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Frontiers in Neuroendocrinology 26 (2005) 27–40
Frontiers in Neuroendocrinology
www.elsevier.com/locate/yfrne

Social stress: From rodents to primates

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Abstract

Social stress is associated with development of many psychological and physiological disturbances in humans. Animal models are needed to determine the etiology of these diseases and to develop rational clinical therapies to treat those afflicted. Rodent and non-human primate models of social stress have been developed to address these needs and contribute in complementary ways to the understanding of social stress. In this review, we provide an overview of common rodent and non-human primate models of social stress used in the laboratory with a focus on social hierarchy models. The implications of the current findings on understanding of the development of stress-related disease will also be discussed.

Keywords: Social stress; Dominance; Subordination; Rat; Mouse; Non-human primate; Animal model

1. Introduction

Humans face social stress to varying degrees on an almost daily basis. Interpersonal relationships are dependent upon the interactions between people and on an individual's "position" in society. Social stress derived from these interactions can be one of the most important sources of stress in human life and may also play a critical role in the development of stress-related disorders and disease. Understanding the mechanisms underlying stress-induced disturbances will ultimately allow for improved clinical therapies and possible preventative strategies to decrease the incidence of these disorders. Laboratory models of stress have been used for many years to examine the behavioral and physiological mechanisms leading to disease conditions resulting from exposure to stress. However, it is often the case that the stress paradigm used in the laboratory bears little resemblance to the natural conditions under which social stress-related disease develops. For example, footshock, restraint, forced swim and/or cold are commonly used to generate stress in the laboratory but do not reliably resemble challenges animals are normally faced within their natural environment and may elicit behavioral and physiological responses different from those resulting from social or psychological stressors [32,42,50,75], such as social defeat or social hierarchy formation.

Increasingly, a greater amount of attention has been focused upon developing animal models that utilize more naturalistic experimental paradigms to model stress that is ethologically relevant to the model organism. Consequently, several animal models of social stress have been developed in order to investigate questions related to the etiology, treatment, and prevention of stress-related disorders. In this review, we provide an overview of common animal models of social stress used in the laboratory and discuss the implications of the current findings on understanding the development of stress-related disease.

1.1. Modeling social stress in the laboratory

Rodents and non-human primates are the most commonly used animals to model social stress since both

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doi:10.1016/j.yfrne.2005.03.001

take advantage of the inherent neuroethological social interactions and behavior of these species. Rodent models of social stress are widely used in the laboratory in part because of their short lifespan enabling investigators to conduct longitudinal studies in a short time span. In addition, they are relatively easy to maintain since they do not require the housing space and other resources as primates and are thus also less costly. Because of the amount of research on rodents, there is a vast literature documenting the behavior of rats and mice as well as some of their genetic correlates. This extensive database enables investigators to make direct genetic manipulations via knockout and transgenic technology furthering the understanding of stress disorders.

Non-human primates are highly dependent on social interaction and relationships and therefore are a useful model for studying social stress and the resulting effects. Their neuroanatomy and neurophysiology are also considered to be more analogous to those of humans contributing to construct validity of the models. The life span of many non-human primates is sufficiently long enabling investigators to conduct studies during specific critical periods, such as the neonatal or adolescent stages, without facing restrictive time constraints as occurs with rodents. A substantial literature documents the behavior of various species of non-human primates in the wild as well as in the laboratory providing an established baseline on which to superimpose experimental interventions.

In evaluating animal models of human disorders, it is important to determine the validity of the model relative to potential clinical applications. In this regard, both rodent and non-human primate models have face validity (i.e., the models reproduce the comparable symptoms as occur in human conditions) and varying degrees of predictive validity (i.e., animals respond similarly to some drugs as humans under the same conditions). However, the non-human primate model has the additional advantage in sharing more of the same endocrine and neural substrates with humans. Both animal models have their place in biomedical research and contribute to the overall "big picture" in different ways.

1.1.1. Social defeat

There are several models of social stress that are used in the laboratory and most can be categorized into one of two broadly defined groups: the resident-intruder and the social hierarchy or colony model. The resident-intruder paradigm of social defeat is a popular animal model of social stress typically utilized in rats and mice. It is based on the initial occupation and establishing of a territory by a resident male such that the male subsequently and rigorously defends the territory against unfamiliar male intruders. Rats and mice are naturally social animals, and this model is thus thought to be applicable to the study of mechanisms contributing to social stress-related disorders. However, it is important to note the caveat that the resident-intruder paradigm often does not reflect natural environmental conditions. Depending on the specific social defeat paradigm used, the experimenter can manipulate test conducting parameters to generate the desired outcome in resident-intruder models. For example, the resident is usually selected for high body weight and aggression to give it a greater advantage in defending its territory. In many cases, the resident male is also housed with a female, a procedure that increases aggression in male rats [24]. Residents are typically used repeatedly, thereby giving them experience of victory and further increasing their aggressiveness. Thus, the social defeat model may also be more similar to an acute stress akin to a post-traumatic stress disorder (PTSD) rather than chronic social stress experienced on a daily basis under normal living conditions.

1.1.2. Social hierarchy

Social stress is common in many animal species and typically results from competition for resources such as space, access to a reproductive partner, food, or water. A number of animal models have been developed to capitalize on the natural tendency of different species to form social hierarchies when housed in groups, including sugar gliders [37,48], rats [2,3,8,9,18,19,25,89,94], mice [22], and non-human primates [26,41,72,79,83,86,101]. Establishing and maintaining dominance in a group setting is psychologically and physically stressful for all parties, including both the dominant and the subordinate animals. Furthermore, since animals are group-housed for extended periods of time, the members of the group are continuously exposed to stress as opposed to the intermittent acute exposures often used in social defeat paradigms. In this review, we will focus primarily on social stress resulting from group housing and social hierarchy formation in rodent and non-human primate models.

Many studies have been done using rodent models, and some of the findings have been extended into non-human primates. The animal model that this review focuses on is the visible burrow system (VBS) model of social hierarchy and chronic psychosocial stress with references to other rodent studies. Briefly, the VBS model involves housing mixed-gender (four or five males and two females) groups of rats in a semi-naturalistic burrow environment continuously for 14 days or more. Within a period of 3–4 days after colony formation, a dominance hierarchy forms among the males of the group resulting in 1 dominant and 3 or 4 subordinate animals. Controls are single males pair-housed with a single female. For a more detailed description see [8,90].

The VBS model has the advantage of forming stable hierarchies over time; i.e., it has been used for investigating the effects of single (typically 14 days) as well as