



Stress-dependent opioid and adrenergic modulation of newly retrieved fear memory



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ARTICLE INFO

Article history:

Received 16 August 2013

Revised 18 November 2013

Accepted 21 November 2013

Available online 27 November 2013

Keywords:

Reconsolidation

Modulation

Updating

Stress

Opioid

Adrenergic

Retrieval

ABSTRACT

Recent studies on the effect of stress on modulation of fear memory in our laboratory have uncovered endogenous opioid and adrenergic based modulation systems, working in concert, that limit the strengthening or weakening of newly *acquired* fear memory during consolidation under conditions of mild or intense stress, respectively. The present study sought to determine if similar stress-dependent modulation, mediated by endogenous opioid and adrenergic systems, occurs during reconsolidation of newly *retrieved* fear memory. Rats underwent contextual fear conditioning followed 24 h later by reactivation of fear memory; a retention test was administered the next day. Stress was manipulated by varying duration of recall of fear memory during reactivation. In the first experiment, vehicle or the opioid-receptor blocker naloxone was administered immediately after varied durations (30 or 120 s) of reactivation. The results indicate that (1) reactivation, in the absence of drug, has a marked effect on freezing behavior—as duration of reactivation increases from 30 to 120 s, freezing behavior and presumably fear-induced stress increases and (2) naloxone, administered immediately after 30 s (mild stress) or 120 s (intense stress) of reactivation, enhances or impairs retention, respectively, the next day. In the second experiment, naloxone and the β -adrenergic blocker propranolol were administered either separately or in combination immediately after 120 s (intense stress) reactivation. The results indicate that separate administration of propranolol and naloxone impairs retention, while the combined administration fails to do so. Taken together the results of the two experiments are consistent with a protective mechanism, mediated by endogenous opioid and adrenergic systems working in concert, that limits enhancement and impairment of newly retrieved fear memory during reactivation in a stress-dependent manner.

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1. Introduction

Consolidation of fear memory, the process by which newly acquired memories related to fear are stabilized and stored, is not a one-time process; it may recur during subsequent retrieval of the initially consolidated memory by a process referred to as memory reconsolidation (Abel & Lattal, 2001; Sara, 2000). Various post-retrieval pharmacological manipulations previously used to characterize consolidation have been used to determine the

cellular and molecular mechanisms underlying reconsolidation. These studies have indicated that, like storage and modulation of newly acquired fear memory during consolidation, *de novo* protein synthesis (Nader, Schafe, & Le Doux, 2000) and stress-related hormones and transmitters, including glucocorticoids (Cordero, Merino, & Sandi, 1998; Tronel & Alberini, 2007), norepinephrine (Debiec & LeDoux, 2004; Przybylski, Roulet, & Sara, 1999), opioids (Meilandt, Barea-Rodriguez, Harvey, & Martinez, 2004) and acetylcholine (Boccia, Acosta, Blake, & Baratti, 2004), are essential for storage and modulation of newly retrieved fear memory during reconsolidation.

Recent studies on stress-dependent modulation of newly acquired fear memory in our laboratory, using β -adrenergic and opioid-receptor blockers, have uncovered endogenous adrenergic and opioid based modulation systems, working in concert, that limit the strengthening or weakening of newly *acquired* fear memory during consolidation under conditions of mild or intense stress, respectively (Schneider, Simson, Atapattu, & Kirby,

Abbreviations: LSD, Least Significant Difference; veh, vehicle; nal, naloxone; pro, propranolol; NR, non-reactivation; ANOVA, analysis of variance; SEM, standard error of the mean.

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2011; Schneider et al., 2009). The present study sought to determine if similar stress-dependent modulation, via adrenergic and opioid modulatory systems working concurrently, occurs during reconsolidation of newly retrieved fear memory. If modulation of newly retrieved memory does indeed parallel modulation of newly acquired memory, then modulation of newly retrieved memory (like modulation of newly acquired memory) should depend on both the level of stress as well as the nature of the receptor blockade accompanying it. Specifically, the following *a priori* predictions concerning modulation of newly retrieved fear memory can be made:

- (1) As with modulation of newly acquired memory, opioid-receptor blockade after mild stress should enhance modulation of newly retrieved memory, while opioid-receptor blockade after intense stress should impair modulation of newly retrieved memory (owing to the blockade-induced loss of a “protective”, stress-dependent opioid-based modulation system that normally “limits” enhancement or impairment of memory under conditions of mild and intense stress, respectively).
- (2) As with modulation of newly acquired memory, β -adrenergic receptor blockade after intense stress should impair modulation of newly retrieved memory (owing to the blockade-induced loss of a “protective”, stress-dependent adrenergic-based modulation system that normally limits impairment of memory under conditions of intense stress).
- (3) As with modulation of newly acquired memory, concurrent opioid and β -adrenergic receptor blockade after intense stress should prevent impairment of modulation of newly retrieved memory suggesting a non-additive interaction between the two modulation systems under conditions of intense stress.

The present study tested these predictions. In contrast to previous experiments on stress-dependent modulation of newly acquired memory in which the level of stress was manipulated shortly after training via stressors such as predator exposure (Diamond et al., 2006), restraint (Klenerova et al., 2003) or forced swim (Schneider et al., 2011), the present study focused on stress-dependent modulation of newly retrieved memory utilizing reactivation of the retrieved fear memory itself (24 h after training) as the stressor. As an agent of stress, reactivated fear memory (freezing behavior) has been validated in studies using activation of the hypothalamo–pituitary–adrenal axis as a physiological index of stress intensity (Antoniadis & McDonald, 1999). During retrieval of fear-related memory, stress-related hormones and neurotransmitters, including glucocorticoids, norepinephrine (NE) and opioids, act in limbic nuclei, including the amygdala and hippocampus, to regulate the strength of retention (de Quervain, Roozendaal, & McGaugh, 1998; Meilandt et al., 2004; Murchison et al., 2004; Roozendaal, Hahn, Nathan, de Quervain, & McGaugh, 2004). Thus, reactivated fear memory not only meets the criteria of a stressor but produces neurochemical effects (particularly with respect to glucocorticoids, adrenergic and opioid action) consistent with a potential modulator of retention. In the present study pharmacological blockade was initiated immediately after reactivation of fear memory; a retention test to measure memory strength was administered the next day.

2. Material and methods

2.1. Subjects

The subjects ($N = 99$) were male Long-Evans hooded rats weighing 240–280 g at the start of the experiment. The rats were housed

two to a cage with access to food and water ad libitum. The colony room was maintained at 20 °C and was illuminated on a 12-h light–dark cycle (lights on at 9:00 a.m.). All experiments were conducted between 10:00 a.m. and 12:00 p.m. at the nadir of the diurnal cycle for glucocorticoids (Krieger, 1974) minimizing the extent to which fluctuations in endogenous levels of stress-dependent hormones influence the results. The experimental protocol was approved by Swarthmore College’s Institutional Animal Care and Use Committee and was in compliance with the National Research Council Guide for the Care and Use of Laboratory Animals.

2.2. Apparatus

Rats were trained and tested in a fear conditioning apparatus that consisted of a trough-shaped compartment (42 L \times 28 H \times 20 W cm at the top; 42 L \times 28 H \times 8 W cm at the base) with a hinged plastic top and stainless steel plates making up the floor and sidewalls. A constant-current Lafayette Master Shocker (Model 2400SS; Lafayette, IN) was connected to the floor of the compartment. The training apparatus was located in a quiet, dimly illuminated room, and was cleaned with water followed by acetone before all training and testing trials.

2.3. Drug administration and drug doses

The rats were injected intraperitoneally with vehicle (0.9% saline, 2 ml/kg), the β -adrenergic antagonist dl-propranolol hydrochloride (10 mg/kg, 2 ml/kg, Sigma Chemical), the opioid antagonist naloxone hydrochloride (3 mg/kg, 2 ml/kg, Sigma Chemical) or a mixture of propranolol (10 mg/kg) and naloxone (3 mg/kg) in a 2 ml/kg injection volume. The doses of propranolol and naloxone chosen were similar to doses that have previously been shown to be effective in studies on memory modulation (McGaugh, Introini-Collison, & Nagahara, 1988; Przybyslawski et al., 1999; Schneider et al., 2009, 2011).

2.4. Experimental procedure and treatment

Two experiments were conducted. The timeline for each experiment was as follows: contextual fear conditioning (Day 1), reactivation of fear memory followed immediately by administration of vehicle or drug (Day 2) and a retention test (Day 3). Contextual fear conditioning consisted of placing rats in a dark compartment for 120 s followed by a single footshock (1.0 mA, 0.5 s); reactivation of fear memory consisted of returning the animals to the dark compartment for brief durations (see below for details) in the absence of shock; the retention test consisted of returning the animals to the dark compartment for 6 min in the absence of shock. Freezing behavior, defined by the cessation of movement other than that associated with respiratory function, was monitored by an observer blind to the treatment conditions and served as a measure of fear during reactivation and the retention test.

2.4.1. Experiment 1: stress-dependent effect of naloxone on newly retrieved fear memory

The first experiment (*Experiment 1*) was aimed at determining whether activation of the endogenous opioid system, like its effect on modulation of newly acquired fear memory in previous studies (Schneider et al., 2009), limits enhancement and impairment of newly retrieved fear memory under conditions of weak and intense stress, respectively. Specifically, the effect of naloxone on modulation of newly-retrieved (reactivated) fear memory was determined under conditions of mild and intense stress.

Twenty-four hours after training, animals were randomly assigned to two groups and were placed in the conditioning chamber (to reactivate fear memory) for either 30 s (mild stress) or 120 s

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