Sex-Specific Peculiarities of Cholinergic Regulation of the Cardiovascular System in Normal and Hypertensive Rats

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Cardiovascular sensitivity to atropine and acetylcholine is reduced in renal hypertension. Hypertension in females is more benign and the hypotensive effects of acetylcholine in them are less attenuated than in males. Cardiovascular sensitivity to cholinergic effects in females is higher in health and hypertension, which improves their resistance to cardiovascular pathology.

Key Words: *cardiovascular system; atropine; acetylcholine; hypertension; sex-specific differences*

Appurtenance to male gender is an acknowledged independent risk factor for cardiovascular diseases, which renders special importance to studies of mechanisms providing resistance to these diseases with consideration for the gender factor. An important protective role is played by the cholinergic system limiting excessive cardiovascular reactions in stress via suppression of activity of the sympathoadrenal system, activation of NO production [5], and antiarrhythmic effects [12]. Attenuation of the parasympathetic effects on the cardiovascular system (CVS) is an unfavorable prognostic sign in cardiovascular diseases [12], while moderate predominance of parasympathetic effects on CVS is cardioprotective in experimental myocardial infarction [15]. The data on sex-specific characteristics of cholinergic regulation are scanty. The parasympathetic effects on CVS predominated in females and the sympathetic effects in males in experiments *in vitro* and in anesthetized animals [7] and in humans [8,14]. It remains unclear how the efficiency of cholinergic regulation of CVS is modified in cardiovascular disease and whether these changes are gender-dependent.

We studied the reactions of the CVS to blockade and intensification of cholinergic effects in normotensive and hypertensive female and male albino rats.

MATERIALS AND METHODS

Experiments were carried out on 43 normotensive (12 females and 10 males, acetylcholine groups; 11 females and 10 males, atropine groups) and 32 hypertensive (8 females and 8 males, acetylcholine groups; 8 females and 8 males, atropine groups) albino rats. Renal hypertension was induced as described previously [9] by clumping the left renal artery under Nembutal narcosis (40 mg/1000 g). After 7 weeks, blood pressure monitoring (by the catheter method) was performed in hypertensive rats under conditions of cholinergic blockade and stimulation, using a multichannel measuring and computing complex (PowerLab/400 ML401). Cholinergic effects were blocked and stimulated with atropine sulfate (0.2 mg/100 g) and acetylcholine

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chloride (ACC; 0.3 μg/100 g; Pharma), respectively, infused through a venous catheter. Intact (but not sham-operated) rats served as the control, because according to our data, blood corticosterone level normalized in rats as early as 24 h after surgical stress [1].

The data were processed by the Statistica 5.0 software using Wilcoxon, Mann—Whitney, and ANOVA-2, Duncan tests. The differences were considered significant at $p<0.05$.

RESULTS

Atropine blockade of the cholinergic system in normotensive animals was associated with lasting tachycardia without appreciable changes in the mean blood pressure (BP_m). The amplitude of heart rate increase during 40-min observation in females was significantly higher than in males (23-29 and 15-17%, respectively; $p<0.05$) and heart rate normalized more rapidly also in females (Fig. 1, *a*). Basal heart rate values in females and males were 375±5 and 400±5 bpm, respectively ($p<0.05$).

Stimulation of cholinergic effects by ACC infusion caused a sharp transient drop of heart rate and BP_m, more pronounced in females. During the first minute of observation (the period of maximum hemodynamic effects of ACC), the females exhibited more pronounced reduction of pulse rate and BP_m than males (heart rate: 61 and 27%, $p<0.05$; BP_m: 74 and 40%, $p<0.05$; Fig. 2, *a*, Fig. 3, *a*). Heart rate recovery against the background of more pronounced bradycardia was longer in females than in males. On the other hand, despite sharply pronounced hypotensive effect in females, normalization of BP_m in them, similarly as in males, was over by minute 5 of observation, which attests to effective work of compensatory mechanisms in males and even more so in females.

Hence, blockade and stimulation of cholinergic effects were associated with changes in cardiovascular activity by the cardiac (atropine) and cardiac and vascular (ACC) components, more pronounced in females. These data attest to a more important role of cholinergic mechanisms in cardiovascular regulation in females, which is in line with the results obtained *in vitro* and in narcotized animals [7].

Similarly as in our previous studies [2], females were more resistant to renal blood flow disorders. The BP_m value 7 weeks after clumping of the renal artery reached 128±3 mm Hg in females and 151±7 mm Hg in males ($p<0.05$), corresponding to 125% ($p<0.05$) and 144% ($p<0.05$) of the basal levels, respectively (102±1 and 105±4 mm Hg; $p>0.05$).

Cardiac and vascular effects of atropine and ACC were changed in hypertension, and in many cases depended on animal gender. Cardiac sensitivity to atropine decreased under conditions of hypertension, the reduction being approximately the same in females and males, as a result of which tachycardia in hypertensive females (similarly as in normal ones) was more pronounced in females than in males. Positive chronotropic effects of atropine during 60-min observation were 19-21% ($p<0.05$) in hypertensive females and 9-10% ($p<0.05$) in hypertensive males (Fig. 1, *b*). Similarly as in normal animals, heart rate more rapidly returned to normal in females.

Infusion of atropine to hypertensive rats (in contrast to normotensive animals) gave rise to a

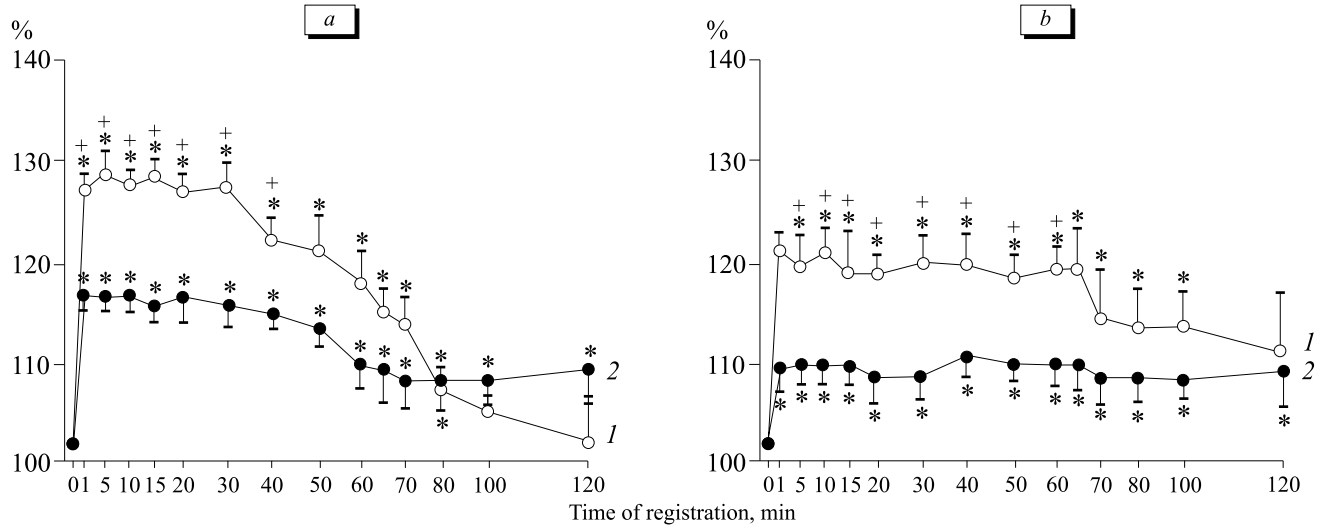

Fig. 1. Changes in heart rate in normotensive (*a*) and hypertensive (*b*) rats injected with atropine. Here and in Fig. 2, 3: *1*) females; *2*) males. $p<0.05$ compared to: *initial level, +males.

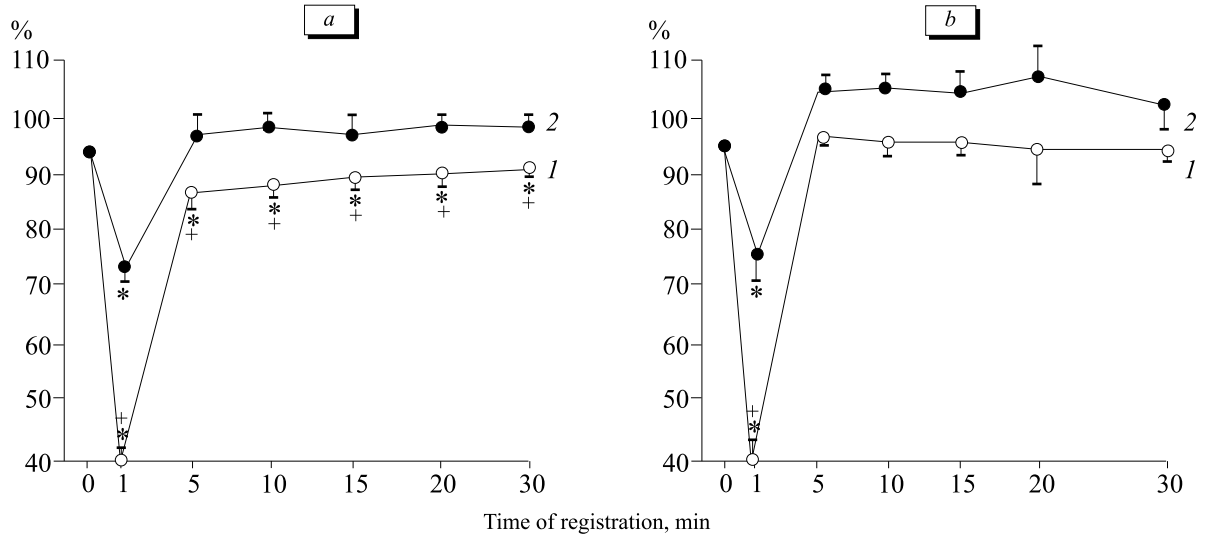

Fig. 2. Changes in heart rate in normotensive (*a*) and hypertensive (*b*) rats in response to ACC.

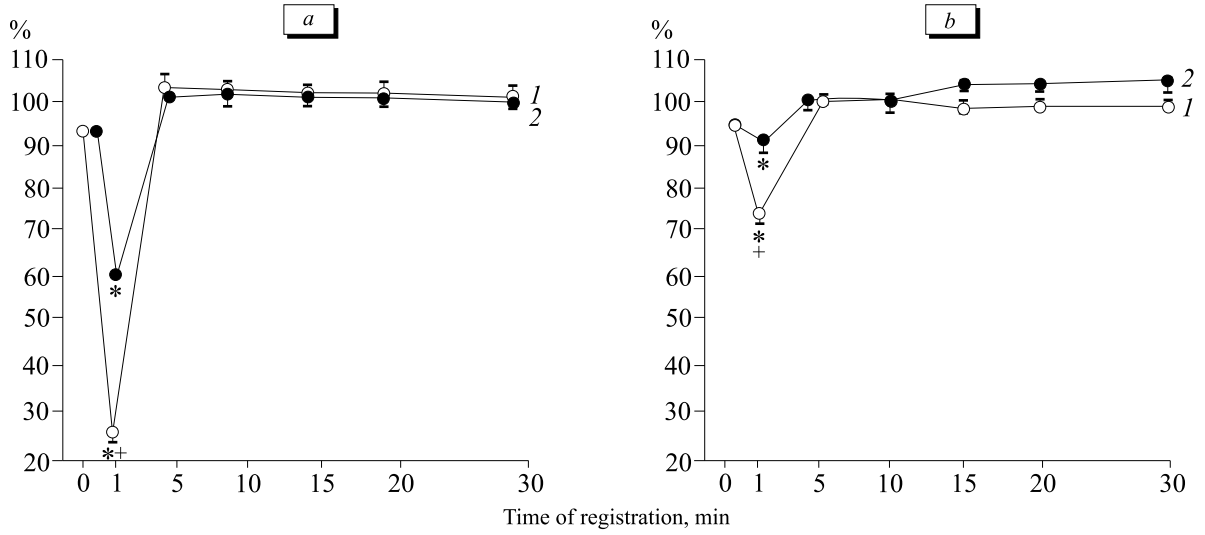

Fig. 3. Changes in BP_m in normotensive (*a*) and hypertensive (*b*) rats in response to ACC.

trend to lasting (during 80 min of observation) hypotension in females and a significant reduction of BP_m in males (by 8-15% over 120 min; $p<0.05$). Obviously, vasoconstrictor effects on blood vessels increased under conditions of cholinergic system blockade. Since adrenal production of epinephrine inducing lasting depressive reactions in hypertensive rats [3] sharply increases in hypertension [4], hypertension, more pronounced in males, is associated with more manifest hypotensive reactions to atropine.

Vascular reactivity to ACC decreased significantly in hypertensive rats, more markedly in males than in females, in the absence of appreciable changes in cardiac sensitivity to ACC (Fig. 2, *a*, *b*). During the first minute of ACC action, BP_m decreased by 27% in females ($p<0.05$) and only by 9% in males ($p<0.05$), that is, the amplitude of hypotensive reactions to ACC was 2.7 times lower in females and 4.4 times in males in hypertensive animals *vs.* normotensive ones (Fig. 3, *a*, *b*).

On the whole, our data indicate reduced cardiovascular sensitivity to cholinergic effects in experimental renal hypertension, which was also observed in rats with hereditary hypertension [6]. This can be explained by increased sympathoadrenal activity in hypertension [4,6,11] and impaired synthesis of NO in health augmenting the cholinergic effects [10]. More benign form of hypertension in females was associated with significant reduction of the hypotensive effects of ACC. The sensitivity of CVS to cholinergic effects is higher in females than

in males in health and hypertension, which is in line with the results of *in vitro* experiments [13]. These differences can be due to estrogen effects [7] and to NO, its production being higher in normal and hypertensive females than in males, as was shown previously [2]. Hence, our results suggest that attenuation of cholinergic effects on the CVS plays an important role in the development of hypertension, while more effective cholinergic regulation of CVS in females in comparison with males improves the resistance of females to hypertension and other cardiovascular diseases in health and disease.

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