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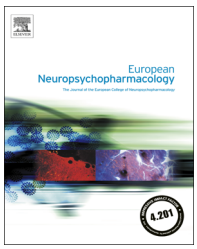

Evidence supporting the match/mismatch hypothesis of psychiatric disorders

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Abstract
Chronic stress is one of the predominant environmental risk factors for a number of psychiatric disorders, particularly for major depression. Different hypotheses have been formulated to address the interaction between early and adult chronic stress in psychiatric disease vulnerability. The match/mismatch hypothesis of psychiatric disease states that the early life environment shapes coping strategies in a manner that enables individuals to optimally face similar environments later in life. We tested this hypothesis in female Balb/c mice that underwent either stress or enrichment early in life and were in adulthood further subdivided in single or group housed, in order to provide aversive or positive adult environments, respectively. We studied the effects of the environmental manipulation on anxiety-like, depressive-like and sociability behaviors and gene expression profiles. We show that continuous exposure to adverse environments (matched condition) is not necessarily resulting in an opposite phenotype compared to a continuous supportive environment (matched condition). Rather, animals with mismatched environmental conditions behaved differently from animals with matched environments on anxious, social and depressive like phenotypes. These results further support the match/mismatch hypothesis and illustrate how mild or moderate aversive conditions during development can shape an individual to be optimally adapted to similar conditions later in life.

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1. Introduction

Chronic stress is one of the predominant environmental risk factors for a number of psychiatric disorders, particularly for major depression (De Kloet et al., 2005). While it has been predicted that depression will be the leading cause for burden of disease worldwide by 2030 (WHO/Wonca, 2008), the underlying mechanisms of the disease etiology are still unclear. One important aspect, related to stress and depression vulnerability, lies in different coping strategy repertoires of each individual (Koolhaas et al., 1999), or in other words, how could similar stressors exert a very wide spectrum of effects in different individuals. These differences seem grounded in both genetic background and specific environmental conditions (Caspi et al., 2003).

The interplay between experiences during sensitive developmental periods and the later adult environment seems to be a crucial factor in shaping individual variability in stress coping strategies. There are two main hypotheses that have been formulated to address this interaction. The cumulative stress or multiple hit hypothesis states that higher numbers of stressful events during early stages of life increase vulnerability to stressors later in life (McEwen, 2003). Accordingly, the effects of a environment are additive and result in an increased allostatic load, which in turn leads to a higher risk for developing psychiatric disorders. More recently, the match/mismatch hypothesis of psychiatric disease has been formulated, which states that the early life environment shapes coping strategies in a manner that enables individuals to optimally face similar environments later in life (Belsky and Pluess, 2009; Ricon et al., 2012; Schmidt, 2011). From an ethological and evolutionary perspective, this last hypothesis is plausible: individuals raised in a stressful environment will likely also face a stressful environment in adulthood and need to be adapted to deal with this aversive situation. This conceptual framework could also help to explain many cases in which individuals that are exposed to high levels of stress show comparable behavioral performances to individuals who have never exposed to stress (Champagne et al., 2008; Oomen et al., 2010). However, it still remains unclear whether and under which conditions early programming will result in adaptive or maladaptive coping reactions during adulthood.

While the cumulative stress and the match/mismatch hypothesis seem to be conceptually different and mutually exclusive, there is substantial clinical and preclinical evidence for both. It was therefore proposed that both hypotheses may be integrated and could be applicable depending e.g. on the genetic background of the individual (Nederhof and Schmidt, 2012). In this framework, individuals with a highly inert adaptive capacity would suffer more under mismatched environments, while individuals with a low capacity would have the highest disadvantage following cumulative stress exposures. For example it could be hypothesized that females under different estrous cycles could differ in adaptive capacity, which is also supported by reports on varying stress or drug effects according to the estrous phase (Frye and Walf, 2002; Mourlon et al., 2011; Palanza et al., 2001).

This would apply for example to the important aspect of gender, as women are reported to suffer more often from depression than men (Holden, 2005; Kessler, 2003). In particular, women can be more responsive to environmental challenges, according to different phases of their menstrual cycle, as indicated by the recognition of the premenstrual dysphoric disorder (PMDD) as a disorder in the recent DMS V and its short term treatment with SSRIs (American Psychiatric Association, 2013).

A number of genetic risk factors for stress-related psychiatric disorders were described, including some polymorphisms of genes encoding for neurotrophic factors. Differences in expression levels of brain plasticity genes may lead to different behavioral responses to the same load of stress. This generates subsets of individuals that are able to effectively respond to environmental changes, while some others show no adaptation or no response at all, leading to maladaptation. In particular, *brain-derived neurotrophic factor* (BDNF), a brain plasticity marker, has been extensively investigated and correlated with stress response and major depression (for review see Duman and Monteggia, 2006). Interestingly in the context of adaptation, BDNF showed an U-shaped curve correlation with corticosterone, where moderate levels of corticosterone are inducing an increase in BDNF levels, whereas high levels of corticosterone do not induce any change in BDNF (Schaaf et al., 1997). In general, high levels of corticosterone and reduced levels of BDNF are both associated with increased levels of stress; however it has been shown that rats subjected to moderate concentrations of corticosterone, BDNF levels are increased whereas at higher concentration of corticosterone BDNF levels return comparable to control levels (Schaaf et al., 1997). This and similar findings are suggesting that the correlation between stress effects and "stress markers" is not always linear, but rather follows a U shaped curve distribution.

Furthermore, other neuronal systems have been correlated with stress vulnerability. Many candidates have been identified, but often the results were contradictory or not reproducible (for an example (Karg et al., 2011) further commented in (Hardy and Low, 2011; Blakely and Veenstra-VanderWeele, 2011). Recently SLC6A15, a neuron-specific neutral amino acid transporter (also known as v7-3 or B^0AT2), was proposed as a strong candidate gene for vulnerability to stress and major depression (Kohli et al., 2011; Schuhmacher et al., 2013).

To test the match/mismatch in individuals with different levels of responsiveness to stress effects, we here studied the interaction of early life experience and adult environment in the development of anxiety-like and depression-like behavior in female Balb/c mice. We hypothesized that animals which experienced either matched supportive environments or matched aversive environments (i.e. matched environments), would exhibit lower anxiety-like and depressive-like behavior compared to animals with mismatched early and adult life environments. Furthermore, we investigated the expression of stress vulnerability related genes in the brain, like BDNF and SLC6A15.

2. Experimental procedures

2.1. Animals and breeding procedures

Male and female Balb/c mice ($n=30$/sex) were purchased from Charles River, Germany. The experiments were carried out in accordance with European Communities Council Directive 2010/63/EU. All efforts were made to minimize animal suffering during