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Psychosocial stress induces hyperphagia and exacerbates diet-induced insulin resistance and the manifestations of the Metabolic Syndrome

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Summary Stress and hypercaloric food are recognized risk factors for obesity, Metabolic Syndrome (MetS) and Type 2 Diabetes (T2D). Given the complexity of these metabolic processes and the unavailability of animal models, there is poor understanding of their underlying mechanisms. We established a model of chronic psychosocial stress in which subordinate mice are vulnerable to weight gain while dominant mice are resilient. Subordinate mice fed a standard diet showed marked hyperphagia, high leptin, low adiponectin, and dyslipidemia. Despite these molecular signatures of MetS and T2D, subordinate mice fed a standard diet were still euglycemic. We hypothesized that stress predisposes subordinate mice to develop T2D when synergizing with other risk factors. High fat diet aggravated dyslipidemia and the MetS thus causing a pre-diabetes-like state in subordinate mice. Contrary to subordinates, dominant mice were fully protected from stress-induced metabolic disorders when fed both a standard- and a high fat-diet. Dominant mice showed a hyperphagic response that was similar to subordinate but, unlike subordinates, showed a significant increase in VO_2, VCO_2, and respiratory exchange ratio when

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compared to control mice. Overall, we demonstrated a robust stress- and social status-dependent effect on the development of MetS and T2D and provided insights on the physiological mechanisms. Our results are reminiscent of the effect of the individual socioeconomic status on human health and provide an animal model to study the underlying molecular mechanisms.

1. Introduction

Type 2 diabetes (T2D) is multifactorial and polygenic. The initiation of the disease requires the combination of underlying genetic predisposition and several environmental factors, including hypercaloric diet and physical inactivity (Stumvoll et al., 2005; Kahn, 1994). A historical notion linking diabetes and stress was originally formulated by Willis in 1675 and Cannon (1929). Recent meta-analyses have revealed that a plethora of emotional stressors can be found in association with increased risk of T2D (Mooy et al., 2000; Räikkönen et al., 2007). The Whitehall II study clearly established a link between lifetime stress exposure and the development of the Metabolic Syndrome (MetS) and insulin resistance (Chandola et al., 2006). Other important studies such as the National Health and Nutrition Examination Survey (NHANES) also clearly established a connection between individual socioeconomic status health and mortality. Interestingly the effect of (objective or subjective) socioeconomic status (SES) is particularly relevant for T2D and MetS (Brunner, 2007; Mackenbach et al., 1997; McEwen and Mirsky, 2002; Singh-Manoux et al., 2005). Given the intrinsic complexity and unavailability of appropriate animal models, there is a poor understanding of the underlying molecular mechanisms linking SES, stress, MetS, and T2D related phenotypes. Convincing evidence is now provided for the positive association between hypercortisolemia, increased body weight, and insulin resistance (Kyrou et al., 2006; Shpilberg et al., 2012). Chronic stress (McEwen, 1998; Sapolsky et al., 2000; Koolhaas et al., 2011) associated with elevation of glucocorticoids and catecholamine levels can be characterized by visceral fat accumulation and insulin resistance (Bjorntorp and Rosmond, 2000; Dallman, 2010; Dallman et al., 1993). Also, elevated glucocorticoid level stimulates gluconeogenesis, opposes insulin effects, and prevents insulin secretion (Sapolsky et al., 2000; Dallman, 2010; Dallman et al., 1993). Available animal models of chronic stress link sympathetic nervous system and hypothalamic—pituitary—adrenal (HPA) axis hyperactivity with obesity, hyperphagia, craving of ''comfort foods'', and hypercholesterolemia (Bartolomucci et al., 2009; Scott et al., 2012; Chuang et al., 2010a,b; Sun et al., 2012; Tamashiro et al., 2007; Surwit, 1993; Moles et al., 2006; Foster et al., 2006; Kuo et al., 2007). However, most of the animal models of chronic stress are associated with weight loss (or weight gain only in the recovery phase) and few models are associated with features of MetS and T2D. Furthermore current rodent models of T2D are limited to genetic manipulations or pharmacological effects (Leiter, 2009; Brüning et al., 1997). Although very useful to test mechanisms, these models do not incorporate important aspects of the etiology of the human disease. Primate studies show a remarkable similarity with the human disease but the primate is not amenable for mechanistic studies (Shively et al., 2009; Wilson et al., 2008). Social subordination stress has long been considered ideal to mimic the impact of psychosocial stress on human pathologies (Koolhaas et al., 2011; Scott et al., 2012; Sapolsky, 2005; Bartolomucci, 2007). We have previously validated a mouse model of chronic psychosocial stress. Subordinate (SUB) mice show a depression-like phenotype and consistently manifest hyperphagia, weight gain, and hyperactivation of the HPA-axis (Bartolomucci et al., 2005, 2009; Dadomo et al., 2011). Conversely, dominant (DOM) mice show sympathetic hyperactivity and weight loss despite being hyperphagic (Bartolomucci et al., 2005, 2009). The aim of the present study was to test whether stress-induced neuroendocrine changes sensitizes for MetS and T2D and to determine if the metabolic consequences of stress are rank dependent. Our data showed that chronic stress in SUB led to features of MetS and T2D when combined with a hypercaloric diet. Conversely, DOM showed a remarkably healthy phenotype in the presence of hyperphagia, which was associated with increased energy expenditure.

2. Methods

2.1. Experimental outline

All experiments consisted of 5-day baseline phase followed by 4 weeks of chronic psychosocial stress. During baseline and the 1st week of stress all mice were fed a standard diet (STD), while during the 2nd, 3rd and 4th week of stress mice were randomized to a STD or a high fat diet (HFD). Between day 21 and 23 a subgroup of animals underwent a glucose tolerance test (GTT), insulin tolerance test (ITT) or indirect calorimetry. Plasma markers of MetS and hormones were measured in a subgroup of mice after overnight fasting. The experiment was replicated 2 times in mice fed STD and 3 times in mice fed HFD. Data were pooled after a preliminary analysis revealed no difference between the replicates.

3. Animals and diet

Subjects were three-to-four months old male CD1 mice derived from outbred stocks obtained from Charles River Italy or from Charles River USA. Mice were reared in a 12:12 h light:dark cycle at $22 \pm 2\,^{\circ}C$. Animal experiments were conducted at University of Parma (Italy) and University of Minnesota (USA) and approved by ethical committees of University of Parma and by Institutional Animal Care and Use Committee, University of Minnesota. Mice were fed a standard (4RF21, Mucedola 3.9 kcal/g, 6.5% kcal from fat or D12405B, Research Diet 3.85 kcal/g, 10% kcal from fat) or a high fat (HFD Mucedola modified 4RF21, 5.2 kcal/g, 45% kcal from fat or D12451 Research Diet, 4.73 kcal/g, 45% kcal from fat). Food intake was quantified every other day for the entire duration of the experiment and averaged