Psychoneuroendocrinology (2010) **35**, 635—643

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High susceptibility to chronic social stress is associated with a depression-like phenotype

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Received 21 June 2009; received in revised form 2 September 2009; accepted 1 October 2009

KEYWORDS
Chronic stress;
Vulnerability;
Resilience;
HPA axis;
Depression

Summary Chronic stress is a key risk factor for a variety of diseases, including depression. There is a large degree of individual variation in the ability to recover successfully from a chronic stress exposure, but the determinants of this individual stress susceptibility are still poorly understood. We recently developed a novel mouse paradigm for chronic social stress during adolescence, which closely mimics the human condition of chronic social stress in respect to construct, face and predictive validity. By applying this chronic stress model to a large number of animals we aimed at identifying individuals that are either resilient or vulnerable to the persistent effects of chronic social stress exposure. Animals showing markedly elevated basal corticosterone levels 5 weeks following the end of the stress paradigm were considered ''vulnerable'', whereas individuals recovering quickly and being indistinguishable from controls were classified as ''resilient''. Stress vulnerability was associated with an increased level of corticotropin-releasing hormone in the paraventricular nucleus, decreased hippocampal mineralocorticoid receptor expression as well as increased anxiety- and depression-like behavior compared to resilient and control animals. In summary, we show that by using a large cohort of animals it is possible to select individuals that are vulnerable or resilient to the lasting effects of chronic social stress. The vulnerable phenotype mimics many aspects of stress-related human affective disorders and this may be used as a novel approach to study depression in an animal model, ultimately contributing to a better understanding and treatment of stress-related disorders.

1. Introduction

Chronic social stress represents a major risk factor for a variety of diseases, including depression (Kendler et al., 2002, 2006; De Kloet et al., 2005; Shekhar et al., 2005; Bale, 2006). Hyperactivity of the hypothalamic—pituitary—adrenal (HPA) system is one of the most robust and consistent neurobiological findings in patients with major depression

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doi:10.1016/j.psyneuen.2009.10.002

(Holsboer, 2003b; Ising et al., 2007). Moreover, an increased reactivity of the HPA axis was already shown for healthy individuals at high-risk for depression (Modell et al., 1998). Chronic or traumatic stress experiences that occur during vulnerable developmental time periods, such as childhood abuse, are correlated with an increased risk for psychiatric disease (Goodyer et al., 2000; Corcoran et al., 2003) and permanent HPA axis alteration (Heim and Nemeroff, 2001).

Although the effects of chronic stress have been shown to be a risk factor for psychiatric diseases, it is important to note that stress is neither necessary nor sufficient to cause the disease (Nestler et al., 2002). In fact, the majority of individuals do not develop a serious illness after prolonged exposure to severe stress (Wang, 2005). To date, it is still largely unclear why some individuals are more susceptible to develop long-term effects induced by chronic social stress exposure while others seem to be resilient and recover quickly (Charney, 2004). The possibility to identify high-risk individuals early on before stress exposure would open up a variety of intervention strategies that could ultimately avert long-term pathophysiological consequences.

Stress susceptibility can be assessed using different physiological or behavioral readouts. Recently, Krishnan et al. (2007) illustrated that stress susceptibility based on social avoidance in mice is characterized by an increase of the brain derived neurotrophic factor (BDNF) in the nucleus accumbens. Further, Bergström et al. (2007) separated rats by sucrose intake — an animal model for anhedonia — following chronic mild stress exposure. So far, however, there have been no studies investigating basal corticosterone levels and HPA axis activity as a main readout for stress susceptibility in animals, even though there is abundant evidence supporting the importance of this parameter in humans.

To assess individual differences in stress susceptibility, we hypothesized that animals that recover quickly from a chronic stress exposure are ''resilient'' to adverse and lasting stress effects, while individuals that fail to recover for weeks after the stress exposure are ''vulnerable'' (Fig. 1a and b). To test this hypothesis, we recently developed a novel paradigm for chronic social stress in mice, which can be used with a large number of animals and closely mimics the human condition of chronic stress with respect to face, construct and predictive validity (Schmidt et al., 2007; Sterlemann et al., 2008). Since the stress paradigm is carried out during the adolescent and early adult period of the animals, the time of stress exposure coincides well with the period of increased stress vulnerability described in humans (Paus et al., 2008). We show that highly stress susceptible individuals display a depression-like phenotype, including increased corticotropin-releasing hormone expression, enhanced anxiety and increased despair behavior. Our data support the hypothesis that only a subpopulation of individuals exposed to chronic stress is unable to cope successfully with this situation. With the identification of those stress-susceptible animals, our approach opens up the possibility to study the genetic and neurobiological mechanisms underlying stress-related disorders as depression in detail.

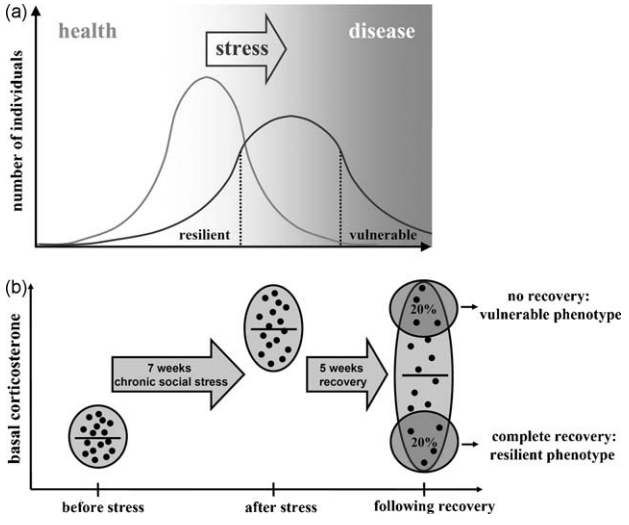

Figure 1 Concept of stress vulnerability. (a) If a healthy population of individuals is exposed to chronic stress, the Gaussian distribution of the health status shifts towards disease. However, also following stress many individuals remain healthy (left part of the curve; resilient), while others are largely and lastingly affected (right part of the curve; vulnerable). (b) We hypothesized that chronic stress exposure will result in a stressed phenotype measured by basal corticosterone levels in most individuals. However, following 5 weeks of recovery, we expected a much higher variation of this phenotype. Animals that fully recover during this period are regarded as resilient to the stress exposure, while animals that are lastingly affected are considered vulnerable.

2. Methods and materials

2.1. Animal housing

Male CD1 mice were used for all experiments. Animals were 24—26 days old at the day of arrival and were kept on a 12L:12D cycle (lights-on at 0700 h). Food and water was provided *ad libitum*. The experiments were carried out in accordance with European Communities Council Directive 86/609/EEC. All efforts were made to minimize animal suffering during the experiments. The protocols were approved by the committee for the Care and Use of Laboratory Animals of the Government of Upper Bavaria, Germany.

2.2. Chronic stress paradigm

The chronic social stress procedure was performed as described previously (Schmidt et al., 2007). In this paradigm, mice are exposed to a highly unstable social and hierarchical situation during the adolescence and young adult period. Briefly, after a habituation period of five days following arrival, the group composition in each cage was changed twice a week for 7 weeks; each time it was made sure that four mice from different cages were put together in a new, clean cage. The rotation schedule was randomized to minimize the likelihood of a repeated encounter with the same mice throughout the experiment. Control mice remained with the same cage mates. During the recovery period, all