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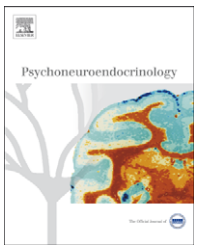

Mice selected for high *versus* low stress reactivity: A new animal model for affective disorders

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Summary
Affective disorders such as major depression are among the most prevalent and costly diseases of the central nervous system, but the underlying mechanisms are still poorly understood. In recent years, it has become evident that alterations of the stress hormone system, in particular dysfunctions (hyper- or hypo-activity) of the hypothalamic–pituitary–adrenal (HPA) axis, play a prominent role in the development of major depressive disorders. Therefore, we aimed to generate a new animal model comprising these neuroendocrine core symptoms in order to unravel parameters underlying increased or decreased stress reactivity.

Starting from a population of outbred mice (parental generation: 100 males and 100 females of the CD-1 strain), two breeding lines were established according to the outcome of a 'stress reactivity test' (SRT), consisting of a 15-min restraint period and tail blood samplings immediately before and after exposure to the stressor. Mice showing a very high or a very low secretion of corticosterone in the SRT, i.e. animals expressing a hyper- or a hypo-reactivity of the HPA axis, were selected for the 'high reactivity' (HR) and the 'low reactivity' (LR) breeding line, respectively. Additionally, a third breeding line was established consisting of animals with an 'intermediate reactivity' (IR) in the SRT.

Already in the first generation, i.e. animals derived from breeding pairs selected from the parental generation, significant differences in the reactivity of the HPA axis between HR, IR, and LR mice were observed. Moreover, these differences were found across all subsequent generations and could be increased by selective breeding, which indicates a genetic basis of the respective phenotype. Repeated testing of individuals in the SRT furthermore proved that the observed differences in stress responsiveness are present already early in life and can be regarded as a robust genetic predisposition.

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Tests investigating the animal's emotionality including anxiety-related behavior, exploratory drive, locomotor activity, and depression-like behavior point to phenotypic similarities with behavioral changes observed in depressive patients. In general, HR males and females were 'hyperactive' in some behavioral paradigms, resembling symptoms of restlessness and agitation often seen in melancholic depression. LR mice, on the other hand, showed more passive-aggressive coping styles, corresponding to signs of retardation and retreat observed in atypical depression.
Several morphometric and neuroendocrine findings further support this view. For example, monitoring the circadian rhythm of glucocorticoid secretion revealed clearly increased trough levels in HR mice, resulting in a flattened diurnal rhythm, again adding to the neuroendocrine similarities to patients suffering from melancholic depression.
Taken together, our results suggest that distinct mechanisms influencing the function and regulation of the HPA axis are involved in the respective behavioral and neurobiological endophenotypes. Thus, the generated HR/IR/LR mouse lines can be a valuable model to elucidate molecular genetic, neuroendocrine, and behavioral parameters associated with altered stress reactivity, thereby improving our understanding of affective disorders, presumably including the symptomatology and pathophysiology of specific subtypes of major depression.

1. Introduction

Stress-related disorders such as major depression (MD) are among the most prevalent and costly diseases of the central nervous system. About 240 million people are affected worldwide, reflecting a high lifetime prevalence of about 17% (Wong and Licinio, 2001; Nestler et al., 2002; Kessler et al., 2003). In general, mood disorders are a major cause of morbidity as they show a high rate of recurrence ($>50\%$) and the duration of a depressive episode can be more than 2 years in about 30% of the patients, also involving a high risk for suicide (Wong and Licinio, 2001; Nestler et al., 2002; Kessler et al., 2003). Apart from the tremendous suffering of the affected individuals and their families, depressive disorders also cause a high economic burden (year 2000 estimated total costs of MD in the USA: 83.1 billion $ Greenberg et al., 2003). Furthermore, a considerable comorbidity with other psychiatric disorders (e.g. anxiety and substance abuse) is observed and MD has been identified as a risk factor for other clinical conditions such as obesity, cardiovascular, and neurodegenerative disorders (Kessler et al., 2003; Rumsfeld and Ho, 2005; Swaab et al., 2005; Bornstein et al., 2006).

Clinical features of MD encompass mood changes, vegetative dysfunctions, motor deficits, and cognitive impairments. According to current diagnostic algorithms (DSM-IV), patients attributed to major depression have depressed mood, diminished interest or pleasure in enjoyable activities/stimuli (e.g. sex, food, social interaction), disturbed sleep (insomnia or hypersomnia), decreased or increased appetite, significant changes in weight, psychomotor agitation or retardation, cognitive impairments, feelings of worthlessness and inappropriate guilt, and often recurrent suicidal ideation. Thus, the current diagnosis of MD is, in contrast to other diseases, not based on objectifiable signs or diagnostic markers and includes a highly variable, sometimes even contrasting set of symptoms. Therefore, attempts have been made to define 'subtypes' of depression with potentially distinct pathophysiology and response to treatment. Two quite common and clinically important subtypes of MD are the 'melancholic' (also termed 'endogenous' or 'typical') and the 'atypical' form of depression. Melancholia is associated with non-reactive mood, anxiety, insomnia (including early morning awakening), loss of appetite and weight, as well as marked psychomotor changes, involving hyperarousal and agitation (Gold and Chrousos, 2002; Nestler et al., 2002; Hasler et al., 2004a; Antonijevic, 2006). Atypical depression seems to be distinctly different, as it is characterized by reactive/labile mood, hypersomnia (oversleeping), increased appetite and weight gain, as well as lethargy and fatigue (Nierenberg et al., 1998; Angst et al., 2002; Gold and Chrousos, 2002; Nestler et al., 2002; Antonijevic, 2006).

In recent years, it has become evident that pathological alterations in the stress hormone systems play a major role in the development of depressive disorders. The activity of the sympathetic nervous system as well as the hypothalamic–pituitary–adrenal (HPA) axis is dysregulated in depressed patients and restored by successful antidepressant treatment during remission (findings of human and animal studies including discussions on potential mechanisms are reviewed in: Holsboer, 2000; Wong and Licinio, 2001; Gold and Chrousos, 2002; Nestler et al., 2002; Hasler et al., 2004a; Cryan and Holmes, 2005; de Kloet et al., 2005; Bale, 2006; Müller and Holsboer, 2006).

In particular, dysfunctions (hyper- or hypo-activity) of the HPA axis in patients suffering from mood disorders are a firmly established finding in biological psychiatry. About 50% of patients suffering from MD (mainly of the melancholic subtype) present a hyperactive HPA system resulting in hypercortisolism (see reviews cited above). The production and secretion of glucocorticoids (mainly cortisol in humans and corticosterone in murine rodents) from the adrenal cortex is regulated by the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which, in turn, is stimulated by corticotrophin-releasing hormone (CRH) and arginine-vasopressin (AVP) derived from parvocellular neurons of the paraventricular nucleus (PVN) of the