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Research Report

Maternal and genetic factors in stress-resilient and -vulnerable rats: A cross-fostering study

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ABSTRACT

Early environmental factors can modulate the development of the hypothalamic–pituitary–adrenal (HPA) axis response to stress, together with subsequent brain functions and emotional behaviors. Two rat strains, Sprague–Dawley (SD) and Fischer 344 (F344), are known to exhibit differences in HPA axis reactivity and anxiety behavior in response to restraint stress in adulthood. To investigate the contribution of maternal influences in determining HPA axis and behavioral responses to stress, a cross-fostering study was performed using stress-resilient (SD) or stress-susceptible (F344) strains. We found that SD rats adopted by either an SD (in-fostered) or an F344 (cross-fostered) dam and F344 rats adopted by an SD dam (cross-fostered) showed a suppression of the HPA axis response following 14 days of repeated restraint stress. In contrast, F344 rats adopted by an F344 dam (in-fostered) did not show such HPA axis habituation. We also found that F344 rats adopted by an F344 dam showed increased anxiety-related behaviors in social interaction and novelty-suppressed feeding tests as a result of the 14 days of restraint stress, while SD rats adopted by either an SD or an F344 dam and F344 rats adopted by an SD dam showed normal anxiety-related behaviors under the same experimental conditions. These results suggest that while genetic differences between SD and F344 strains account for some of the variations in stress vulnerability, maternal factors also contribute.

1. Introduction

The hypothalamic–pituitary–adrenal (HPA) axis controls the production and release of adrenal glucocorticoids in response to stress and the daily circadian rhythm. Dysfunction of the HPA axis is known to be associated with vulnerability to a number of psychiatric diseases, including major depression and anxiety disorders (de Kloet et al., 2005; Seckl and Holmes, 2007). Although glucocorticoids act in the brain to restore physiological and behavioral homeostasis after stress exposure, it is believed that the activation of the stress response can be deleterious when the intensity or frequency of stressors exceeds a certain individual-specific threshold, which can then lead to a variety of mental disorders (McEwen, 2002, de Kloet et al., 2005).

Chronically stressed animals often exhibit suppressed or decreased HPA axis responses upon re-exposure to the same, or homotypic, stressor. This decrement, termed habituation, has been observed with various stress paradigms, including

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restraint stress (Melia et al., 1994; Dhabhar et al., 1997; Ma et al., 1999; Cole et al., 2000; Viau and Sawchenko, 2002; Girotti et al., 2006; Uchida et al., 2008). This plasticity in the regulation of HPA activity as a consequence of repeated stress is thought to protect the organism from the potentially damaging effects of hypercorticosteroidism (Armario et al., 2004). To date, however, the mechanism underlying such HPA habituation has not been fully elucidated.

Different strains of mouse or rat have different neuroendocrine, physical and behavioral phenotypes that are heritable and stable (Dhabhar et al., 1995, 1997; Fernandes et al., 2004; Hovatta et al., 2005). In particular, Fischer 344 (F344) rats have been widely used in the study of HPA axis function (Kosten and Ambrosio, 2002). F344 rats are known to consistently present an exaggerated acute stress-induced corticosterone secretion relative to Sprague–Dawley (SD) and Lewis strains (Dhabhar et al., 1995, 1997; Uchida et al., 2008). F344 rats have also been reported to exhibit no habituation of HPA axis activity during repeated restraint stress (RRS) episodes (Dhabhar et al., 1997; Uchida et al., 2008). Further, we have previously reported that repeatedly restrained F344 rats exhibited increased anxiety-related behavior, while repeatedly restrained SD rats exhibited normal anxiety behavior (Uchida et al., 2008). These observations suggest that F344 rats are a useful genetic animal model to understand the adaptation to repeated stress and the susceptibility to anxiety disorder and depression.

A growing body of evidence suggests that maternal factors can affect long-term behavioral and neuroendocrine consequences in rodents (Liu et al., 1997, 2000; Meaney, 2001; Francis et al., 2003). Early life adversity is one of the most prominent environmental factors associated with an increased risk of developing mood and anxiety disorders (Heim and Nemeroff, 2001; Widom et al., 2007). It is believed that the HPA axis can be affected by abnormal maternal behavioral patterns, and this can modulate the subsequent stress responses of the offspring. Indeed, early environmental factors have been reported to modify the development of the HPA axis, together with subsequent brain functions and emotional behaviors (Francis et al., 2002; Plotsky and Meaney, 1993; Liu et al., 2000; Weaver et al., 2004). These observations raise the possibility that genetically determined stress vulnerability in F344 rats may be affected by maternal factors. However, there is no published evidence demonstrating the effect of maternal factors on the development of stress vulnerability and resiliency in F344 and SD rats, respectively.

In the present study, to assess whether epigenetic maternal factors contribute to the differential behavioral and neuroendocrine responses to stress in F344 and SD strains, we examined the effects of cross-fostering on the HPA axis response to stress and anxiety- and depression-related behaviors after RRS.

2. Results

2.1. *Effect of cross-fostering on neuroendocrine response to restraint stress*

A previous report showed the deleterious effects of body weight gain, adrenal weights, and plasma corticosterone levels in restrained F344 rats, but not in restrained SD rats (Uchida et al., 2008). To examine the effects of cross-fostering on the neuroendocrine responses to acute and repeated restraint stress, we measured changes in daily body weights, adrenal weights, and plasma corticosterone levels. Experimental design is shown in Fig. 1. Changes in body weight for rats across 6 days of pre-stress and during the 14-day stress period are shown in Fig. 2. In the non-restrained groups, there was no significant effect of pup strain [$F_{(1,456)}=0.81$, $p>0.05$] or dam [$F_{(1,456)}=0.157$, $p>0.05$] upon body weight gain among the four groups (Fig. 2A). In the restrained groups, there were significant effects of pup strain [$F_{(1,437)}=4.57$; $p<0.01$], dams [$F_{(1,437)}=1.84$; $p<0.05$], and their interaction [$F_{(1,437)}=1.84$; $p<0.05$] upon body weight gain (Fig. 2B). In the in-fostered groups, body weight gain of restrained F344–F344 rats was significantly less than that of restrained SD–SD rats ($p<0.05$) after the 5th restraint stress presentation. The body weight gain of restrained F344–SD cross-fostering rats was significantly greater than that of restrained F344–F344 rats ($p<0.05$), whereas the body weight gain of restrained SD–F344 cross-fostering rats was comparable to restrained SD–SD rats ($p>0.05$).

Adrenal weights of rats from the 14th restraint stress sessions are shown in Fig. 3A, which shows a significant effect of the pup strain × dam × stressor condition [$F_{(1,55)}=5.58$, $p<0.05$]. Post hoc comparisons indicated that the adrenal

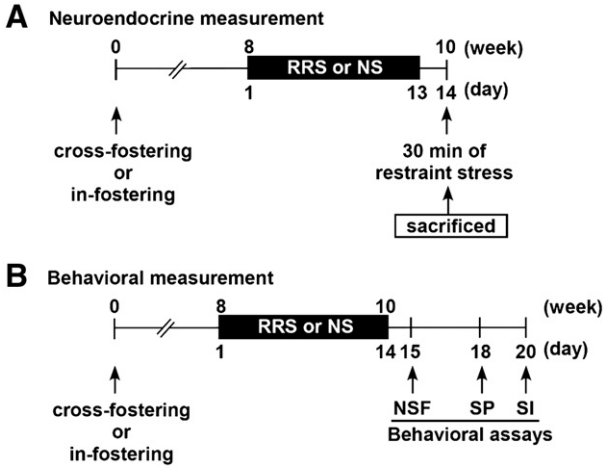

Fig. 1 – Experimental design. Cross- and in-fostering were carried out on postnatal day 1. Adult rats (postnatal day 56–60) were individually subjected to 2-h repeated restraint stress (RRS) for 14 consecutive days. Non-restrained rats (NS) were handled every day during weighing. (A) Plasma corticosterone levels of the rats subjected to 13th restraint stress sessions were measured 30 min after the initiation of restraint stress on day 14. Acutely stressed rats were left for 13 days without RRS exposure, and plasma corticosterone levels were measured 30 min after the initiation of restraint stress on day 14. *n* in each group between 6 and 8. (B) Cross- and in-fostered rats subjected to RRS or NS were tested for anxiety- and depression-related behaviors on days 15 (novelty-suppressed feeding test, NSF), 18 (sucrose preference test, SP), and 20 (social interaction test, SI) of the experiment (n in each group between 12 and 16).