Neurobiology of Learning and Memory 90 (2008) 495–503

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

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

Chronic stress modulates the use of spatial and stimulus-response learning strategies in mice and man

Lars Schwabe [a,b,*], Sergiu Dalm [b], Hartmut Schächinger [a], Melly S. Oitzl [b]

[a] Division of Clinical Physiology, Institute of Psychobiology, University of Trier, Germany
[b] Division of Medical Pharmacology, Leiden/Amsterdam Center for Drug Research and Leiden University Medical Center, University of Leiden, The Netherlands

ARTICLE INFO

Article history:
Received 6 June 2008
Revised 21 July 2008
Accepted 21 July 2008
Available online 26 August 2008

Keywords:
Multiple memory systems
Chronic stress
Spatial learning
Stimulus-response learning

ABSTRACT

Acute stress modulates multiple memory systems in favor of caudate nucleus-dependent stimulus-response and at the expense of hippocampus-dependent spatial learning and memory. We examined in mice and humans whether chronic stress has similar consequences. Male C57BL/6J mice that had been repeatedly exposed to rats ("rat stress") used in a circular hole board task significantly more often a stimulus-response strategy (33%) than control mice (0%). While velocity was increased, differences in latency to exit hole, distance moved or number of holes visited were not observed. Increased velocity and performance during retention trials one day later indicates altered emotionality and motivation to explore in rat stressed mice. Forty healthy young men and women were split into "high chronic stress" and "low chronic stress" groups based on their answers in a chronic stress questionnaire ("Trier Inventory of Chronic Stress"—TICS) and trained in a 2D task. A test trial immediately after training revealed that participants of the "high chronic stress" group used the S-R strategy significantly more often (94%) than participants of the "low chronic stress" group (52%). Verbal self-reports confirmed the strategy derived from participants' choice in the test trial. Learning performance was unaffected by the chronic stress level. We conclude that one consequence of chronic stress is the shift to more rigid stimulus-response learning, that is accompanied by changes in motivational factors in mice.

1. Introduction

Memory consists of multiple systems which differ regarding the processed kind of information, the performed operations and the underlying neural structure (Gabrieli, 1998; Squire, 2004). "Cognitive" memory supports the acquisition of flexible, consciously accessible knowledge, such as the memory of your last birthday party, and is based on the medial temporal lobe, in particular the hippocampus (Eichenbaum, 2004; Scoville & Milner, 1957). "Habit" memory, on the other hand, processes simple stimulus-response (S-R) associations, such as "stop your car when the traffic lights are red". It is not necessarily accessible and relies on the caudate nucleus (Jog, Kubota, Connolly, Hillegaart, & Graybiel, 1999; Knowlton, Mangels, & Squire, 1996).

Hippocampus- and caudate-based systems work in parallel and process information simultaneously (Mizumori, Yeshenko, Gill, & Davis, 2004). The nature of interactions between these systems has been described as cooperative by some authors (Voermans et al., 2004) and competitive by others (Poldrack & Packard, 2003) raising the question which factors coordinate their use. Recent findings suggested that stress plays a critical role in the modulation of multiple memory systems. Acute stress prior to training in a task that could be acquired by a hippocampus-based spatial and a caudate-based S-R strategy favored caudate-based learning both in rodents and humans (Kim, Lee, Han, & Packard, 2001; Packard & Wingard, 2004; Schwabe et al., 2007). This stress-induced modulation of hippocampus-dependent and caudate-dependent systems is assumed to be mediated by the amygdala (Packard & Wingard, 2004). Effects of prolonged or repeated periods of stress on the modulation of caudate-dependent and hippocampus-dependent learning have not been studied yet. This, however, would be particularly valuable since chronic stress has been related to psychiatric disorders such as depression (for a review: Willner, 1997).

Chronic stress impairs hippocampus-dependent learning and memory (Bodnoff et al., 1995; Kleen, Sitomer, Killeen, & Conrad, 2006). Non-hippocampal memory systems respond differently. Working memory was not affected after repeated restraint stress (Kleen, Sitomer, Killeen, & Conrad, 2006), but fear memory was even strengthened following a prolonged stress period (Conrad, Magarinos, LeDoux, & McEwen, 1999). Interestingly, Wright and Conrad (2005) demonstrated in chronically stressed rats that salient intramaze cues prevented impaired performance in a spatial Y-

* Corresponding author. Address: Department of Cognitive Psychology, Ruhr-University Bochum, Universitaetsstrasse 150, 44789 Bochum, Germany. Fax: +49 234 3214308.
E-mail address: Lars.Schwabe@ruhr-uni-bochum.de (L. Schwabe).

1074-7427/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.nlm.2008.07.015

maze task. We suggest that the introduction of intramaze cues allowed for S-R learning and thus, compensated for impairment of spatial functions. Consequently, we hypothesize that chronic stress modulates multiple memory systems in favor of caudate-based and at the expense of hippocampus-based learning.

To test this hypothesis, we used experimental designs that provide a single proximal and multiple distal cues for learning the task, i.e., allowing stimulus-response learning and spatial learning. Changing the position of the proximal cue in the last trial of the learning session revealed the used strategy in mice and humans. First, we examined in mice the effect of chronic stress (i.e., by repeatedly exposing the mouse to a rat, but separated by a partition) on the use of spatial and S-R learning strategies during the acquisition of a circular hole board task, followed by a retention test 24 h later. Second, we examined in humans the influence of self reported chronic stress as assessed by the Trier Inventory of Chronic Stress on the learning strategy used in a 2D spatial task in which the position of a win-field could be acquired by spatial and S-R strategies.

2. Materials and methods

2.1. Mouse study

2.1.1. Animals

Male C57BL6/j mice (12 weeks old; purchased from Charles River, The Netherlands) were single-housed in a temperature- (21 ± 1 °C) and humidity-controlled room on a 12 h light/dark cycle (lights on at 07:00) with *ad libitum* access to food and water. Behavioral experiments were performed in the same room. Three times during the week before training started, mice were "pretrained" to climb through an S-shaped tube into their home cage after weighing. Experiments were approved by the Local Committee for Animal Health, Ethics and Research of the University of Leiden. Animal care was conducted in accordance with the EC Council Directive of November 1986 (86/009/EEC).

2.1.2. Experimental design

Five days prior to the beginning of the rat stress, general activity and exploratory behavior of mice were assessed on the circular hole board. Animals were randomly assigned to one of two conditions: control ($n = 12$) and "rat stress" ($n = 12$; see below). Mice of the rat stress group were repeatedly exposed to a rat for 1–2 h a day during 2 weeks. Seven days after the last rat exposure mice started with the circular hole board (CHB) task. Twenty-four hours after training retention performance was tested. Testing took place between 08:00 and 12:30. One day later, mice were sacrificed between 08:00 and 10:00. The experimenter was unaware of the previous treatment of the animals. Behavior was recorded on videotape and analyzed by EthoVision 1.95 (Noldus Information and Technology BV, Wageningen, The Netherlands). This image analysis system sampled the position of an animal 12.5 times per second; to calculate the distance moved we chose for a minimal distance between samples of 3 cm.

2.1.3. Rat stress paradigm

In nature, mice and rats avoid each other. Exposure to a rat is highly stressful for a mouse (Linthorst, Flachskamm, Barden, Holsboer, & Reul, 2000). In the first week, mice were exposed to male Wistar rats on five consecutive days (1–2 h per day resulting in 9 h in the first week). In the second week, mice were confronted with rats on Tuesday and Thursday for 1 h. This time schedule was chosen to increase unpredictability and uncontrollability which are key stress components (Dickerson & Kemeny, 2004). Rats were placed in a cage with a grid floor and Plexiglas walls on the top of two mouse cages which were covered by a grid. Thus, mice and rats could hear, see and smell, but not touch each other. During exposure to rats mice were kept in another cage than their home cage (but always the same cage for confrontation with rats) without food and water. The rat stress took place during the light phase (07:00–19:00) in a room adjacent to the housing room. Previous studies using the same stress protocol showed that it induces reliable features of chronic stress expressed, e.g., by reduced body weight, changes in corticosterone secretion and alteration in hippocampal corticosteroid receptor expression, strain-dependent alterations in learning and memory and motivation to explore (Grootendorst, de Kloet, Dalm, & Oitzl, 2001a; Grootendorst, de Kloet, Vossen, Dalm, & Oitzl, 2001b). Mice of the control group (naïve) were housed in their home cage.

2.1.4. Learning task

2.1.4.1. Apparatus. The circular hole board (CHB) is a revolvable white Plexiglas plate (diameter: 110 cm) with 12 holes (diameter: 5 cm) at equal distance to each other, 10 cm from the rim. It is situated 1 m above the floor (see Fig. 1A; light intensity at the level of the platform 120 lux). Holes can be closed by a lid at a depth of 5 cm. Whether a hole is open or not can be recognized by the mouse if it puts its head over the edge of the hole. If open, the hole provides access to the home cage of the mouse via an S-shaped

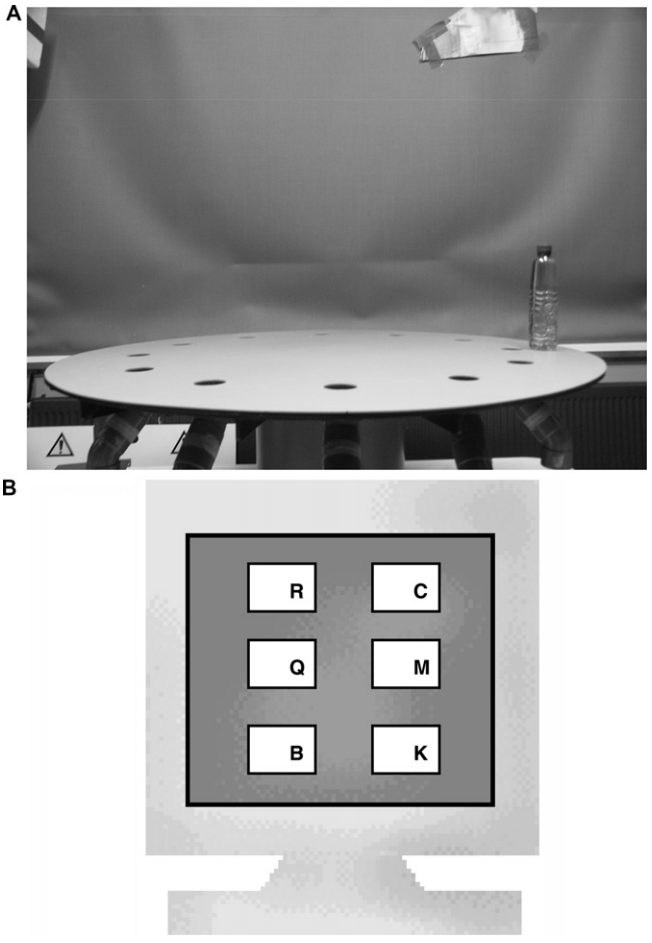

Fig. 1. Apparatus used in the mouse (A) and human study (B). Mice were trained to find an exit hole. They could use either a spatial (room cues) or a stimulus-response strategy (bottle). Relocation of the bottle in the test trial revealed the used strategy. In the human study, participants could identify the position of a "win-field" with a spatial (right column, second row) or a stimulus-response (stimulus: letter M) strategy. Changing the arrangement of the letters in the test trial allowed revealed the employed strategy.