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Review

Adaptation of the hypothalamus–pituitary–adrenal axis to daily repeated stress does not follow the rules of habituation: A new perspective

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ABSTRACT

Repeated exposure to a wide range of stressors differing in nature and intensity results in a reduced response of prototypical stress markers (i.e. plasma levels of ACTH and adrenaline) after an acute challenge with the same (homotypic) stressor. This reduction has been considered to be a habituation-like phenomenon. However, direct experimental evidence for this assumption is scarce. In the present work we demonstrate in adult male rats that adaptation of the hypothalamus–pituitary–adrenal (HPA) axis to repeated stress does not follow some of the critical rules of habituation. Briefly, adaptation was stronger and faster with more severe stressors, maximally observed even with a single exposure to severe stressors, extremely long-lasting, negatively related to the interval between the exposures and positively related to the length of daily exposure. We offer a new theoretical view to explain adaptation to daily repeated stress.

Contents

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1. Adaptation to repeated stress as a habituation process, evidences and contradictions

Exposure to different types of stressors results in a wide range of physiological and behavioral responses, some of them related to the particular nature of the stressor. Activation of the hypothalamus–pituitary–adrenal (HPA) axis constitutes one of the prototypical responses to all kind of stressors. The HPA axis, along with a few set of other physiological responses (i.e. plasma levels of prolactin, adrenaline and glucose) appear to be good markers of the intensity of emotional or predominantly emotional stressors (Armario et al., 2012; Kvetnansky et al., 2009; Martí and Armario, 1998). When animals are daily exposed to the same stressor for several days or a few weeks, reduction of the response of the HPA axis and other physiological variables, mainly plasma levels of adrenaline and hyperglycemia, has been very often observed (Martí and Armario, 1998), suggesting that those variables that are sensitive to the intensity of stressors are also sensitive to repeated experience with the stressors. The progressive reduction of the HPA and adrenaline response to repeated exposure to the same stressor was initially termed adaptation, but later on, the term habituation has been more widely accepted on the assumption that adaptation to the same (homotypic) daily repeated stressor appears to follow the rules of habituation (i.e. De Boer et al., 1990; Ma and Lightman, 1998; Natelson et al., 1988).

Reduction of the HPA response to daily repeated stress is not always achieved and is likely to involve different processes depending on the nature of the stressors. We can broadly distinguish between physical (systemic) stressors that represent a direct challenge to homeostasis and survival (i.e. hypovolemia, infection), and psychological (emotional) stressors that represent potential, not actual, danger (i.e. an unknown unprotected environment, predator odor). Although most laboratory stressors have some physical component (exercise and hypothermia after forced swim, minor tissue damage/inflammation after footshock, altered temperature and intense struggle after restraint or immobilization), under typical laboratory conditions the physical component do not represent any challenge for survival. In addition, the pattern of brain c-fos expression strongly suggests that they are more alike to emotional than physical stressors and therefore we call them predominantly emotional stressors. Adaptation to physical and emotional stressors probably encompasses markedly different processes (see Armario, 2015) and the present work will focus on emotional or predominantly emotional stressors.

Habituation has been defined as a response decrement that results from repeated exposure to a stimulus and does not involve either sensorial adaptation or sensorial/motor fatigue. Although it was originally considered as a primitive, non-associative type of learning, more recent views about habituation emphasize that it represents a wide range of phenomena, distinguish between short-term (STH) and long-term habituation (LTH) and considers the possibility that some of these phenomena may also involve associative processes (Cristofferssen, 1997; Grissom and Bhatnagar, 2009; Rankin et al., 2009; Thompson, 2009). It is obvious that factors involved in adaptation to daily repeated stress are likely to be closer to LTH than STH. There is a consensus among researchers about the main characteristics of habituation (Rankin et al., 2009):

(1) Repeated application of a stimulus results in a progressive decrease in some parameters of the response to an asymptotic level.
(2) If the stimulus is withheld after response decrement, the response recovers at least partially (spontaneous recovery).
(3) After multiples series of stimulus repetitions and spontaneous recovery, the response decrement becomes successively more rapid and/or more pronounced.
(4) Other things being equally, more frequent stimulation results in more rapid and/or pronounced response decrement, and more rapid spontaneous recovery.
(5) Within a stimulus modality, the less intense the stimulus, the more rapid and/or more pronounced the behavioral decrement. Very intense stimuli may yield no significant observable decrement.
(6) The effects of repeated stimulation may continue to accumulate even after the response has reached an asymptotic level. This effect of stimulation beyond asymptotic level can alter subsequent behavior, for example, delaying the onset of spontaneous recovery.
(7) Within the same stimulus modality, the response decrement shows some stimulus specificity.
(8) Presentation of a different stimulus results in an increase of the decremented response to the original stimulus. This phenomenon is termed dishabituation.
(9) Upon repeated application of the dishabituating stimulus, the amount of dishabituation is reduced (habituation of dishabituation).
(10) Some stimulus repetition protocols may result in properties of the response decrement that last hours, days or weeks. This persistence of aspects of habituation is termed long-term habituation.

The hypothesis that adaptation to repeated stress is an habituation-like phenomenon neither has been theoretically developed nor is strongly supported by experimental evidence (Grissom and Bhatnagar, 2009). To our knowledge, only a few papers have generated information directly concerning to the hypothesis of habituation to repeated stress in rats. In a first paper comparing stressors differing in intensity (handling, restraint prone and restraint supine) the authors concluded that the stronger the stressors the lower the magnitude of corticosterone reduction after repeated stress (Natelson et al., 1988). However, there is strong evidence to suggest that plasma corticosterone neither appropriately reflect plasma ACTH nor adaptation to daily repeated stress for two main reasons (Armario, 2006; Armario et al., 2012): (i) saturation of adrenal cortex secretion of glucocorticoids with intermediate levels of ACTH; and (ii) increase in maximum adrenal cortex glucocorticoid secretion after a history of chronic exposure to severe stressors. In another report, De Boer et al. (1990) studied how the interval between stressor exposure (24 versus 72 h) could affect adaptation of corticosterone, noradrenaline, adrenaline and glucose to five repeated exposure to a novel environment (cylinder) containing a low level of water. They found a progressive reduction of the response of all these variables after repeated stress, which was more pronounced with the 24 h than the 72 h interval. This is in contrast to the lower LTH observed after massed (six 30 min sessions of noise on one day) as compared with spaced (six daily 30 min

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