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Sex differences in social stress-induced pressor and behavioral responses in normotensive and prehypertensive rats

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Abstract. This study investigated sex differences in chronic social stress-induced pressor and behavioral responses in normotensive and prehypertensive rats. Adult Wistar and borderline hypertensive (BH) rats (offspring of Wistar dams and spontaneously hypertensive sires) of both sexes were exposed to crowding stress (200 cm^2/rat, 5 rats/cage) for 6 weeks. Controls were kept 4 rats/cage (480 cm^2/rat). Blood pressure (BP) and open field activity were determined before experiment and after 1, 3 and 6 weeks of stress. Basal BP of BH rats was higher than in Wistar ($p < 0.001$) in both males and females. Horizontal and vertical activity of BH males and females was elevated *vs.* Wistar ($p < 0.01$) and females in both phenotypes were more active than the respective males ($p < 0.01$). Crowding resulted in delayed between-session habituation and significant elevation of BP only in BH males (143 ± 2 *vs.* 134 ± 3 mmHg in controls after 6-week crowding). No changes of BP were observed in crowded females of both phenotypes regardless of their delayed between-session habituation. Thus chronic social stress produced by crowding seems to represent a significant risk factor for development of stress-related hypertension only in males with genetic predisposition to high blood pressure while females of both phenotypes responded to stress by impaired between-session habituation.

Key words: Borderline hypertension — Open field behavior — Sex differences — Habituation — Crowding

Introduction

Although the modern lifestyle in industrial cities with a high population density is a risk factor in the development of lifestyle diseases involving cardiovascular diseases and mental disorders, the role of stress in the etiology of these disorders is not satisfactorily understood.

Several studies have addressed the effect of stress on the cardiovascular system and behavior. In many cases, experimental animals or humans were exposed to a single stress event or to relatively short-term repeated stress, showing prominent pressor reaction, stress-induced tachycardia, altered vascular responses (Li et al. 1997; Sgoifo et al. 1999; Knuepfer et al. 2001; van den Buuse et al. 2001; Junior and Cordellini 2007; Hayashi et al. 2009), gene expression (Hudecova et al. 2007; Novakova et al. 2007; Tillinger et al. 2008) or receptor signaling (Adameova et al. 2009). However, exposure to chronic social stress, which is more relevant to the human situation, produced ambiguous results. In mice, psychosocial stimuli produced by crowding-induced sustained hypertension (Henry and Stephens-Larson 1984). A social stress paradigm, in which male rats were housed with different females, failed to affect blood pressure (Lemaire and Mormede 1995). On the other hand, Henry et al. (1993) presented evidences that chronic social stress, produced by group housing, caused an increase of blood pressure in Long-Evans rats but not in Wistar-Kyoto (WKY) rats. In humans, crowded residents had greater increases in blood pressure and heart rate and higher levels of urinary catecholamines during performance of a challenging task than non-crowded residents (Fleming et al. 1987). Elevation of blood pressure was observed in prisoners when they were transferred from single occupancy cells to the multiple occupancy dormitories, supporting the crowding theory (D'Atri et al. 1981). Behavioral changes are usually observed

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immediately after stress, but in many cases they persist after discontinuation of the stressful stimuli (Hashiguchi et al. 1997). Behavioral alterations can be manifested in activity level, emotionality and anxiety, as well as in learning and memory processes (Ramos and Mormede 1998; Hata et al. 2001; Keeney et al. 2001; Krskova et al. 2009). In addition to discrepancies mentioned above, sex and family history of hypertension represent other important issues that may interact with environmental factors and participate in development of cardiovascular disorders.

Sex differences were also seen in a variety of behavioral and mental disorders, including the prevalence of affective disorders and anxiety in women (Kornstein et al. 1995; Simonds and Whiffen 2003). Despite of inconsistent information available in literature, animal studies suggest that sex differences exist in fear and anxiety-related behaviors in the open field test, the elevated plus maze, the defensive prod-burying test, acoustic startle reflex, conflict procedures, swim-stress as well as in social behavior (Frye and Walf 2002; Gulinello et al. 2003; Vendruscolo et al. 2004; Shepard et al. 2009).

We have used crowding stress, a model that exposes rats to continuous social interactions and evokes stress reaction with prominent psychosocial components mimicking emotional state alterations (Bugajski 1999). Crowding, similarly to other stressful events, affects physiological processes including responses of the central nervous system and habituation, which represents a waning of the reflex response to repeated presentations of a stimulus (Staddon and Higa 1996). However, the response depends on the intensity and duration of crowding as well as on the amount of crowded subjects in the cage. Although crowding is a relatively weak stressor, chronic exposure may induce behavioral changes (Aureli and de Waal 1997) with sex related differences as well as cardiovascular alterations (Bernatova et al. 2007).

The purpose of this study was to elucidate the sex differences in open field behavior and blood pressure in adult normotensive and borderline hypertensive (BH) rats in response to chronic social stress produced by crowding.

Materials and Methods

Animals

All rats used in the study were born in our certified animal facility. BH rats were F1 offspring of normotensive (Wistar) dams and spontaneously hypertensive sires (Bernatova and Csizmadiova 2006). Rats were housed at 22–24°C on a 12 : 12 h dark/light cycle (07.00–19.00 h lights on) and maintained on a standard pellet diet and tap water *ad libitum*. All experiments were in accordance with the institutional guidelines and they were in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

Blood pressure (mean ± SEM) of Wistar dams used in the study was 106 ± 3 mmHg. Blood pressure of spontaneously hypertensive sires was 179 ± 6 mmHg. After weaning (25th day), rats were kept in groups of 4 rats *per* cage (35/55/20 cm, 480 cm^2/rat), males separately from females, and siblings were preferably kept together until the beginning of the experiment.

Stress model

Two weeks before experimentation, the rats were handled and accustomed to the procedure of blood pressure recording. Adult males and females, 15 weeks old, were randomly divided into the control and stressed groups. Control rats were kept in groups of 4 rats/cage (35/55/20 cm, 480 cm^2/rat). Rats exposed to crowding stress were kept in groups of 5 rats/cage (25/40/15 cm), where their living-space was reduced to 200 cm^2/rat for six weeks (Bernatova and Csizmadiova 2006). In both, control and stressed group, males were kept separately from females and there were preferably no siblings in the same cage. In both cardiovascular phenotypes eight control and ten stressed rats (males and females, respectively) were used. All rats had food and water *ad libitum*.

Blood pressure and biometric parameters

Blood pressure was determined non-invasively by tail-cuff plethysmography before experiment (basal) and after 1, 3 and 6 weeks of experiment. Body mass was recorded before and at the end of experiment. Combined adrenal glands wet weight and left ventricular wet weight were determined and adrenal gland-to-body mass ratio (as an indirect marker of stress exposure) and left ventricle-to-body mass ratio were calculated for each group of rats.

Test of behavior

Open field test was used to determine exploratory behavior in a new environment. Investigation took place before the experiment (basal values) and during experiment after the first, the third and the sixth week of experiment. At the beginning of test, rats were placed in the center of the open field sized 80 × 60 × 40 cm (Pechanova et al. 2006). Test started 5 seconds later and endured 6 minutes. Activity of rats was recorded by web camera (QuickCamPro Logitech with 640 × 480 resolution). Later, horizontal and vertical motor activities, immobility, grooming and defecation rate were evaluated by experienced experimenter. Open field was cleaned with 2% solution of benzyldimethyldodecylammonium bromide (Ajatine®) after each animal. Between-session

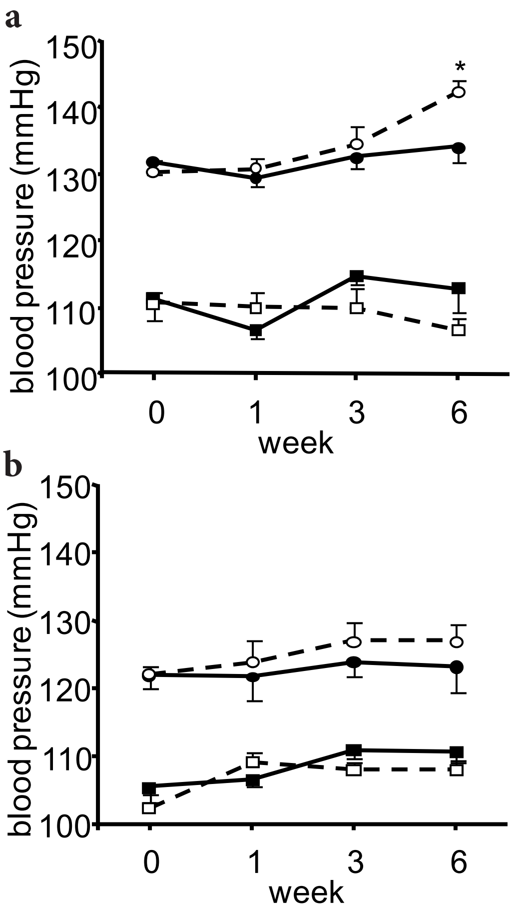

Figure 1. Blood pressure of male (a) and female (b) Wistar and borderline hypertensive rats. Solid line, controls; dashed line, stressed group; square, Wistar rats; circles, borderline hypertensive rats. The results are expressed as means ± S.E.M.; * $p < 0.01$ *vs.* control.

habituation was determined as the reduction of the activity in the open field during repeated open field test compared to the first exposure to this test.

Statistical analysis

The results were analyzed by multi-factorial analysis of variance and the Bonferroni's *post-hoc* test and they were considered to differ significantly if $p < 0.05$. Results were expressed as means ± S.E.M.

Results

Blood pressure and biometric parameters

Basal blood pressure of all BH males (130 ± 2 mmHg, n = 18) was significantly higher than that of all Wistar males (111 ± 3 mmHg, n = 18, $p < 0.0001$). Similarly, basal blood pressure of all BH females (122 ± 2 mmHg, n =18) was significantly higher than that of all Wistar females (103 ± 3 mmHg, n = 18, $p < 0.0001$). Significant differences in the average value of blood pressure in course of experiment were observed between Wistar males and females (111 ± 2 mmHg *vs.* 106 ± 1 mmHg, $p < 0.02$) as well as between BH males and females (133 ± 3 mmHg *vs.* 123 ± 4 mmHg, $p < 0.01$). In rats exposed to stress, the elevation of blood pressure was observed in crowded BH males as compared to the control ($p < 0.01$, Fig. 1a). On the other hand stress failed to affect significantly blood pressure of Wistar males and females as well as of crowded BH females (Figs. 1a,b).

Original and final body mass, adrenal gland-to-body mass ratios and relative left ventricular mass are presented in the Table 1. Significant increase of body mass in course of experiment was observed in all males while no elevation of body mass was found in females. Stress resulted in the increase of adrenal gland-to-body mass ratio only in BH males ($p < 0.04$ *vs.* control), however, stress failed to affect significantly left ventricle-to-body mass ratio.

Horizontal motor activity

In both males and females, horizontal activity of BH rats was significantly increased during all experiment as com-

Table 1. Selected biometrical parameters

	Males				Females			
	Wistar		BHR		Wistar		BHR	
	control	stress	control	stress	control	stress	control	stress
Original BM (g)	290 ± 4	290 ± 11	311 ± 7	306 ± 11	220 ± 5^x	220 ± 4^x	211 ± 6^x	208 ± 12^x
Final BM (g)	350 ± 7$^+$	339 ± 14$^+$	376 ± 13$^+$	363 ± 8$^+$	235 ± 7^x	221 ± 2^x	223 ± 5^x	224 ± 4^x
Adrenal/BM (mg/100 g)	7.8 ± 0.3	7.5 ± 0.4	5.4 ± 0.6	6.8 ± 0.2*	15.3 ± 0.3^x	15.8 ± 0.5^x	13.7 ± 0.4^x	15.8 ± 0.5^x
LV/BM (mg/100 g)	127 ± 8	143 ± 9	160 ± 6$^\#$	155 ± 4	146 ± 5	145 ± 7	152 ± 5	157 ± 7

BHR, borderline hypertensive rats; BM, body mass; LV, left ventricle; The results are expressed as means ± S.E.M. $^+$ $p < 0.002$ *vs.* original body mass, * $p < 0.04$ *vs.* the respective control group, ^{x} $p < 0.01$ *vs.* the respective male group, $^\#$ $p < 0.02$ *vs.* Wistar control group.

pared with Wistar (Table 2); females (control and stressed, respectively) were more active than males (Table 2). After the first week of experiment, horizontal activity decreased significantly by approximately 73% in control Wistar males ($p < 0.05$) and by about 53% ($p < 0.05$) in control BH males. While decrease of horizontal activity of stressed Wistar males was similar to that observed in controls, delayed decrease was observed in stressed BH rats compared to control (Fig. 2a).

In females, a significant decrease in horizontal activity was observed in control Wistar on weeks 1 and 3 and in control BH rats on weeks 3 and 6 compared to basal values (Fig. 2b). However, no significant differences were found in both stressed Wistar and BH females compared to basal values.

Vertical activity

Vertical activity of BH rats was significantly increased during all experiments as compared to Wistar in both males and females; females (control and stressed, respectively) were more active than males (Table 2). After the first week of experiment, vertical activity decreased significantly by approximately 76% in control Wistar males ($p < 0.05$) and by about 66% ($p < 0.05$) in control BH males. In stressed Wistar males, there was similar decrease of vertical activity as it was observed in the control group. A delayed decrease in vertical activity was observed in stressed BH males (on weeks 3 and 6) compared to control BH males (Fig. 3a).

In female control Wistar rats there was a significant decrease of the vertical activity in both week 1 and 3 (by approximately 69%, $p < 0.01$) compared to basal values. In contrast to the control group, there were no significant differences compared to basal values in crowded female Wistar rats (Fig. 3b). There was decrease of the activity in control BH females on weeks 3 (by approximately 62%, $p < 0.01$) and 6 (by approximately 58%, $p < 0.01$) compared to basal value. In stressed BH females the reduction of vertical activity was observed only after 6 weeks of stress by approximately 45% ($p < 0.05$) compared to basal value.

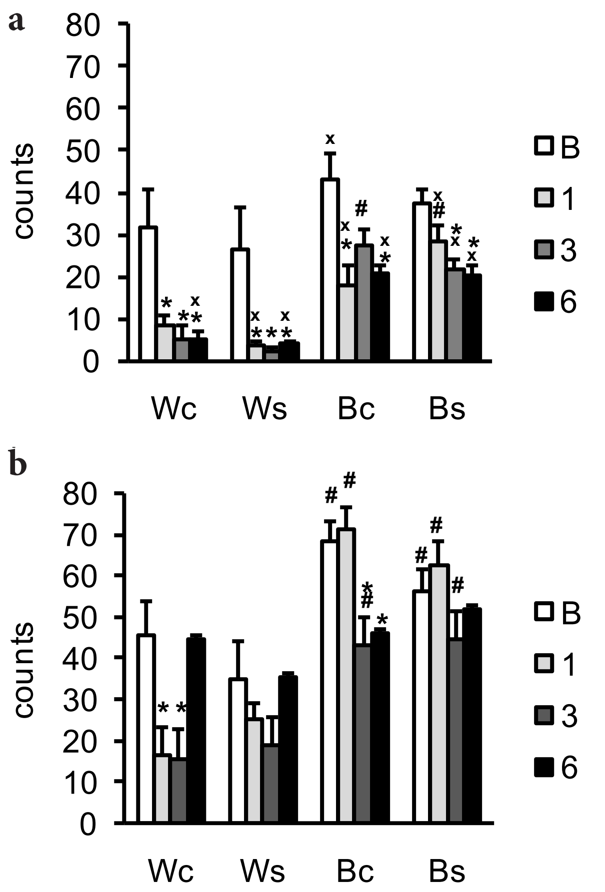

Figure 2. Horizontal motor activity of male (a) and female (b) rats. Wc, Wistar control; Ws, Wistar stressed; Bc, borderline hypertensive controls; Bs, borderline hypertensive stressed rats; B, basal level of the group; 1,3,6 – weeks of the experiment. The results are expressed as means ± S.E.M.; * $p < 0.05$ *vs.* basal level of the group; $^{\#}$ $p < 0.04$ *vs.* Wistar of the same sex in the same experimental conditions; ^{x} $p < 0.03$ *vs.* females of the same phenotype in the same experimental conditions.

Table 2. Stress- and phenotype-dependent differences in horizontal and vertical activity of male and female normotensive Wistar and borderline hypertensive rats (BHR)

		Horizontal activity (counts)	Vertical activity (counts)
males	Wistar	10.8 ± 1.7	4.3 ± 0.7
	BHR	26.4 ± 1.4 $^{\#}$	13.6 ± 1.1 $^{\#}$
females	Wistar	29.6 ± 2.0 ^{x}	11.5 ± 0.9 ^{x}
	BHR	55.3 ± 2.2 $^{\# x}$	29.6 ± 1.7 $^{\# x}$
males	control	19.9 ± 1.9	8.6 ± 1.1
	Stress	18.7 ± 1.8	10.1 ± 1.5
females	control	44.7 ± 2.9 ^{x}	21.4 ± 1.9 ^{x}
	Stress	41.2 ± 2.3 ^{x}	19.8 ± 1.5 ^{x}

Results represent average values of the respective activity during whole experiment and they are expresses are mean ± S.E.M. $^{\#}$ $p < 0.05$ *vs.* Wistar of the same sex; ^{x} $p < 0.05$ *vs.* the respective male group.

Immobility, grooming and defecation

Similar immobility was observed in Wistar and BH males in both the control and stressed group (Fig. 4a). Females expressed less immobility than males in all groups investigated except of control Wistar females compared to control Wistar males.

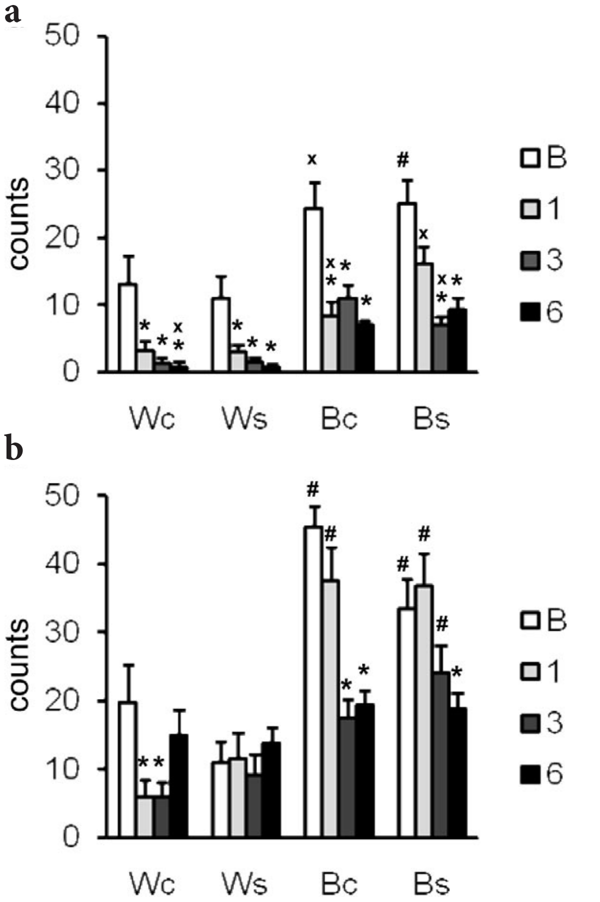

Figure 3. Vertical motor activity of male (a) and female (b) rats. The results are expressed as means ± S.E.M.; * $p < 0.05$ *vs.* basal level of the group; # $p < 0.04$ *vs.* Wistar of the same sex in the same experimental conditions; x $p < 0.03$ *vs.* females of the same phenotype in the same experimental conditions. The abbreviations as in Fig. 2.

No differences in grooming were observed between males and females as well as between stressed and control rats (Fig. 4b).

Significantly lower defecation was observed in BH rats of both sexes as compared to the respective Wistar group (Fig. 4c). Interestingly, no defecation was observed in BH females in both control and stress conditions.

Discussion

This study investigated the sex differences in open field behavior and blood pressure in normotensive and Wistar-mothered borderline hypertensive rats in response to chronic social stress produced by crowding. The key finding of the study was that chronically stressed BH males, in contrast to controls, displayed delayed reduction of the intensity

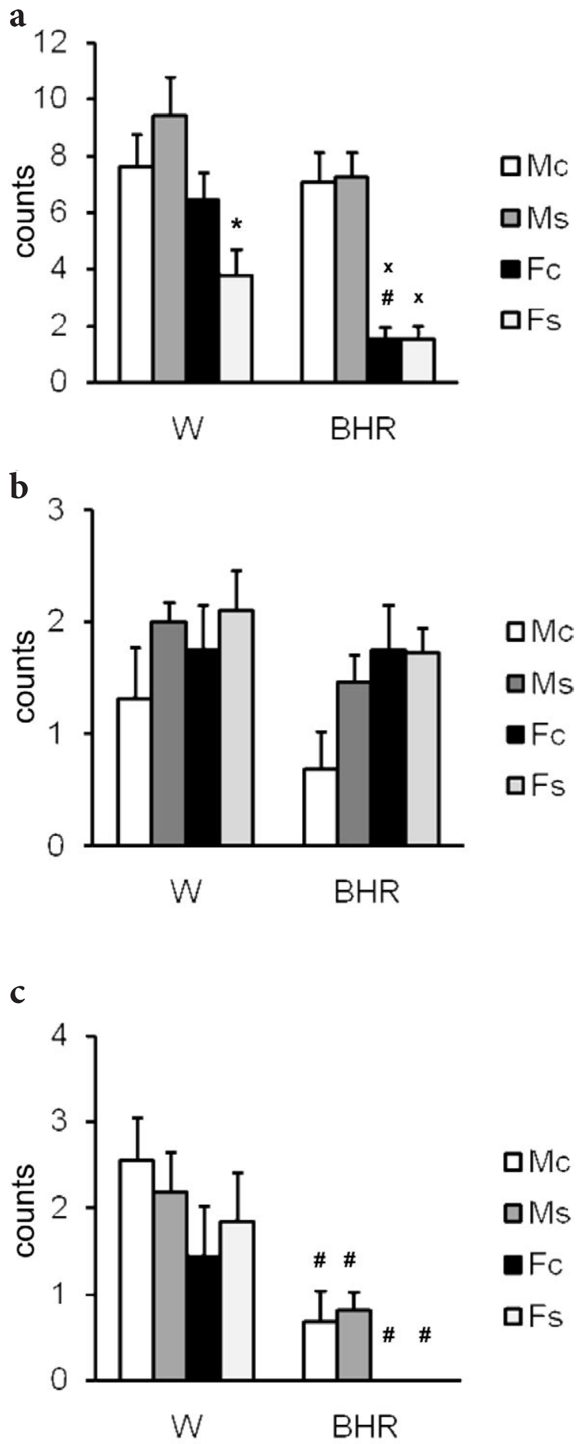

Figure 4. Immobility (a), grooming (b) and defecation (c) of males and females. W, Wistar; BHR, borderline hypertensive rats; Mc, control males; Ms, stressed males; Fc, control females; Fs, stressed females. The results are average values during whole experiment (i.e. basal, 1, 3 and 6 weeks) and they are expressed as means ± S.E.M.; * $p < 0.03$ *vs.* control level of the same sex and phenotype; # $p < 0.002$ *vs.* Wistar of the same sex and group; x $p < 0.0001$ *vs.* males of the same phenotype and group.

of exploration during repeated exposure to the open field indicating slowed-down or delayed habituation in the new environment. This phenomenon was associated with increase of their blood pressure and elevation of relative adrenal gland mass. These alterations were not observed in normotensive males or in both normotensive and BH females.

We also found that rats with borderline hypertension were more active in open field test (in both horizontal and vertical activity) than normotensive rats, and females of both phenotypes were more active than the respective males. The highest levels of motor activity were observed in BH females and it corresponded with their lowest immobility. Moreover, emotional reactivity expressed as a defection rate was reduced in borderline hypertensive rats, with more pronounced manifestation in females (zero defection rate). This suggests that emotional reactivity of rats to stressful stimuli in new environment, determined by their level of explorative behavior and emotional reactivity, was related to sex as well as to level of blood pressure.

Sexual dimorphism of blood pressure has been observed in both normotensive and hypertensive subjects (Antonicelli et al. 2000) as well as in rats (Reckelhoff et al. 1998). Although the mechanisms responsible for sex differences in blood pressure control are not clear, there is evidence on the involvement of sex hormones in cardiovascular regulation. For example, estrogens were shown to inhibit renin release and angiotensin converting enzyme, while testosterone was shown to stimulate the renin-angiotensin system (Reckelhoff 2001). Additionally, pharmacogenetic analysis showed that, in males, blood pressure was controlled by two loci on chromosomes 1 and 5 through the sympathetic nervous system. On the other hand, baseline blood pressure in females was controlled by two loci on chromosomes 3 and 7 and the effect of these loci was not mediated by the renin-angiotensin system, sympathetic nervous system or L-Arg/NO system (Ueno et al. 2003). Similar sex-related differences in pressor control might be responsible for an elevation of blood pressure in stress-exposed BH males due to greater impact of the sympathetic nervous system to pressor control in males compared to females. Additionally, data suggest an involvement of other (epi)genetic factors because no alterations in blood pressure were observed in normotensive males in this particular model of stress.

Regarding behavioral effects literary data suggest that elevated blood pressure itself does not produce hyperactivity because unilateral renal clips in WKY or Sprague-Dawley rats did not alter locomotor activity (Whitehorn et al. 1983). Additionally, no correlation between the activity score and the level of the blood pressure was seen in F1 and F2 hybrid population of spontaneously hypertensive rats (SHR) and WKY suggesting that different genetic factors were involved in the transmission of hypertensive trait and hyperactivity trait (Hendley et al. 1983). On the other hand, increased open field activity was observed in both SHR and rats with developed L-NAME-induced hypertension (Pechanova et al. 2006).

In BH rats, obtained by mating of spontaneously hypertensive females and normotensive males (Fuchs et al. 1998), hyperactivity can be induced also by hyperactive behavior of their hypertensive mother, especially during the nursing period. Van den Buuse and de Jong (1988) showed that already at a young age, when blood pressure differences between WKY rats and SHR were small, marked behavioral changes were present in SHR. Thus the altered behavior could play a role in the development of hypertension in SHR (van den Buuse and de Jong 1988). However, there is only a little information on behavior of BH rats. Cierpial and McCarty (1987) found differences in locomotor activity of WKY, BH rats and SHR (17–30 days old) in an exploratory maze; activity levels of BH rats were between the values of WKY (the lowest activity) and SHR (the highest activity). On the other hand, Sagvolden et al. (1992) demonstrated that the offspring of spontaneously hypertensive dams and WKY sires were as hyperactive as their hypertensive mothers. In this study we used Wistar-mothered BH rats because we were interesting in the effect of genetic predisposition and chronic social stress on blood pressure and behavior in adulthood. This approach eliminated possible "unfavorable" effect of altered prenatal environment (Mastorci et al. 2009) on cardiovascular regulation and stress responsiveness of offspring in adulthood (Woodworth et al.1990; Porter et al. 2004). Although blood pressure of Wistar-mothered BH rats was lower than that of SHR-mothered BH rats (Bernatova et al. 2007), both sexes of BH rats were hyperactive compared to normotensive rats in this study.

Exploratory behavior and its habituation in rats is also known to be sexually dimorphic. Males have a lower intensity of exploratory behavior and more rapid habituation than females (Pare and Redei 1993; McCormick et al. 2005). Pare and Redei (1993) showed that normotensive WKY females were more active in the open field test compared to males. The same authors demonstrated that one stress session resulted in significant immobility in the open field test for males, whereas 5 sessions were required to produce similar immobility in females WKY (Pare and Redei 1993). Higher activity levels in the open field test were also found in females of Long-Evens rats (Brotto et al. 2000). Our study utilized older rats than those used in former studies and our findings suggest that sex differences in activity levels remain present also in older rats. We suggest that the higher intensity of exploration and its slower habituation in females could have played an important role from the evolutionary point of view. The female, as a potential mother, should get acquainted more profoundly than the male with the unknown, possible dangerous environment, so as to secure a quiet course of pregnancy, delivery and care of pups. This could be the reason why females spend more time with exploration and why the decrease of activity (habituation) is not so rapid compared to males, and stays relatively constant during several days (Dubovicky et al. 1999). With regard to neuroendocrine activation, greater increases in plasma levels of adrenocorticotropin (ACTH) and corticosterone were found in females subjected to restraint stress, than it was found in males (Aloisi et al. 1994) suggesting accentuated stress response in females. We found significantly higher adrenal gland-to-body mass ratio in females of both phenotypes than in corresponding males. However, chronic crowding induced the elevation of adrenal gland-to-body mass ratio (indirect marker of stress response) only in crowded BH males.

In this study, chronic crowding stress of adult rats failed to affect the overall horizontal and vertical activity regardless of sex and predisposition to hypertension. Crowding also failed to affect habituation of open field activities in normotensive males, similarly as it was observed in our previous study using chronic restraint (Dubovicky and Jezova 2004). However, differences were observed in habituation of behavioral response of males with borderline hypertension; their between-session habituation was delayed or slowed-down in comparison with non-crowded BH males. Since habituation is a fundamental learning in which organism learns not respond to redundant non-significant stimuli (Groves and Thompson 1970), in our case new environment represented by open field, disability or reduction of habituation may represent an indication of other pathophysiological processes including development of hypertension.

In this study we found elevation of blood pressure, delayed habituation and elevation of relative adrenal gland mass only in crowded BH males suggesting that behavioral disturbance interacting with genetic predisposition to high blood pressure may be a factor leading to gradual development of stress-induced hypertension in males. However any changes in blood pressure and relative adrenal gland mass were observed in crowded females although marked exploratory activity was seen in both phenotypes. This, in contrast to males, suggests the dissociation of behavioral and cardiovascular responses as well as reduced influence of genetic factors on development of stress-induced hypertension in females exposed to chronic crowding.

On balance then, the results indicate that behavior of rats in the open field was related to the interaction of sex and cardiovascular phenotype. Females of both phenotypes were more active than males and more susceptible to behavioral changes during crowding. However, reduced habituation of crowded females was not associated with elevation of blood pressure. On the other hand, crowding stress resulted in delayed habituation associated with the increase of blood pressure and relative adrenal gland mass in BH males. Thus chronic social stress produced by crowding seems to represent more significant risk factor for development of stress-related hypertension in males (especially with genetic predisposition to high blood pressure) while females of both phenotypes responded to stress by impaired between-session habituation.

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References

Adameova A., Abdellatif Y., Dhalla N. S. (2009): Role of the excessive amounts of circulating catecholamines and glucocorticoids in stress-induced heart disease. Can. J. Physiol. Pharmacol. **87,** 493–514; doi:10.1139/Y09-042

Aloisi A. M., Steenbergen H. L., van de Poll N. E., Farabollini, F. (1994): Sex-dependent effects of restraint on nociception and pituitary-adrenal hormones in the rat. Physiol. Behav. **55,** 789–793; doi:10.1016/0031-9384(94)90061-2

Antonicelli R., Gesuita R., Paciaroni E. (2000): Sexual dimorphism in arterial hypertension: an age-related phenomenon. Arch. Gerontol. Geriatr. **29,** 283–289; doi:10.1016/S0167-4943(99)00041-2

Aureli F., de Waal F. B. (1997): Inhibition of social behavior in chimpanzees under high density conditions. Am. J. Primatol. **41,** 213–228; doi:10.1002/(SICI)1098-2345(1997)41:3<213::AID-AJP4>3.0.CO;2-#

Bernatova I., Csizmadiova Z. (2006): Effect of chronic social stress on nitric oxide synthesis and vascular function in rats with family history of hypertension. Life Sci. **78,** 1726–1732; doi:10.1016/j.lfs.2005.08.005

Bernatova I., Csizmadiova Z., Kopincova J., Puzserova A. (2007): Vascular function and nitric oxide production in chronic social-stress-exposed rats with various family history of hypertension. J. Physiol. Pharmacol. **58,** 487–501

Brotto L. A., Barr A. M., Gorzalka B. B. (2000): Sex differences in forced-swim and open-field test behaviours after chronic administration of melatonin. Eur. J. Pharmacol. **402,** 87–93; doi:10.1016/S0014-2999(00)00491-X

Bugajski J. (1999): Social stress adapts signaling pathways involved in stimulation of the hypothalamic-pituitary-adrenal axis. J. Physiol. Pharmacol. **50,** 367–379

Cierpial M. A., McCarty R. (1987): Preweanling behavioral development in spontaneously hypertensive, borderline hypertensive, and Wistar-Kyoto normotensive rats. Dev. Psychobiol. **20,** 57–69; doi:10.1002/dev.420200109

D'Atri D. A., Fitzgerald E. F., Kasl S. V., Ostfeld A. M. (1981): Crowding in prison: the relationship between changes in housing mode and blood pressure. Psychosom. Med. **43,** 95–105

Dubovicky M., Jezova D. (2004): Effect of chronic emotional stress on habituation processes in open field in adult rats. Ann. N. Y. Acad. Sci. **1018,** 199–206; doi:10.1196/annals.1296.023

Dubovicky M., Skultetyova I., Jezova D. (1999): Neonatal stress alters habituation of exploratory behavior in adult male but not female rats. Pharmacol. Biochem. Behav. **64,** 681–686; doi:10.1016/S0091-3057(99)00166-5

Fleming I., Baum A., Davidson L. M., Rectanus E., McArdle S. (1987): Chronic stress as a factor in physiologic reactivity to challenge. Health Psychol. **6,** 221–237; doi:10.1037/0278-6133.6.3.221

Frye C. A., Walf A. A. (2002): Changes in progesterone metabolites in the hippocampus can modulate open field and forced swim test behavior of proestrous rats. Horm. Behav. **41,** 306–315; doi:10.1006/hbeh.2002.1763

Fuchs L. C., Hoque A. M., Clarke N. L. (1998): Vascular and hemodynamic effects of behavioral stress in borderline hypertensive and Wistar-Kyoto rats. Am. J. Physiol. **274,** R375–382

Groves P. M., Thompson R. F. (1970): Habituation: a dual-process theory. Psychol. Rev. **77,** 419–450; doi:10.1037/h0029810

Gulinello M., Orman R., Smith S. S. (2003): Sex differences in anxiety, sensorimotor gating and expression of the alpha4 subunit of the GABAA receptor in the amygdala after progesterone withdrawal. Eur. J. Neurosci. **17,** 641–648; doi:10.1046/j.1460-9568.2003.02479.x

Hashiguchi H., Ye S. H., Morris M., Alexander N. (1997): Single and repeated environmental stress: effect on plasma oxytocin, corticosterone, catecholamines, and behavior. Physiol. Behav. **61,** 731–736; doi:10.1016/S0031-9384(96)00527-6

Hata T., Nishikawa H., Itoh E., Funakami Y. (2001): Anxiety-like behavior in elevated plus-maze tests in repeatedly cold-stressed mice. Jpn. J. Pharmacol. **85,** 189–196; doi:10.1254/jjp.85.189

Hayashi N., Someya N., Maruyama T., Hirooka Y., Endo M. Y., Fukuba Y. (2009): Vascular responses to fear-induced stress in humans. Physiol. Behav. **98,** 441–446; doi:10.1016/j.physbeh.2009.07.008

Hendley E. D., Atwater D. G., Myers M. M., Whitehorn D. (1983): Dissociation of genetic hyperactivity and hypertension in SHR. Hypertension **5,** 211–217

Henry J. P., Liu Y. Y., Nadra W. E., Qian C. G., Mormede P., Lemaire V., Ely D., Hendley E. D. (1993): Psychosocial stress can induce chronic hypertension in normotensive strains of rats. Hypertension **21,** 714–723

Henry J. P., Stephens-Larson P. (1984): Reduction of chronic psychosocial hypertension in mice by decaffeinated tea. Hypertension **6,** 437–444

Hudecova S., Kubovcakova L., Kvetnansky R., Kopacek J., Pastorekova S., Novakova M., Knezl V., Tarabova B., Lacinova L., Sulova Z., Breier A., Jurkovicova D., Krizanova O. (2007): Modulation of expression of Na^+/Ca^{2+} exchanger in heart of rat and mouse under stress. Acta Physiol. (Oxf) **190,** 127–136; doi:10.1111/j.1748-1716.2007.01673.x

Junior U. L., Cordellini S. (2007): Differential vascular adaptive response to stress exposure in male and female rats: role of gonadal hormones and endothelial cells. Stress **10,** 27–36; doi:10.1080/10253890601135426

Keeney A. J., Hogg S., Marsden C. A. (2001): Alterations in core body temperature, locomotor activity, and corticosterone following acute and repeated social defeat of male NMRI mice. Physiol. Behav. **74,** 177–184; doi:10.1016/S0031-9384(01)00541-8

Knuepfer M. M., Purcell R. M., Gan Q., Le K. M. (2001): Hemodynamic response patterns to acute behavioral stressors resemble those to cocaine. Am. J. Physiol. Regul. Integr. Comp. Physiol. **281,** R1778–1786

Kornstein S. G., Schatzberg A. F., Yonkers K. A., Thase M. E., Keitner G. I., Ryan C. E., Schlager D. (1995): Gender differences in presentation of chronic major depression. Psychopharmacol. Bull. **31,** 711–718

Krskova L., Vrabcova M., Talarovicova A., Zeman M. (2009): Influence of up-regulated renin-angiotensin system on the exploration, anxiety-related behavior and object recognition. Acta Biol. Hung. **60,** 369–383; doi:10.1556/ABiol.60.2009.4.4

Lemaire V., Mormede P. (1995): Telemetered recording of blood pressure and heart rate in different strains of rats during chronic social stress. Physiol. Behav. **58,** 1181–1188; doi:10.1016/0031-9384(95)02064-0

Li S. G., Lawler J. E., Randall D. C., Brown D. R. (1997): Sympathetic nervous activity and arterial pressure responses during rest and acute behavioral stress in SHR versus WKY rats. J. Auton. Nerv. Syst. **62,** 147–154; doi:10.1016/S0165-1838(96)00119-1

Mastorci F., Vicentini M., Viltart O., Manghi M., Graiani G., Quaini F., Meerlo P., Nalivaiko E., Maccari S., Sgoifo A. (2009): Long-term effects of prenatal stress: changes in adult cardiovascular regulation and sensitivity to stress. Neurosci. Biobehav. Rev. **33,** 191–203; doi:10.1016/j.neubiorev.2008.08.001

McCormick C. M., Robarts D., Kopeikina K., Kelsey J. E. (2005): Long-lasting, sex- and age-specific effects of social stressors on corticosterone responses to restraint and on locomotor responses to psychostimulants in rats. Horm. Behav. **48,** 64–74; doi:10.1016/j.yhbeh.2005.01.008

Novakova M., Bruderova V., Sulova Z., Kopacek J., Lacinova L., Kvetnansky R., Vasku A., Kaplan P., Krizanova O., Jurkovicova D. (2007): Modulation of expression of the sigma receptors in the heart of rat and mouse in normal and pathological conditions. Gen. Physiol. Biophys. **26,** 110–117

Pare W. P., Redei E. (1993): Sex differences and stress response of WKY rats. Physiol. Behav. **54,** 1179–1185; doi:10.1016/0031-9384(93)90345-G

Pechanova O., Jendekova L., Kojsova S., Jagla F. (2006): Possible role of nitric oxide in the locomotor activity of hypertensive rats. Behav. Brain. Res. **174,** 160–166; doi:10.1016/j.bbr.2006.07.021

Porter J. P., Phillips A., Rich J., Wright D. (2004). Effect of chronic stress on the cardiac baroreflex in the post-weanling rat. Life Sci. **75,** 1595–1607; doi:10.1016/j.lfs.2004.03.018

Ramos A., Mormede P. (1998): Stress and emotionality: a multidimensional and genetic approach. Neurosci. Biobehav. Rev. **22,** 33–57; doi:10.1016/S0149-7634(97)00001-8

Reckelhoff J. F. (2001): Gender differences in the regulation of blood pressure. Hypertension **37,** 1199–1208

Reckelhoff J. F., Zhang H., Granger J. P. (1998): Testosterone exacerbates hypertension and reduces pressure-natriuresis in male spontaneously hypertensive rats. Hypertension **31,** 435–439

Sagvolden T., Hendley E. D., Knardahl S. (1992): Behavior of hypertensive and hyperactive rat strains: hyperactivity is not unitarily determined. Physiol. Behav. **52,** 49–57; doi:10.1016/0031-9384(92)90432-2

Sgoifo A., Koolhaas J., De Boer S. F., Musso E., Stilli D., Buwalda B., Meerlo P. (1999): Social stress, autonomic neural activation, and cardiac activity in rats. Neurosci. Biobehav. Rev. **23,** 915–923; doi:10.1016/S0149-7634(99)00025-1

Shepard K. N., Michopoulos V., Toufexis D. J., Wilson M. E. (2009): Genetic, epigenetic and environmental impact on sex differences in social behavior. Physiol. Behav. **97,** 157–170; doi:10.1016/j.physbeh.2009.02.016

Simonds V. M., Whiffen V. E. (2003): Are gender differences in depression explained by gender differences in co-morbid anxiety? J. Affect. Disord. **77,** 197–202; doi:10.1016/S0165-0327(02)00113-1

Staddon J. E. R., Higa J. J. (1996): Multiple time scales in simple habituation. Psychopharmacol. Rev. **103,** 720–733

Tillinger A., Myslivecek J., Novakova M., Krizanova O., Kvetnansky R. (2008): Gene expression of adrenoceptors in the hearts of cold-acclimated rats exposed to a novel stressor. Ann. N. Y. Acad. Sci. **1148,** 393–399; doi:10.1196/annals.1410.024

Ueno T., Tremblay J., Kunes J., Zicha J., Dobesová Z., Pausova Z., Deng A. Y., Sun Y., Jacob H. J., Hamet P. (2003): Gender-specific genetic determinants of blood pressure and organ weight: pharmacogenetic approach. Physiol. Res. **52,** 689–700

van den Buuse M., Lambert G., Fluttert M., Eikelis N. (2001): Cardiovascular and behavioural responses to psychological stress in spontaneously hypertensive rats: effect of treatment with DSP-4. Behav. Brain Res. **119,** 131–142; doi:10.1016/S0166-4328(00)00349-1

van den Buuse M., de Jong, W. (1988): Open-field behaviour and blood pressure in spontaneously hypertensive rats. Clin. Exp. Hypertens. A10, 667–684; doi:10.3109/10641968809033917

Vendruscolo L. F., Pamplona F. A., Takahashi R. N. (2004): Strain and sex differences in the expression of nociceptive behavior and stress–induced analgesia in rats. Brain Res. **1030,** 277–283; doi:10.1016/j.brainres.2004.10.016

Whitehorn D., Atwater D. G., Low W. C., Gellis J. E., Hendley E. D. (1983): Independence of blood pressure and locomotor hyperactivity in normotensive and genetically hypertensive rat. Behav. Neural. Biol. **37,** 357–361; doi:10.1016/S0163-1047(83)91501-7

Woodworth C. H., Knardahl S., Sanders B. J., Kirby R. F., Johnson A. K. (1990): Dam strain affects cardiovascular reactivity to acute stress in BHR. Physiol. Behav. **47,** 139–144; doi:10.1016/0031-9384(90)90052-6

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