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Behavioral and physiological characterization of male mice under chronic psychosocial stress

Alessandro Bartolomucci[a,b,*], Tiziana Pederzani[a], Paola Sacerdote[c], Alberto E. Panerai[c], Stefano Parmigiani[a], Paola Palanza[a]

[a]*Dipartimento di Biologia Evolutiva e Funzionale, Università di Parma, Parco area delle scienze 11A, 43100 Parma, Italy*
[b]*Istituto di Psicologia, Università di Milano, Via T. Pini 1, 20134 Milano, Italy*
[c]*Dipartimento di Farmacologia, Chemioterapia e Tossicologia Medica, Università di Milano, Via Van itelli 32, 20129 Milano, Italy*

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Summary Social stress is a major factor in the etiology of several psychopathologies, with individuals greatly differing in vulnerability. The development of appropriate animal models of social stress is, thus, a major challenge of modern bio-medical research. Adult male mice were subjected to a new model of chronic psychosocial stress in which resident/intruder dyads live chronically in sensory contact and physically interact on a daily basis. Four behavioral categories were identified: Resident Dominants (RD), Resident Subordinates (RS), Intruder Dominants (InD), Intruder Subordinates (InS). Here we investigated: behavior during aggressive interactions; gross physiological components of mice metabolism; organ physiology; response to dexamethasone suppression test (DST). RD and InD mice showed persistently high levels of aggression. All four categories of mice showed robust lack of suppression of corticosterone level when challenged with the DST. Although food intake was not altered under chronic stress, body weight decreased in RD and InD mice while increased in InS and, even more so, in RS mice, suggesting an alteration of their metabolic functions. In conclusion, social status and territory ownership were factors determining individual vulnerability to stress exposure. Our model could, thus, be regarded as a valid model to investigate the biological basis of the individual differences in the response to stressful events.

1. Introduction

The impact of stressful events in the etiology of several psychopathologies is one of the most developed fields of research in biomedical sciences. Kind of stimulus, duration, intensity and predictability of the stressor applied are all relevant factors determining the development of a

*Corresponding author. Tel.: +39-0521-905636; fax: +39-0521-905657.
E-mail address: bartolomucci@biol.unipr.it (A. Bartolomucci).

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chronic stress state (Natelson et al., 1988; Mormede et al., 1988; Koolhaas et al., 1997; Stefanski and Engler, 1998). Recently, the concept of Allostasis has been proposed and predictions formalized by McEwen (1998). This concept is particularly useful because it permits a formal distinction between the adaptive stress responses (allostasis) which allows to cope with a challenge, and the overload of the organism physiological functions due to continuous activation of the adaptive coping machinery. The cumulative effect of over-activity of the allostatic system has been termed 'Allostatic load' (McEwen, 1998; McEwen and Wingfield, 2003). According to this view, and to several experimental evidences, it is now clear that an overload is more likely to develop when stressors of social nature will chronically challenge the organism following an unpredictable schedule (Blanchard et al., 2002; van Kampen et al., 2002). Indeed, models of social stress are currently considered the best available models of human psychopathological disorders, including major depression (Blanchard et al., 1995; van Kampen et al., 2002).

However, not all individuals exposed to chronic stress develop diseases and psychopathologies, i.e. individual differences in the occurrence of allostatic load are common, particularly in the human literature (Manuck et al., 1991; Sapolsky, 1994; Cohen and Herbert, 1996). Therefore, the development of appropriate animal models to investigate the biological basis of individual differences in vulnerability to social stress is a major challenge of modern bio-medical research. Within this framework we recently proposed an ethologically oriented model of chronic psychosocial stress (Bartolomucci et al., 2001), which is adapted from those previously developed with tree shrews and mice (Fuchs et al., 1996; Kudrayvtseva, 2000). In this paradigm, resident/intruder dyads live chronically in sensory contact and physically-interact on a daily base. In the beginning of the stress protocol, the social relations between the resident and the intruder mouse undergoes dynamic changes such that both the resident and the intruder may acquire the dominant social rank. Accordingly, animals subjected to this procedure of social stress can be divided in four subcategories named: Resident Dominant (RD), Resident Subordinate (RS), Intruder Dominant (InD) and Intruder Subordinate (InS). Therefore, our model offers the opportunity to investigate whether territory ownership (being resident in a territory) and social status (being dominant or subordinate), as well as their interaction (e.g. a resident becoming dominant or subordinate) are factors affecting the individual vulnerability to stress. In previous investigations we reported several physiological and behavioral alterations in mice under social stress (Bartolomucci et al., 2001, 2003b, c). When compared to control group housed mice (Bartolomucci et al., 2001, 2002, 2003a), the socially stressed animals showed: (i) high plasma corticosterone concentration, marked hyperthermia and tachycardia; (ii) RD and InD had high behavioral re-activity to novelty and low anti-KLH IgG; (iii) RS had major immune impairments, having low splenocytes proliferation (to ConA and KLH), Type 2 cytokines production and anti-KLH-IgG; (iv) InS showed a strong depression of locomotor activity (RS not yet investigated as far as locomotor activity is concerned).

The aim of the present study was to obtain information on metabolism (food intake, body weight and epididymal fat), organ physiology (internal organs weight) of mice under chronic social stress. As well, the behavior of resident and intruder mice during the daily fight was analyzed in detail. The choice was determined by the growing interest in underpinning the relationships between stress exposure, psychopathologies and metabolic alterations (Bjorntorp, 2001). In addition, to investigate the possible origin of the elevated plasma corticosterone (Bartolomucci et al., 2001), mice were submitted to dexamethasone suppression test (DST), a widely used test for HPA-axis functionality in both, pre-clinical and clinical research (Carrol, 1982; Barden et al., 1997).

2. Methods

2.1. Animals

Subjects were adult males Swiss CD-1 mice from an outbreed stock originally obtained from Charles River Italia (Calco, Italy). Mice were born and reared in a colony room at the University of Parma at 20 2°C in a 12-hr light–dark cycle (lights on 0700–1900). After weaning (25–28 days of age) they were housed in same-sex- groups of siblings (4–7 per cage) in Plexiglas cages (45 × 25 × 20 cm) with wood shaving bedding. The cages were changed weekly. All animal experimentation was conducted in accordance with the European Communities Council Directive of 24 November 1986 (86/EEC) and approved by the Italian Institute of Health.

2.2. Chronic psychosocial stress

The procedure has been originally described by Bartolomucci et al. (2001). Adult male mice to