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The temporal impact of chronic intermittent psychosocial stress on high-fat diet-induced alterations in body weight

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Summary
Background: Chronic stress and diet can independently or in concert influence the body's homeostasis over time. Thus, it is crucial to investigate the interplay of these parameters to gain insight into the evolution of stress-induced metabolic and eating disorders.
Methods: C57BL/6J mice were subjected to chronic psychosocial (mixed model of social defeat and overcrowding) stress in combination with either a high- or low-fat diet for three or six weeks. To determine the evolution of stress and dietary effects, changes in body weight, caloric intake and caloric efficiency were determined as well as circulating leptin, insulin, glucose and corticosterone levels and social avoidance behaviour.
Results: Exposure to stress for three weeks caused an increase in weight gain, in caloric intake and in caloric efficiency only in mice on a low-fat diet. However, after six weeks, only stressed mice on a high-fat diet displayed a pronounced inhibition of body weight gain, accompanied by reduced caloric intake and caloric efficiency. Stress decreased circulating leptin levels in mice on a low-fat diet after three weeks and in mice on a high-fat diet after three and six weeks of exposure. Plasma levels of insulin and markers of insulin resistance were blunted in mice on high-fat diet following six weeks of stress exposure. Social avoidance following chronic stress was present in all mice after three and six weeks.
Conclusions: This study describes the evolution of the chronic effects of social defeat/over-crowding stress in combination with exposure to high- or low-fat diet. Most importantly, we demonstrate that a six week chronic exposure to social defeat stress prevents the metabolic effects of high-fat diet, by inhibiting an increase in weight gain, caloric intake and efficiency

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and insulin resistance as well as in plasma leptin and insulin levels. This study highlights the importance of considering the chronic aspects of both parameters and their time-dependent interplay.

1. Introduction

In situations of chronic stress humans show changes in eating behaviour and alterations in body weight (Lattimore and Maxwell, 2004; Wallis and Hetherington, 2009). It is well known that chronic stress has a major impact on metabolic, endocrine and psychological functions (McEwen, 2000; de Kloet et al., 2005; Koolhaas et al., 2011). Exposure to chronic stress can lead to an increase in the consumption of calorie-dense high-fat foods, thereby increasing the risk to develop obesity or on the other hand can lead to stress-induced anorexia (Lo Sauro et al., 2008; Block et al., 2009; De Vriendt et al., 2009).

Several animal models describe the correlation between chronic stress and obesity. In mice chronic stress increases the consumption of palatable foods depending on the social status of the animal thereby increasing its risk for weight gain, obesity and metabolic syndrome when fed a high-fat or cafeteria diet (Moles et al., 2006; Bartolomucci et al., 2009). Furthermore, chronic stress was found to aggravate the obese phenotype caused by the consumption of high-fat diet, with an increase of abdominal fat deposits, disruptions in lipid synthesis and a rise in neuropeptide Y levels (Kuo et al., 2007, 2008; Chuang et al., 2010a). Dallman et al. have developed a model describing the reciprocal relationship between diet, obesity and stress, wherein stress can induce ''comfort eating'' in a feed forward loop and the consumption of these diets can lead to a blunted response to stress in a feedback loop (Pecoraro et al., 2004; Dallman et al., 2005; Dallman, 2010; Maniam and Morris, 2010). However, on the other hand several other rodent studies describe a pronounced anorexic phenotype as a response to repeated stress exposure with inhibited body weight gain or pronounced body weight loss and reduced caloric intake (Martí et al., 1994; Weninger et al., 1999; Kim et al., 2003).

The underlying reason for the divergent feeding-related phenotypes in rodent models of chronic stress can be manifold. Indeed, differences in the variety of stress and feeding protocols applied with different types of stressors, diets, protocol durations, strains of animals and stress intensities being amongst the most critically important factors. Overall, one can conclude that chronic stress will interact with diet to alter feeding and metabolic parameters relevant to obesity and other eating disorders.

Another important aspect is the chronic nature of both features studied. The effects of stress as well as the impact of dietary manipulations on the metabolic homeostasis develop in a temporal fashion which may influence the net effect on physiology. Chronic exposure to a variety of diets with a high fat content causes a range of metabolic and endocrine changes over time (Hariri and Thibault, 2010). Best described in models of diet-induced obesity, prolonged feeding leads to an augmentation of body fat deposition, accompanied by the gradual development of leptin and insulin resistance (Park et al., 2005; Morrison et al., 2009). Furthermore, long-term ingestion of high-fat diet can alter depression-like behaviour (Abildgaard et al., 2011) and the response to antidepressant treatment (Isingrini et al., 2010). Similarly, alterations in the hypothalamic pituitary adrenal (HPA) axis, the central regulator of stress effects, develop over time, with an acute hyperactivity and a chronic dysregulation with abnormal peripheral to central feedback [for review see: Makino et al., 2002; McEwen, 2007].

The hormone leptin modulates homeostasis at the interface of both diet and stress. It plays a key role in the regulation of body weight and food intake, with leptin deficiency in the ob/ob mouse leading to pronounced obesity, type 2 diabetes and hyperphagia (Lindström, 2007; Finger et al., 2010, 2011). Leptin is released into the bloodstream in proportion to the body's adipose state, and induces anorexigenic effects in a feedback function via hypothalamic neurons [for review see: Belgardt and Brüning, 2010]. Diet-induced obese animals present with a central insensitivity to these anorexigenic effects of leptin although circulating leptin levels in these animals are high (Morrison et al., 2009). In contrast, exposure to chronic stress causes a decrease in circulating leptin levels (Lu et al., 2006; Chuang et al., 2010b), and the potential role of leptin as an antidepressant has been described (Lu, 2007).

However, despite the strong links between diet and stress there is a paucity of studies investigating the temporal evolution and interplay of stress-induced and diet-induced effects. Thus, in this study we investigate the time-dependent modulation of body weight gain, caloric intake and efficiency as well as circulating leptin levels in response to chronic intermittent psychosocial stress of combined social defeat and overcrowding and concomitant exposure to high-fat diet.

2. Methods

2.1. Animals

In this study two cohorts of male C57BL/6J mice (cohort 1, 6 weeks of stress: $n = 37$, 7 weeks of age; cohort 2, 3 weeks of stress: $n = 39$, 7 weeks of age) and one group of male CD1 mice ($n = 50$, 9 weeks of age) were used. All mice were obtained from Harlan, UK. On the date of arrival all mice were singly housed in standard holding cages ($33 \times 15 \times 13\ cm^3$) for seven days. The holding room was temperature ($21 \pm 1\ ^\circ C$) and humidity ($55 \pm 10\%$) controlled and under a 12-h light/dark cycle (lights on 0700 h). All experiments were conducted in accordance with the European Directive 86/609/EEC, the Recommendation 2007/526/65/EC and approved by the Animal Experimentation Ethics Committee of University College Cork. All efforts were made to minimise animal suffering and to reduce the number of animals used.