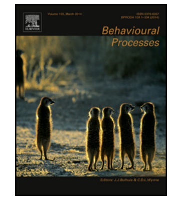
Behavioural Processes 105 (2014) 6–14

Contents lists available at ScienceDirect

Behavioural Processes

journal homepage: www.elsevier.com/locate/behavproc



Influence of trait anxiety on the effects of acute stress on learning and retention of the passive avoidance task in male and female mice

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A R T I C L E   I N F O

Article history:
Received 10 June 2013
Received in revised form 25 January 2014
Accepted 14 February 2014
Available online 21 February 2014

Keywords:
Acute stress
Memory
Mice
Passive avoidance conditioning
Sex differences
Trait anxiety

A B S T R A C T

The influence of anxiety on the effects of acute stress for the acquisition and retention of passive avoidance conditioned task was evaluated in male and female mice. Animals were categorized as high-, medium-, and low-anxiety according to their performance in the elevated plus-maze test. Subsequently, half of the mice in each group were exposed to an acute stressor and assayed in an aversive conditioning test two days later. Exposure to restraint stress before inhibitory avoidance conditioning had a differential impact on the conditioned response of males and females according to their trait anxiety. The acute stressor significantly altered the conditioned response of mice with a high-anxiety level. The long-term effect of the stressor varied for each sex; high-anxiety stressed males showed an enhanced conditioned response with respect to their controls, whereas high-anxiety stressed females presented an impaired performance. These results lead us to believe that the characterization of individuality is an important factor in understanding the interaction between stress and memory for each sex; the trait anxiety of our animals modulated the effects of stress on the conditioned response so that males and females performed in contrasting manners to the same environmental stimuli and experimental conditions.

1. Introduction

Learning and memory processes have been shown to be highly susceptible to modulation by stress (Henckens et al., 2009; Luksys and Sandi, 2011; Shors, 2006). In some situations, stress impairs learning, whereas in others it increases the ability to learn and remember (Salehi et al., 2010). Indeed, an extremely stressful event can provoke psychopathologic alterations of memory in humans (e.g., flashback in post-traumatic stress disorder; Yehuda et al., 2010). Numerous reviews deal with the relation between stress and learning (Bangasser and Shors, 2010; Bisaz et al., 2009; Conrad, 2010; Luksys and Sandi, 2011; Roozendaal, 2002; Sandi and Pinelo-Nava, 2007; Schwabe et al., 2010). Although the exact nature of the effects of stress on learning is still unclear (Schwabe et al., 2011), such reviews have highlighted the importance of a number of key factors for understanding the impact of stress on memory function.

Among the critical factors that have been underlined are the duration, intensity, and source of the stressful episode, as well as timing with regard to the memory phase, and the learning system employed (Sandi and Pinelo-Nava, 2007). The duration of the stressor refers to the time for which the stressor lasts; in this context, the differential effects of acute vs. chronic stress have attracted great interest. While the impact of chronic stress has been widely investigated, the influence of acute stress on memory function has been the focus of less attention (Bisaz et al., 2009). Stress intensity has long been known to be highly relevant, and there is a consensus that the relationship between stress intensity and memory can be explained by an inverted U-shaped function (i.e., both low and high stress levels impair memory, whereas intermediate levels facilitate it; Salehi et al., 2010). The source of stress is also important and determines whether it is intrinsic (if owing to elements related to the cognitive task) or extrinsic (if owing to conditions completely unrelated to the cognitive task; that is, temporally dissociated from such a task). When the act of training is intrinsically stressful, as it is during fear conditioning, the learning process tends to be facilitated by stress. However, when training is not stressful, or the stressful experience occurs long after training, the consequences are less predictable (Sandi and Pinelo-Nava, 2007). The moment at which stress is experienced with regard to a particular memory phase is also relevant, given that the effects on consolidation and retrieval of memory vary depending on the moment when the stressor is present (Joels et al., 2006; Roozendaal, 2002; Schwabe et al., 2010). Memory performance is enhanced by stress or pharmacologically elevated glucocorticoid concentrations after learning, but exposure to stress or the administration of glucocorticoids shortly before a retention test

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http://dx.doi.org/10.1016/j.beproc.2014.02.009
0376-6357/

reduces memory performance in both humans and rodents. It has also been reported that stress may disrupt memory reconsolidation in humans, increasing resistance to extinction (Schwabe and Wolf, 2011). These findings suggest that stress leads to a rather rigid, less flexible behavior, which has important implications for anxiety disorders related to aberrant instrumental responses.

Another key factor is the category of learning under evaluation (implicit/no-declarative learning, explicit/declarative learning, non-associative learning, etc.). While acute stress is generally highly disruptive for the processing of working memory, it can facilitate implicit learning (Luethi et al., 2009). Furthermore, there are tasks in which learning occurs under stressful conditions, including procedures in which it is induced by footshocks, such as in fear conditioning to a cue and/or context, and passive and active avoidance tasks (Bisaz et al., 2009).

Recently, the maladaptive nature of the stress response has been characterized by the absence of an anticipatory response (unpredictable) or a hindered recovery (uncontrollable) of the neuroendocrine reaction (Koolhaas et al., 2011). Subsequently, the terms "controllability" and "predictability" define a stressor and are considered cognitive, perceptual aspects and key mediators of the psychophysiological impact of stress. However, there are other significant influences on the effects of stress on learning/memory processes that have been the subject of less research, such as the subject's sex or level of anxiety.

There are numerous reports of sex differences in basic learning processes (Andreano and Cahill, 2009; Dalla and Shors, 2009; Ribeiro et al., 2010). Studies with animals have shown that sex differences with respect to performance are influenced by natural differences in activity levels. Female rats, which are generally more active than males, perform better in tasks that require activity, such as active avoidance, and do quite poorly in those that require immobility, such as fear conditioning or passive avoidance (Shors, 2002). These differences are most evident in tasks with strong emotional contexts, where different fear responses and stress effects could be determinant (Beck and Luine, 2010; Ribeiro et al., 2010; Shors, 2006). In this way, stressful experiences can also elicit very different behavioral responses in males and females.

Numerous studies have shown that chronic stress has an impaired effect on the performance of males in spatial learning tasks, while it improves performance by females (Beck and Luine, 2002; Bowman et al., 2003; Bowman, 2005; Luine et al., 1994; Kitraki et al., 2004). This differential effect according to sex could be due to differences with respect to hippocampal functioning, particularly under conditions of stress, since such tasks involve the hippocampus. It seems that the hippocampus of females is substantially more resistant than that of males to the morphological (Galea et al., 1997; Kitraki et al., 2004; Shors et al., 2001, 2004) and physiological (Bronzino et al., 1996; Maren et al., 1994; Yang et al., 2004) changes induced by chronic stress. Thus, chronic stress increases emotionality and impairs cognition in male animals, whereas it alleviates emotionality and enhances cognition in females depending on the learning task and stressor (ter Horst et al., 2012).

However, when the effects of an acute stressor are evaluated, female adult rats exhibit a more robust and longer-lasting increase in glucocorticoids and behavioral impairment (McCarthy and Konkle, 2005; Shors, 2002). Studies have also shown that the ability of female rats to learn an associative response is severely undermined after exposure to an acute stressful event (Dalla and Shors, 2009; Shors, 2004; Wood and Shors, 1998), while the performance of males is enhanced after exposure to the same stressful event (Beylin and Shors, 2003; Conrad et al., 2004; Shors, 2004; Wood et al., 2001).

It is known that emotionally arousing experiences create stronger memories than the more neutral ones (Chen et al., 2012; McGaugh, 2004; Roozendaal and McGaugh, 2011). Adaptive behavior is directly linked to interactions between memory and emotions, particularly anxiety; in fact, there are indications that anxiety and memory are closely linked processes (Podhorna and Brown, 2002). The moderate anxiety level is known to facilitate efficient learning of a conditioned passive avoidance reflex, while high and low levels lead to suppression of memory (Dubrovina and Tomilenko, 2007).

Taking the aforementioned literature into account, the present study was designed to examine the influence of trait anxiety on the effects of acute stress on the acquisition and retention of passive avoidance conditioning in male and female mice. To this end, we first evaluated the anxiety level of mice prior to exposing them to stress in order to categorize them according to their trait anxiety, which is an individual's predisposition to respond, and not state anxiety which is a transitory emotion in response to stress (Endler and Kocovski, 2001).

We chose immobilization (restraint), as it is one of the most widely employed experimental methods of inducing stress in rodents (Buynitsky and Mostofsky, 2009). Moreover, its physiological effects on rodents have been determined by blood-derived assays or direct measurements of cortical microdialysis (Armario et al., 2008; Buynitsky and Mostofsky, 2009), which have demonstrated that a single exposure to restraint is a severe acute stressor that induces long-term behavioral consequences (Armario et al., 2008). We also used the passive avoidance conditioned task, as it induces learning through punishment, which provokes a high emotional state in the subject. Finally, we ran hot-plate test, a very widely used behavioral model of nociception (Wahlsten, 2011), to confirm that the differences among experimental groups were due to the animals' trait anxiety and/or stress and not to their differences in pain sensitivity.

We hypothesized that the animals would vary in their acquisition and retention of the aversive task according to their sex and their anxiety level prior to exposure to an acute stressor such as restraint. We expected the high-anxiety mice to be more affected by the stressor, and contrasting effects to be manifested in each sex; namely, that the conditioned response would be weaker in females and stronger in males.

2. Materials and methods

2.1. Subjects

A total number of 92 male and 80 female mice of the CD1 outbred strain were acquired commercially from Charles River (Barcelona, Spain). The animals arrived at the laboratory weighing 26-28 g in the case of males and 22-24 g for females. They were housed in groups of four in plastic cages (27 cm length × 27 cm width × 15 cm height) for seven days prior to initiating experiments, under the following conditions: constant temperature (21 ± 2 °C), a reversed light schedule (white lights on: 24-12 h), as well as food and water available ad libitum. Procedures involving mice and their care conformed to national, regional, and local laws and regulations, which are in accordance with the Directive 2010/63/EU of the European Parliament and of the council of September 22, 2010, on the protection of animals used for scientific purposes.

2.2. Apparatus

The elevated plus-maze (Cibertec, S.A., Madrid, Spain) was comprised of two open and two enclosed arms (30 × 5 cm and 30 × 15 × 5 cm, respectively), both of which extended out from a common central square (5 × 5 cm) and were elevated 50 cm above floor level on five pedestals. The maze floor was made of black Plexiglas, while the walls of the enclosed arms were made of clear Plexiglas. The illumination in the experimental room consisted of