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Short Communication

Peripherally administered oxytocin modulates latent inhibition in a manner consistent with antipsychotic drugs

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HIGHLIGHTS

- Oxytocin is proposed to be therapeutic for schizophrenia.
- Facilitation of latent inhibition is predictive for antipsychotic drugs.
- We tested oxytocin's effect in rats with deficient latent inhibition.
- Oxytocin facilitated latent inhibition consistent with antipsychotics.
- Results support a therapeutic potential of oxytocin for schizophrenia.

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ABSTRACT

Background: Peripherally administered oxytocin (OT) has produced antipsychotic drug (APD)-like effects in animal tests that are predictive of APD efficacy. However, these effects have mainly been demonstrated using animal models of schizophrenia-like deficits in prepulse inhibition (PPI) of the startle reflex. Another schizophrenia-relevant abnormality that is the basis of a predictive animal test for APD efficacy is deficient latent inhibition (LI). LI is the normal suppression of a classically conditioned response when the subject is pre-exposed to the conditioned stimulus (CS) before it is paired with the unconditioned stimulus (UCS). Conditioned taste aversion (CTA), the normal avoidance of ingesting a food or liquid by animals when its taste is associated with an aversive experience, was used to test whether OT facilitates LI consistent with APDs.

Methods: Brown Norway rats, known to naturally display attenuated LI, were aversively conditioned on two consecutive exposures to flavored drinking water (0.1% saccharin) by pairing it with malaise-inducing lithium chloride injections. Concurrent with conditioning, rats received subcutaneous OT (0.02, 0.1, 0.5 mg/kg) or saline. Some rats were pre-exposed to the flavored water prior to its aversive conditioning (pre-exposed) while others were not (non pre-exposed). Two days after aversive conditioning the amount of flavored water consumed during a 20-min session was recorded.

Results: As expected, LI, defined as greater consumption by pre-exposed vs. non pre-exposed rats was only weakly exhibited in Brown Norway rats and OT enhanced LI by reducing CTA in pre-exposed rats in a dose-dependent manner, with the 0.02 mg/kg dose producing the strongest effect.

Conclusions: The facilitation of LI by OT is consistent with the effects produced by APDs and provides further support for the notion that OT has therapeutic potential for schizophrenia.

1. Introduction

Oxytocin (OT) is a nonapeptide that modulates several neurotransmitter systems in the brain via receptors located in brain regions implicated in schizophrenia such as the nucleus accumbens and hippocampus [1]. Although it has been reported that 1% or less of peripherally administered OT crosses the blood–brain barrier [2], a recent study demonstrated that intraperitoneal and intranasal administration OT in rodents produces a rapid increase in brain OT levels [3]. This is consistent with findings from a large number of studies, which show that peripheral administration of OT produces various effects that are centrally mediated. For example, peripherally administered OT alters various aspects of social behavior and fear in rodents [4,5]. Similarly, our laboratory has

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Table 1
Overview of the experimental design. D3, D5, D7: on these days all rats received regular water during their 20-min daily drinking session.

DAY	D1 and D2	D3	D4	D6	D8
	Water restriction	Pre-exposure	Conditioning and drug treatment #1	LI testing #1	LI testing #2
Procedure	All rats have 20 min access to water.	PE rats have 20 min access to flavored water. NPE and NC rats have 20 min access to regular water.	All rats have 20 min access to flavored water. All rats then given IP injections of LiCl except NC rats (saline injections). All rats then given SC injection of a dose of OT or saline.	All rats receive flavored water for 20 min. Conditioning and drug treatment #2 Rats given same IP and SC injections as on D4.	All rats receive flavored water for 20 min.

Abbreviations: NC = non conditioned group, NPE = non-pre-exposed group, PE = pre-exposed group, SAC = saccharine, LiCl = lithium chloride.

demonstrated that subcutaneously (SC) administered OT enhances prepulse inhibition of the startle reflex (PPI), a centrally mediated index of sensorimotor gating an important feature of normal information processing [6,7], consistent with OT activity in the brain.

PPI is deficient in schizophrenia and certain other neuropsychiatric disorders [8]. Peripherally administered OT enhances PPI deficits induced by psychotomimetic drugs and PPI deficits naturally exhibited in the Brown Norway (BN) rat strain [6,7]. The facilitation of reduced PPI is consistent with the effects of antipsychotic drugs (APDs) and suggests that OT may have therapeutic potential for schizophrenia. Indeed, several recent preliminary studies in humans in which OT was administered intranasally support this notion that OT has anti-schizophrenia properties [9]. However, to date the question of whether OT has therapeutic potential for schizophrenia and related disorders remains open. Thus there is a need for further pre-clinical and clinical studies to address this question.

Like PPI, latent inhibition (LI) is a schizophrenia-relevant brain process that is sensitive to drugs with APD efficacy. LI is the normal suppression of a classically conditioned response if the subject is pre-exposed to the conditioned stimulus (CS) before it is paired with the unconditioned stimulus (UC) [10]. It is thought to reflect an adaptive allocation of attention away from irrelevant stimuli and there is evidence that LI regulation is abnormal in schizophrenia [11]. Specifically, LI has been found to be absent or reduced in schizophrenia patients who are early in the course of the disorder, whereas in patients with a long-standing schizophrenia LI seems to be intact [11,12] but see [13]. Weiner and Arad [14] have proposed two ways LI is likely perturbed in schizophrenia, a deficit in LI and excessive persistence of LI, each with a distinct underlying mechanism. This may account for the apparent transitory nature of LI deficits in schizophrenia as these deficits manifest early in the course of the disorder but are masked in later stages by the emergence of excessive persistence of LI.

LI deficits as often seen in the acute stages of schizophrenia can be modeled in animals by various manipulations. For example, administration of dopamine enhancing drugs such as amphetamine concomitant with conditioning disrupts LI. In contrast, the Brown Norway (BN) rat has been found to exhibit low LI [15], in addition to other schizophrenia relevant phenotypes such as low PPI [7,16].

When administered concurrent with the pairing of the CS and UC in animal models of deficient LI (drug-induced or natural deficits), first and second generation APDs enhance LI [14]. This APD-induced facilitation of LI is thought to be mediated by the regulation of brain dopamine [17]. Psychotropic drugs that lack APD activity in humans generally do not facilitate LI in animal models [18] suggesting that LI deficit animal models have predictive validity for the therapeutic effects of APDs.

In order to further investigate the therapeutic potential of OT for schizophrenia, we tested its effects on LI in BN rats.

2. Experimental methods

2.1. Animals

Thirty-seven BN rats (170–300 g at testing) (Harlan, San Diego, CA) were housed individually in clear plastic chambers in a climate-controlled room under a 12 h light/dark schedule, with food and water provided ad libitum. Behavioral testing was begun 7 days after the animals' arrival, and was conducted during the light phase of their light/dark schedule. All studies described in this publication were carried out in accordance with The Declaration of Helsinki and/or with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

2.2. Procedures

An overview of the LI procedure is shown in Table 1. Throughout this experiment, all rats were water deprived except for 20 min a day during which they were allowed to drink ad libitum from bottles filled with 100 ml of water. At the end of the 20 min, water bottles were removed and the amount of water consumed measured. Animals were allowed unrestricted access to food at all times in their home cages. Rats were acclimated to this drinking schedule for 2 consecutive days and then were split into nine groups, matched based upon their average water intake. Four of the groups chosen at random were designated to be pre-exposed (PE) to the conditioned stimuli (flavored water) and the remaining five groups were not pre-exposed (NPE).

On the third day (D3), rats assigned to the PE groups received water flavored with 0.1% saccharin for their 20-min drinking session, while the NPE rats continued to receive unflavored water. The fourth day (D4) was the first conditioning day and on that day all rats were given-flavored water for 20 min. Thirty minutes before being presented with the flavored water the four PE groups and four of the NPE groups were randomly assigned to receive either subcutaneous (SC) saline or one of three doses of SC OT (0.02, 0.1, 0.5 mg/kg). The doses of OT were based on earlier studies that our lab conducted examining the effects of various doses of SC administered OT on motor activity and drinking under fluid deprived conditions. Doses above 0.5 mg/kg reduced drinking (Unpublished data). Thus, we avoided testing doses higher than 0.5 mg/kg. Twenty minutes later, immediately after the drinking session, each rat in these groups was administered one of the four oxytocin doses, then a SC injection of lithium chloride (0.15 M, 1.33% body weight), a dose that produces a transient malaise [19]. The final NPE group received two injections of SC saline after the drinking session and served as a non-conditioned control group.

The next day (D5) all rats were allowed to drink regular water during their 20-min drinking session. Day 6 (D6) served as both a LI test day and a second conditioning day. On that day all rats