EFFECT OF ATRIAL NATRIURETIC PEPTIDE AP II ON MORPHOLOGY AND FUNCTION OF THE ADRENAL CORTEX IN ALBINO RATS

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The adrenals are one of the target organs of atrial natriuretic peptides (ANP) [10]. A high density of receptors for ANP is found in the glomerular zone of the adrenal cortex [12]. Atrial peptides lower basal and stimulated aldosterone production in vitro and in vivo [9, 11, 13]. Despite the abundance of data on the effect of ANP on adrenocortical function, information on their effect on morphology and proliferation of adrenocorticocytes is sporadic and contradictory. According to some data [10] natriuretic peptides stimulates DNA synthesis in a primary culture of cells of the zona glomerulosa of the bovine adrenal cortex. In vivo, injection of atriopeptin for 7 days led to atrophy of cells of the zona glomerulosa of the albino rat adrenal cortex [13].

The aim of the present investigation was to study the effect of ANP on physiological regeneration and on some parameters of the morphology and function of the adrenal cortex in vivo.

EXPERIMENTAL METHOD

As the representative of the natriuretic peptide family we chose the 23-amino-acid peptide atriopeptin AP II, which possesses the principal structural characteristics and biological properties of ANP [3]. AP II was obtained by classical methods of peptide chemistry in solution at the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR. Atriopeptin was injected intraperitoneally in a single dose of 10 or 100 μg/kg. Animals of the control group received an intraperitoneal injection of an equal volume (0.2 ml) of the solvent, namely sterile isotonic sodium chloride solution. The process of physiological regeneration in the zona glomerulosa and zona fasciculata of the adrenal cortex was studied 4 and 24 h after injection of the peptide. The animals were given an intraperitoneal injection of ^{3}H-thymidine in a dose of 0.6 μCi/g 1 h before sacrifice. Histological preparations were obtained by methods described previously [5]. Physiological regeneration was judged by monitoring parameters of DNA synthesis: its index of labeled nuclei (ILN, ‰) and the labeling intensity (LI: the mean number of grains of silver above the nucleus). The plasma aldosterone concentration was determined by radioimmunoassay 1 h after injection of atriopeptin, with the aid of standard kits from "Sorin" (Italy) on a "Gamma-800" apparatus. Karyometry was carried out on an "Integral-2MT" television image analyzer. The area of maximal cross section of nuclei entirely present in the section was determined, using techniques in [1, 8] for guidance. In each preparation 70 nuclei in adrenocorticocytes of the zona glomerulosa and zona fasciculata of the adrenal cortex were measured. The experimental results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

Injection of AP II into rats in a dose of 10 μg/kg led to an increase in the index of labeled nuclei in the zona glomerulosa of the adrenal cortex by 1.5 times after 4 h (Table 1). No significant changes in labeling intensity, which

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TABLE 1. Effect of AP II on DNA Synthesis and Dimensions of Cell Nuclei in Zona Glomerulosa and Zona Fasciculata of Albino Rat Adrenal Cortex

Experimental conditions	Zona glomerulosa			Zona fasciculata		
	ILN, ‰	LI	area of section of nucleus	ILN, ‰	LI	area of section of nucleus, μ^2
Control	4,3±0,4	19,0±0,9	32,1±0,5	3,3±0,5	21,3±2,2	37,3±1,1
4 h	6,6±0,6*	20,1±1,6	32,6±0,9	4,3±0,7	20,6±1,1	38,4±1,3
24 h	3,4±0,3	20,4±1,3	32,5±0,6	2,5±0,4	22,7±1,0	39,8±0,4
Control	7,7±1,1	22,5±1,5	33,3±0,5	6,2±0,7	26,2±1,7	37,2±0,8
4 h	5,4±0,8	25,4±1,3	32,8±0,7	3,5±0,4*	31,5±2,4	36,2±0,8
24 h	9,1±1,9	19,7±1,7	32,3±0,6	4,8±0,8	21,9±1,8	37,8±0,8

Legend. *$p < 0.05$ compared with control.

indirectly characterizes the rate of DNA replication, could be recorded. After 24 h, parameters of DNA synthesis did not differ from the control. The increase in the number of cells in the S period at the early stage of the investigation was evidently due to the direct action of atriopeptin on the adrenocorticocytes, for according to data in the literature, natriuretic peptide can stimulate DNA synthesis in a primary culture of cells from the zona glomerulosa of the adrenal cortex [10]. The population of receptors for ANP in the zona glomerulosa consisted mainly of the B type, bound with guanylate cyclase [15]. Activation of the receptors led to an increase in the intracellular cGMP level – the messenger involved in transmission of the mitogenic signals [2]. Consequently, the stimulating action of atriopeptin on adrenocorticocytes proliferation in the zona glomerulosa can take place through specific binding sites.

According to the results of radioimmunoassay AP II (10 μg/kg) caused a significant fall in the plasma aldosterone concentration of the rat (Fig. 1). A combination of activation of physiological regeneration in the zona fasciculata and inhibition of aldosterone production under the influence of ANP is in agreement with the rule put forward by Peter (1924), namely that relations between the functional and proliferative activity of cells are antagonistic [6].

After injection of AP II in a dose of 100 μg/kg no significant changes in DNA synthesis in the zona glomerulosa of the adrenal cortex could be recorded during the period of testing (Table 1). Atriopeptin, in this dose, likewise had no effect on the plasma aldosterone concentration (Fig. 1). ANP, like certain other regulatory peptides, thus exhibits the phenomenon of "sliding" of the effect when the dose is increased [4].

The effect of AP II on proliferative processes in the zona fasciculata of the adrenal cortex was different in character. In a dose of 10 μg/kg AP II did not change the parameters of DNA synthesis at the times of testing. When AP II was given in a dose of 100 μg/kg, we recorded a fall of 1.7 times in ILN after 4 h, but no effect after 24 h. It can be tentatively suggested that differences in the character of the action of AP II on physiological regeneration of the zona glomerulosa and zona fasciculata of the adrenal cortex are due to differences in representation of the specific binding sites of ANP on adrenocorticocytes. A high density of receptors for ANP has been found in the zona glomerulosa [12]. In the zona fasciculata specific binding sites of atrial peptides either are absent [12] or are present in small numbers [7]. The possibility that the action of AP II on the zona fasciculata of the adrenal cortex is mediated through ACTH cannot be ruled out, because ANP can inhibit production of peptide derivatives of pro-opiomelanocortin in primary culture of anterior pituitary cells [14].

According to the results of karyometric analysis AP II, in doses of both 10 and 100 μg/kg, had no effect on the dimensions of the adrenocorticocyte nuclei at the times of testing, possible evidence that atriopeptin has no antitrophic action on cells of the adrenal cortex under these conditions.

The experimental results indicate that administration of AP II can affect physiological regeneration of the adrenal cortex in vivo. The character of changes in proliferative processes depended on the dose of atriopeptin and was opposite in different zones of the adrenal cortex.

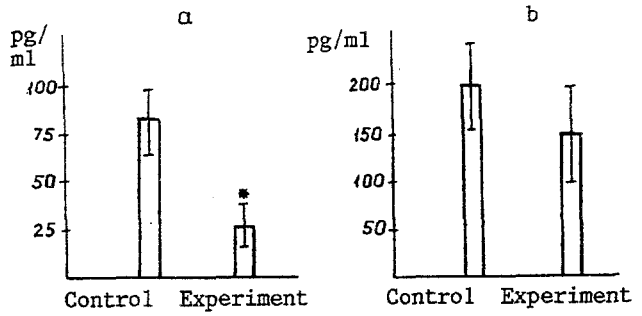

Fig. 1. Effect of AP II on plasma aldosterone level in albino rats: a) dose 10 μg/kg, b) dose 100 μg/kg. *$p < 0.05$, compared with control.

In our previous investigations we demonstrated the activating action of AP II in doses of 10 and 100 μg/kg on DNA synthesis in the intestinal epithelium, and the absence of any effect on DNA replication in the corneal epithelium of albino rats. It can be tentatively suggested that the character of the action of AP II on proliferation depends on the specific pattern of reception of atrial peptides in different tissues.

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