Comparative Analysis of Effects from Prolonged Peripheral and Intracerebral Administrations of Angiotensin II in Rats

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Variations in arterial pressure and food and water consumption were studied in rats during and after their prolonged continuous exposure to angiotensin II using osmotic minipumps. Subcutaneously administered angiotensin-II (300 μg over 7 days) induced long-lasting hypertension followed by hypotension. Angiotensin-II administered into a lateral cerebral ventricle (3 μg over the same period) led to a significant fall in arterial pressure. The peripheral and intracerebral angiotensin-II administrations were both accompanied by increased water consumption.

Key Words: *angiotensin II; arterial pressure; water consumption; osmotic minipumps*

Angiotensin II (AT-II) has long been known to play an important part in the humoral regulation of arterial pressure (AP) and in drinking behavior in animals and humans by interacting with specific receptors located in various organs and tissues. More recently, evidence has been obtained that there exist a peripheral system and a cerebral renin-angiotensin system, each of which appears to perform distinct functions, including those of regulating AP and drinking behavior [6,11].

It is now certain that exogenously administered endogenous regulatory peptides exert a complex integrative effect on the body, involving: 1) direct interaction of the peptide in question with specific receptors with a resultant modulation of their sensitivity; 2) alterations in the activity of the enzymes catalyzing the synthesis and degradation of the respective peptides; 3) stimulation or inhibition of the synthesis and secretion of other biologically active compounds such as peptides and transmitters [10].

In view of this, we thought it important to compare in this study the effects from long-term peripheral and intracerebral administrations of AT-II in rats.

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MATERIALS AND METHODS

The study was conducted on 60 male Wistar rats weighing 300-350 g. For prolonged administration of AT-II (synthetic human AT-II; Berlin Chemie), osmotic minipumps were used (model 2001; Alzet), ensuring continuous delivery of AT-II for 7 days.

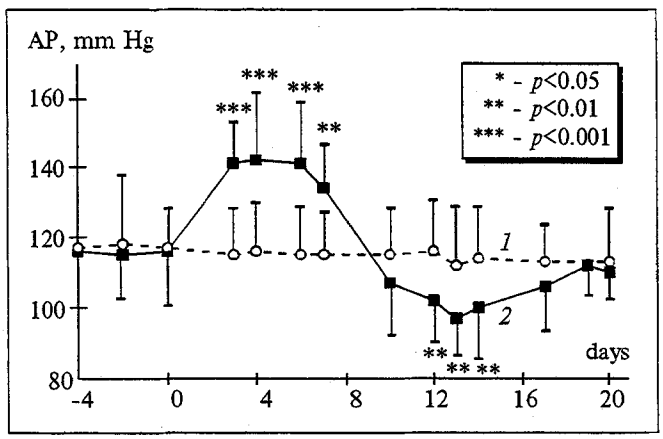

Fig. 1. AP variation in rats exposed to AT-II for 7 days continuously by the subcutaneous route. Levels of significance shown here also apply to Figs. 2, 3, and 4. *1)* - control, *2)* - test.

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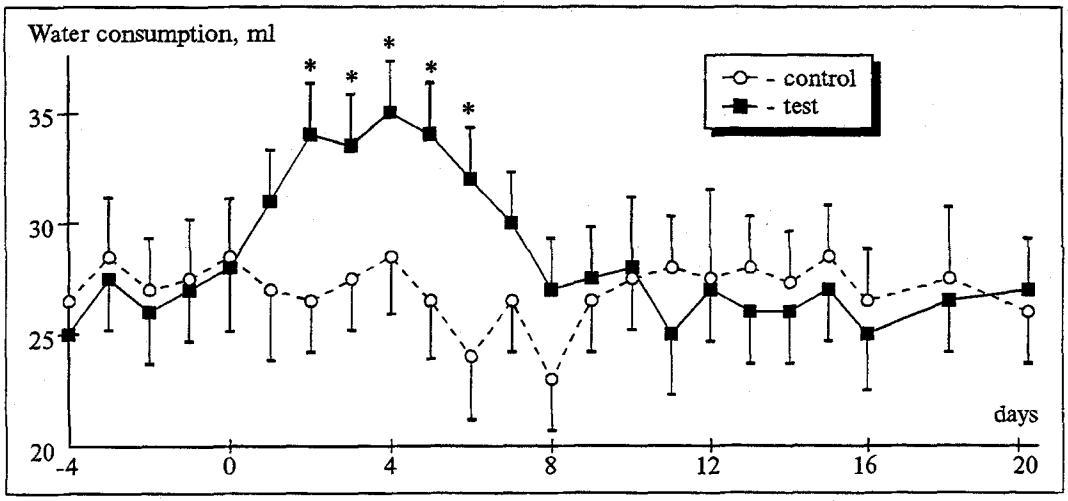

Fig. 2. Variation in water consumption by rats exposed to AT-II for 7 days continuously by the subcutaneous route.

An osmotic minipump was implanted into each rat subcutaneously in the supraclavicular region under light ether anesthesia and, in the rats slated to receive AT-II intracerebrally, it was connected via a polypropylene catheter to a cannula implanted in a lateral cerebral ventricle.

In the first experimental series, test rats (n=26) were exposed to AT-II subcutaneously for 7 days (1.5 μg/ml, delivered from the minipump at a rate of 1 μl/h, the total dose being 300 μg); in the second series, test rats (n=14) were exposed to AT-II intraventricularly over the same period (15 ng/μl for a total dose of 3 μg). In the control groups (9 rats in the first series and 11 in the second), minipumps filled with physiological saline were implanted.

All rats were monitored for food and water consumption, systolic AP, and body weight for 7 days before and 20 days after minipump implantation. Systolic AP was measured indirectly using an AP-212 pulse sensor (RTF) placed over the caudal artery.

The location of the cannula in the lateral cerebral ventricle was verified by a photographic method on frozen brain sections.

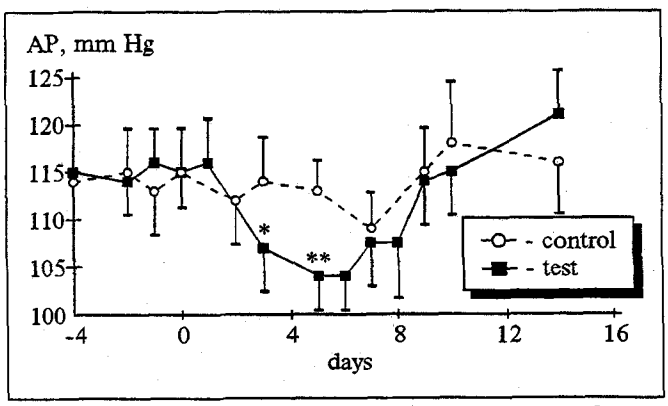

Fig. 3. AP variation in rats exposed to AT-II for 7 days continuously by the intraventricular route.

The results were treated statistically using Student's t test.

RESULTS

In the first experimental series, significant AP elevations by 25-30 mm Hg on average (by 50-70 mm Hg in some rats) occurred on days 2-3 after the start of subcutaneous AT-II infusion, and the AP remained at this level during the subsequent 4-5 days, i.e., until no more AT-II was delivered from the minipump. During the following 2-3 days the pressure returned to normal and then fell significantly by 10-15 mm Hg on average (by 15-20 mm Hg in some rats) before returning to normal again 5-6 days later. In the control group, variations in AP never exceeded 6 mm Hg (Fig. 1).

The test rats also showed significant increases in water consumption throughout the period of subcutaneous AT-II administration (Fig. 2). No significant changes in the quantity of consumed food or in body weight were detected.

The observed hypertensive action of subcutaneously infused AT-II agrees with the results reported by other authors [8,9], but its delayed hypotensive effect, discovered in this study, deserves special consideration. This effect appears to be due to the fact that the prolonged elevation of AP, which is one of the most important self-regulating bodily constants, results in the mobilization of compensatory physiological mechanisms whereby AP is brought back to normal [1,4]. It has been also demonstrated that the AT-II-induced vascular spasm is modulated by vascular endothelium and accompanied by the release of an endothelial relaxing factor and by a rise in prostaglandins with potent vasodilatory properties [7]. In addition, there is evidence that prolonged exposure to AT-II leads to

reduced activity of plasma renin with a consequent lowering of endogenous AT-II [15].

Prolonged entry of AT-II into the body has been shown to result in augmented excretion of water and electrolytes [8] and in increased diffusion of peripheral AT-II across the histohematic and blood-brain barriers [3,12], which makes it accessible to the central AT-II receptors. These observations probably explain why, in our study, rats were consuming increased amounts of water during the entire period of AT-II release from the subcutaneously implanted osmotic minipumps.

In the second experimental series, significant AP reductions (by 10-15 mm Hg on average and by 20-25 mm Hg in some rats) were recorded starting on day 2 or 3 of intraventricular AT-II infusion (Fig. 3). Water consumption by the test rats was significantly increased throughout the period of their exposure to AT-II (Fig. 4).

The hypotensive effect of AT-II that develops during its constant infusion into a lateral cerebral ventricle is of special interest. There have been only occasional reports of a short-term depressive action of AT-II following its one-time introduction into the nucleus of the solitary tract [13], the dorsal nucleus of the vagus [5], or the ventromedial hypothalamic nucleus [2], i.e., into structures containing large numbers of AT-II receptors and endings of catecholaminergic neurons. AT-II is known to alter substantially the activity of the catecholaminergic systems in the brain. In addition, microinjections of norepinephrine or epinephrine into the solitary tract nucleus have been found to be followed by inhibition of the descending sympathetic pathways and by depressive effects [13]. It has been suggested that the depressive effects of low AT-II doses are mediated by the solitary tract nucleus [13], and this is presumably one of the physiological mechanisms through which the hypotensive effect of AT-II is realized during its prolonged infusion into a lateral cerebral ventricle.

It has been shown in numerous experiments that exogenously administered AT-II modulates the activity of various components of the cerebral renin-angiotensin system, markedly enhances the secretion of hypophyseal peptide hormones (ACTH, vasopressin, oxytocin), and raises the concentration of corticosteroids and catecholamines [14]. It should be stressed that the levels of these physiologically active substances, which are directly involved in the maintenance of AP, are regulated by a feedback

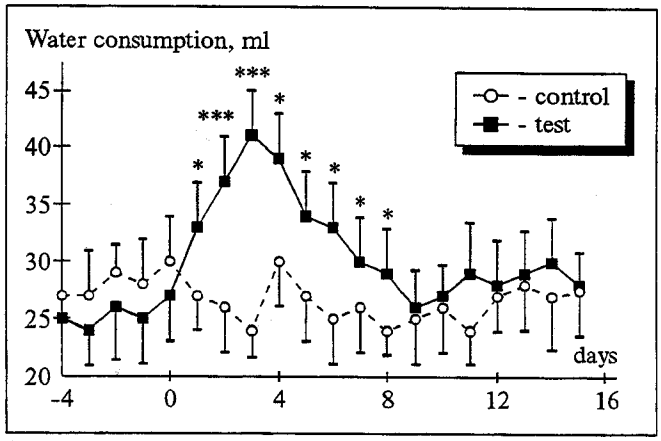

Fig. 4. Variation in water consumption by rats exposed to AT–II for 7 days continuously by the intraventricular route.

mechanism. It is therefore possible that the continuous entry of AT-II into the lateral ventricles in low (close to physiological) doses leads to a diversity of neurohumoral changes whose integration results in the development of long-lasting hypotension.

REFERENCES

1. P. K. Anokhin, *Biology and Neurophysiology of the Conditioned Reflex* [in Russian], Moscow (1968).
2. P. A. Pernyakov, *Effects of Exposing the Hypothalamus to Various Agents on Nociceptive Hemodynamic Responses (Author's synopsis of dissertation)* [in Russian], Kazan (1987).
3. B. J. Rolls and E. T. Rolls, *Thirst,* Cambridge Univ. Press, London (1982).
4. K. V. Sudakov, *General Theory of Functional Systems* [in Russian], Moscow (1984).
5. D. Diz, K. L. Barnes, and C. M. Ferrario, in: *Proc. 10th Scientific Meeting of the International Society of Hypertension. Interlaken, Switzerland* (1984), pp. 17-18.
6. D. Ganten, R. E. Lang, E. Lehmann, and Th. Unger, *Biochem. Pharmacol.*, **22**, 3523-3530 (1984).
7. C. A. Gruetter, E. T. Ryan, S. M. Lemke, *et al.*, *Europ. J. Pharmacol.*, **146**, 85-95 (1988).
8. J. E. Hall and J. P. Grander, *Fed. Proc.*, **42**, 589-596 (1983).
9. J. L. Huelsemann, R. B. Sterzel, D. E. McKenzie, and C. S. Wilcox, *Hypertension*, **7**, 374-379 (1985).
10. F. S. LaBella, J. D. Geiger, and G. B. Glavin, *Peptides*, **6**, 645-660 (1985).
11. F. A. O. Mendelsohn, R. Quirion, J. M. Saavedra, *et al.*, *Proc. Nat. Acad. Sci. USA, Ser. Biol. Sci.*, **81**, 1575-1579 (1984).
12. M. J. Phillips, *Ann. Rev. Physiol.*, **49**, 413-435 (1987).
13. R. Retting, D. P. Healy, and M. P. Printz, *Brain Res.*, **364**, № 2, 233-240 (1986).
14. R. Rettig, R. E. Lang, W. Rascher, *et al.*, *Clin. Sci.*, **63**, 269-283 (1982).
15. R. C. Vari, S. Zinn, K. M. Verburg, and R. H. Freeman, *Hypertension*, **9**, № 4, 345-349 (1987).