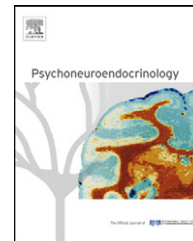




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Behavioural consequences of two chronic psychosocial stress paradigms: Anxiety without depression

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Summary Chronic stress, in particular chronic psychosocial stress, is a risk factor in the aetiology of various psychopathologies including anxiety- and depression-related disorders. Therefore, recent studies have focussed on the development of social-stress paradigms, which are believed to be more relevant to the human situation than non-social-stress paradigms. The majority of these paradigms have been reported to increase both anxiety- and depression-related behaviour in rats or mice. However, in order to dissect the mechanisms underlying anxiety or depression, animal models are needed, which specifically induce one, or the other, phenotype. Here, we study both short- (1 d after stressor termination) and long-term (4 d or 7 d after stressor termination) behavioural and physiological consequences of two well-validated chronic psychosocial stress models: social-defeat/overcrowding (SD/OC) and chronic subordinate colony housing (CSC). We demonstrate that SD/OC and CSC result in different physiological alterations: SD/OC more strongly affecting body-weight development, whereas CSC more strongly affects adrenal and pituitary morphology. Both stressors were shown to flatten circadian locomotor activity immediately after stress termination, which normalized 7 d later in SD/OC group but reversed to hyperactivity during the dark phase in the CSC group. Importantly, neither stress paradigm resulted in an increase in depression-related behaviour as assessed using the forced swim test, tail suspension test and saccharin preference test at any time-point. However, both stress paradigms lead to an anxiogenic phenotype; albeit with different temporal profiles and not towards a novel con-specific (social anxiety). CSC exposure elevates anxiety-related behaviour immediately after stressor termination, which lasts for at least 1 wk. In contrast, the anxiogenic phenotype only develops 1 wk after SD/OC termination. In conclusion, both models are unique for

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uncovering the molecular underpinnings of anxiety-related behaviour without conflicting depression-based alterations.

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Introduction

Despite substantial research efforts in the last decades, the aetiology of stress-based disorders such as major depression and anxiety remains poorly understood. This has led to a resurgence of interest in developing more relevant animal models than the majority currently employed. Therefore, given the evidence purporting chronic social stress to be a risk factor for the development, not only of cardiovascular and inflammatory diseases, but also of depression and anxiety in vulnerable individuals (Cryan and Slattery, 2007), recent attempts have focussed on the development of chronic social stress paradigms (Blanchard et al., 1995; Keeney and Hogg, 1999; Bartolomucci et al., 2003; Fuchs and Flugge, 2003; Stefanski et al., 2003; Engler et al., 2005; Berton et al., 2006; Reber et al., 2006, 2007; Tsankova et al., 2006; Krishnan et al., 2007; Schmidt et al., 2007). Such paradigms are believed to be more relevant to the human situation than non-social stress paradigms (e.g. repeated restraint (Cryan and Slattery, 2007)) and, thus, can better reveal the behavioural, neuroendocrine or immunological consequences of chronic stress.

Thus, the use of social defeat/subordination (De Goeij et al., 1992; Amstislavskaya and Kudryavtseva, 1997; Avgustinovich et al., 1997; Bartolomucci et al., 2001; Keeney et al., 2001; Stefanski, 2001; Bartolomucci et al., 2003; Berton et al., 2006; Reber et al., 2006, 2007; Miczek et al., 2008; Savignac et al., 2010; Denmark et al., 2010) and social instability (Engler et al., 2005; Bailey et al., 2006; Schmidt et al., 2007; Kemme et al., 2008; Sterlemann et al., 2008; Engler et al., 2008; Bailey et al., 2010) paradigms in the last decades have revealed numerous behavioural and physiological consequences that occur following chronic psychosocial stress exposure. The majority of these stressors have been reported to increase both anxiety- and depression-related behaviour (Keeney and Hogg, 1999; Blanchard et al., 2001; Berton et al., 2006; Krishnan et al., 2007; Schmidt et al., 2007). This is perhaps not surprising, given the high comorbidity between anxiety- and depression-related disorders, with approximately half of the patients diagnosed with major depressive disorder (MDD) also meeting criteria for comorbid anxiety (Kennedy, 2008). In addition, approximately 50% of patients with generalised anxiety disorder display symptoms of depression, while this level drops dramatically for other anxiety disorders, such as post-traumatic stress disorder and specific phobias (Hirschfeld, 2001; Kessler et al., 2006; Mackenzie et al., 2011). As in humans, behavioural alterations induced by the above mentioned social stressors persist for a long-time after the termination of the stressor (Fuchs, 2005; Berton et al., 2006; Krishnan et al., 2007; Kennedy, 2008). Thus, such models allow us to enhance our knowledge of underlying mal-adaptations caused by chronic stressor exposure. For example, chronic social defeat in mice was shown to result in an anxious-like phenotype, to induce an anhedonic state, and to reduce their

social approach, for at least one month after stress exposure. In contrast, behaviour in traditional depression tests such as the forced swim test (FST) and tail suspension test (TST) were not altered (Berton et al., 2006; Krishnan et al., 2007). Such findings demonstrate not only the comorbid phenotype observed after social stress exposure, but also the need in preclinical models to assess multiple behavioural readouts. However, they also highlight a drawback of the models currently used to assess stress-related psychopathologies. In order to really dissect the mechanisms underlying anxiety or depression, animal models are needed, which specifically induce one phenotype. There are two main rationales for this approach: (i) despite the high comorbidity between anxiety and depression, there are a large percentage of patients who suffer from only one or the other disease and (ii) such a model is likely to make analysis of the underlying pathophysiology of the disorder simpler. To date, only the social disruption model has been reported to cause increased anxiety in the absence of enhanced depression-related behaviour (Kinsey et al., 2007). However, only FST and TST, and not anhedonic-like behaviours were assessed.

We have previously reported the physiological and immunological consequences of exposure to two chronic psychosocial stress paradigms: social defeat/overcrowding (SD/OC) and chronic subordinate colony housing (CSC) (Reber et al., 2006, 2007, 2008; Reber and Neumann, 2008; Veenema et al., 2008; Singewald et al., 2009; Schmidt et al., 2010; Reber et al., 2011). The SD/OC model combines exposure to repeated social defeat over 3 wk with periods of overcrowding and single-housing, which adds a component of social instability. In contrast, the CSC model consists in housing 4 experimental mice together with a dominant, and larger, resident for 3 wks. Thus, while CSC reflects a continuous form of chronic stress, SD/OC rather mimics an intermittent chronic stressor, but both cause numerous alterations in stress-related physiological and immunological parameters (Reber et al., 2006, 2007, 2008; Veenema et al., 2008; Singewald et al., 2009; Schmidt et al., 2010; Reber et al., 2011). Interestingly, the increased level of pro-inflammatory cytokines observed following CSC is evident for at least 8 d (Reber et al., 2008). These results, coupled with those from the other chronic stress paradigms, suggest that it is likely that SD/OC and CSC induce lasting behavioural changes. In this context it has repeatedly been demonstrated that CSC exposure leads to an anxious-like phenotype immediately after stressor termination (Reber et al., 2007, 2008; Reber and Neumann, 2008; Veenema et al., 2008; Singewald et al., 2009). However, the effect of CSC on depression-related behaviour remains unknown, and no studies have examined the behavioural consequences of SD/OC, at least in the context of a standard diet (Finger et al., 2011a,b).

Therefore, in the present study we aimed to assess the impact of these two well-validated, clinically-relevant, psychosocial stress paradigms on both short- and long-term anxiety- and depression-related behaviour.

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