Investigating the impact of Oxytocin on irritability in children and adolescents with disruptive behavior and mood disorders

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Abstract

Background: Irritability is a significant mental health issue in pediatric population with various psychiatric diagnoses. One of the established neurobiological mechanisms of irritability is increased activation in the neural areas of acute threat response system. OXT, with its most commonly suggested mechanism as reduction of reward processing, can be potentially a mechanism-based treatment option for irritability, targeting the key neural areas.

Objective: To determine the efficacy of OXT intranasal administration for high levels of irritability in pediatric population with various psychiatric diagnoses.

Methods: Randomized double-blind clinical trial of OXT intranasal administration (3 weeks) for children and adolescents (10-18 years old) with ADHD, CD, ODD, and DMDD. Neuroimaging modalities (fMRI and MEG) are applied to visualize the neural changes in the target areas of acute threat response system.

Results: 26 participants were recruited. 24 of 26 completed the clinical trial. OXT administration demonstrated significant reduction of the key neural areas of acute threat response system (mPFC and PAG) in target areas of acute threat response system, compared to placebo in youths with high levels of irritability. MEG captured effectively the key neural areas (amygdala) activation to negative emotional stimuli.

Conclusion: Not only the neuroimaging modalities successfully captured the increased activations in acute threat response system for youths with high levels of irritability, they also demonstrated reduction of the key neural areas of acute threat response system after OXT intervention, compared to placebo. OXT can be a promising mechanism-based treatment modality for high levels of irritability in youths with various psychiatric diagnoses.

Introduction

Irritability in pediatric population can be defined as an increased propensity to exhibit anger relative to one’s peers. Children and adolescents with irritability demonstrate increased level of aggression/violent behavior, especially reactive aggression. An important translational neurobiological model of irritability implicates hyper-activation in acute threat processing (i.e. heightened response of the neural areas to emotional stimuli, especially negative emotional stimuli), and/or abnormal fluctuating non-reward processing (Leibenluft, 2017).

Irritability manifests across various psychiatric diagnoses of pediatric population, including Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), and Disruptive Mood Dysregulation Disorder (DMDD). For those diagnoses, dimensional approach to irritability (especially in regard to targeting of underpinning neurobiological mechanism) may be of inherent identification of neurobiology and development of common-target-oriented treatment.

Chronic irritability is related to negative long-term outcomes (disruptive behavior, aggression/violence, delinquency, substance abuse, and depression/anxiety). Considering the high prevalence of irritability in pediatric population, it is a significant concern that there is remarkably little evidence-based treatment, and even less of treatment that is mechanism-based.

One potentially promising compound for treatment of irritability in pediatric population is intranasal oxytocin (OXT). Previous studies have shown that the most consistent neural impact of OXT administration implicates reduction of hyperactivity in the acute threat response system. These have been demonstrated in various psychiatric diagnoses (Borderline Personality Disorder, Generalized Anxiety Disorder, Post-Traumatic Stress Disorder). In addition to children and adolescents with Disruptive Behavior Disorder (DBD) show abnormal pattern of methylation on OXT receptors. However, OXT has not been investigated for this population.

Objective: To determine the efficacy of oxytocin on irritability in pediatric population and determine its relation to reduction of increased activation in the acute threat response system.

Hypothesis: Administration of OXT will be associated with improvement in levels of irritability as well as a decreased in the heightened response of acute threat response system to emotional stimuli. There will be a positive correlation between the level of reduction in response of acute threat response system to emotional stimuli following OXT intervention and the level of improvement in symptom profiles of irritability.

Methods

The study was designed as a double-blind randomized clinical trial of OXT intranasal administration. Two neuroimaging modalities (fMRI and MEG) have been applied. A total of 26 participants were recruited. 24 of 26 completed the clinical trial. OXT administration demonstrated significant reduction of the key neural areas of acute threat response system, compared to placebo in youths with high levels of irritability. MEG captured effectively the key neural areas (amygdala) activation to negative emotional stimuli.

Conclusion: Not only the neuroimaging modalities successfully captured the increased activations in acute threat response system for youths with high levels of irritability, they also demonstrated reduction of the key neural areas of acute threat response system after OXT intervention, compared to placebo. OXT can be a promising mechanism-based treatment modality for high levels of irritability, as a mechanism-based treatment modality.

Progress/Future Direction

1. Continue recruitment/conduction of current clinical trial of OXT intranasal administration, focusing on the neural as well as clinical changes.
2. Future NIMH grant application:
   (1) U01
   (2) First in Human and Early Stage Clinical Trials of Novel Investigational Drugs or Devices for Psychiatric Disorders (FOA: PAR-18-427)
(3) Proof of Concept Study

Acknowledgements

The project described was supported by the National Institute Of General Medical Sciences, 1U54GM115458. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References