Role of Sex Hormones in Cardiovascular Resistance to Atropine in Rats at Rest and during Stress

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 141, No. 3, pp. 270-272, March, 2006
Original article submitted March 25, 2005

Castration of males and females reduces the sensitivity of cardiac chronotropic function to atropine and potentiates the vascular component in the reaction to atropine in females (during stress) and males (at rest and during stress). Our results show that estrogens and androgens increase the sensitivity of the cardiovascular system to cholinergic influences at rest and during stress.

Key Words: *cardiovascular system; sex hormones; stress; atropine*

Higher resistance to pathologies of the cardiovascular system (CVS) in women are related to more favorable cardiohemodynamics under stress conditions [3,12], which can be explained by the existence of sex-related peculiarities of the nervous and humoral regulation of CVS. In women stress is characterized by more pronounced release of catecholamines [13] and their more potent effect on the heart rhythm [6], but the duration of pressor responses in females is shorter than in males [6,13], which attests to more effective control over activity of the sympathoadrenal system in female organism [7]. Activity of the sympathoadrenal system decreases under the influence of estrogens. These hormones activate the parasympathetic nervous system and reduce the sympathetic influences on CVS [11]. Cardioprotective activity of estrogens [2] is associated with modulation of autonomic regulation and their peripheral effects on the heart and vessels [2,4].

The data on the effect of androgens on CVS and mechanisms of its regulation are scanty and contradictory. Testosterone promotes the development of hypertension [8,10]. On the other hand, it improves coronary blood flow during coronary artery diseases. This hormone produces the positive effect on mechanical function of the heart, which is related to activation of expression of α-myosin heavy chains [2,9].

Here we studied the effect of castration in females and males on sensitivity of CVS to cholinergic blockade at rest and during stress.

MATERIALS AND METHODS

Experiments were performed on intact (10 females and 10 males) and castrated (10 females and 10 males) Sprague-Dawley rats. Castration was performed as described elsewhere [2]. One day after laparotomy the concentration of corticosterone in the adrenal glands and plasma did not differ from normal [1]; this allowed using intact rats as controls (without sham-operation). The animals were narcotized with calipsol (60-80 mg/kg intraperitoneally) 3 weeks after castration. Polyethylene catheters were implanted into the abdominal aorta to record hemodynamic parameters. Cholinergic antagonist atropine sulfate (0.2 mg per 100 g) was administered via polyethylene catheters inserted into the femoral vein. Blood pressure was recorded continuously using a PowerLab/400 ML401 computer-aided multichannel measuring-calculating complex and Chart 4 software (ADInstruments Ltd.). Over the next 2 days the experimental animals received atro-

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pine and were subjected to 60-min immobilization stress (IS). The data were processed using Statistica 5.0 software. The influence of individual factors on hemodynamic parameters was determined by analysis of variance (ANOVA). Multiple comparison procedures involved Duncan rank test. The differences were significant at $p<0.05$.

RESULTS

Cholinergic blockade in intact females and males was accompanied by a significant increase in the heart rate (HR), which remained high until the end of the study (120 min after atropine administration). Basal HR in females was higher than in males. However, no interstrain differences were revealed in the degree of tachycardia (40% increase, $p<0.05$). From the 5th minute after treatment until the end of study, the absolute value of HR in intact males was lower than in females. HR in males more rapidly returned to normal than in females.

Mean blood pressure (BP_M) in females was slightly elevated over 40 min after atropine administration (5%, $p<0.05$). Atropine had little effect on BP_M in males.

At rest the cholinergic antagonist caused tachycardia and mild hypertensive response in females, but not in males. These findings attest to higher sensitivity of female CVS to parasympathetic blockade, which is consistent with the results of our previous experiments [6] and published data [5].

Under combined influence of IS and atropine, HR in females increased less significantly than in males (37 and 48%, respectively, $p<0.05$). In contrast to intact females, stressed females demonstrated less pronounced tachycardia in response to atropine and more rapid recovery of HR compared to males. The severity of stress-induced hypertension in atropine-treated females was lower than in males (113-110 and 122-119%, respectively, $p<0.05$). It should be emphasized that the hypertensive response in males was longer than in females.

Thus, the cholinergic influences on CVS depend on sex and state of animals. Judging from HR and BP_M responses at rest, females are more resistant to cholinergic blockade than males. However, males are more resistant to stress than females.

Castration of females increased basal HR and BP_M by 14.5 ($p<0.05$) and 7% ($p<0.05$), respectively. In males, castration increased HR by 13% ($p<0.05$), but had no effect on basal BP_M.

The chronotropic effect of atropine in castrated females was 2-fold lower than in intact animals over 120 min postinjection (Fig. 1). The hypertensive response to atropine did not differ in intact and

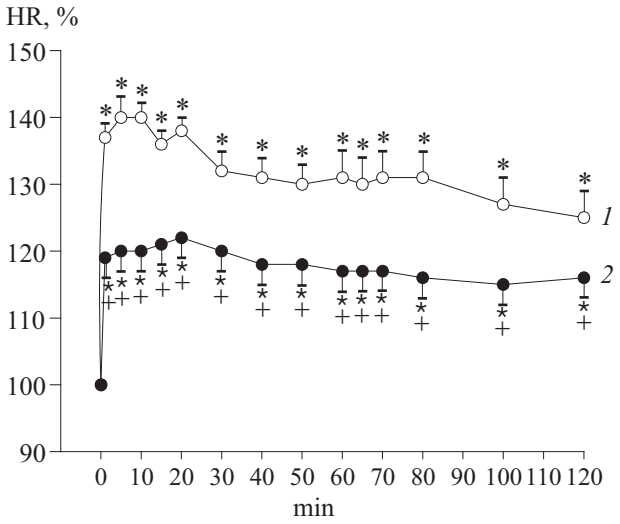

Fig. 1. HR in intact (*1*) and castrated female rats (*2*) after atropine administration. Here and in Fig. 2: $p<0.05$: *compared to basal level; +compared to intact animals.

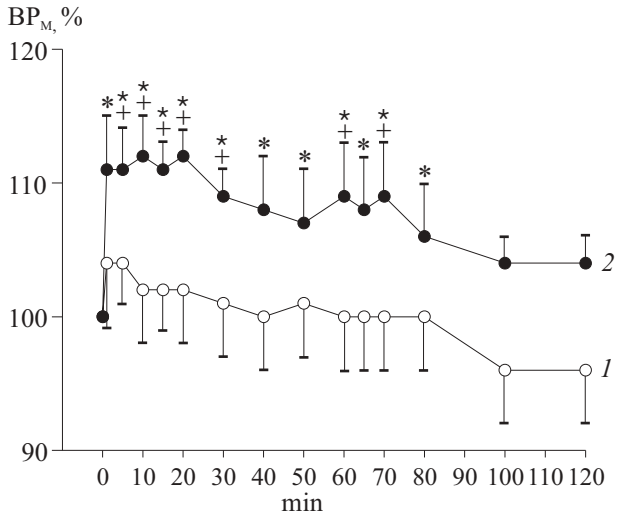

Fig. 2. BP_M in intact (*1*) and castrated male rats (*2*) after administration of atropine.

castrated females. The absolute value of HR in castrated males was higher than in intact animals. However, the degree of tachycardia in castrated males over the first minutes after treatment was lower than in intact animals (128 and 137%, respectively, $p<0.05$). In contrast to intact males, administration of atropine was accompanied by severe hypertension in castrated males (Fig. 2).

Castration abolished the chronotropic effect of atropine in stressed males, which reflects the decrease in cholinergic influences on the regulation of the heart rhythm. After IS and atropine injection, the degree of tachycardia in castrated males was lower than in intact animals (35-32 and 48-42%, respectively, $p<0.05$). However, HR in intact and castrated females increased similarly during IS (38%).

Study of BP_M showed that castration is accompanied by an increase in the sensitivity of female and male CVS to atropine. We revealed an increase in the amplitude and duration of hypertensive responses. During treatment the absolute values of HR (females) and BP_M (females and males) in castrated animals were higher than in intact animals.

Our results suggest that in females and males castration has the same effect on CVS sensitivity to cholinergic blockade at rest and during stress. Estrogen deficiency decreases the sensitivity of cardiac chronotropic function to cholinergic blockade at rest, but increases the vascular response of CVS to atropine during stress. Androgen deficiency increases the vascular response to cholinergic blockade at rest and during stress, but decreases the chronotropic effect of atropine during stress.

Experiments with castrated animals showed that estrogens and androgens potentiate the negative chronotropic effect of parasympathetic nerves at rest and during stress, respectively. The vascular response of CVS to cholinergic blockade decreases under the influence of estrogens (stress conditions) and androgens (at rest and during stress). Our findings suggest that female and male sex hormones can limit cardiovascular activity at rest and during stress. During stress the autonomic balance is shifted to a relative predominance of the sympathetic influences on CVS.

We conclude that the modulatory effect of estrogens and androgens on CVS is mainly mediated by autonomic regulation. Hormone deficiency has adverse consequences on the function of CVS in females and males.

This work was partially supported by the BRHE program (grant No. SR-006-X1).

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