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Preclinical experimental stress studies: Protocols, assessment and comparison

Anjana Bali, Amteshwar Singh Jaggi *

Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala 147002, India

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ABSTRACT

Stress is a state of threatened homeostasis during which a variety of adaptive processes are activated to produce physiological and behavioral changes. Preclinical models are pivotal for understanding these physiological or pathophysiological changes in the body in response to stress. Furthermore, these models are also important for the development of novel pharmacological agents for stress management. The well described preclinical stress models include immobilization, restraint, electric foot shock and social isolation stress. Stress assessment in animals is done at the behavioral level using open field, social interaction, hole board test; at the biochemical level by measuring plasma corticosterone and ACTH; at the physiological level by measuring food intake, body weight, adrenal gland weight and gastric ulceration. Furthermore the comparison between different stressors including electric foot shock, immobilization and cold stressor is described in terms of intensity, hormonal release, protein changes in brain, adaptation and sleep pattern. This present review describes these preclinical stress protocols, and stress assessment at different levels.

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* Corresponding author. Mobile: +91 9501016036.
E-mail addresses: anjubali.123@gmail.com (A. Bali), amteshwarjaggi@yahoo.co.in (A.S. Jaggi).

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1. Introduction

Hans Selye, Father of stress, described stress as a non-specific phenomenon representing the intersection of symptoms produced by a wide variety of noxious agents. Selye employed various conditions, including fasting, extreme cold, and others as stressors to produce the representative stress response, and defined that the determinants of the stress response are non-specific (Selye, 1950, 1998). However, John Wayne Mason modified the original concept of Selye by incorporating the importance of psychosocial stressors and the emotional aspects of stress. He defined stress response as a specific hormonal, behavioral and physiological response rather than the non-specific response as advocated by Selye (Mason, 1968, 1970). The stress response is an orchestrated process which involves various mechanisms for physiological and metabolic adjustments in the body to cope with the demands of a homeostatic challenge (Bali and Jaggi, 2013). These changes occur at the psychological (emotional and cognitive), behavioral (fight and flight), and biological level (altered autonomic and neuroendocrine function). According to Richard Lazarus, an appraisal of an event is essential for a psychosocial situation to be stressful, and argued that cognitive processes of appraisal are central in determining whether a situation is potentially threatening or not. In other words, stress response develops when the demands on the organism perceived by the individual exceed its ability to cope (Lazarus, 1966).

Acute stress triggers cascade of biological events mainly due to activation of two major pathways i.e. hypothalamic–pituitary–adrenal (HPA) axis and sympathetic adreno-medullary system. However, repeated exposure of a same stressor is generally associated with general adaptation syndrome (a phase of resistance to the homologous stressful condition). However, during persistent exposure of stress, the initial “adaptive response” may change to “maladaptation” in which biological and behavioral responses are counter-productive to the organism. Furthermore, repeated exposure of same stressor (chronic stress) sensitizes the HPA axis and exposure to novel, unpredictable stressor may cause long lasting dysregulation of the HPA axis (Gray et al., 2013; Herman, 2013). Accordingly, over-activation of these systems during persistent stress tends to produce the deleterious effects in the body. In fact, the lack of turning off the physiological response to a stressor (when it is not required) produces allostatic load/overload leading to the development of pathophysiological changes (Karatsoreos and McEwen, 2011; McEwen, 2007). Stress has been postulated to be involved in the pathophysiology of a variety of diseases including anxiety, depression, dementia and other diseases.

Animal models are pivotal for understanding the pathophysiological changes occurring in the disease and for the development of novel pharmacological agents for stress management. Accordingly, diverse animal models, acute as well as chronic, have been created to simulate the stress condition in animals akin to humans. These include immobilization (Bhatia et al., 2011; Rabasa et al., 2011), restraint (Jackson and Moghaddam, 2006), electric foot shock (Bali et al., 2013; Rabasa et al., 2011) and social isolation stress (Serra et al., 2008) and have been used more frequently by different scientists to evaluate the anti-stress activity of pharmacological interventions. The assessment of stress in animals as a part of research activity is also of paramount importance and is done at various levels including the behavioral, biochemical and physiological levels. Stress-induced animal behavioral assessment is usually done using several well-established behavioral paradigms, including open field test, social interaction test and hole board test. Quantitative estimation of plasma corticosterone and ACTH levels at the biochemical level; while determination of body weight, adrenal gland weight, and gastric ulceration at the physiological level is also carried by different scientists as indices of stress (Bhatia et al., 2011; Manchanda et al., 2011). The present review discusses the different experimental stress protocols in animals and stress assessment at biochemical, behavioral and physiological levels.

2. Stress protocols employed in preclinical studies

There have been a number of preclinical models for inducing stress in animals (Jaggi et al., 2011). However, more commonly employed models in preclinical studies include immobilization, restraint, electric foot shock, social isolation stress and are described below.

2.1. Immobilization stress

Kvetnansky and coworkers developed a gold standard protocol for inducing stress in laboratory animals by immobilizing rats/mice for a stipulated period of time. Thereafter, it has become one of the most frequently employed stress models for rodents. A typical immobilization procedure involves fixing the four limbs of mouse/rat in the prone position on the plain board with an adhesive tape. The head is also fixed with a metal loop over the neck area to limit the head motion. This model has been widely used to induce both acute as well as chronic stress by varying the duration of immobilization stress. Immobilization is a complex stressor and has both physical as well as psychological dimensions. The struggling and muscular exertion during immobilization is an intense form of physical exercise. During the first exposure to immobilization stress, rats or mice struggle vigorously to free themselves for 5–10 min. After that time, they stop struggling and remain motionless. However, on repeated immobilization exposures for many days, the animals tend to develop signs of habituation to stressor and stop struggling much earlier. The struggling and muscular exertion in the process to free itself comprises the physical components of stress. On the other hand, limited movement during immobilized position and exposure in an open area comprises the psychological stress (Kvetnansky and Mikulai, 1970).