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Genetic predisposition for high stress reactivity amplifies effects of early-life adversity

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ABSTRACT

A dysregulation of the hypothalamus-pituitary-adrenocortical (HPA) axis and the experience of early-life adversity are both well-established risk factors for the development of affective disorders, such as major depression. However, little is known about the interaction of these two factors in shaping endophenotypes of the disease. Here, we studied the gene-environment interaction of a genetic predisposition for HPA axis dysregulation with early-life stress (ELS), assessing the short-, as well as the long-lasting consequences on emotional behavior, neuroendocrine functions and gene expression profiles. Three mouse lines, selectively bred for either high (HR), intermediate (IR), or low (LR) HPA axis reactivity, were exposed to one week of ELS using the limited nesting and bedding material paradigm. Measurements collected during or shortly after the ELS period showed that, regardless of genetic background, ELS exposure led to impaired weight gain and altered the animals' coping behavior under stressful conditions. However, only HR mice additionally showed significant changes in neuroendocrine stress responsiveness at a young age. Accordingly, adult HR mice also showed lasting consequences of ELS, including hyperactive stress-coping, HPA axis hyperreactivity, and gene expression changes in the *Crh* system, as well as downregulation of *Fkbp5* in relevant brain regions. We suggest that the genetic predisposition for high stress reactivity interacts with ELS exposure by disturbing the suppression of corticosterone release during a critical period of brain development, thus exerting lasting programming effects on the HPA axis, presumably via epigenetic mechanisms. In concert, these changes lead to the emergence of important endophenotypes associated with affective disorders.

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1. Introduction

Major Depressive Disorder (MDD) is one of the most prevalent and costly psychiatric disorders (Ferrari et al., 2013; Greenberg et al., 2015). Among the large number of patients diagnosed with MDD, there exist smaller clinical subgroups, which can be distinguished by their opposing vegetative symptoms (for example: motor agitation or retardation, insomnia or hypersomnia, weight loss or gain) (Antonijevic, 2006; Gold, 2014; Gold and Chrousos, 1999, 2002; Lamers et al., 2012). In addition, patients suffering from these different subtypes of MDD also show opposite symptoms regarding the function of their hypothalamus-pituitary-adrenocortical (HPA) axis, one of the main neuroendocrine systems controlling the body's stress response (Joëls and Baram, 2009; Nemeroff, 1996; Sapolsky et al., 1984). Specifically, the atypical depression subtype is associated with blunted cortisol release in response to stressors, while patients with the psychotic or melancholic depression subtype show stress hyper-reactivity with extreme cortisol release and a flattened profile in their diurnal glucocorticoid secretion (Antonijevic, 2006; Gold and Chrousos, 1999, 2002). Thus, due to its central role in the systemic regulation of the stress response, a dysfunctional HPA axis may be a critical factor in the etiology of both depression subtypes (Gold, 2014; Holsboer, 1999; Lamers et al., 2012). However, a genetic predisposition for high or low HPA axis reactivity alone is probably not sufficient to cause a psychiatric disorder; severe negative experiences or other stressful environmental factors are thought to play an equally important role (Provençal and Binder, 2015). Until today, it remains poorly understood how a genetic predisposition for HPA axis dysregulation and environmental stressors interact, and what the short- and long-term consequences are.

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The Stress Reactivity (SR) mouse model offers a good starting point to investigate this gene × environment (G × E) interaction. This genetic animal model consists of three independent, CD1-derived mouse lines, selectively bred for either high (HR), intermediate (IR), or low (LR) HPA axis reactivity in response to a psychological stressor, thereby mirroring the HPA axis dysregulation endophenotypes described in the melancholic/psychotic and the atypical depression subtypes, respectively (Heinzmann et al., 2014; Touma et al., 2008, 2009). Compared to the IR line, which serves as reference line, HR mice have lower bodyweight, show disturbed circadian activity patterns and increased REM sleep, display hyperactive stress-coping behavior and show cognitive deficits, corresponding to symptoms of melancholic/psychotic depression. In contrast, LR mice have increased bodyweight, show passive coping behavior, as well as intact sleep and cognitive function, akin to symptoms of atypical depression (Fenzl et al., 2011; Heinzmann et al., 2014; Knapman et al., 2010a,b, 2012; Touma et al., 2008, 2009). Thus, the SR mouse model is an appropriate tool to investigate the interaction of a genetic vulnerability for disturbances in the stress hormone system and environmental stressors.

Exposure to early-life stress (ELS) is a well-established environmental risk factor for affective disorders (Baram et al., 2012; Heim et al., 2002; Kessler et al., 2005; Penza et al., 2003). During the early postnatal period, the central nervous system is still highly plastic, so that the environment can profoundly and lastingly shape the brain and the neuroendocrine system (Everson-Rose et al., 2003; Lehmann et al., 2002; Oomen et al., 2010a,b; Plotsky and Meaney, 1993; Wilson et al., 2005). Recent evidence from animal models and human data suggests that this process involves epigenetic modifications at several target sites, including the genes coding for the glucocorticoid receptor (*Gr*), vasopressin (*Avp*), corticotropin-releasing hormone (*Crh*), and FK506 binding protein 5 (*Fkpb5*) (Bockmühl et al., 2015; Klengel et al., 2012; Provençal and Binder, 2015; Radtke et al., 2015; Weaver et al., 2004; Zimmermann et al., 2015). A dominant factor in a mouse pup's early-life environment is the dam. Via her maternal behavior, she has a profound influence on her pups' brain development (Caldji et al., 2004; Meaney, 2001). For example, the amount of maternal licking and grooming can change the behavior of the offspring by altering their brain function and HPA axis responsiveness (Champagne et al., 2003; Francis et al., 1999; Liu et al., 1997; Sarro et al., 2014).

Also in humans, the mother acts as a powerful regulator of the development of the infant's physiological regulatory systems, including the HPA axis (Als et al., 2004; Hane and Fox, 2006) and the quality of the mother-child relationship is highly predictive of the child's trajectory regarding mental and cognitive health (Belsky and Fearon, 2002; Bowlby, 1958; Masur et al., 2005). For the development of a secure attachment relationship maternal sensitivity and responsiveness are of critical importance (McElwain and Volling, 2004). Fragmentation and unpredictability of maternal care are therefore important triggers of ELS and predictors of mental health deficits in children. In rodents such fragmented and unpredictable maternal care can be experimentally induced by reducing the amount of the nesting and bedding material available to nursing dams (Molet et al., 2014; Rice et al., 2008), thus permitting controlled studies of the consequences of ELS.

In our study, we combined the genetic predisposition for HPA axis hyper- or hypo-reactivity of the SR mouse lines with exposure to ELS to investigate the interaction of these two risk factors at the level of physiology, behavior, neuroendocrine function and gene expression in the brain. We aimed to (i) study the long-lasting consequences of this G × E interaction, including key endophenotypes of affective disorders, and (ii) examine the short-term effects of ELS-exposure, which may be involved in mediating the long-term outcomes. Therefore, we exposed mice of the three SR mouse lines to ELS and studied the pups and the adult animals using a battery of tests for emotional behavior, HPA axis reactivity and recovery, as well as expression profiles of candidate genes in relevant brain nuclei. Additionally, factors influencing the animals' stress experience during the ELS paradigm, such as maternal behavior, nest temperature, and nest quality were monitored throughout the experiment. This experimental design allowed us to detect endophenotypes associated with the development of long-lasting consequences of ELS, which can contribute to the ongoing search for intervention targets after early-life adversity.

2. Methods

All presented work is in accordance with the accepted standards of humane care and use of experimental animals and was approved by the appropriate local authority. The supplementary material provides additional descriptions of methods and experimental procedures.

2.1. Animals and housing conditions

In all experiments, animals from the SR mouse model were used (Touma et al., 2008). A detailed description of the breeding procedure used to generate and maintain this mouse model is provided in the supplementary material, section 1.1. Animals were housed under standard laboratory conditions (stable 12 h light/dark cycle (lights on at 8 a.m.), 22 ± 2 °C, 55 ± 10% humidity, standard diet chow and water *ad libitum*).

2.2. Experimental design

We used a 3 × 2 factorial design: Three SR breeding lines (HR, IR, and LR) and two environmental conditions (early-life stress (ELS) and standard housing (STD)), resulting in a total of six experimental groups. The data presented here was generated from five independent cohorts of experimental animals, derived from breeding generations XXIII–XXVIII of the SR mouse model, focusing on either the long-lasting effects of ELS in adulthood (cohorts I and II) or on the short-term effects in the pups (cohorts III, IV and V).

2.3. Breeding of experimental cohorts

For each cohort, 48 breeding pairs were used, i.e. 16 male-female pairs per mouse line. The cages of pregnant primiparous females were inspected daily at 5 p.m. for the delivery of pups and the day a litter was discovered was defined as postnatal day 0 (P0). On P2, litters were culled to seven pups, consisting of six males and one female, when possible. Only litters with a total number of at least six pups and including at least four males were included in the study to ensure a comparable early-life situation for pups from different litters.

2.4. Early-life stress paradigm

Dams and their offspring were randomly assigned to either the ELS or the STD condition ($N = 8$ dams per line and condition). We used a stress paradigm based on limiting the resources of nesting and bedding material, described by Rice et al. (2008). This paradigm creates a chronic ELS environment that has been described as more naturalistic and creating fewer metabolic side-effects than repeated maternal-separation (Molet et al., 2014). Briefly, on P2, dams assigned to the ELS condition were placed, together with their litter, into a polycarbonate type II cage fitted with an aluminum grid floor (mesh dimensions 0.4 × 0.9 cm, catalog no. 57398; McNichols Co., Tampa, U.S.A). A reduced amount of sawdust bedding material (~20 g) was spread underneath the aluminum grid and half a

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