assess their inhibitory effect on the development of motion sickness.

Research-Manufacturing Center *Gidrobios*, Russian Ministry of Public Health, Moscow. (Presented by I. P. Ashmarin, Member of the Russian Academy of Medical Sciences)

MATERIALS AND METHODS

The experiments were carried out on male Wistar rats weighing 160-230 g. The animals were conditioned in the passive avoidance reaction (PAR) [12]. Immediately after the completion of conditioning, the rats were subjected to SHF EMR (wavelength 12.6 cm, frequency 2375 MHz, specific density of the power current 1 mW/cm^2, exposure time 1 hour). The control animals were conditioned and subjected to sham-irradiation. The method was described by us in detail earlier [4,5].

Motion sickness was modeled by placing the rats for 1-1.5 hours on a modified NASA device [11] permitting the animals to be rotated in two perpendicular planes with a frequency of 0.33 Hz. The degree of motion sickness was assessed by recording the amount of food consumed by the animals during 2 and 24 hours after rotation (modified method [15]).

ACTH fragments (4-10) and (5-10) (Serva), ACTH (4-9) analog (ORG-2766, Organon), and semax were injected intraperitoneally in a dose range of 0.05-0.1 mg/kg 3-5 min before the start

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Table 1. Effect of ACTH Fragments and Their Analogs on Amnesia Induced in Rats by SHF EMR

Experimental conditions	Total number of rats	Number of rats showing retrograde amnesia (PAR test)		
		immediately after irradiation	1 hour after irradiation	24 hours after irradiation
Saline plus sham–irradiation (control 1)	30	5 (17%)	6 (20%)	8 (27%)
Saline plus SHF EMR (control 2)	30	23 (77%)°°°	19 (63%)°°°	15 (50%)°
ACTH (4–10) plus sham–irradiation	10	1 (10%)	1 (10%)	1 (10%)
ACTH (4–10) plus SHF EMR	20	7 (35%)**	6 (30%)*	6 (30%)
ACTH (5–10) plus sham–irradiation	10	1 (10%)	2 (20%)	2 (20%)
ACTH (5–10) plus SHF EMR	20	8 (40%)**°	8 (40%)*	7 (35%)
ORG–2766 plus sham–irradiation	10	1 (10%)	1 (10%)	1 (10%)
ORG–2766 plus SHF EMR	17	6 (35%)**	5 (29%)*	3 (18%)*
Semax plus sham–irradiation	10	1 (10%)	1 (10%)	1 (10%)
Semax plus SHF EMR	18	6 (33%)**	6 (33%)*	4 (22%)*

Note. Here and in Table 3: one asterisk (or circle) corresponds to $p<0.05$, two correspond to $p<0.01$, and three correspond to $p<0.001$ when compared with control 2 and control 1, respectively (Fisher's exact method).

Table 2. Comparison of Anti–Motion Sickness Activity of Various Preparations in Rats (Assessed by Measurement of Food Consumption) ($M \pm m$)

Preparation (dose, mg/kg) (n=6-10)	Food consumption (% of control level) after rotation
Control (saline)	63±6
Scopolamine (0.1)	86±7*
Diprazin (50)	81±5*
ACTH (5–10) (0.1)	95±6**
Semax (0.1)	140±5**

Note. Food consumption before rotation is taken as 100%; *$p<0.05$; **$p<0.01$ in comparison to the control (Student's test).

of rotation and/or immediately after the completion of PAR conditioning.

RESULTS

As can be seen from Table 1, SHF EMR exposure lasting 1 hour induces a retrograde amnesia in the rats revealed in the PAR test; the severity of amnesia diminished over 24 hours. The proportion of rats with retrograde amnesia was 77% ($p<0.001$) immediately after irradiation, 63% ($p<0.001$) one hour later, and 50% ($p<0.05$) 24 hours later. All peptides tested improved the retention of memory to a certain degree and more or less efficiently alleviated (by 1.9-2.3 times) the amnestic effect of SHF EMR. ORG-2766 and semax proved to be most effective, reliably ($p<0.05$) completely preventing amnesia development 24 hours after irradiation.

In the next series of experiments (Table 2) the vestibuloprotective activity of the peptides was assessed. It was shown that ACTH (5-10) and semax practically completely prevent the development of motion sickness in the rats. The anti-motion sickness activity of ACTH (5-10) slightly (unreliably) exceeded the activity of established vestibuloprotectors, i.e., scopolamine (0.1 mg/kg) and diprazin (50 mg/kg). Semax in a dose of 0.1

Table 3. Effect of ACTH Fragments and Their Analogs on Rotation–Induced Amnesia in Rats

Experimental conditions	Total number of rats	Number of rats showing retrograde amnesia (PAR test)		
		immediately after rotation	1 hour after rotation	24 hours after rotation
Saline plus sham–rotation (control 1)	30	7 (23%)	7 (23%)	9 (30%)
Saline plus rotation (control 2)	32	20 (62%)°°°	18 (56%)°°	17 (53%)°
ACTH (5–10) plus sham–rotation	10	2 (20%)	2 (20%)	2 (20%)
ACTH (5–10) plus rotation	20	7 (35%)*	7 (35%)	7 (35%)
ORG–2766 plus sham–rotation	10	1 (10%)	1 (10%)	1 (10%)
ORG–2766 plus rotation	19	6 (32%)*	5 (26%)*	5 (26%)*
Semax plus sham–rotation	10	1 (10%)	1 (10%)	1 (10%)
Semax plus rotation	20	6 (30%)*	6 (30%)*	5 (25%)*

mg/kg proved to be reliably ($p<0.01$) more effective than all the mentioned compounds.

One would assume that peptides possessing strong vestibuloprotective properties could also show antiamnestic activity in motion sickness. The experiments conducted showed (Table 3) that the peptides under study alleviated the rotation-induced amnesia by a factor of 1.8-2.1 ($p<0.05$). As in the case of SHF EMR-induced amnesia, the highest activity was exhibited by semax and ORG-2766, which, in contrast to ACTH (5-10), reliably ($p<0.05$) completely prevented the amnesia that was observed in the rats 2 and 24 hours after rotation.

Thus, the results of the present study show that ACTH fragments and their analogs possess marked antiamnestic and vestibuloprotective properties. Preparations with prolonged action, semax and ORG-2766, are more efficient than native ACTH fragments. In light of recent findings on the anti-ischemic and antihypoxic activity of semax in human being and animals [10], it can be recommended that this preparation undergo trials as a vestibuloprotector in human beings.

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