



# Social overcrowding as a chronic stress model that increases adiposity in mice



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Adrb1

**Abstract** Stress is a widely recognized risk factor for psychiatric and metabolic disorders. A number of animal models utilizing various stressors have been developed to facilitate our understanding in the pathophysiology of stress-related dysfunctions. The most commonly used chronic stress paradigms include the unpredictable chronic mild stress paradigm, the social defeat paradigm and the social deprivation paradigm. Here we assess the potential of social crowding as an alternative chronic stress model to study the effects on affective behaviors and metabolic disturbances. Ten-week-old male C57BL/6 mice were housed in groups of four (control) or eight (social crowding; SC) in standard cage for 9 weeks. Exploration, anxiety- and depressive-like behaviors were assessed in the open field test, the elevated T-maze, the novelty-suppressed feeding test and the forced swim test. SC mice exhibited a modest anxiety-like phenotype without change in depressive-like behaviors. Nine weeks of social crowding did not affect the body weight, but robustly increased adiposity as determined by increased mass of fat depots. Consistent with the increased fat content, serum leptin was markedly elevated in the SC mice. Specific changes in gene expression were also observed in the hypothalamus and the white adipose tissue following SC housing. Our study demonstrates the potential of social crowding as an alternative model for the study of stress-related metabolic and behavioral dysfunctions.

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## 1. Introduction

Chronic stress has been shown to affect metabolic, endocrine and psychological functions both in animal studies and in human population-based and clinical studies

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(McEwen, 2000; de Kloet et al., 2005; Block et al., 2009; De Vriendt et al., 2009; Wallis and Hetherington, 2009; Koolhaas et al., 2011). Substantial evidence indicates that chronic stress is a risk factor for affective and metabolic disorders (McEwen et al., 2012; Hunter and McEwen, 2013; Sinha and Jastreboff, 2013). In a Finnish study by Marniemi et al. (2002), monozygotic twins discordant for obesity were assessed for differences in hormonal, physiological and psychological parameters. Notably, the obese co-twins showed higher index of psychosocial stress perception compared to their lean co-twins (Marniemi et al., 2002). In humans, the effect of stress on feeding and body weight appears to be bidirectional (Gibson, 2006; Serlachius et al., 2007; Torres and Nowson, 2007; Block et al., 2009). Why some people lose and others gain weight in response to stress is not fully understood and is likely to involve many factors (Stone and Brownell, 1994; Epel et al., 2004). One explanation is the balance between an increase in  $\beta$ -adrenergic activation, the body's main fat-burning mechanism (leading to weight loss), and the increased intake of sugar- and fat-rich comfort foods (resulting in weight gain) (Dallman et al., 2003; Dodt et al., 2003; Kuo et al., 2008). The observation that those who are initially overweight are more inclined to increase body weight when stressed whereas those who are of normal- or under-weight do not led Dallman to propose that difference in metabolic outcomes might be the results of higher insulin concentration in people with higher body mass index (Dallman, 2010).

Similar to humans, animal models of chronic stress have produced variable and even opposite phenotypes of food intake, body weight gain and adiposity. Several studies described a pronounced anorexic phenotype following repeated stress exposure. Using an unpredictable chronic mild stress (UCMS) model, Michel et al. (2005) observed reduced weight gain and adiposity in stressed mice on a high-fat diet. A similar observation was made by Kim et al. (2003) with rats subjected to 8 weeks of UCMS (Kim et al., 2003). Other types of chronic stressors, such as repetitive daily restraint, turpentine abscess, surgical stress and immobilization have also been reported to reduce food intake in rodents (Marti et al., 1994; Weninger et al., 1999). On the other hand, several studies also demonstrated that chronic psychosocial stress models such as the social defeat/sensory contact model, lead to hyperphagia and increased body weight gain and adiposity (Bhatnagar and Vining, 2003; Moles et al., 2006; Bartolomucci et al., 2009). In Syrian hamsters, social crowding (for female) and intermittent or chronic social defeat and footshock (for male) also lead to increases in food intake, body mass and adiposity (Borer et al., 1988; Meisel et al., 1990; Foster et al., 2006; Solomon et al., 2007). Long-term social isolation has also been shown to accelerate body weight gain and adiposity in mice, although this effect appears to be strain-dependent (Nonogaki et al., 2007). Chronic stress was also found to increase consumption of more palatable food, which are typically high in fat and/or sugar content (Gibson, 2006; Zellner et al., 2006; O'Connor et al., 2008; Roberts et al., 2013) and aggravate diet-induced obesity (Kuo et al., 2007, 2008). Studies of mice subjected to chronic social defeat stress identified ghrelin signaling in catecholaminergic neurons as a critical mechanism for stress-induced food-reward behavior and the associated body weight gain (Lutter et al., 2008; Chuang

et al., 2011; Patterson et al., 2013). However, there were also reports of a lack of effect or even reduced body weight gain in stressed mice fed high-fat diet (Michel et al., 2005; Bartolomucci et al., 2009; Finger et al., 2012).

The highly variable metabolic phenotypes observed in the different studies have been attributed to differences in the types of stressors, diets, protocol durations, strains of animals and stress intensities. The variability also reflects the complexity of the interaction between stress and metabolic processes and highlights the importance of the development and thorough characterization of different stress models. In this study, we used high-density living as a mild form of chronic social stress due to overcrowding. We assessed the affective behaviors and body composition changes following 1 and 2 months of social crowding, respectively.

## 2. Materials and methods

### 2.1. Animals

Ten weeks old male C57BL/6 mice (Charles River Laboratories, Wilmington, MA, USA) were housed in groups of four (control; 3 cages) or eight (social crowding; 2 cages) in standard cages (31 cm  $\times$  17 cm  $\times$  14 cm) for 9 weeks. All mice were kept under a 12 h light/dark cycle (lights on at 0600 h), with free access to water and standard chow diet (11% fat, 28% protein, 61% carbohydrate, caloric density 3.4 kcal/g, Research Diets). Mice were transferred to clean cages when the bedding became too soiled, which were 1–2 weeks for the control group and twice weekly for the social crowding (SC) group. Mice were weighed at week 1, 4 and 8. All use of animals was approved by the Ohio State University Animal Care and Use Committee, and was in accordance with the NIH guidelines.

### 2.2. Behavioral analysis

After 1 month of housing in the different conditions, mice were subjected to behavioral testing in the following order: (1) open field test on day 30, (2) elevated T-maze on day 35, (3) forced swim test on day 37 and (4) novelty suppressed feeding on day 40. All tests were conducted during the light phase.

### 2.3. Open field test (OF)

To assess exploration and general motor activity, mice were placed individually into the center of an open square arena (60 cm  $\times$  60 cm, enclosed by walls of 48 cm). Each mouse was allowed 10 min in the arena, during which time its activity was recorded and analyzed by TopScan (Clever Sys Inc, Vienna, VA, USA). Specifically, the parameters measured include distances traveled in the periphery and in the center of the arena (36 cm  $\times$  36 cm), the total distance traveled, and the time spent in the center of the arena. The total distance traveled provides a measure of exploratory activity while the time and distance ratio of arena center exploration provide an indication of anxiety level. In addition, the number of fecal boli was counted as an additional measure of physiological response to anxiety. The arena was cleaned with 30% ethanol between trials to remove any odor cues.

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