Regulation of Hemodynamic Parameters under Conditions of Systemic Administration of Angiotensin II and Angiotensin IV to Rats after Carotid Glomectomy

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 152, No. 7, pp. 12-14, July, 2011
Original article submitted April 13, 2010

Systemic administration of angiotensin II was followed by an increase in systolic BP and HR in rats with carotid glomectomy, the time of attaining maximum values in treated animals was much higher than in sham-operated controls. Injection of angiotensin IV slightly reduced systolic BP in sham-operated animals and increased it in rats with carotid glomectomy. The involvement of the local renin-angiotensin system of the carotid body in systemic mechanisms of hemodynamics regulation is discussed.

Key Words: *hemodynamics; angiotensins II and IV; chemoreceptors of the carotid body; carotid glomectomy*

The renin-angiotensin system (RAS) is involved in the regulation of water-salt metabolism and associated hemodynamic parameters in the body [2,9]. Physiologically active components of RAS, angiotensins (AT-II, AT-III, and AT-IV), circulate in the blood and are widely distributed in peripheral organs and brain structures (local RAS) [12]. Chemoreceptor cells in the peripheral vascular chemosensory apparatus of the carotid body (CB) regulate chemical composition of the blood and contain all components of the local RAS and receptors for AT-II and AT-IV [8,10]. Our previous studies demonstrated the major role of CB in the formation of AT-II-induced thirst and salt appetite and center-peripheral interactions between the cerebral and carotid RAS [4,5].

Here we studied the role of CB in the regulation of hemodynamic parameters under conditions of systemic administration of AT-II and AT-IV.

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MATERIALS AND METHODS

Experiments were performed on male Wistar rats (n=35) weighing 250-350 g. The role of CB in the regulation of hemodynamic parameters (systolic BP, SBP; and HR) was evaluated by the method of bilateral surgical removal of CB (carotid glomectomy) [1], which results in complete elimination of afferent chemosensory activity. Control animals were sham operated. The surgeries were performed under ether anesthesia. SBP and HR in awake rats were measured by the indirect method with a NIBP system (AD Instrument). The animals were placed in plastic cages. AT-II (300 μg, Sigma), AT-IV (400 μg/kg, American Peptides), and physiological saline were injected intraperitoneally. All experiments were conducted according to the Helsinki declaration on the welfare of animals. SBP and HR were expressed as a percentage of the baseline values. SBP and HR were interpolated with cubic splines to adjust the data to the same time grid. The results were analyzed by Student's t test. The differences were significant at $p<0.05$.

0007-4888/11/1521-0009

RESULTS

In sham-operated rats, SBP rapidly increased after systemic injections of AT-II, reached a maximum, and then progressively decreased to baseline by minutes 60-70 postinjection (Fig. 1, *a*). In glomectomized rats, SBP reached the maximum 25 min after AT-II injection (by 10 min longer than in controls; Fig. 1, *a*). HR in sham-operated rats increased and returned to the baseline by the 90th minute. The time of attaining the maximum HR in glomectomized rats (plateau curve) was by 35 min longer than in control animals (Fig. 1, *b*). The differences between the maximum values of SBP and HR in treated and control animals were statistically insignificant ($p>0.05$). Therefore, AT-II increases BP and HR in glomectomized and sham-operated animals. However, in treated animals these parameters reached the maximum values later than in controls.

Administration of AT-IV to sham-operated rats was not followed by significant changes in SBP (as compared to the baseline). SBP tended to decrease over 50 min after injection (Fig. 2, *a*). AT-IV injection to glomectomized animals produced a rapid increase in SBP. SBP in treated rats significantly differed from the baseline and the corresponding value in sham-operated animals (Fig. 2, *a*). AT-IV had little effect on HR in treated and control rats (Fig. 2, *b*). The minor increase in HR was probably related to experimental conditions [3].

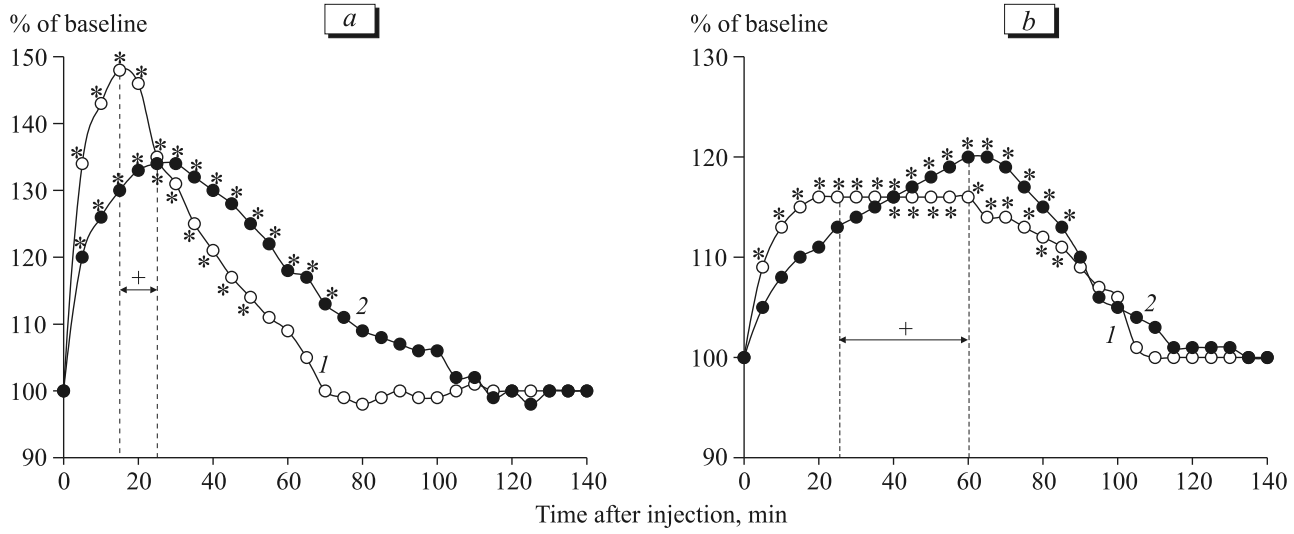

Fig. 1. Increase in SBP (*a*) and HR (*b*) in glomectomized rats after administration of AT-II. *1*) control (sham operation); *2*) treatment (carotid glomectomy). Dotted line: time of attaining the maximum value after injection. $^{+}p<0.01$ between the time of attaining the maximum values in control and treated animals. $^{*}p<0.05$ compared to baseline.

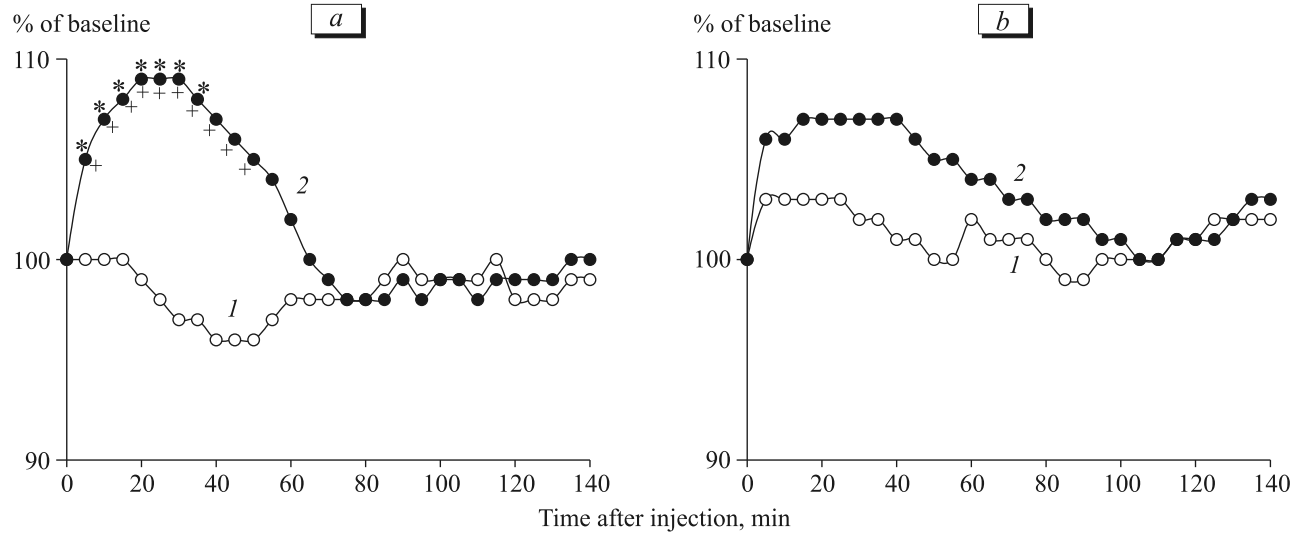

Fig. 2. Changes in SBP (*a*) and HR (*b*) in glomectomized rats after administration of AT-IV. *1*) control (sham operation); *2*) treatment (carotid glomectomy). $p<0.05$: compared to: *baseline, $^{+}$control.

Control injections of physiological saline had no significant effects on SBP and HR in treated and control animals. In contrast to the effect of systemic treatment with AT-II, AT-IV injection did not induce thirst in freely moving rats [3].

We previously studied the effect of carotid glomectomy on AT-II-induced thirst and salt appetite [4,5]. Published data show that glomus cells of CB express AT1 and AT2 receptors binding AT-II [7,10]. These data indicate that the chemoreceptor apparatus of CB plays an important role in the regulation of water-salt metabolism (with the involvement of RAS). Hemodynamic parameters of the body associated with water-salt metabolism also depend on RAS activity [2,3]. It can be hypothesized that the increase in blood AT-II concentration is followed by activation of peripheral and central targets of this peptide. These changes contribute to the increase in SBP and HR. CB is involved in systemic mechanisms of AT-II-dependent hypertension and tachycardia. This structure provides a rapid increase in SBP and HR. The increase in these hemodynamic parameters is significantly delayed in glomectomized rats. Activation of AT-II receptors in CB is followed by an increase in afferent impulses from the carotid chemoreceptor apparatus [7,10]. These impulses probably reach the brain structures that regulate hemodynamic parameters. AT-II probably affects the bioelectric properties of chemoreceptor cells in CB and induces the reflex activation of efferent channels for regulation of cardiac function [11]. It provides the initial increase in hemodynamic parameters.

AT-IV injections increased SBP in glomectomized rats, but decreases it in sham-operated animals. Binding of AT-IV to AT4 receptors in glomus cells of CB is probably followed by changes in chemosensory activity of these cells and reflex decrease in SBP. In the absence of CB, AT-IV cannot bind to AT4 receptors of glomus cells. Under these conditions, the increase in AT-IV concentration in the blood activates cardiac function due to systemic tonic mechanisms.

Our results suggest that binding of AT-II to chemosensory cells of CB is followed by a rapid reflex increase in SBP and HR. During binding to AT-IV, these cells produce a reflex inhibitory effect on SBP. The increase of SBP in the absence of CB is mediated by other systemic AT-IV-sensitive mechanisms. The reflex centrifugal regulation of cardiac function under conditions of CB activation probably involves the efferent sympathetic and parasympathetic channels [11].

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