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Oxytocin Facilitates the Extinction of Conditioned Fear in Humans

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ABSTRACT

BACKGROUND: Current neurocircuitry models of anxiety disorders posit a lack of inhibitory tone in the amygdala during acquisition of Pavlovian fear responses and deficient encoding of extinction responses in amygdala–medial prefrontal cortex circuits. Competition between these two responses often results in a return of fear, limiting control over anxiety. However, one hypothesis holds that a pharmacologic strategy aimed at reducing amygdala activity while simultaneously augmenting medial prefrontal cortex function could facilitate the extinction of conditioned fear.

METHODS: Key among the endogenous inhibitors of amygdala activity in response to social fear signals is the hypothalamic peptide oxytocin. To address the question whether oxytocin can strengthen Pavlovian extinction beyond its role in controlling social fear, we conducted a functional magnetic resonance imaging experiment with 62 healthy male participants in a randomized, double-blind, parallel-group, placebo-controlled design. Specifically, subjects were exposed to a Pavlovian fear conditioning paradigm before receiving an intranasal dose (24 IU) of synthetic oxytocin or placebo.

RESULTS: Oxytocin, when administered intranasally after Pavlovian fear conditioning, was found to increase electrodermal responses and prefrontal cortex signals to conditioned fear in the early phase of extinction and to enhance the decline of skin conductance responses in the late phase of extinction. Oxytocin also evoked an unspecific inhibition of amygdalar responses in both phases.

CONCLUSIONS: Collectively, our findings identify oxytocin as a differentially acting modulator of neural hubs involved in Pavlovian extinction. This specific profile of oxytocin action may open up new avenues for enhancing extinction-based therapies for anxiety disorders.

Keywords: Fear extinction, fMRI, Oxytocin, Psychophysiology, Skin conductance

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An ability to detect and avoid danger is essential for all species. It is likewise essential to adapt flexibly to new life circumstances in which a situation previously predicting danger no longer has this association. Facilitating this process has strong therapeutic implications for anxiety disorders (1), which are among the most common mental illnesses with a lifetime prevalence of up to 25% (2). Together with supportive pharmacotherapy, exposure-based behavioral interventions currently represent the "gold standard" for treating anxiety disorders (3). However, a substantial percentage of patients do not benefit from established therapeutic approaches (4,5).

Procedurally, exposure therapy is very similar to Pavlovian extinction (6), which can be modeled experimentally by the progressive decrement of a conditioned fear response (CR) when a conditioned stimulus (CS) is repeatedly presented in the absence of a noxious unconditioned stimulus (US) with which it has previously been paired (7,8). The return of fear after extinction owing to reinstatement, renewal, or spontaneous recovery serves as behavioral evidence that extinction does not erase the original fear, but rather involves new and independent inhibitory learning that competes with the original CS-US association (6). Current neurocircuitry models suggest that Pavlovian extinction is orchestrated by the medial prefrontal cortex (PFC) and surrounding areas, the amygdala, and their functional interactions (9,10). Consistent with the assumption that deficient extinction may contribute to the development and preservation of pathologic anxiety, patients with anxiety disorders typically present a neural pattern of medial PFC hypoactivation paralleled by amygdala hyperactivation, which normalizes after exposure therapy (11,12).

Informed by translational research on the neurocircuitry of extinction, innovative approaches for augmenting exposure therapy with pharmacologic agents have evolved (3,13,14). Specifically, animal studies have identified the oxytocin (OXT) system as a promising pharmacologic target for therapeutic interventions aimed at attenuating anxiety disorders (15–17). Investigators have shown OXT to modulate key nodes implicated in both anxiety disorders and Pavlovian extinction, including the amygdala and prefrontal areas, which is consistent with rich OXT receptor expression in these regions (18,19). Intranasal OXT administration has been found to reduce amygdala responses to social fear stimuli and to increase

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amygdala–medial PFC functional interplay (20–23). When administered after Pavlovian fear conditioning, intranasal OXT attenuates the negative evaluation of previously conditioned faces (24) and enhances the recall of extinction assessed with fear potentiated startle responses (25). Taken together, there is substantial evidence implicating OXT in the inhibition of anxiety; however, it remains unclear whether these effects or additional mechanisms might promote extinction learning.

We report a randomized, double-blind, parallel-group, placebo-controlled proof-of-concept study using a Pavlovian fear conditioning and extinction procedure with concomitant functional magnetic resonance imaging (MRI) and psychophysiologic assessments in 62 healthy men to examine the potential of OXT to modulate extinction learning. First, we hypothesized that OXT would specifically increase reactivity to the fear-conditioned stimulus in prefrontal regions implicated in extinction learning (7). Second, we predicted that neural activity in fear-associated brain areas such as the amygdala as well as electrodermal responses to the fear-associated stimulus (CS+) would be diminished. Given previous findings of phase-dependent modulation of fear extinction (26–28) and a selective effect of OXT on fear-potentiated startle during the earliest stage of extinction training (25), we also expected OXT specifically to modulate early extinction learning.

METHODS AND MATERIALS

Participants

Participants included 62 healthy, right-handed men (mean age ± SD, 24.61 ± 4.28 years) who gave written, informed consent. The study was approved by the institutional review board (Identifier: 329/12) and carried out in compliance with the latest revision of the Declaration of Helsinki. The study was registered in the ClinicalTrials.gov database (Identifier: NCT02156661) provided by the U.S. National Institutes of Health. Subjects were free of current and past physical or psychiatric illness, as assessed by medical history and the Mini-International Neuropsychiatric Interview (30); were nonsmokers, were naïve to prescription-strength psychoactive medication, and had not taken any over-the-counter psychoactive medication in the past 4 weeks. Subjects were not told the aim of the study. At the end of the experiment, they received a detailed debriefing and monetary compensation.

Experimental Design

We applied a randomized, placebo-controlled, double-blind, between-subject design. We preferred a parallel-group design over a crossover within-subject design to avoid potentially confounding effects of repetitive fear conditioning. Volunteers were randomly assigned to either intranasal administration of OXT (Syntocinon Spray; Novartis, Basel, Switzerland), 3 puffs per nostril, each with 4 IU OXT for a total dose of 24 IU, or placebo (PLC), sodium chloride solution, in accordance with current guidelines (31). Screening of the subjects was conducted before the test sessions. Participants completed a comprehensive neuropsychological test battery to control for possible pretreatment differences in cognitive performance, Beck Depression Inventory, and the Anxiety Sensitivity Index (32,33). The experimental groups did not differ in demographic variables or neuropsychological performance (Table 1).

Functional MRI Conditioning and Extinction Paradigm

We used an adapted version of a validated functional MRI fear-conditioning procedure (34). Briefly, during the procedure, neutral conditioned stimuli (CS+) were paired with an aversive US (electric shock) in 70% contingency, whereas other neutral stimuli were never paired with the US (non–fear-associated stimulus [CS−]). To account for previous findings suggesting that OXT specifically modulates processing of social stimuli, we included a social CS pair (two neutral faces from the Karolinska face database; face CS+, face CS−) and a

Table 1. Demographics and Neuropsychological Performance

	OXT Group, Mean (SD)	PLC Group, Mean (SD)	*t*	*df*	*p*
Age (Years)	25.20 (4.46)	24.03 (4.08)	1.068	59	.290
Education (Years)	16.77 (2.47)	16.23 (2.34)	.833	54	.409
SST[a]					
Median reaction time (msec)	491.65 (158.68)	443.00 (115.16)	1.381	60	.172
Stop signal reaction time (msec)	198.71 (143.99)	197.06 (137.48)	.046	60	.963
Proportion of correct stops	.52 (.14)	.51 (.08)	.088	60	.930
PAL[a]					
Total errors	23.52 (19.40)	17.87 (15.77)	1.257	60	.214
Mean errors to success	2.10 (3.76)	1.35 (1.68)	1.002	60	.320
SWM 8[a]					
Between errors	5.16 (7.49)	6.48 (9.31)	−0.616	60	.540
Strategy score	13.26 (4.25)	12.45 (3.14)	.878	60	.383
ASI[b]	15.10 (8.36)	17.13 (10.66)	−.832	59	.409
BDI[c]	2.71 (3.54)	2.65 (3.14)	.080	57	.937

ASI, Anxiety Sensitivity Index; BDI, Beck Depression Inventory; OXT, oxytocin; PAL, paired associates learning task; PLC, placebo; SST, stop signal task; SWM, spatial working memory task.

[a]Used to measure subjects' ability to inhibit a reaction, their visual memory, and their ability to retain spatial information, using the Cambridge Neuropsychological Test Automated Battery.

[b]Used to assess anxiety sensitivity.

[c]Used to measure depressive symptoms.