EFFECT OF ARGININE-VASOPRESSIN ON EXCITABILITY AND FATTY ACID CONTENT OF BRAIN STRUCTURES OF NEUROTIC RATS

P. A. Nerush

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Neuropeptides play a direct role in the regulation of higher mental function [2, 4, 5]. The use of neuropeptides of the vasopressin group during learning and in pathology of higher nervous activity (alcoholic encephalopathy) is firmly established [8, 11]. It has been shown that vasopressin delays extinction of a negative emotional reaction [8]. Investigations on isolated adipocytes [1] have revealed the stimulating action of arginine-vasopressin on isolation of free fatty acids.

The aim of this investigation was to study the action of arginine-vasopressin on excitability of certain structures of the limbico-reticular complex in the frontal region of the neocortex, and also to determine concentrations of free fatty acids in them under conditions of an experimental neurotic state.

EXPERIMENTAL METHOD

Experiments to study excitability of the structures were conducted on 15 male rats weighing 230-250 g with bipolar electrodes (diameter 0.1 mm) implanted chronically into the frontal cortex (FC: coordinates A-2, D-2, H-0.5), the dorsal region of the hippocampus (DH: P-2, D-1, H-3.5), and the midbrain reticular formation (RF: P-6.5, D-2, H-7), taking data from a stereotaxic atlas [13]. The reference electrode was inserted into the frontal bone near its boundary with the nasal bone. The rats were used in the experiments 12 days after the operation to implant the electrodes. Parameters of the functional state of the brain structures were their bioelectrical activity and level of excitability, recorded in unrestrained animals. Excitability of the brain formations was determined from the ratio of the primary components of the corresponding behavioral reactions, developing in response to stimulation of these structures by square pulses of threshold value, and changes in cortical electrical activity accompanying them (after-discharges for FC and DH, an arousal reaction for the midbrain RF). Brain structures were stimulated by means of an ELS-2 stimulator with the following parameters: for FC and DH the following frequency of the square pulses was 50 Hz, their duration 1 msec, duration of stimulation 5 sec; for RF the frequency 200 Hz, duration 0.5 msec and 5 sec respectively. Quantitative determination of free fatty acids in the cerebral cortex (CC), hippocampus (H), and midbrain (MB) was carried out by gas chromatography, using a "Shimadzu" chromatograph by the method in [12]. In this part of the work, the test were carried out on 29 noninbred male albino rats weighing 180-200 g, obtained from the Rappolovo nursery. This group of animals was divided into four series: intact (seven animals), intact + arginine-vasopressin (seven animals), neurosis (seven animals), and neurosis + arginine-vasopressin (eight animals). To form a neurosis a model of neurogenic stress was used (a conflict between afferent excitations) [3]. This model is based on the appearance of a state of indeterminacy in the animals. The neurosis was induced in an electrode cage with programing system. The neurotic state was formed in the course of 2.5 weeks, with an exposure of 2 h daily. In the group of animals undergoing neurophysiological tests, neurosis was induced after determination of their initial level of excitability for each structure. The action of arginine-vasopressin (AVP; 1 μg/kg, intraperitoneally) was studied both in intact animals and against the background of established neurosis, 30 min after injection of the peptide. The results were subjected to statistical analysis [7].

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TABLE 1. Effect of AVP (1 μg/kg body weight) on Level of Excitability of Brain Structures during Neurosis

Experimental conditions	Frontal cortex	Dorsal hippocampus	Reticular formation
Intact animals	—12,2±1,1*	—5,2±0,6	—7,6±0,8
Neurosis	—6,0±0,7***	—8,0±0,4**	—5,7±0,7

Legend. Level of excitability (— denotes lowering) of brain structures shown as percentages of initial values. *p < 0.05; **p < 0.01; ***p < 0.001.

TABLE 2. Level of Free Fatty Acids (FFA) in Parts of Brain of Rats with Experiment Neurosis (mmoles/g tissue)

Brain structure		FFA											
		control (n = 7)						neurosis (n = 7)					
		myristic	palmitic	stearic	oleic	linoleic	arachidonic	myristic	palmitic	stearic	oleic	linoleic	arachidonic
Cerebral cortex	M	0,07	7,19	12,46	13,56	0,34	0,48	0,03*	7,68	7,22*	14,65	0,68*	1,06**
	m	0,01	0,15	3,26	1,14	0,08	0,06	0,01	0,75	0,62	0,53	0,10	0,15
	%							—57	+7	—42	+8	+100	+120
Hippocampus	M	0,01	5,35	7,66	18,84	0,29	2,08	0,02**	6,36	8,79	16,69	0,76**	1,38*
	m	0,001	0,21	0,50	2,72	0,04	0,19	0,001	0,67	1,13	1,90	0,11	0,18
	%							+100	+19	+15	—11	+162	—34
Midbrain	M	0,38	5,80	18,9	32,29	0,50	4,45	0,04***	5,81	8,25*	30,96	0,82*	1,95*
	m	0,001	0,63	3,23	3,3	0,10	0,33	0,005	0,64	1,13	0,83	0,04	0,21
	%							+89	+0,2	—56	—4	+64	—56

Legend. Here and in Table 3: *p < 0.05; *p < 0.01; ***p < 0.001.

EXPERIMENTAL RESULTS

The effect of AVP was studied after stable initial values of parameters of the functional state of the brain formations had been established. In intact animals the threshold of excitability of FC averaged 12.43 ± 0.94 V; of DH 6.73 ± 0.2 V, and of RF 4.83 ± 0.16 V.

The state of neurosis was accompanied by increased excitability of the brain structures. Under these circumstances the excitability of FC was increased by 15 ± 1.2% ($p < 0.01$), of DH by 12.4 ± 0.4% ($p = 0.05$), and of the midbrain RF by 17.5 ± 2.8% ($p < 0.001$).

Data on the effect of AVP on the level of excitability of the various structure studied in intact and neurotic rats are given in Table 1.

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They show that excitability of the test structures was changed in different ways by AVP, Against the background of neurosis the effect of AVP was seen more clearly, as shown by elevation of the threshold of responses of the brain structure to stimulation.

It has recently been shown that lipids can perform widely different functions, including helping to maintain the enzymic activity of membrane proteins. The lipid phase of the membrane is responsible for more specific protein–lipid interaction, which promotes the formation of particular conformations of the protein and its functioning in the membrane.

Data on changes in the content of free fatty acids (FFA) in the brain structures studied in intact and neurotic rats under the influence of AVP are given in Tables 2 and 3. The fatty acid spectrum of the lipids in neurotic animals showed an increase in the concentrations of linoleic acid, as well as opposite changes in arachidonic acid in CC and subcortical formations of the end brain. In the midbrain a statistically significant decrease was observed in concentrations of myristic and stearic acids. Changes in FFA in the brain of the neurotic rats can be explained from the point of view of the hypothesis regarding the role of cerebral hypoxia in the pathogenesis of neuroses [10].

TABLE 3. Changes in Level of Free Fatty Acids in Parts of Rat Brain under the Influence of AVP (1 μg/kg, intraperitoneally) during Experimental Neurosis (mmoles/g tissue)

Brain structure		FFA											
		control + AVP (n = 7)						neurosis + AVP (n = 8)					
		myristic	palmitic	stearic	oleic	linoleic	arachidonic	myristic	palmitic	stearic	oleic	linoleic	arachidonic
Cerebral cortex	M	0,16***	16,20***	14,13	25,87***	0,36	1,20***	0,19***	15,27**	15,43***	29,84***	0,52	1,76*
	m	0,01	0,88	0,41	0,69	0,02	0,08	0,02	0,66	0,54	0,81	0,10	0,22
	%	+129	+125	+13	+91	+6	+150	+ by 5.3 times	+99	+110	+104	—24	+66
Hippocampus	M	0,13***	15,0***	15,79***	42,84***	0,20***	4,75***	0,12***	13,65***	17,02***	42,80***	0,26**	4,83***
	m	0,01	0,37	0,39	0,96	0,01	0,18	0,01	0,87	1,03	1,97	0,07	0,32
	%	+ by 13 times	+180	+106	+127	—31	+128	+ by 6 times	+115	+94	+156	—66	+250
Midbrain	M	0,16***	11,36***	15,65	53,94***	0,36	15,76***	0,12***	9,61***	13,40*	47,35**	0,26***	14,21***
	m	0,01	0,28	0,39	1,52	0,01	0,42	0,01	0,41	1,29	3,49	0,05	0,64
	%	—58	+96	—17	+67	—28	+254	+200	+65	+62	+53	—68	+ by 4 times

In intact rats AVP caused a sharp increase (by 1.5-2.5 times) in concentration of arachidonic, palmitic, and oleic acids The myristic acid concentration was increased in CC and H but reduced in MB; the linoleic acid concentration was red in H and MB.

In neurotic rats the character of the changes in FFA under the influence of AVP differed from the situation in pure neurosis. This is shown by a rise of the arachidonic acid level in H and MB by 2.5 and 6 times and, to a lesser degree, in CC — by 66% ($p < 0.05$). Concentrations of myristic (by 2-5 times), palmitic, stearic, and oleic acids also were increased.

Thus in neurotic rats AVP reduced the excitability of structures of the limbicoreticular complex and frontal neocortex involved in the realization of memory processes. The ability of vasopressin analogs to raise the threshold of response to stimulation of the medial septal nucleus in conscious rabbits also was noted by other workers [6].

It has been suggested that the different effects of neuropeptides on brain structures can be attributed to the uneven distribution of peptide receptors [9].

The increase in FFA concentration under the influence of AVP is in accordance with facts relating to this effect on fatty acid excretion by isolated adipocytes [1], which ultimately was due to the property of vasopressin of enhancing membrane fluidity [15]. The action of AVP also is realized through intracellular biochemical processes [14]. AVP increases the cAMP concentration in the neuron, and this is accompanied by release of intracellular Ca^{2+}, a triggering factor during cerebral hypoxia.

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