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The stress response to sensory contact in mice: genotype effect of the stimulus animal

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Summary Male wild house mice selectively bred for long and short attack latency (LAL and SAL, respectively) were previously shown to respond differently to chronic sensory contact stress with another SAL male. In the present study, it was investigated whether the genotype of the opponent played a role in the differential stress response of LAL and SAL mice. To this end, a LAL or SAL male was housed either under standard conditions (i.e. with a female), single, or in sensory contact with another LAL or SAL male for a period of 5 days. This period was chosen in order to study stress response adaptations. Although social isolation (singly housed) already induced changes in some physiological markers, in particular in LAL mice, the highest number of stress-induced changes was observed in LAL and SAL males living opposite a male of the other genotype. This was indicated in LAL mice by higher corticosterone levels, adrenal hypertrophy, and reduced seminal vesicle weight, and in SAL mice by higher ACTH levels and adrenal hypertrophy. Some mechanisms through which LAL and SAL mice could perceive each other as being different are proposed in the discussion, but it remains unclear why these mice show a differential stress response depending on the genotype of the opponent. In conclusion, it was demonstrated that a psychosocial stressor triggered line-specific changes in LAL and SAL mice, which were shown to be determined by the genotype of the stressor. These results open a new avenue to investigate mechanisms underlying genotypic-dependent stress responses.

1. Introduction

In order to study individual differences in stress responsiveness and in the susceptibility for stress-related psychopathologies, genetically selected strains or lines of rats and mice are frequently

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used (Gomez et al., 1996; Steimer et al., 1997; Jones et al., 1998; Landgraf and Wigger, 2002). We have used wild house mice that are selectively bred for long attack latency (LAL, low to non-aggressive) and short attack latency (SAL, high aggressive). Several studies have shown that this genetic property is part of a fundamental difference in behavioral strategy towards environmental stimuli. LAL mice are characterized by a 'passive' coping style, and SAL mice by an 'active' coping style (Benus et al., 1989, 1991a,b; Sluyter et al., 1996). In the defensive burying test, for example, LAL mice suppress their activity when exposed to the shock prod, while SAL mice respond actively by burying the shock prod with bedding material (Sluyter et al., 1996).

Furthermore, this line difference in attack latency was recently found to be associated with differences in the serotonergic (5-HT) system and in the regulation of the Hypothalamic–Pituitary–Adrenal (HPA) axis under basal and acute stress conditions. LAL mice have a lower 5-HT_{1A} receptor expression and function in the hippocampus than SAL mice (Korte et al., 1996; Van Riel et al., 2002). In addition, the corticosterone output in LAL mice was found to be more sensitive to ACTH, but showed less day–night variation than in SAL mice (Veenema et al., 2003a). Moreover, LAL mice showed a higher and prolonged stress-induced increase in plasma corticosterone than SAL mice (Veenema et al., 2003a). These results suggest a line-difference in HPA responsiveness to chronic stress.

Indeed, we could recently demonstrate that LAL and SAL mice differ in stressor susceptibility when they were exposed to chronic psychosocial stress (Veenema et al., 2003b). Living in sensory (visual, auditory, and olfactory, but not tactile) contact with a SAL male for 25 days, induced stress symptoms (such as decreased body weight, elevated plasma ACTH and corticosterone levels and decreased hippocampal mineralocorticoid receptor [MR] mRNA expression) in LAL, but not in SAL males (Veenema et al., 2003b).

It is, however, unclear whether the genotype of the male opponent in the sensory contact model matters. To investigate this, LAL and SAL males were housed for 5 days either under standard conditions (i.e. one male with one female), single, opposite a LAL male, or opposite a SAL male. The experimental period of 5 days was chosen in order to study sub-acute effects of housing condition on the stress response. Stress responsiveness was evaluated by measuring body weight, plasma corticosterone, plasma ACTH and thymus, adrenal and seminal vesicle weights were measured as well as the behavior of the mice in the partitioned cage.

2. Methods

2.1. Animals

The two mouse lines, which were genetically selected for attack latency, originated from a colony of wild house mice (*Mus musculus domesticus*) maintained at the University of Groningen, The Netherlands, since 1971. The mice were housed in perspex cages ($17\times11\times13$ cm^3) in a room with a 12:12 light/dark cycle (lights on from 00.30 to 12.30 h). Standard laboratory chow and water were available ad libitum. The mice were weaned at 3–4 weeks of age, and were paired male–female at the age of 6–8 weeks. At the age of 92–100 days, male mice were tested for their attack latency as described by Van Oortmerssen and Bakker (1981). Briefly, genetically selected LAL and SAL males are confronted with a standard non-aggressive opponent male of an inbred albino strain (MAS-Gro) at the border of their home cage. The time it takes before a SAL or LAL mouse attacks the non-aggressive opponent is measured on three consecutive days. The attack latency score is the mean of these daily scores. Neither LAL nor SAL mice experienced a social defeat. Only non-attacking LAL mice, and only SAL mice with an attack latency of less than 50 s were used for the experiments. The LAL males came from the 38–40th generation, and the SAL males from the 63–65th generation of selection (this difference in generation between LAL and SAL mice is the result of unsuccessful breeding of LAL mice at the beginning of the selection). LAL and SAL males were at the age of 17 weeks ($\pm$2 weeks) at the start of the experiments. All experiments were in accordance with the regulations of the Committee for Use of Experimental Animals of the University of Groningen (DEC no. 2326).

2.2. Experimental procedure

The experiment (see Fig. 1) was designed to study the effect of genotype of the opponent on the stress response in LAL and SAL males. Therefore, a LAL or SAL male was living for 5 days in a partitioned cage ($75\times29\times27$ cm^3) either single (single: LAL $n=8$; SAL $n=9$), opposite a LAL male (LAL opp: $n=6$ per line), or opposite a SAL male (SAL opp: LAL $n=8$; SAL $n=7$). A perforated (diameter of 5 mm) transparent partition separated the cage into two equal halves and allowed the mice to see, hear and smell each other. This partition was not removed during the experiments, i.e. the two males had never physical contact with each other. Control LAL