BIOPHYSICS AND BIOCHEMISTRY

Effects of Angiotensin II on DNA Synthesis in the Myocardium and Epithelial Tissues in Newborn Rats

E. Yu. Zhivotova and S. S. Timoshin

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 126, No. 12, pp. 643-645, December, 1998
Original article submitted June 21, 1998

The effects of angiotensin II on DNA synthesis in the myocardium and epithelial tissues of the skin and intestine were studied in 7-day-old albino rats by autoradiography. Angiotensin II significantly increase the labeling index of the nuclei and labeling intensity in myocardial cells and intensified cell proliferation in epithelial tissues. Thus, angiotensin II stimulates proliferative processes in the myocardium and epithelial tissues of the skin and intestine in newborn rats.

Key Words: *angiotensin II; DNA synthesis; myocardium; skin; intestine*

Recent studies indicate that angiotensin II (AT-II) regulates arterial pressure, maintains electrolytic homeostasis, and displays the properties typical of growth regulators [5,7]. AT-II was initially considered to be a factor responsible for angiogenesis and stimulation of reproductive processes in vascular smooth muscles [4]. Further studies revealed its ability to stimulate proliferation of mammatrophs in the adenohypophysis in adult rats [12] and astroglial cells [13]. AT-II induces the proliferation in the adrenal glomerular zone in adult rats. AT-II stimulates the proliferation of cultured cranial osteoblasts [6], human skin fibroblasts [8], and cultured cardiac fibroblasts in newborn rats [11], and inhibits the synthesis of DNA in cultured NIH3T3 fibroblasts [9] and CHO-K1 cells [14]. The majority of these studies were performed on cultured cells.

We studied the effects of AT-II on the DNA synthesis in various cellular populations in newborn rats.

MATERIALS AND METHODS

Experiments were performed on 29 outbred albino rats which received daily (from the second day to the sixth day) intraperitoneal injections of the AT-II octapeptide at a dose of 100 μg/kg. Animals injected with the same volume of sterile isotonic NACl (0.02 ml/10 g body mass) served as a control. Groups of control and treated rats were composed by the method of brood separation to decrease the genetically determined differences between various broods. The DNA synthesis in the studied tissues was analyzed auto-radiographically 24 h after the last injection. All rats received ^{3}H-thymidine in a dose of 1 mCi/g body mass and were then killed by decapitation (1 h later). Autoradiographs were prepared as described [2]. The labeling index of the nuclei (LIN, %) and the labeling intensity (LI, mean number of silver grains over the nucleus) were differentially calculated in myocardial tissues of the left and right atria, left and right ventricles, and interventricular septum by using histotopographic heart preparations. Epithelial and connective tissue cell were not considered. Duodenal crypts were analyzed to estimate the number of DNA- synthesizing enterocytes. The intensity off skin cell proliferation was determined by measuring the number of labeled cells in the auricular basal epidermis. Results were statistically analyzed by the Student's *t* test.

RESULTS

Indices of the DNA synthesis in the control group (Table 1) were similar to those described previously

Central Research Laboratory of Far-Eastern State Medical University, Khabarovsk

0007-4888/98/0012-1213$20.00

TABLE 1. Effects of Repeated Injections of AT-II on DNA Synthesis in the Myocardium and Epithelium in Seven-Day-Old Rats (*M±m*)

Experimental object	LIN, %		LI	
	control	AT-II	control	AT-II
Myocardial zones				
Left atrium	4.85±0.21	5.82±0.17*	14.11±0.37	16.13±0.59*
Right atrium	4.97±0.3	5.66±0.26	14.56±0.53	16.51±0.43*
Left ventricle	7.15±0.42	8.23±0.25*	15.93±0.44	17.48±0.48*
Right ventricle	4.5±0.21	5.39±0.23*	13.93±0.48	15.68±0.55*
Interventricular septum	7.58±0.48	8.78±0.28*	15.92±0.64	17.44±0.38*
Epithelial tissues				
Intestine	35.14±0.18	41.68±1.13*	13.87±0.41	14.53±0.45
Skin	6.45±0.24	7.54±0.26*	14.45±0.8	14.57±0.5

Note: *$p<0.05$ compared with control.

[3] and found in our earlier studies [1]. AT-II increased significantly the LIN in the left atrium, left ventricle, interventricular septum, and right ventricle (Table 1). The most (20%) and the least pronounced (11.3%) changes were observed in the left and right atria, respectively.

The increase in the LI accompanied increased in the number of ^{3}H-thymidine-labeled nuclei confirmed high rate of DNA synthesis. the LI increased by 11.8%. The maximum increase in the LI and LIN was observed in the left atrium. Thus, AT-II induced stimulatory effects on myocardial cells during the early postnatal ontogenesis.

The AT-II-induced activation of physiological regeneration occurred not only in the myocardium but also in epithelial tissues (Table 1). AT-II increased significantly the LIN in the intestinal epithelium (the endoderm derivative). We did not reveal statistically significant changes of the LI (Table 1).

Similar changes were observed in the skin epithelium (the ectoderm derivative). AT-II increased significantly the number of cells in the cell cycle. The LI remained constant. These data demonstrate similar reactions of epithelia of various origin to peripheral administration of AT-II during the early postnatal ontogenesis.

The stimulatory effect of AT-II on proliferative processes is mediated by receptors of the first type [11]. Receptors of the second type were also reported to be involved in this effect of AT-II [9]. However, the stimulatory effect of AT-II is not inhibited by the antagonists of both types of these receptors [10]. Therefore, the mechanism of stimulatory effects of AT-II on the DNA synthesis in animals requires further investigations.

REFERENCES

1. E. N. Goncharova, N. P. Mel'nikova, and S. S. Timoshin, *Byull. Eksp. Biol. Med.*, **123**, No. 2, 212-215 (1993).
2. O. I. Epifanova and V. V. Terskikh, *Autoradiography in Studies of Cell Cycles* [in Russian], Moscow (1982).
3. P. P. Rumyantsev, *Cardiomyocytes in Reproduction, Differentiation, and Regeneration* [in Russian], Leningrad (1982).
4. R. K. Dubey, *J. Pharmacol. Exp. Ther.*, **269**, No. 1, 402-408 (1994).
5. I. C. Haznedaroglu, S. Tuncer, and M. Gursoy, *Med. Hypotheses.*, **46**, No. 6, 507-510 (1996).
6. Y. Hiruma, *Biochem. Biophys. Res. Commun.*, **230**, No. 1, 176-178 (1997).
7. W. R. Huckle and H. S. Earp, *Prog. Growth Factor Res.*, **5**, No. 2, 177-194 (1994).
8. G. Nickenig, *J. Mol. Med.*, **75**, No. 333, 217-222 (1997).
9. Y. Ozawa, *Biochem. Biophys. Res. Commun.*, **228**, No. 2, 328-333 (1996)
10. M. Pawlikowski and J. Kunert-Radek, *Ibid.*, **232**, No. 2, 292-293 (1997).
11. W. Schorb, *Circ. Res.*, **72**, No. 6, 1245-1254 (1993).
12. T. Shinkai and H. Ooka, *Peptides*, **16**, No. 1, 25-29 (1995).
13. C. Sumners, *Glia*, **11**, No. 2, 110-116 (1994).
14. T. J. Thekkumkata, *Mol. Cell. Biochem.*, **152**, No. 1, 77-86 (1995).