EXPERIMENTAL BIOLOGY

Involvement of Angiotensin II System Components in Regulation of DNA Synthesis in Pyloric Epithelium of Albino Rats

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 129, No. 2, pp. 214-216, February, 2000
Original article submitted January 12, 2000

Effects of intraperitoneal injections of angiotensin II and oral intake of cosaar (angiotensin II receptor blocker) and ednite (angiotensin-converting enzyme inhibitor) on DNA synthesis in the pyloric portion of the stomach was studied in adult albino rats by autoradiography with ^{3}H-thymidine. Proliferative processes in the studied tissue were enhanced 24 h after single injection of the peptide in a dose of 50 μg/kg and 4 h after injection of 100 μg/kg peptide. Treatment with cosaar and ednite for 2 weeks led to normalization of stress-activated epithelial proliferation in the pyloric part of the stomach.

Key Words: *angiotensin II; cosaar; ednite; stomach; DNA synthesis*

New data on the involvement of the angiotensin II (AT) system in the regulation of proliferative processes were recently obtained [6,7,10].

Previously we demonstrated that AT stimulates DNA synthesis in newborn rats in tissues not directly involved in cardiovascular function (epitheliocytes and smooth muscle cells of the small intestine, skin epitheliocytes) [2,4]. In this study we investigated the effects of AT, AT receptor blockers, and AT-converting enzyme inhibitors on DNA synthesis in the pyloric part of the stomach in adult rats.

MATERIALS AND METHODS

Experiments were performed on random-bred male albino rats weighing 140-160 g. The animals received AT in doses of 50 or 100 μg/kg intraperitoneally 4 and 24 h before sacrifice or were injected 5 times with 100 μg/kg AT. Controls were injected with an equivalent volume of NaCl solution.

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In an additional experimental series, the animals were for 2 weeks administered (through a metal tube) 10 mg/kg AT receptor antagonist cosaar (Merck) and AT-converting enzyme inhibitor ednite (Gedeon Richter). These doses are most often used to evaluate their effects on physiological functions [5,8].

For evaluating DNA synthesis in the pyloric part of the stomach the rats were intraperitoneally injected with ^{3}H-thymidine in a dose of 0.6 μCi/g (volume activity 145 gBq/liter, molar activity 1530 gBq/liter) 1 h before sacrifice. Autoradiographs were made as described previously [1]. Labeled nuclei index (LNI) was expressed in percent, labeling intensity (LI) as the mean number of silver grains above the nucleus. The results were statistically processed using Student's *t* test.

RESULTS

In a dose of 50 μg/kg, AT activated DNA synthesis 24 h after single injection, which was seen from a significant increase in LNI (8.63±0.46% *vs.* 7.29±0.34% in the control, $p<0.05$). In a dose of 100 μg/kg AT

0007-4888/00/0002-184$25.00

TABLE 1. Effect of AT in a Dose of 100 μg/kg on Proliferative Processes in the Pyloric Epithelium of Rats (*M±m*)

Parameter	Control	AT injections		
		4 h	24 h	5 times
LNI, %	8.67±0.32	10.11±0.46*	10.35±0.28*	11.7±0.42*
LI	16.7±0.7	16.91±0.63	19.13±1.27	23.8±0.91*

Note. *$p<0.05$ vs. control.

TABLE 2. Effects of Cosaar and Ednite on Proliferative Processes in the Pyloric Epithelium of Rats (*M±m*)

Parameter	Control	Intact	Cosaar	Ednite
LNI, %	10.07±0.89	8.46±0.48	6.84±0.56*	7.31±0.36*
LI	27.51±0.56	26.83±1.18	25.4±1.18	24.7±0.88

Note. *$p<0.05$ *vs.* intact animals.

significantly increased LNI both 24 and 4 h after injection. Five injections of the peptide in a dose of 100 μg/kg led to a significant increase in LNI and LI, which indicated accelerated passage of the cell through S-period (Table 1).

In a special experimental series intragastric administration of 0.9% NaCl solution and the manipulation itself slightly increased the number of DNA-synthesizing nuclei in the pylorus, probably due to stress. Previous studies revealed a compensatory intensification of proliferative processes in the gastric epithelium in rats subjected to chronic stress [3]. The fact that in the present study this increase presented just as a tendency may be explained by low intensity of stress.

Administration of ednite and cosaar decreased LNI in comparison with the effect of isotonic NaCl. No differences from intact animals were observed (Table 2).

In fact, we can speak about normalization of proliferative processes in the stomach. Results of experiments with ednite and cosaar require further explanations.

Exogenous AT induced cascade reactions in the organism, which resulted in the formation of substances activating proliferative processes [9]. That is why inhibition of DNA synthesis after administration of AT receptor blocker and AT inhibitor indicated the involvement of AT in the regulation of DNA production in newborn and adult rats.

The ability of cosaar to normalize proliferative processes suggest that the promotor effect of AT is realized via AT_1-receptors [11], although this point remains to be studied.

In our experiments AT-converting enzyme inhibitor ednite prevents poststress activation of DNA synthesis in the gastric epithelium, which is in line with published data [12].

These results are of practical importance: AT-converting enzyme inhibitors and AT receptor blockers are the drugs of choice in the treatment of essential hypertension and cardiovascular failure. These conditions are often concomitant with gastrointestinal disease often associated with impairement of proliferative processes.

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