Opioid antagonism modulates oxytocin-induces anxiolytic-like behavior: Implications for Treatment of Substance Use Disorders

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Anxiety disorders are leading causes of disability worldwide and are major contributors to substance use disorders (SUDs). Together, these disorders affect ~20% of the population and disproportionately affect women. A previous study by our lab demonstrated that intracerebroventricular oxytocin (500 ng) reduced anxiety-like behavior in male and female mice, with increased efficacy in males. Additionally, others have shown that mu-opioid receptor (MOR) activation can reduce anxiety-like behavior and early studies suggest that the opioid receptors regulate the oxytocin system in relation to the stress response. Thus, we hypothesized that modulation of the opioid system mediates the anxiolytic-like response to oxytocin treatment. To determine whether endogenous opioids mediated anti-stress effects of oxytocin, we administered an opioid receptor antagonist, naloxone (1-4 mg/kg) prior to an effective dose of oxytocin (500 ng) in both males and females. Contrary to our initial hypothesis, our studies demonstrated that naloxone potentiated the anxiolytic-like effect of oxytocin. Using mu-opioid receptor-selective antagonist, CTAP and kappa-opioid receptor-selective antagonist norbinaltorphimine, we demonstrated that mu-opioid receptor blockade potentiated the anxiolytic-like effect of oxytocin, whereas kappa-opioid receptor blockade inhibited oxytocin-induced anxiolytic-like effects. Our findings also indicated that blockade of the opioid system may eliminate observed sex differences in oxytocin sensitivity. As current clinical trials and treatment strategies include naltrexone (an opioid receptor antagonist), and in preliminary studies, oxytocin, these findings have clinical implications for the prevention and treatment of SUDs. Ongoing studies to further elucidate the neural mechanisms underlying the observed behavior include electrical recording and morphological observations from the central amygdala, a brain region important for emotion regulation.