EFFECT OF VASOPRESSIN ANALOG ON CHEMOREACTIVE PROPERTIES OF SENSORIMOTOR CORTICAL NEURONS

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An essential role in learning and memory processes is played by modifications of the membrane chemoreactive properties of neurons involved in engram formation [2, 3, 7]. With the obtaining of extensive data on the effect of neuropeptides, including vasopressin and its analogs, on integrative brain activity [1, 6, 8, 9, 12] the question of the mechanisms of this effect has arisen and investigations into the action of neuropeptides on chemoreactive properties of central neurons are necessary.

The object of this investigation was to study the effect of systemic adminstration of the vasopressin analog desglycylargininevasopressin (DG-AVP), synthesized at the Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, on chemoreactive properties of sensorimotor cortical neurons.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats weighing under 250 g, immobilized with D-tubocurarine chloride (10 mg/kg). A miniature micromanipulator was secured to the skull above the sensorimotor cortex by means of acrylic glue, so that a three-barreled composite microelectrode with a tip under 10 μ in thickness could be inserted in steps of 6 μ down to the level of layer IV-V of the sensorimotor cortex. The barrels of the electrode were filled with 3M NaCl, 2M acetylcholine (ACh), pH 4.0, and a 0.2 M solution of noradrenalin (NA) bitartrate. The electrode barrels were filled 30-40 min before the experiment. Mediators were applied to these neurons by currents 10-20 nA for 30 min, and the holding current did not exceed 4-5 nA. Unit activity was recorded for 1.5-2 min before, during, and for 1.5-2 min after application of mediators to the neurons. Spontaneous discharges (for 60 sec) and activity of the neurons during microiontophoresis (for 30 sec) of mediators before and after subcutaneous injection of 10 μg DG-AVP were subjected to statistical analysis.

In 40 rats 165 sensorimotor cortical neurons were tested. Reactivity to NA and ACh was studied under normal conditions in 114 neurons and in experiments with neuropeptides on 51 cells. Bursting activity was compared in 28 cells under normal and 51 cells under experimental conditions. The animal remained in the experiments for 2-4 h.

EXPERIMENTAL RESULTS

The mean spontaneous firing rate before injection of DG-AVP was 2.06 ± 0.1 spikes/sec and after injection 2.2 ± 0.3 spikes/sec, i.e., it was practically unchanged. By contrast with this, the distribution of the neurons before responding to ACh and NA and after the injection of DG-AVP showed significant changes. As Fig. 1 shows, after injection of DG-AVP the number of activated neurons increased significantly ($P < 0.05$) and the number of neurons inhibited by application of ACh decreased; the number of neurons not responding to ACh remained virtually unchanged. After injection of DG-AVP responses of the neurons to NA also changed: the relative number of activated cells decreased significantly and the number of cells not

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responding to NA increased. Besides changes in responses of the neurons to ACh and NA, estimated from changes in the mean discharge frequency, marked changes also were found in the structure of activity, both spontaneous and after application of the mediators. These changes consisted of considerable strengthening of bursting activity after injection of DG-AVP. Bursts consisting of 2-3, 4-6, and 7-10 spikes with maximal duration of up to 0.3, 0.6, and 1 sec respectively, were chosen for statistical evaluation of these changes.

It will be clear from Table 1 that under the influence of the peptide the number of neurons with a bursting type of activity increased. There was a greater increase (by 30%) in the number of neurons whose activity included long bursts of 7 to 10 spikes under these circumstances (incidentally, both long and short bursts could be recorded from the same neuron, so that the total number of neurons with bursting activity exceeded 100%). The number of bursts consisting of 4 to 6 and, in particular, of 7 to 10 spikes also increased considerably under the influence of DG-AVP. A general tendency for bursting activity to be intensified by DG-AVP was found during microiontophoretic application of the mediators and in the after-period after its end. On examination of the corresponding data in Table 1 the first fact to attract attention is the appearance of long bursts of spikes during application of NA to neurons which did not exhibit this kind of bursting activity before injection of DG-AVP. This change in firing pattern continued after the end of application of NA. Another noteworthy fact is that application of ACh to the neuron immediately after application of NA, against the background of the action of DG-AVP, gave rather different results from those before injection of DG-AVP. For instance, before injection of DG-AVP application of ACh to the neurons before application of NA reduced the number of bursts consisting of 4 to 6 spikes by more than half (from 4.8 to 2.3) compared with their number in response to application of ACh alone. On the other hand, the number of neurons in whose activity such bursts took place was virtually unchanged. Against the background of reaction of DG-AVP the number of bursts under these conditions was reduced not by half, but only by 29%, but the number of neurons in whose activity such bursts were observed fell by 40%. Clear differences between the effects of ACh application to neurons after NA application can be seen by comparing the corresponding values before and after injection of DG-AVP with respect to bursts consisting of 7 to 10 spikes (Table 1).

Under the influence of systemic injection of 10 μg DG-AVP the character of the spontaneous discharge of the neurons, their response to microiontophoretic application of ACh and NA, and the modulating action of NA application on subsequent responses of the neuron to ACh

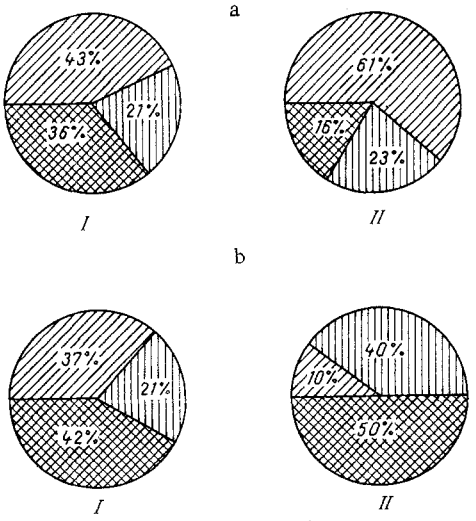

Fig. 1. Distribution of neurons (in %) by direction of responses to microiontophoretic application of ACh (a) and NA (b) before (I) and after (II) intraperitoneal injection of DG-AVP. Oblique shading — increase in spike activity; vertical shading — decrease in spike activity; cross-hatching — no change in spike activity.

TABLE 1. Character of Bursting Activity of Rat Sensorimotor Cortical Neurons after Subcutaneous Injection of DG-AVP and Microiontophoretic Application of ACh and NA to Neurons (M ± m)

Experimental conditions	Parameter studied	Before application of mediators, 60 sec			During application of mediators, 30 sec				After application of mediators, 60 sec		
		number of spikes in burst			mediator	number of spikes in burst			number of spikes in burst		
		2—3	4—6	7—10		2—3	4—6	7—10	2—3	4—6	7—10
Normal	Number of bursts	19,3±1,71	3,4±0,37	0,9±0,16	ACh	16,6±1,7	4,8±0,4	2,0±0,6	18,0±1,6	3,3±0,8	4,07±0,54
					NA	3,7±1,0	15±0,1	0	12,5±2,1	3,5±0,8	0
	Number of neurons exhibiting bursting activity, %				ACh after NA	12,1±3,0	2,3±0,8	0	26,0±3,2	5,6±0,5	3,0±0,2
					ACh	91	52	21	100	52	26
		80	50	17	NA	100	18	0	62	15	0
					ACh after NA	100	50	0	100	50	16
During action of DG-AVP	Number of bursts	16,0±1,12	7,6±0,34*	7,1±0,29*	ACh	14,0±0,9	4,5±0,3	5,5±0,3*	21,0±1,0	6,5±0,5*	6,2±0,4
					NA	8,3±1,2	3,1±0,5*	2,0±0,4	12,0±1,7	2,0±0,3	2,0±0,4
	Number of neurons exhibiting bursting activity, %				ACh after NA	14,0±3,0	3,2±0,2	5,0±1,3	28,0±3,0	4,2±1,0	4,6±1,0
		92	60	47*	ACh	94	82*	70*	91	80*	58*
					NA	100	63*	18*	60	40	25
					ACh after NA	100	50	37*	100	75	40

Legend.* $P < 0.05$ compared with corresponding value of parameter before injection of DG-AVP.

were thus all changed. All these effects may be the result of changes in the chemoreactive properties of large neuron populations and of a correspondng change in the structure of interneuronal relationships, notably changes in the efficiency of the "organizing" influences of interneurons. The redistributions of spike trains arising under these conditions are reflected in a general intensification of bursting activity, with the predominant increase in the efficiency of mechanisms responsible for the formation of long bursts of spikes. The effects observed may be the result of both the direct and the indirect (through the brain noradrenergic system) action of DG-AVP on neuron membranes. This last hypothesis is based on data showing the effect of noradrenergic mechanisms of the brain on chemoreactive properties of neurons [4, 5] and the recently discovered role of the brain noradrenergic system in the realization of the effects of vasopressin [10, 11]. Changes in the chemoreactive properties of neurons after systemic injection of vasopressin analog discovered in the present investigation confirm to some degree the suggestion that this mechanism is involved in the action of vasopressin (and, perhaps, other neuropeptides) on learning and memory processes.

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