

Individual differences in novelty-seeking and emotional reactivity correlate with variation in maternal behavior

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Abstract

Numerous studies have demonstrated that Sprague–Dawley rats exhibit a wide range of locomotor reactivity when placed in a novel environment. High Responder (HR) rats show exaggerated locomotor response to novelty, enhanced neuroendocrine stress reactivity, decreased anxiety-like behavior, and propensity to self-administer psychostimulants, compared to the less active Low Responder (LR) animals. Few studies have explored the early environmental factors which may underlie the HR–LR differences in emotional reactivity. Considering the enormous impact of maternal care on rodent neurodevelopment, we sought to examine maternal behavior in HR–LR dams to determine whether they exhibit differences which could contribute to their offspring's differential temperaments. Females, like males, can be classified as HR versus LR, showing marked differences in novelty-induced locomotor activity and anxiety-like behavior. HR–LR mothers behaved differently with their pups during the first two postpartum weeks. LR dams spent greater time licking and nursing their pups compared to HR dams, with the most prominent differences occurring during the second postpartum week. By contrast, when non-lactating HR–LR females were presented with orphaned pups, the pattern of maternal response was reversed. HR females were more responsive and showed greater maternal care of the novel pups compared to LR females, which were probably inhibited due to fear of the unfamiliar pups. This underscores the critical interplay between the female's emotional phenotype, her hormonal status and her familiarity with the pup as key factors in determining maternal behavior. Future work should explore neural and hormonal mechanisms which drive these HR–LR differences in maternal behavior and their impact on the development of the offspring.

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Introduction

Outbred Sprague–Dawley rats display a variety of behavioral responses when placed in a novel situation, with some rats (High Responders (HR)) actively exploring the new environment, and others (Low Responders (LR)) showing a blunted locomotor response. Numerous studies have demonstrated a high correlation between novelty-induced locomotor activity, drug-taking and other risk-taking behaviors, as well as

neuroendocrine stress-reactivity (Piazza et al., 1989, 1991a; Hooks et al., 1991; Kabbaj et al., 2000). HR rats exhibit exaggerated stress-induced corticosterone secretion (Piazza et al., 1991a, Kabbaj et al., 2000), increased behavioral reactivity to psychostimulants (Piazza et al., 1989, 1991a; Hooks et al., 1991), diminished fear and anxiety-like behavior (Kabbaj et al., 2000, Stead et al., 2006b), and increased aggressive behavior (Abraham et al., 2006) compared to their LR counterparts. Neurochemical and neural gene expression differences appearing to contribute, at least in part, to these observed HR–LR behavioral phenotypes (Piazza et al., 1991b, Hooks et al., 1994a,b; Kabbaj et al., 2000; Kabbaj, 2004). Many of these features are homologous to novelty-seeking and impulsive behavioral traits shown in humans to predispose to propensity

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for drug abuse (Zuckerman and Neeb, 1979; Cloninger, 1987). Thus, the HR–LR trait may tap into the broad dimension of behavioral disinhibition versus behavioral control—a dimension that has been implicated in the vulnerability versus resilience to numerous psychiatric and addictive disorders (Ball et al., 2005).

While numerous studies have evaluated behavioral and biological differences between adult HR–LR animals, there is a paucity of information regarding what heritable or non-genetic environmental factors may contribute to the development of the HR–LR phenotypes. A vast literature clearly illustrates the profound impact of early life experience on emotional temperament and neuroendocrine reactivity (Levine et al., 1957, 1967; Levine, 1962; Denenberg et al., 1967; Zarrow et al., 1972; Hofer, 1973; Russell, 1973; Ladd et al., 2000; Sanchez et al., 2001; Arnold and Sivi, 2002). While we recently showed that the HR–LR trait appears to be heritable (Stead et al., 2006b), we also wanted to ascertain whether early maternal influences could also modulate the phenotype. Given the broad behavioral differences between HR–LR animals, we hypothesized that HR–LR mothers may differentially interact with their young offspring, and that this differential treatment may in turn contribute to emergence of the well-characterized adult HR–LR behavioral, neuroendocrine, and neuronal phenotypes.

In the present study we screened a group of male and female rats using exploration in a novel environment as an index of the HR–LR trait. We also ascertained anxiety-like behavior in the HR–LR groups to confirm that both male and female HR–LR rats show similar behavioral phenotypes. Next, we mated HR male–female pairs and LR male–female pairs and evaluated maternal behavior of HR–LR lactating dams as they cared for their litters during the first 2 postpartum weeks. In a follow-up study we examined maternal response of non-lactating HR–LR females when presented with novel orphaned pups, the so-called “maternal sensitivity test” initially designed and described by (Fleming and Sarker, 1990). Maternal behavior is largely driven by hormonal changes that occur during late pregnancy and parturition. Non-lactating female rats are generally fearful of novel pups (Fleming and Rosenblatt, 1974a,b; Fleming et al., 1979), but their aversion can be mitigated with a hormonal regimen that mimics the changes in estrogen and progesterone typical of pregnancy and partition (Fleming et al., 1989). Alternatively, non-lactating females can eventually exhibit maternal behavior in the absence of hormonal priming if they are able to habituate to the novel pups through frequent exposure to them (Fleming and Sarker, 1990; Rosenblatt et al., 1994; Bridges et al., 1996).

Our results show that HR–LR mothers behave differently with their litters during the first two postpartum weeks, with LR mothers being significantly more attentive to their pups than HR mothers. However, maternally-experienced HR–LR females presented with orphaned pups beyond the lactation period have a pattern of maternal response that is reversed, with HR females showing greater maternal care of the novel pups than LR females. The HR females’ increased willingness to approach the novel pups is likely related to their general novelty-seeking and

exploratory tendencies. The pattern of maternal behaviors is consistent with the individual differences in the HR–LR behavior phenotypes originally described in male rats.

Materials and methods

Animals

Forty-two male and sixty female Sprague–Dawley rats (Charles River Wilmington, MA, USA) were housed in separate rooms in groups of three per $43 \times 21.5 \times 25.5$ -cm polycarbonate cage (Nalgene, $24 \times 45 \times 20$). The rooms were kept under constant temperature (25 ± 2 °C) and lighting conditions. Males were kept in a 12 h light:12 h dark cycle. Females were housed in a room with a 14 h light:10 h dark cycle (lights on 6:00 am–8:00 pm) to promote reliable reproductive cycles. Rats were provided with rat chow and tap water *ab libitum*, and maintained in accordance with the *NIH Guidelines for the Care and Use of Laboratory Animals*. The University of Michigan Animal Use Committee approved all animal protocols utilized.

HR/LR classification: screening for locomotor response to novelty

Prior to mating, male and female rats were screened for locomotor response to novelty. Animals were acclimated to housing conditions for a minimum of 7 days. Starting on the eighth day, female rats were subjected to daily vaginal smears to monitor estrous cycle for 1 week. Locomotor testing was performed during the D1 phase of the estrous cycle. Horizontal and rearing activity was monitored by computer in 5 min intervals over 60 min by placing animals into clear acrylic $43 \times 21.5 \times 25.5$ cm (high) cages equipped with infrared photocell emitters mounted 2.3 and 6.5 cm above the grid floor. Male and female rats were tested separately, and all testing was performed between 8:00 and 11:30 am. Total locomotion scores for each rat were calculated by adding the total number of horizontal and rearing movements. Rats that exhibited locomotor scores in the highest third of the sample population were classified as high responders (HR), whereas animals with scores in the lowest third of the population were classified as low responders (LR). Animals whose scores fell in the middle third of the population were classified as intermediate responders (IR) and were not used for subsequent studies.

Light–Dark test

One week after locomotor testing, the HR–LR males and females ($N=8$ per group) were subjected to the Light–Dark test to assess anxiety-like behavior. The test apparatus was a $30 \times 60 \times 30$ cm Plexiglas shuttle-box divided into two equal-sized compartments by a wall with a 12-cm-wide open door. One compartment was painted white and brightly illuminated (100 lx), and the other compartment was painted black with very dim light. Rows of five photocells located 2.5 cm above the stainless steel grid floor monitored the rats’ locomotor activity and time spent in each compartment. A microprocessor recorded the number of photocell beams interrupted, and the time spent in each compartment during the 5 min test. Rats were initially placed in the dark compartment at the beginning of the test. Male and female rats were tested on different days after careful cleansing of the apparatus to devoid it from odors. Females were tested during the D1 phase of the estrous cycle. All testing was performed between 8:00 and 11:30 am.

Mating HR–LR animals

One week after light–dark testing, HR–LR females were paired for 10 days with HR–LR males, respectively. Conception was verified by the presence of a vaginal plug. Pregnant females were individually housed on the calculated eighteenth day of gestation, and litters were culled to 8 healthy pups (4 males, 4 females) shortly after birth. After the initial handling of cages at birth, the mothers and litters were not disturbed in order to minimize disruption of mother–pup interactions, except for weekly cage change. Pups were weaned on postnatal day 21 and grouped 4 animals per cage according to sex, with water and food available *ab libitum*.

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