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Neonatal Stress Alters Habituation of Exploratory Behavior in Adult Male but not Female Rats

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DUBOVICKÝ, M., I. ŠKULTÉTYOVÁ AND D. JEŽOVÁ. *Neonatal stress alters habituation of exploratory behavior in adult male but not female rats.* PHARMACOL BIOCHEM BEHAV **64**(4) 681–686, 1999.—The effect of monosodium-L-glutamate (MSG) administration in the neonatal period on habituation of exploratory behavior related to gender differences was investigated. Rats of both sexes were intraperitoneally treated with MSG (4 mg/g) or hypertonic saline (10% NaCl) on postnatal days 2, 4, 6, 8, and 10. On postnatal day 65, the animals were tested in an open-field test during 4 consecutive days, once daily in 6-min sessions. The rapidity of habituation of exploratory behavior during repeated exposure to the open field (interrupted habituation) and over individual sessions (uninterrupted habituation) was evaluated by using the method of linear regression. Compared to intact controls, there were no significant differences found in interrupted habituation, neither in males nor in females. Uninterrupted habituation in neonatally treated males was slowed down in the first 2 days of testing. No differences in adult behavior between treated groups (MSG and hypertonic saline) were observed, i.e., there were no late effects specific for neonatal MSG administration. In females, uninterrupted habituation was not affected. Males proved to be more sensitive to neonatal stress associated with injections of MSG or hypertonic saline than females, and showed feminine-like habituation in the new environment. © 1999 Elsevier Science Inc.

Rat Monosodium-L-glutamate Open field Exploratory behavior Habituation Gender differences Neonatal stress Handling

HABITUATION is a waning of the reflex response to repeated presentations of a stimulus (33). It has been widely observed with many different stimuli and responses in various species, ranging from protists to humans (4,6,23,30). Habituation of exploratory behavior in a new environment is manifested by a gradual decrease in the intensity of locomotor (horizontal movement of the animal) as well as vertical activity (rearing). This can be measured by means of repeated exposure of animals to a new environment (interrupted habituation) or during each individual testing (uninterrupted habituation) (22). Evaluation of habituation rate of exploratory behavior has been frequently used in psychopharmacology as well as in developmental toxicology (13,14).

Exploratory behavior in rodents is found to be sexually dimorphic. Females show higher locomotor activity, a lower level of emotionality, and slower habituation than their male counterparts (9,12,28). Strain differences are also described (5,34). Habituation processes can be altered by means of various pharmacological challenges (10,11), and in many cases, these changes are shown to be sex specific (9,14,29).

During neonatal development in rats, treatment with monosodium-L-glutamate (MSG) was found to induce neurotoxic lesions in the hypothalamus and other brain regions, resulting in consequent alterations in hormone release, metabolism, and reproductive function (17,24,36). Some authors observed sex-specific impairment of hypothalammic monoamine release (31), growth hormone secretion (38), dopamine level in the median eminence (27), and of blood pressure (8). Gender-related differences were found also in behavioral responses. Neonatal male rats showed higher susceptibility to glutamate-induced dysfunction of sexual and ingestive behavior (35). Reduced exploratory behavior with a more robust ef-

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fect in male rats and impairment in a complex learning task in males but not in females were reported by Grimm and Frieder (15). According to the results of our previous study (11), the effects of neonatal MSG treatment on habituation processes appear to be also gender related.

The purpose of this study was to evaluate the effects of neonatal treatment of MSG on habituation of exploratory behavior using a more complex approach involving assessment of both interrupted and uninterrupted habituation with regard to the gender differences.

METHOD

Animals

Female SPF (Specific patogen-free conditions) Sprague–Dawley rats (Charles River Laboratories, WIGA, Sulzfeld, Germany) were mated and housed individually until delivery of pups. After weaning on postnatal day (PD) 21, the offspring were separated according to treatment and sex. A constant temperature of 23–25°C and a 12 L:12 D cycle (lights on 0600–1800 h) were maintained in the animal room. Standard pellet diet and tap water were provided ad lib.

Treatment

Pups of both genders (a total of 30 males and 30 females obtained from eight litters, seven to eight pups per litter) were injected intraperitoneally with MSG (Merck KgaA, Darmstadt, Germany) dissolved in 0.9% NaCl in dose of 4 mg/g body weight on PD 2, 4, 6, 8, and 10. Littermate controls (hypertonic saline controls—HS) received an equivalent volume of 10% NaCl (saline isoosmotic to MSG solution) at the same time intervals as MSG-treated rats. The other control group (intact controls—IC) remained with their mothers without any handling.

Behavioral Test

Spontaneous exploratory behavior (locomotor activity) and its habituation were evaluated in an open-field test. At the age of 65 days, all animals were exposed to the open field in 6-min sessions once daily during 4 consecutive days at the same time schedule between 1300–1700 h over 2 weeks (males were tested in the first week and females during the second week). Gradual decrease of the activity during individual sessions represented an uninterrupted habituation. Interrupted habituation represented the decrease of the activity during repeated exposure of animals to open field over 4 days of testing. The rat was placed in the center of the open field sized 42 × 42 cm, constructed of transparent glass. Movement through a photocell beam sent a single pulse to the computer. For further details see Dubovický et al. (12).

Statistical Analysis

The exponential function $Y(t) = Y_o e^{-kt}$ (Y = amount of activity in individual session in the case of interrupted habituation assessment or amount of activity in individual minutes of session in the case of uninterrupted habituation assessment, k = individual rate of habituation, t = number of sessions in the case of interrupted habituation assessment or time of session in the case of uninterrupted habituation) was used as a model of the habituation course of locomotor activity in individual animals, and was determined by using the method of linear regression (12,16). Thus, the individual rate of habituation (k-value) expresses the rapidity of locomotor activity decline during repeated exposure of animals to open field or during individual sessions. The intensity of locomotor activity in individual sessions and k-values for habituation related to treatment and gender were analyzed by two-way ANOVA using the statistics package STATGRAPHICS 7.1, Manugistics, Inc., Rockville, MD. The results are presented as means ± SEM ($p \leq 0.05$).

Ethics Statement

In experimental part of our study the Principles of Laboratory Animal Care (NIH publication No. 85-23, revised 1985) and the Law of National Council of Slovak Republic on Protection of Animals (No. 115/1995, pp. 1250–1255) were followed.

RESULTS

Table 1 shows the results concerning the intensity of locomotor activity in individual days of testing. In neonatally treated males, the treatment related increase of the activity was found during the first 2-days, $F(2, 54) = 6.202$, $p = 0.0038$. Overall activity of females was not affected by neonatal treatment. Intact males showed significantly decreased locomotor activity compared to that in intact females, $F(1, 72) = 15.262$, $p = 0.0002$. In the groups of neonatally treated rats, there were no significant differences between males and females.

Interrupted habituation of motor activity during 4 days of testing was not altered in neonatally treated rats, either in males or in females. This was demonstrated by lack of statistically significant differences in habituation rates compared to intact controls. Compared to females, males proved to habituate more rapidly in a new environment, but the differences in interrupted habituation rates between males and females failed to be statistically significant (Table 2).

In males, a gradual decrease of motor activity during sessions was evident in all experimental groups in each day of testing (Fig. 1A). During the first 2 days of testing, uninterrupted habituation was slowed down, compared to intact controls. The mean rates of habituation were signifi-

TABLE 1

INTENSITY OF LOCOMOTOR ACTIVITY EXPRESSED AS AN ACTIVITY COUNTS IN INDIVIDUAL DAYS OF TESTING IN NEONATALLY TREATED RATS OF BOTH GENDERS

Days	Treatment	Males	Females
	Intact control	1724.10 ± 119.35	2078.92 ± 58.75
1	Hypertonic saline	1859.59 ± 102.53	2102.27 ± 117.62
	Glutamate	2000.31 ± 119.65	1976.85 ± 75.38
	Intact control	891.10 ± 195.94	1438.02 ± 124.75
2	Hypertonic saline	1002.67 ± 149.57	1225.59 ± 212.20
	Glutamate	1515.02 ± 134.43	1573.46 ± 125.26
	Intact control	917.42 ± 200.79	1162.72 ± 157.32
3	Hypertonic saline	820.81 ± 152.37	995.88 ± 220.08
	Glutamate	974.42 ± 181.21	1042.65 ± 160.84
	Intact control	649.64 ± 130.46	1190.03 ± 165.81
4	Hypertonic saline	624.29 ± 117.82	707.73 ± 161.26
	Glutamate	918.63 ± 143.91	1075.16 ± 178.12

Means ± SEM, n/group = 10. Differences between intact controls and neonatally treated rats on the first 2 days of testing and between intact males and females were statistically significant (two-way ANOVA, $p < 0.01$).

cantly lower in both neonatally treated groups, $F(2, 54) = 3.980$, $p = 0.0244$. On the third and fourth testing days, no significant changes were found in habituation rates of neonatally treated animals compared to controls (Fig. 1B). In females, as in males, a gradual decrease of motor activity was observed during sessions both in controls and in neonatally treated animals in each session (Fig. 2A). Yet in females, no significant changes related to the treatment were found in habituation rates on any individual day of testing (Fig. 2B).

Concerning gender differences in uninterrupted habituation of motor activity, intact males habituated more rapidly than intact females on all individual days of testing. Habituation rates were higher in males compared to those in females, $F(1, 72) = 12.174$, p = 0.0008. Habituation rates in intact males tended to increase during the 4 days of testing, but this rise failed to be statistically significant. In females, relatively constant mean values of habituation rates persisted all over the testing period (Fig. 3).

In the groups of animals neonatally treated with hypertonic saline or MSG, the habituation rates were slightly lower in males compared to those in females in the first 2 days of testing. On the third day, the mean values of habituation rates were almost similar in both genders, while on the fourth day the rates decreased in females but not in males. However, these changes failed to be statistically significant. Habituation rates inceased during testing in both treated groups in males as well as in females [hypertonic saline: $F(3, 72) = 5.880$, $p = 0.0012$; MSG: $F(3, 72) = 5.074$, $p = 0.003$] (Figs. 4 and 5).

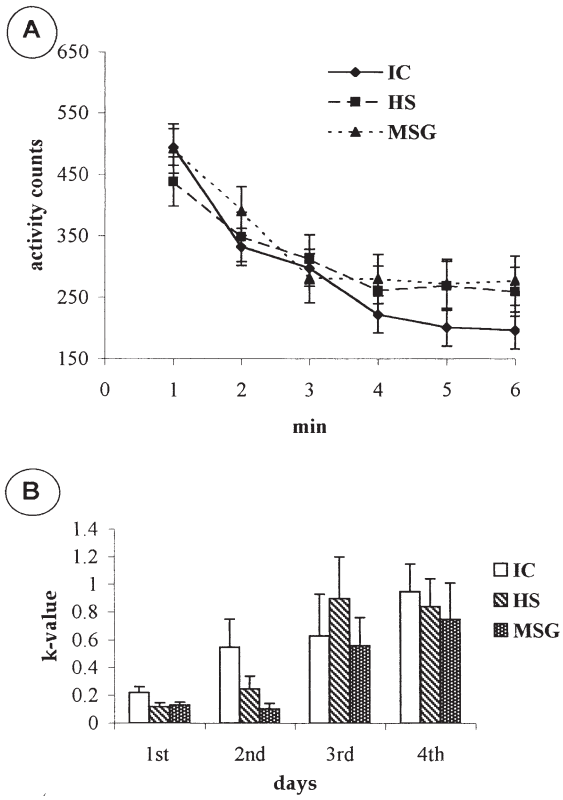

FIG. 1. Decrease of intensity of motor activity during the first day of testing (A) and habituation rates on individual days of testing (B) in neonatally treated male rats (means ± SEM, *n*/group = 10). IC—intact control, HS—hypertonic saline control, MSG—rats treated with a dose of 4 mg/g of monosodium-L-glutamate, k-value—individual rates of habituation. Differences between intact controls and neonatally treated rats on the first 2 days of testing were statistically significant (two-way ANOVA, $p < 0.05$).

DISCUSSION

The study showed that neonatal stress associated with MSG or hypertonic saline treatment resulted in increased intensity of locomotor activity and slow down of its uninterrupted habituation in the open-field test in adult male rats. No differences in adult behavior between treated groups (MSG and hypertonic saline) were observed, i.e., there were no late effects specific for neonatal MSG administration. In contrast, in neonatally treated females, the locomotor activity and its habituation were not altered.

Information on habituation processes in relation to neonatal MSG treatment and handling is practically lacking. Results of the presented study are in keeping with our previous experiments (11) showing that neonatal treatment with MSG or hypertonic saline increased the intensity of exploratory behavior and slowed down the habituation in adult male rats but not in females. In the earlier study, the rapidity of habituation was evaluated by means of a simple habituation index expressed as a percentage of locomotor activity within the first 90 s in relation to the total 6-min activity. The more complex approach used in the present study including the evaluation of habituation over 4 days of testing allowed to reveal greater details in gender-related changes in habituation of exploratory behavior in neonatally treated animals.

Exploratory behavior and its habituation in rats is known to be sexually dimorphic. Males have a lower intensity of exploratory behavior and more rapid habituation than females (12,25). 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.

Marked gender differences related to neurotoxic action of MSG during early postnatal development were, for example, found in the open-field behavior as well as in the acquisition of a complex learning task task with marked effects in males but not in females (15). MSG-treated males showed more susceptibility with respect to the effect of 2-deoxy-D-glucose on feeding behavior (2). In our study, males proved to be more sensitive to neonatal handling/injection than fe-

TABLE 2

RATES OF INTERRUPTED HABITUATION EXPRESSED AS k-VALUES IN NEONATALLY TREATED RATS OF BOTH GENDERS

Treatment	Males	Females
Intact control	0.36 ± 0.08	0.23 ± 0.06
Hypertonic saline	0.40 ± 0.05	0.34 ± 0.05
Glutamate	0.34 ± 0.07	0.29 ± 0.08

Means ± SEM, *n*/group = 10.

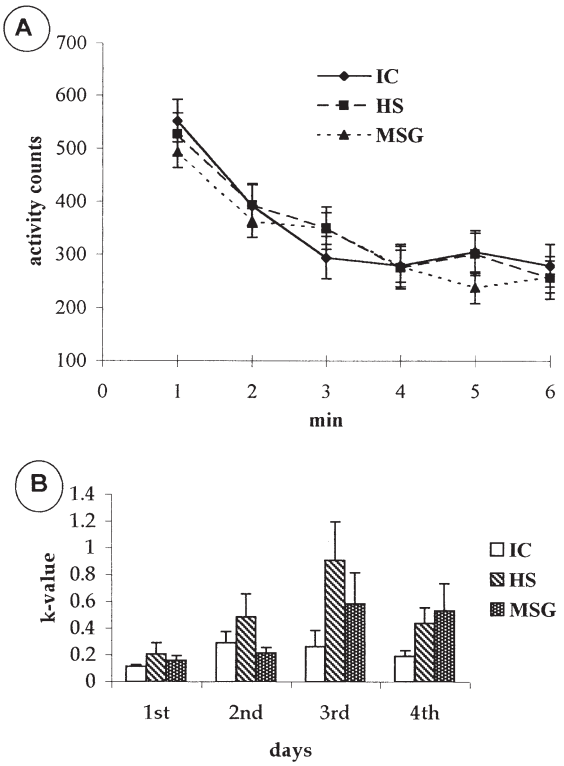

FIG. 2. Decrease of intensity of motor activity during the first day of testing (A) and habituation rates on individual days of testing (B) in neonatally treated female rats. (For further details, see Fig. 1).

males, and showed feminine habituation during individual sessions. Behavioral reactivity of females was not affected; moreover, their habituation seemed to be masculine. To date, it is not known which factors are responsible for gender differences in behavior-disrupting effects after neonatal MSG treatment. More severe and widespread neuron damage in the basomedial hypothalamus, also including the suprachiasmatic nucleus in males (35), as well as effects of sex hormones may contribute to these differences (3).

On evaluating results of neonatal stress studies, it should be considered that the MSG solution used was hypertonic. Short handling and administration of hypertonic solutions

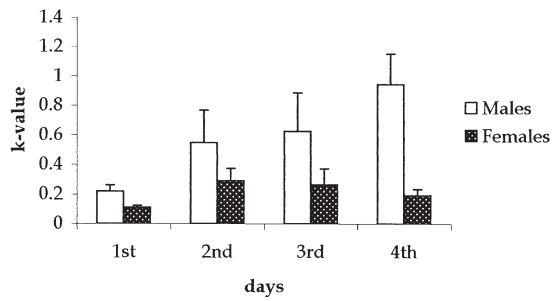

FIG. 3. Comparison of habituation rates between males and females in intact controls on individual days of testing (means ± SEM, *n*/group = 10). Differences between males and females were statistically significant (two-way ANOVA, $p < 0.01$).

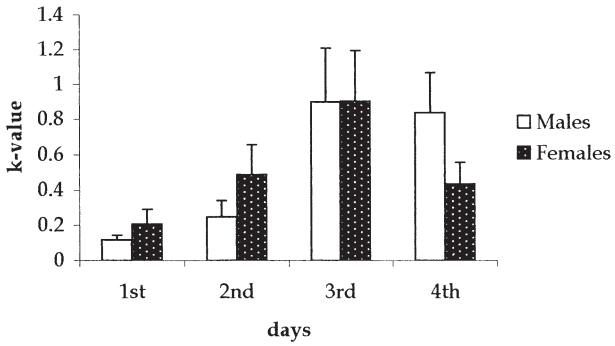

FIG. 4. Comparison of habituation rates between males and females in hypertonic saline controls on individual days of testing (means ± SEM, *n*/group = 10).

were found to be stressful stimuli (19). These facts could play an important role in the disrupting effect of MSG on behavioral reactivity and habituation to novelty.

Interestingly, in our neonatal males, administration of hypertonic saline exerted a similar effect as did MSG. Actually, MSG-treated males did not differ compared to hypertonic saline control. Despite the fact that the postnatal period from 2 to 10 days is considered to be stress hyporesponsive (32), the agonists of glutamate receptors stimulate adrenocorticotropin (ACTH) release not only in adult rats (18) but also in neonatal rats (7,21). Treatment with MSG or hypertonic saline was found to induce a rise of proopiomelanocortin gene transcription, as well as ACTH and corticosterone levels also during the stress hyporesponsive period, while the changes proved to be more pronounced after MSG administration (20). It has been shown that neonatal exposure to ACTH administration or to certain stress stimuli produced physiological and behavioral changes persisting into adulthood (1,26). Adult neonatally handled rats exhibited low anxiety-like behavior, expressed as high exploratory behavior, correlated with low secretion of corticosterone in response to stress (37). The described alterations of male exploratory behavior might be charecterized as a general unspecific sequels of neonatal stress.

In our study, neonatal stress associated with MSG or hypertonic saline treatment resulted in decreased habituation rates in males comparable to the levels of female habituation

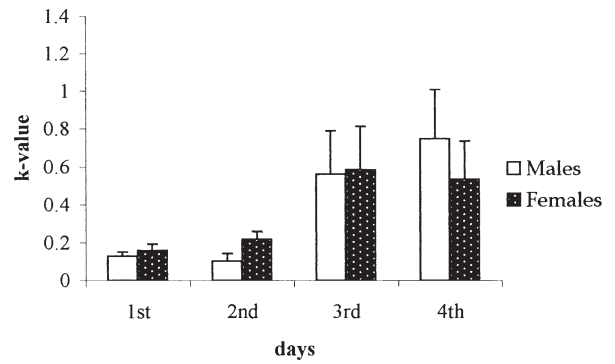

FIG. 5. Comparison of habituation rates between males and females in the MSG-treated rats on individual days of testing (means ± SEM, *n*/group = 10).

rates. Marked gender differences disappeared and males started to habituate in a female-characteristic way. It might be stated that habituation of exploratory behavior became feminized in males after neonatal stress associated with either MSG or hypertonic saline treatment. Unlike males, neonatally stressed females exhibited a slight increase of habituation rates compared to intact controls. Moreover, in intact females there were no significant differences in habituation rates related to individual days of testing (mean values were relatively constant during the 4 days of testing), while in neonatally treated females a significant rise of habituation rates was found during repeated testing. Thus, neonatally treated females seemed to habituate like males, and their habituation showed certain signs of masculization.

Although, the terms feminization and masculization are mostly used concerning the consequences of adverse effects of prenatal administration of sex hormones, it cannot be excluded that some elements of behavior could be feminized in males and masculinized in females due to various influences operative during neurobehavioral development period.

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