



# Effects of intranasal oxytocin on social anxiety in males with fragile X syndrome

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**Summary** Fragile X syndrome (FXS) is a rare inherited genetic disorder causing severe intellectual disability and autistic-like symptoms. Individuals with FXS, males in particular, often exhibit extreme eye gaze avoidance and hyperarousal when they encounter stressful social situations. We investigated whether oxytocin (OT), a hormone with prosocial and anxiolytic effects, could alleviate symptoms of social anxiety in this population. A randomized double-blind placebo-controlled single-dose trial was performed with intranasal administration of placebo, 24 IU OT and 48 IU OT. Measures of eye gaze frequency, heart rate, respiratory sinus arrhythmia (RSA), heart rate variability (HRV) and salivary cortisol were obtained during a structured social challenge conducted 50 min following OT administration. Ten low-functioning males with FXS (aged 13–28 years) traveled to Stanford for the initial visit: 8 completed the study. Eye gaze frequency improved significantly in response to the 24 IU OT dose and salivary cortisol levels decreased significantly in response to the 48 IU OT dose. There was no effect of OT on heart rate, RSA or HRV although individual plots of the heart rate data suggested that OT increased heart rate in some participants and decreased heart rate in others. These findings suggest that intranasal administration of OT may ameliorate some symptoms of social anxiety in patients with FXS. Further double-blind placebo-controlled studies of OT, conducted in combination with behavioral treatment programs, may be warranted.

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## 1. Introduction

Fragile X syndrome (FXS) is a rare inherited genetic disorder occurring in approximately 1 in every 3–4000 live births

(Crawford et al., 1999; Turner et al., 1996). The syndrome arises from disruption in expression of the fragile X mental retardation gene 1 (*FMR1*) caused by amplification of a CGG repeat in the 5' untranslated region (Verkerk et al., 1991). In normal alleles, a CGG repeat within *FMR1* varies from 6 to 50. Expansions of ~50–200 repeats are associated with the “premutation” form of FXS whereas larger expansions (200 to thousands) are considered “full mutations” and are typically associated with excessive methylation of cytosines in the *FMR1* promoter. This modification extinguishes

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transcription of the *FMR1* gene into mRNA, stopping translation of the fragile X mental retardation protein (FMRP). FMRP is a messenger RNA-binding brain protein involved in the maturation and elimination of synapses during typical development (O'Donnell and Warren, 2002). Increased FMRP is also observed in association with new learning and response to varying environmental conditions (Irwin et al., 2005). Thus, reduced FMRP in individuals with the full *FMR1* mutation significantly increases risk for both long-term neurodevelopmental and real-time neurofunctional abnormalities. To date, FXS is the most common known form of inherited intellectual disability.

Studies from our laboratory and others indicate that the most common problem behaviors observed in FXS consist of hyperarousal, disturbance in language/communication, and social anxiety (Reiss and Hall, 2007). In males, problematic behaviors often take the form of social deficits with peers, social avoidance, gaze aversion, qualitative abnormalities in communication, unusual responses to sensory stimuli, stereotypic behavior, inattention, impulsivity and hyperactivity. FMRP expression (as quantified by immunocytochemistry) has been linked to many of these phenotypic characteristics of FXS, including social withdrawal, anxiety and depression as well as to quantitative measures of brain development and function (Lightbody and Reiss, 2009).

Individuals with FXS, particularly males, often have abnormally strong physiological and behavioral responses to social stimuli, associated with increased levels of arousal and stress reactivity. For example, Miller et al. (1999) used a laboratory paradigm to study electrodermal responses to auditory, visual, touch, vestibular, and olfactory stimuli to assess sympathetic nervous system activity in children and adults with fragile X syndrome. In this study, increased electrodermal response (EDR) to stimulation and lower rates of habituation to stimulation were found in FXS as compared to age and gender matched control subjects. Other investigators studying spectral analysis of heart beat intervals have found that boys with FXS have increased heart rate and lower parasympathetic activity during experimental challenge (Bocchia and Roberts, 2000; Hall et al., 2009a). For example, in the study by Hall et al. (2009a), males with FXS (8–20 years of age) had higher heart rate, lower amplitude respiratory sinus arrhythmia (RSA) and lower heart rate variability during both a baseline and social interaction, relative to their typically developing siblings. In another study from our group, we reported that children with FXS, especially males, had higher levels of salivary cortisol compared to their non-FXS siblings. Increased cortisol was significantly associated with behavior problems in boys and girls with FXS but not in their unaffected siblings (Hessl et al., 2002). The finding of abnormal cortisol levels in individuals with FXS is complemented by the discovery that FMRP is involved in regulating the glucocorticoid receptor in the hippocampus (Brown et al., 2001).

There is currently no cure for FXS though initial efforts are now being made to intervene at the level of downstream systems altered by reduced levels of FMRP. Examples of such interventions include the use of agents to reduce metabotropic glutamate activity (Bear et al., 2004; Berry-Kravis et al., 2009; Garber et al., 2006) or to re-regulate the cholinergic system (Kesler et al., 2009). Less specific psychotherapeutic and pharmacological interventions targeting specific behaviors are also often used in the clinical setting

for affected individuals (Berry-Kravis and Potanos, 2004). However, studies conducted to date have reported few significant positive effects for these approaches, particularly with respect to increasing appropriate social behavior in individuals with FXS (Hall, 2009).

A potentially promising pharmacotherapy for patients with FXS is the neuropeptide oxytocin (OT), which has a variety of prosocial, antistress, and anxiolytic properties. Briefly, OT is synthesized in the hypothalamus and released into systemic circulation via the posterior pituitary. OT is also released as a neurotransmitter into the central nervous system (CNS), and OT receptors are found in a variety of socially relevant and stress-sensitive neuroanatomical regions. Centrally administered OT facilitates contact-seeking, attachment bond formation, and social memory in rodents (Ferguson et al., 2000; Williams et al., 1992; Witt et al., 1992). Centrally administered OT also diminishes stress-induced adrenocorticotrophic hormone (ACTH) and corticosterone release, and inhibits corticotropin releasing factor (CRF) mRNA expression in the hypothalamus during restraint stress in rats (Windle et al., 2004). Similarly, female mice lacking the oxytocin gene exhibit enhanced corticosteroid responses to psychogenic stressors and enhanced anxiety on the elevated plus-maze compared to wildtype controls (Amico et al., 2004; Mantella et al., 2003).

Recently, several investigators have reported that administration of OT can improve social functioning in patients diagnosed with autism. For example, OT administration has been shown to improve social decision-making (Andari et al., 2010; Hollander et al., 2007), reduce repetitive behaviors (Hollander et al., 2003), increase emotion recognition (Gualetta et al., 2010), and promote visual scanning of faces (Andari et al., 2010) in youth and adult patients with high functioning autism and Asperger's syndrome. When administered intranasally, OT also attenuates the neuroendocrine stress response in rodents and monkeys and alters emotion regulation in humans (Heinrichs et al., 2003; Parker et al., 2005; Windle et al., 2004). Effects of intranasal OT have also been demonstrated with functional neuroimaging (Kirsch et al., 2005) as well as with standardized testing, self-report or expert ratings (Kosfeld et al., 2005). CNS penetration following intranasal administration occurs within minutes and delivery to the brain is thought to occur via an extracellular pathway (e.g., patent intercellular clefts in the olfactory epithelium) (Balin et al., 1986), indicating that the observed behavioral effects of intranasally administered OT result from altered neural function. However, it should be pointed out that while vasopressin has been detected in cerebrospinal fluid (CSF) and plasma within 30 min of intranasal administration (Born et al., 1998, 2002), similar work has not yet been published with intranasally administered OT in humans.

The extant literature strongly suggests that intranasally administered OT is safe and associated with very few adverse effects. Thus, intranasally administered OT is a promising medication to utilize in a clinical trial designed to improve social functioning in persons with FXS. The purpose of the present study was to determine whether administration of intranasal OT could improve socially appropriate behaviors and reduce concomitant social anxiety in males with FXS. Specifically, we hypothesized that individuals with FXS would show significant gains in eye contact frequency, reduced

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