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Oxytocin enhances the expression of morphine-induced conditioned place preference in rats

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Abstract Drug addiction is characterized by drug-seeking and drug-taking and has devastating consequences on addicts as well as on society. Environmental contexts previously associated with drug use can elicit continued drug use and facilitate relapse. Accumulating evidence suggests that the neuropeptide oxytocin might be a potential treatment for behavioral disorders, including drug addiction. Here, we investigated the effects of central oxytocin administration on the acquisition and expression of morphine-induced conditioned place preference (CPP), a model for measuring the rewarding effects of drugs of abuse, in male Wistar rats. Intracerebroventricular (ICV) administration of oxytocin (0.2 μg) or the specific oxytocin receptor antagonist (OTA), desGly-NH_2, d$(CH_2)_5$[Tyr(Me)^2, Thr^4] OVT, (0.75 μg), on the conditioning days did not affect the acquisition of morphine-induced CPP. By contrast, ICV oxytocin, but not OTA, administration immediately prior to the post-conditioning session enhanced the expression of morphine-induced CPP, possibly by activation of oxytocin receptors in the nucleus accumbens shell (NAcSh). The oxytocin enhancement of morphine-induced CPP was not associated with any changes in the locomotor activity of morphine-conditioned rats. Together, these data suggest that central administration of exogenous oxytocin enhances the expression of morphine-induced CPP, at least in part, via activation of oxytocin receptors within the NAcSh.

1. Introduction

Opioids, such as heroin and morphine, are widely used for pain management (Morgan and Christie, 2011), and the increasing number of patients with chronic pain has led to an increase in the use of opioid analgesics (de Leon-Casasola, 2012). However, addiction to opioids is a major public health problem (Compton and Volkow, 2006) and there is a pressing need to understand the mechanisms that underpin opioid addiction to improve the management and treatment of addicts. A particularly problematic aspect affecting the success of treatment of drug addiction is relapse following

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abstinence (Hyman et al., 2006). Repeated drug use can develop a strong association between the rewarding effects of the drug and drug administration environment, and the drug associated-environment can contribute to continued drug use as well as to the high risk of relapse after abstinence (Hyman et al., 2006; Koob and Volkow, 2010).

Oxytocin is a hypothalamic neuropeptide that is particularly important in parturition and lactation after secretion into the bloodstream from the posterior pituitary gland (Brown et al., 2013). In addition to its endocrine roles, oxytocin modulates a wide range of behaviors (Neumann, 2008) and is emerging as a potential treatment for drug addiction (McGregor and Bowen, 2012).

Oxytocin administration inhibits the development of tolerance to the analgesic effects of morphine and heroin (Kovacs et al., 1984, 1985b) and decreases intravenous heroin self-administration (Kovacs et al., 1985a). Peripherally administered oxytocin decreases methamphetamine self-administration, as well as relapse to methamphetamine-seeking in rats (Carson et al., 2010). In addition, intracerebroventricular (ICV) oxytocin inhibits methamphetamine-induced hyperactivity (Qi et al., 2008) and prevents the acquisition of methamphetamine-induced conditioned place preference (CPP) in mice (Qi et al., 2009). Furthermore, ICV oxytocin reduces cue-induced cocaine seeking (Morales-Rivera et al., 2014). Hence, oxytocin appears to be a promising candidate for the treatment of drug addiction. However, whether oxytocin administration has an effect on the power of association between opiates and the drug-associated environment remains unknown.

The medial prefrontal cortex and dorsal hippocampus contribute to oxytocin inhibition of stress-induced reinstatement of methamphetamine CPP (Han et al., 2014). Furthermore, oxytocin administration into the subthalamic nucleus or nucleus accumbens (NAc) core inhibits the acquisition of methamphetamine-induced CPP (Baracz et al., 2011). While the neural circuitry underlying these effects remains to be fully elaborated, the nucleus accumbens shell (NAcSh) is a likely to be a key relay component because it contributes to the execution of drug-related behaviors (Cheer et al., 2007; Witten et al., 2010; Cruz et al., 2014).

Oxytocin receptors are expressed in the NAcSh (Kremarik et al., 1993; Veinante and Freund-Mercier, 1997) and the same neurons that secrete oxytocin from the posterior pituitary gland project to the NAcSh (Knobloch et al., 2012).

Here, we determined the effects of exogenous and endogenous oxytocin on the acquisition and expression of morphine-induced CPP as a measure of learned associations between the rewarding effects of the drug use and drug administration environment (Aguilar et al., 2009).

2. Materials and methods

2.1. Animals

All experimental procedures were approved by the University of Otago Animal Ethics Committee, and were performed in accordance with the New Zealand Animal Welfare Act (1999) and associated guidelines. Adult male Wistar rats at 6—8 weeks of age, weighing 250—300 g, were obtained from University of Otago animal facility. While the best-characterized hormonal roles of oxytocin are in females, the neuromodulator/neurotransmitter roles of oxytocin are evident in both males and females and a recent study by Cox et al. (2013) suggested that 'oxytocin may be a promising treatment for methamphetamine addiction in both males and females'. We limited this study to males to reduce the potential confounding effects of estrous cycles, and to enable comparison of the effects of oxytocin on drug-induced CPP with the previous published reports, which have mostly been in males e.g. (Qi et al., 2009; Baracz et al., 2011). The rats were housed in groups of four at $22 \pm 1\,^{\circ}C$ with free access to water and food. Rats were maintained on a 12 h light/dark cycle (lights on at 0700 h) with all experiments performed during the light phase. All rats were handled daily for one week before and after recovery surgery.

2.2. Drugs

Morphine sulfate (15 mg ml^{-1}; Hospira, Wellington, New Zealand) was diluted in 0.9% saline before subcutaneous (SC) injection at 5 mg kg^{-1} in a 1 ml kg^{-1} volume. Oxytocin (Tocris Bioscience, Bristol, UK) and the selective oxytocin receptor antagonist (OTA), desGly-NH_2, d$(CH_2)_5$[Tyr(Me)^2, Thr^4] OVT (a generous gift of Dr M. Manning, University of Toledo, OH, USA), were diluted in 0.9% saline to the final concentrations used and stored in aliquots at $-20\,^{\circ}C$ until use. All vehicle injections were equivolume 0.9% saline solution.

2.3. Surgery

Rats were anaesthetized with 2—3% halothane in oxygen and placed in a stereotaxic frame (Model 900; Kopf, Tujunga, CA, USA). Prior to the start of surgery, rats were administered carprofen (5 mg kg^{-1}, SC) and strepcin (250 IU, SC). A guide cannula (22-ga, 3 mm length; Plastics One, Roanoke, VA, USA) was implanted into the lateral ventricle using the following stereotaxic coordinates (from bregma: 0.8 mm posterior; 1.3 mm right lateral and 3.0 below the surface of the skull). For bilateral cannula implantation, a double-barreled guide cannula (26-ga, 6.5 mm length; Plastics One) was positioned 1 mm above the NAcSh using the coordinates (from bregma: 1.7 mm anterior; 0.75 mm lateral, and 6.5 mm below the surface of the skull). Stereotaxic coordinates were adapted from the rat brain atlas of Paxinos and Watson (2007). The guide cannula was held in place with dental cement bonded to stainless steel screws inserted into the surface of the skull (Henry Schein Shalfoon, Auckland, New Zealand). A dummy cannula (3 mm length for ICV, 6.5 mm length for intra-NAcSh) was inserted into the guide cannula. Following surgery, the rats were allowed to recover for 3—5 days before being used in experiments.

2.4. Intracranial injections

Oxytocin (0.2 μg), OTA (0.75 μg) or 0.9% saline (2 μl) were injected ICV over 2 min using a microinjector (28-ga, 5 mm length; Plastics One), attached by polyethylene (PE-10) tubing to a 2 μl Hamilton syringe. The dose of oxytocin was based on previous studies that showed ICV oxytocin-induced