Neurobiology of Stress xxx (2016) 1–9

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Social stress models in rodents: Towards enhanced validity

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ARTICLE INFO

Article history:
Received 3 May 2016
Accepted 20 September 2016
Available online xxx

Keywords:
Appraisal stress
Controllability
Predictability
Expectancy
Feedback
Corticosterone
Noradrenaline
Adrenaline

ABSTRACT

Understanding the role of the social environment in the development of stress related diseases requires a more fundamental understanding of stress. Stress includes not only the stimulus and the response but also the individual appraisal of the situation. The social environment is not only essential for survival it is at the same time an important source of stressors. This review discusses the social stress concept, how it has been studied in rodents in the course of time and some more recent insights into the appraisal process. In addition to the factors controllability and predictability, outcome expectancy and feedback of the victim's own actions during the social stress are suggested to be important factors in the development of stress related disease. It is hypothesized that individual differences in the way in which these factors are used in the appraisal of everyday life situations may explain individual vulnerability.

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1. Introduction

During the last decade there is a renewed interest in the use of the social environment in animal models of stress pathology. This is based on the fact that many animal species, including human beings spend most of their daily life in close proximity of conspecifics. It is generally assumed that a focus on social stress enhances the translational value of animal models. In some species, the social environment can be quite complex with a diversity of hierarchical relationships among group members. The general idea is that evolution has shaped these social structures for optimal survival. Living in a social community implies adaptation to the behavior and presence of other group members. In a stable social group, the social relationships are well established and there are no clear signs of stress pathology. From an evolutionary point of view, such a social structure should be optimal for health, reproduction and survival. However, social structures can be quite dynamic and have to be (re)established and maintained. This requires adaptation of the individual colony members and the degrees in which adaptation processes are activated depend of course on the stability of the social structure. Hence, the social structure and environment is not only essential for survival, it can be an important source of social stressors at the same time. In view of this dual nature and evolutionary significance of social structures, it is surprising that many

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http://dx.doi.org/10.1016/j.ynstr.2016.09.003

studies using social stimuli as stressors interpret the data in terms of maladaptation and stress related disease. This biomedical pathophysiological interpretation bias of rodent models of social stress and the limitations of such models of depression have recently been discussed in two papers (Chaouloff, 2013; Gray et al., 2015). A similar discussion on the adaptive or maladaptive significance of stress induced behavioral changes can be found in the clinical literature (Nesse, 2000; Nesse et al., 2016). The present paper will discuss some issues that might help in the interpretation of the adaptive and/or maladaptive significance of the behavioral consequences of social defeat.

Some of the early pioneers of stress research have emphasized the view that stress should be considered as a process that includes the stimulus, the perceptual processing or appraisal of this input and the behavioral and physiological output (J. W. Hennessy and Levine, 1979; Plaut and Friedman, 1982). Still, many studies and preclinical studies in particular seem to neglect this aspect of cognitive, higher level cortical processing of information. To understand social stimuli as stressors, assessing the activation of the so called stress systems such as the Hypothalamic-Pituitary-Adrenocortical (HPA) axis and the Sympathetic nervous – Adrenomedullary (SAM) system is not sufficient. These neuroendocrine systems have an important function in the cardiovascular and metabolic support of any behavioral reaction to salient environmental challenges or opportunities. For example, the response of these systems to rewarding stimuli such as sexual behavior or social victory can be just as high as to aversive stimuli (Buwalda et al., 2012). Similarly, stress systems are highly activated during the use of drugs with a strong euphoric action (Goeders, 2002). Hence, without taking perceptual processes into account, there is a serious risk of misinterpretation. There is also a risk of circular reasoning. Because aversive stimuli and negative affective states are often associated with activation of the neuroendocrine stress systems, i.e. the activation of 'stress' systems and/or measurement of "stress hormone" levels are subsequently used as an indicator or even proof of the negative connotation of social stress exposure. In addition, preclinical studies often define their stimulus as aversive, usually from an anthropomorphic line of reasoning, and interpret the myriad of physiological, neuroendocrine, immune and neurochemical changes that occur in response to it as a stress response. In conclusion, there is a need for indices that allow an answer to the question whether a social stimulus is indeed perceived as a stressor in the sense that it is considered a serious threat to homeostasis and thus to physical health and psychological well-being. This paper will discuss these perceptual processes in more detail; in particular the individual differentiation in outcome expectancy and feedback from the stressful event.

2. Social defeat and the appraisal process

2.1. Controllability, predictability

The terms controllability and predictability are central in the definition of a stressor. These terms date back to a series of elegant experiments by Martin Seligman, Steven Maier and Jay Weiss in the late sixties and early seventies of the last century (Seligman and Maier, 1967; Weiss, 1972). Using a yoked control stress paradigm, these authors concluded that it is not the physical nature of an aversive stimulus that induces somatic diseases such as stomach wall erosions or behavioral disorders such as learned helplessness, but rather the degree in which the stimulus can be controlled and/or predicted by an individual. Although the concept of controllability and predictability has strongly contributed to the present insights in stress physiology and the development of stress-related pathology, there are a few shortcomings in this concept. For example, there is evidence from the human literature that it is not the *actual* control that counts, but the *perceived* control (Salvador, 2005). This important insight necessitates a cautious interpretation of preclinical stress studies based on animal models. Stimuli that are considered as stressors from the anthropomorphic point of view may not necessarily be stressors from the animal point of view. In particular in social stress models, this is not always self-evident. This raises the question how to objectively assess whether a stimulus is perceived as a stressor in terms of predictability and controllability. In a recent paper, we argued that an uncontrollable condition can be distinguished from a controllable one by the adrenaline response and the slow recovery of the activated HPA axis and the SAM system (Koolhaas et al., 2011). This idea is illustrated for example in a comparison of the physiological response of a single social defeat with the response in the animal that wins the social interaction (Fig. 1). Although the magnitude of the acute corticosterone response is virtually identical, the recovery of the response takes almost twice as much time in the loser compared to the victor. The speed of recovery of the HPA axis response is determined by a delayed onset of negative feedback control mechanisms. This delayed onset includes a fast non-genomic action of glucocorticoids on neuronal excitability mediated by both mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) (De Kloet et al., 2008). It is suggested that the stressful nature of a stimulus acts in particular through this fast glucocorticoid action. Also the magnitude of the acute cardiovascular response to winning and losing a social interaction is identical, but the difference is in the recovery phase of this response. The defeated animal shows a delayed recovery (Koolhaas et al., 2011). Using controllable and yoked uncontrollable foot shocks in rats, Swenson and Vogel concluded already in 1983 that a delayed recovery of the corticosterone response and the release of adrenaline characterize an uncontrollable aversive situation (Swenson and Vogel, 1983). A graphic presentation of their original data is given in Fig. 2. Similar results were obtained in carefully controlled experiments using non-social stressors by de Boer and colleagues (de Boer et al., 1990). This central role of adrenaline in the acute stress response is consistent with more recent animal (Kvetnansky et al., 2013) and human research (Esler, 2010) demonstrating that

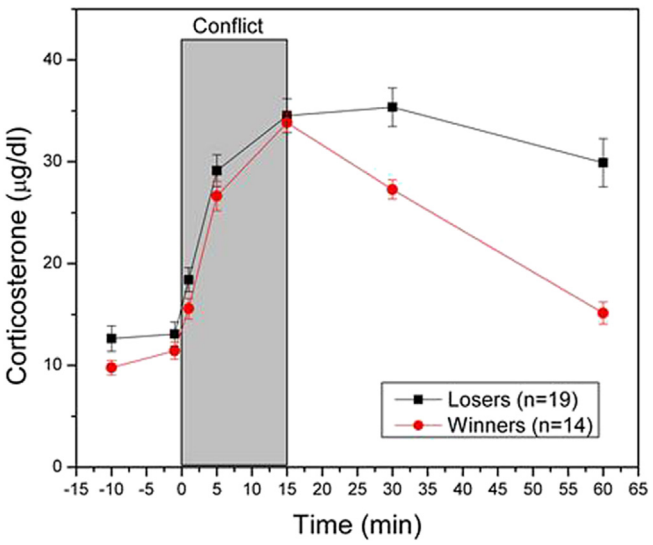

Fig. 1. Course of plasma corticosterone in male rats, before, during and after either winning or losing a social conflict. Animals were provided permanently implanted jugular vein cannula to allow undisturbed blood sampling during the social interaction (Koolhaas et al., 2011).

Please cite this article in press as: Koolhaas, J.M., et al., Social stress models in rodents: Towards enhanced validity, Neurobiology of Stress (2016), http://dx.doi.org/10.1016/j.ynstr.2016.09.003