



## What is stressful for females? Differential effects of unpredictable environmental or social stress in CD1 female mice



Harold Dadomo<sup>a,1</sup>, Laura Gioiosa<sup>a,1</sup>, Jenny Cigalotti<sup>a</sup>, Graziano Ceresini<sup>a</sup>, Stefano Parmigiani<sup>b</sup>, Paola Palanza<sup>a,\*</sup>

<sup>a</sup> Department of Medicine and Surgery, University of Parma, Parma, Italy

<sup>b</sup> Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, Italy

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### ABSTRACT

Stressful life events are a major factor in the etiology of several diseases, such as cardiovascular, inflammatory and psychiatric disorders (i.e., depression and anxiety), with the two sexes greatly differing in vulnerability. In humans and other animals, physiological and behavioral responses to stress are strongly dependent on gender, and conditions that are stressful for males are not necessarily stressful for females. Hence the need of an animal model of social chronic stress specifically designed for females. In the present study we aimed to compare the effects of two different chronic stress procedures in female mice, by investigating the impact of 4 weeks of nonsocial unpredictable, physical stress by the Chronic Mild Stress paradigm (CMS; Exp.1) or of Social Instability Stress (SIS; Exp.2) on physiological, endocrine and behavioral parameters in adult female mice. CMS had a pronounced effect on females' response to novelty (i.e., either novel environment or novel social stimulus), body weight growth and hormonal profile. Conversely, 4 weeks of social instability did not alter females' response to novelty nor hormonal levels but induced anhedonia. Our findings thus showed that female mice were more sensitive to nonsocial stress due to unpredictable physical environment than to social instability stressors. Neither of these stress paradigms, however, induced a consistent behavioral and physiological stress response in female mice comparable to that induced by chronic stress procedures in male mice, thus confirming the difficulties of developing a robust and validated model of chronic psychosocial stress in female mice.

### 1. Introduction

The impact of stressful life events in the etiology of several diseases is widely recognized in clinical and preclinical research (Schmidt et al., 2008). Chronic stress has been described to increase the risk for developing metabolic syndrome (Chandola et al., 2006), cardiovascular and inflammatory diseases (Holmes et al., 2006) and psychopathologies, such as Alzheimer's disease (Wilson et al., 2003), depression and anxiety disorders (Belmaker and Agam, 2008; Cryan and Slattery, 2007; Kendler et al., 1999; Kessler, 1997; Kessler et al., 2005; Lupien et al., 2009; Nestler et al., 2002; Wang, 2005). Many of these stress-related disorders exhibit gender bias in frequency, severity, or response to treatment (Wittchen et al., 2011; Kessler, 2007; Gobinath et al., 2017). Major depression, which is the most prevalent mental disorder worldwide according to the World Health Organization statistics (WHO, 2015), can be caused or enhanced by chronic stress exposure (Belmaker and Agam, 2008; Kendler et al., 1999), presents high comorbidity with

anxiety-related disorders (Hirschfeld, 2001; Kessler et al., 2005; Kennedy, 2008) and is twice as common in women than in men (Gorman, 2006; Kendler et al., 1995, 2002; Kessler, 2007; Tafet and Bernardini, 2003; Wang, 2005; Wittchen et al., 2011).

Animal models involving chronic stress are particularly appropriate for emulating several neuropsychiatric disorders, to determine their underlying mechanisms and to find pharmacological treatment (Chaouloff, 2013; Davis and Pfaff, 2014; Goel and Bale, 2009; Pryce and Fuchs, 2016; Schmidt et al., 2008). However, human and animal data clearly indicate that individuals' perception of the stressfulness of a situation as well as the physiological and behavioral responses to stress are strongly dependent on gender; conditions that are stressful for males are not necessarily stressful for females, and the reverse (Bangasser and Wicks, 2017; Kokras and Dalla, 2014; Kudielka and Kirschbaum, 2005; Palanza, 2001; Palanza and Parmigiani, 2017). The development of appropriate animal models to investigate the biological basis of sex-biased differences in vulnerability to chronic stress is a

\* Corresponding author at: Unit of Neuroscience, Department of Medicine, University of Parma, Laboratory of Behavioral Biology, Viale delle Scienze 11A, 43100 Parma, Italy.  
E-mail address: [paola.palanza@unipr.it](mailto:paola.palanza@unipr.it) (P. Palanza).

<sup>1</sup> Equally contributing authors.

major challenge of modern bio-medical research.

Unpredictability, novelty, lack of control, threat to self-esteem are key factors making people perceive a situation as stressful and eliciting a physiological and psychological stress response (Gruenewald et al., 2004; Hammen, 2005; Havranek et al., 2016; Wood et al., 2015). As Koolhaas et al. (2011) pointed out in their critical re-evaluation of the stress concept, “the term ‘stress’ should be restricted to conditions where an environmental demand exceeds the natural regulatory capacity of an organism, in particular situations that include unpredictability and uncontrollability”. Accordingly, animal models of stress-induced disorders generally use chronic, unpredictable stressors involving either the physical or the social environment.

The chronic mild stress (CMS) procedure is a well-established rodent model for inducing behavioral changes commonly associated with clinical depression (Willner et al., 1992; Willner, 2017a). In this procedure mice or rats are exposed chronically to unpredictable environmental mild stressors such as cold, footshock, restraint, bright light, or forced swimming, resulting in behavioral changes, such as decreased response to rewards (considered a behavioral correlate of the core symptom of depression, anhedonia), decreased locomotor and explorative behavior, impairment of feeding, drinking and sexual behavior (Willner et al., 1987, 1992; Willner, 2017b). The CMS procedure induces several physiological changes (e.g., hypercortisolemia, hypertension) that are clinically associated with depression and many effects of CMS can indeed be reversed by antidepressant agents (Willner et al., 1987, 1996). Thus the CMS procedure appears to have face and predictive validity, at least when involving male mice or rats. A few studies have examined the effects of CMS on female rodents and they produced conflicting data; CMS can have an opposite effect to the expected depressed-like profile and the result was reported as an “anomalous” response to chronic stress (Willner, 2005). On the other hand, Dalla et al. (2005) reported that female rats were more vulnerable to chronic mild stress than males. Following CMS exposure, females showed decreased sucrose intake and open field activity, increased corticosterone levels, alteration in estrous cycle and decreased serotonergic activity in hippocampus and hypothalamus. In males CMS procedure induced only behavioral changes, such as decreased sucrose intake and open field activity (Dalla et al., 2005).

Human studies indicate that social rather than physical stress is associated to depression (Blazer and Hybels, 2005; Kessler, 1997). Thus animal models using unpredictable social stressors are currently considered the best available models of human psychopathological disorders (Blanchard et al., 1995; van Kampen et al., 2002). Chronic stress induced by social defeat and subordination has been a valuable tool to induce depressive-like behavior (Becker et al., 2008; Björkqvist, 2001; Fuchs and Flügge, 2002; Rygula et al., 2005). In male mice, defeat in aggressive encounters and chronic subordination due to unescapable exposure to the dominant animal, induce psychopathological changes and depressive-like behavior in male mice, accompanied by consistent alterations of hormonal, physiological, behavioral, immune and metabolic responses (Bartolomucci et al., 2004, 2005, 2009). Because of its congruence with the human condition, the defeat-induced loss of status in mice and rats has been proposed as a model of loss of self-esteem and depression in humans that parallels human psychiatric disorders related to negative emotions provoked by loss of social role, resources, and adverse social environment (Blanchard et al., 1995; Blanchard et al., 2001; Marrow and Brain, 1998; Willner et al., 1995). These models of defeat-related, psychosocial stress used for male mice (or rats) are, however, not appropriate for females, because female mice do not show high levels of competitive, territorial aggression or a strong dominance relationship when they are not in a reproductive state (Berry and Bronson, 1992; Palanza et al., 2005; Palanza and Parmigiani, 2017).

A number of models of social stress in female rodents have been proposed in order to elicit consistent behavioral, hormonal and metabolic changes. For instance, social deprivation by different lengths of social isolation have been widely used to induce a depressive-like

profile in females (Brain, 1975; Jesberger and Richardson, 1985; Koike et al., 2009; Martin and Brown, 2010; Palanza et al., 2001; Hong et al., 2012), as well as the crowding procedure (Finger et al., 2012; Lin et al., 2015; Reiss et al., 2007). Moreover, social instability stress, consisting either of alternation of crowding and social isolation or housing in an unpredictable social environment, was reported to induce some stress-related changes in female rats and mice (Haller et al., 1999; Jarcho et al., 2016; Schmidt et al., 2010). Results from such studies, however, are often conflicting and the problem is finding a consistent behavioral and physiological profile indicative of stress-related alterations in female mice (Jarcho et al., 2016; Schmidt et al., 2010). Virtually none of the proposed model of physical or social stress is, indeed, recognized to produce a consistent and coherent set of behavioral and physiological responses indicative of depression- and anxiety-like profile in adult female mice. In addition, not all depression and anxiety disorders in women, but also in men, are alike (Goldberg, 2011; Insel et al., 2010; Nandi et al., 2009). Therefore, different rodent models are likely to apply to different expressions of depressive and/or anxiety disorder (Brand et al., 2015; O’Leary and Cryan, 2013). Although women are more vulnerable to several stress-related disorders, such as major depression and anxiety, an apparent paradox is that rodent models are still mostly based on males (Palanza and Parmigiani, 2017; Zucker and Beery, 2010).

The aim of the present study was to compare the effects of two different chronic stress procedures, based on unpredictability of physical or social environment, upon several behavioral and physiological responses of female mice, in order to validate a behavioral procedure that may serve as a female animal model for stress-related depressive or anxiety disorders. Since large variability among different mouse strains is reported for stress responses, anxiety and depression-like behaviors (Belzung and Griebel, 2001; Ibarguen-Vargas et al., 2008; Milner and Crabbe, 2008; Mineur et al., 2006), we examined CD1 outbred mice, which reflect the genetic diversity in natural populations and can be used in behavioral studies in a translational perspective (Vogt et al., 2017; Palanza and Parmigiani, 2017). The ethogram of CD1 mice, among many mouse strains, is similar to that of wild mice, in particular for their social and emotional behavior (Chalfin et al., 2014; Holmes et al., 2000; Parmigiani et al., 1998, 1999). We carried out two experiments investigating the consequences of 4 weeks of either unpredictable CMS (Exp.1) or social instability (Exp.2) on behavioral, metabolic and endocrine parameters in adult female mice. At variance with Haller et al.’s (1999) procedure in rats, which also employed social isolation and crowding, social instability was achieved here by daily switching the cagemates that the experimental female was housed with. Isolation and crowding per se may indeed be stressful conditions for female mice (Beery and Kaufer, 2015; Martin and Brown, 2010; Reiss et al., 2007), while we aimed to evaluate the impact of instability of the social network in group-housed female mice.

We examined the experimental mice in different behavioral test for assessing anxiety, anhedonia, social exploration and novelty responses and evaluated the metabolic consequences of the stress procedures on females’ body weight growth, food intake and glucose plasma level. At the end of the study, we measured plasma Corticosterone (C) and Adrenocorticotrophic hormone (ACTH) and organs’ weight to determine stress-related physiological alterations.

## 2. General methods and materials

### 2.1. Experimental subjects

Experimental subjects were outbred CD1 female mice (*Mus musculus*) derived from Charles River Italia (Calco, Italy), born and reared in our vivarium at the Laboratory of Behavioral Biology at the University of Parma. Animal room temperature was set at  $22 \pm 2^\circ\text{C}$  with a 12 h light-dark cycle (lights on 07:00). Food (4rf21 standard diet, Mucedola, Italy) and water were available ad libitum. After weaning (25 days)

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