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Review Article

Electric foot shock stress adaptation: Does it exist or not?

Anjana Bali [1], Amteshwar Singh Jaggi *

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

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ABSTRACT

Stress adaptation is a protective phenomenon against repeated stress exposure and is characterized by a decreased responsiveness to a repeated stress stimulus. The adaptation is associated with a complex cascade of events, including the changes in behavior, neurotransmitter and gene expression levels. The non-adaptation or maladaptation to stress may underlie the affective disorders, such as anxiety, depression and post-traumatic stress disorder (PTSD). Electric foot shock is a complex stressor, which includes both physical and emotional components. Unlike immobilization, restraint and cold immersion stress, the phenomenon of stress adaptation is not very well defined in response to electric foot shock. A number of preclinical studies have reported the development of adaptation to electric foot shock stress. However, evidence also reveals the non-adaptive behavior in response to foot shocks. The distinct adaptive/non-adaptive responses may be possibly influenced by the type, intensity, and duration of the stress. The present review discusses the existence or non-existence of adaptation to electric foot shock stress along with possible mechanism.

Contents

1. Introduction

Stress is a state of threatened homeostasis during which a variety of adaptive processes are activated to produce a series of physiological and behavioral changes. In response to stress, there is an overactivation of hypothalamic–pituitary–adrenal (HPA) axis and sympathetic adrenomedullary system, which produce their effects by releasing glucocorticoids (corticosterone) and catecholamines (norepinephrine) into the blood, respectively [6]. Initial exposure to a stress stimulus produces behavioral alterations, including the reduced locomotor activity, decreased exploratory behavior and social withdrawal. However, repeated exposure to a same stressor (homotypic) results in a diminished stress response in terms of restoration of behavioral alterations and normalization of neuro-endocrinological changes, as compared to the initial stress response [2,20]. This blunted response to the stress stimulus during repeated exposure is referred as 'stress adaptation' phenomenon and it has been suggested to be a key protection mechanism against repeated stress exposure [35,40–43].

* Corresponding author. Tel.: +91 9501016036 (mobile).
E-mail address: anjubali.123@gmail.com (A. Bali), amteshwarjaggi@yahoo.co.in (A.S. Jaggi).
[1] Tel.: +91 9501016036 (mobile).

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An integrated response to stressful stimuli is an essential component of adaptive process which is critical for the survival of an organism [19,35]. Continuous exposure to stress may trigger homeostatic pathways leading to adaptation against the stress stimuli. Failing to activate the homeostatic pathway may lead to induction of chronic diseases. The adaptation to repeated stress is associated with a complex cascade of molecular events, ranging from release of neurotransmitter to regulation of gene expression. It has been suggested that failure to cope with the stress is the primary determinant for stress-induced behavioral and physiological pathologies. There is utmost need to identify the adaptogenic/homeostatic pathway to cope with stressful situations using valid models of stress.

Electric foot shock is a complex stressor, which includes both physical and emotional components. This stress paradigm comprises acute or chronic exposures of foot shocks of varying intensity and duration on the electrified grid floor in an electric foot shock apparatus [4–6,10,35]. Electric foot shock remains the most widely used stimulus for producing the measured amount of discomfort in animals due to its experimental advantage of control over the intensity and duration. Accordingly, scientists have developed foot shock-based disease models including anxiety [47], posttraumatic stress disorder (PTSD) [25,32] and depression [37]. However, unlike other stresses such as immobilization, restraint and cold immersion, the phenomenon of stress adaptation is not very well defined in response to electric foot shock [35,40–43]. A number of studies have reported the development of adaptation in response to electric foot shock stress in terms of neural, endocrine, and behavioral responses in experimental animals [31,35,48]. However, studies also reveal the differential adaptive or non-adaptive behavior in response to foot shock of variable intensity [13,46] (Table 1). The distinct adaptive/non-adaptive responses may be influenced by the type, intensity, and duration of the stressor along with the time interval between the stressful episodes. The literature for the present review was searched on PUBMED database using the different key words including "repeated foot shock", "foot shock and adaptation" and "foot shock and habituation". Furthermore, the relevant literature was also collected from the cross references of collected papers. Thereafter, the relevant literature was screened to meet the objectives of the present review. The present review discusses the existence or non-existence of adaptation in response to electric foot shock stress along with the possible mechanisms.

2. Evidence for the existence of stress adaptation

There have been a number of studies showing that the repeated application of foot shocks is associated with the development of stress adaptation. Ohi et al. showed the development of behavioral adaptation (in terms of the locomotor and freezing behavior) in male rats, after repeated foot shocks of 2 mA intensity, 1 s duration, 4 s inter-shock interval for 1 h daily for 10 days. The study demonstrated that the reduction in locomotor activity following the application of electric foot shocks was greatest on the 2nd day (−31% of control) and began to restore between the 3rd and 5th days of stress, with significant recovery on the 10th day (−13% of control). Similarly, foot shock-induced duration of freezing behavior (64–83 s) in the initial days (1–2 days) began to shorten on day 4 (17 s) and the shortened duration persisted till the last day of the experiment (10th day) suggesting the development of stress adaptive behavior. Moreover, the loss of body weight on days 1 and 2 following the foot shock stress began to increase on subsequent days of stress exposure (but remained below the control levels) again indicating the adaptive responses [31]. Earlier studies by the different scientists also demonstrated the existence of stress adaptation to repeated foot shocks. Weiss et al. demonstrated the restoration of acute inescapable shock-induced impairment in shuttle avoidance–escape task performance on repeated applications of shocks for 14 days [48]. Irwin et al. did not employ the behavioral response, but measured the brain NE levels to indirectly assess the effects of acute and repeated foot shock stress on stress adaptation [18]. A single foot shock session of 360 shocks (each shock of 150 μA intensity, 2 s duration and 9 s interval) significantly decreased the NE levels in the hypothalamus. However, after three shock sessions, the NE levels were restored and were comparable in normal and foot shock-subjected animals [18]. Similarly, Shanks et al. also reported that the decline of NE associated with an acute inescapable stress was abolished following repeated exposures of inescapable foot shocks for 15 days [38].

Cohen et al. reported that a single foot shock exposure sufficient to induce 'learned helplessness' significantly decreases the β-adrenergic receptor binding in the hypothalamus and increases the α_2 adrenergic receptor binding in the cortical region. However, repeated applications of foot shocks for seven days restored acute stress-induced changes in adrenergic receptor binding on the different brain regions. In fact, there was a significant increase in β-adrenergic receptor binding in the hypothalamus as compared to control following repeated foot shocks. The restoration of adrenergic receptor binding in the brain indicates the induction of stress adaptive pathways in response to foot shock stress [8]. The study of Swenson and Vogel investigated the effects of repeated foot shock stress on the plasma corticosterone concentration in coping and non-coping rats. Coping is usually defined as the behavioral and physiological efforts to master the situation. The authors used the terms 'coping' and 'non-coping' depending upon the controllability of stressor. Rats that could control and terminate the shock were termed as 'coping' and rats that could not terminate the shock were termed as 'non-coping'. In other words, coping rats received escapable shocks, while non-coping rats received inescapable foot shocks. The plasma corticosterone concentration was increased in response to foot shock in both coping and non-coping rats, however, the long lasting responses were observed in non-coping rats. It suggests that the peripheral stress-related changes are minimized and shortened in coping animals, and are augmented and prolonged in non-coping animals [44]. Hanjos-Korcsok et al. described the development of rapid habituation at the behavioral level in response to second electric foot shock (1 mA, 0.2 s duration, delivered for 0.5 min with 1 s interval) after 60 min of the first session of foot shock stress of the same intensity and duration. The second foot shock session was not able to evoke the similar increase in anxiety-related behavior, including the freezing behavior and rearing following first session of foot shock stress [13].

The scientists have employed other stress-associated parameters to demonstrate the existence of adaptation to repeated foot shock stress. The development of anti-nociception in response to acute stress response is very well defined [12] and accordingly, scientists have employed anti-nociception as a parameter to assess the development/non-development of stress adaptation. Nguyen et al. described that a single exposure of foot shock (1 mA, 0.2 Hz, 1 s duration) led to decrease in anti-nociception. However, these responses gradually deceased by repeated exposure of this stressor for five days suggesting the development of stress adaptation [30]. On similar lines, Takahashi et al. also reported that on repeated exposures of foot shocks (2 mA, 0.2 Hz, 1 s duration), there is a gradual decrease in anti-nociceptive behavior, suggesting the development of adaptation to repeated foot shock stress [45]. The study of Holmer et al. describing the effects of repeated foot shocks on the reproductive parameters in male Syrian hamster also favors the existence of stress adaptation. The authors subjected the animals to foot shocks (0.8 mA) for 12 days to study the effect of repeated stress exposure on reproductive behavior. In repeated foot shock-subjected animals, there was only a slight change in sexual behavior in males, who could not escape their stress. The animals that could escape the stress did not experience any decrease in copulation. Although, the results do not clearly demonstrate the existence of adaptation to repeated foot shocks, yet the subtle changes in the sexual behavior suggest the possibility of development of habituation to foot shocks [17]. The changes in corticosterone levels may also be employed to assess the existence or non-existence of adaptation. Daniels et al.