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RESEARCH HIGHLIGHT

Unraveling oxytocin's peripheral vs. central mechanisms

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To date, very few pharmacological treatments for addiction have crossed the bridge of translational relevance. The arduous journey often begins with early victories in preclinical animal settings before becoming bogged down in clinical trials, where numerous factors all too often bring the journey to a dead end. The few compounds that do successfully reach the fabled land of clinical significance are typically agonist substitution treatments for alcohol or opioid addiction. There are currently no compounds that have managed to conquer this bridge in regard to cocaine or methamphetamine addiction. This failure is alarming, as methamphetamine is second only to opioids in the number of emergency room visits and deleterious health consequences [1]. Currently, the neuroactive peptide oxytocin is steadily approaching the bridge with startling speed and efficiency. There are many clinical trials testing intranasal oxytocin as a solo or adjunct therapy for alcohol, opioid, and stimulant addiction. Thus far, reports from these trials demonstrate that oxytocin has some efficacy at reducing craving in alcohol, heroin and cocaine users.

The preclinical research corroborates the clinical findings that systemic administration of oxytocin decreases relapse to cocaine, methamphetamine, heroin, and alcohol seeking (reviewed in [2]). However, one of the biggest criticisms of oxytocin use in rodent models is the peptide's ability, or lack thereof, to cross the blood-brain-barrier (BBB). Like all peptides, oxytocin does not readily cross into the central nervous system (CNS). Only 1–2% of oxytocin synthesized and released by peripheral organs or the posterior pituitary cross the BBB [3, 4]. So, it remains unknown how peripherally administered oxytocin can exert effects on the central nervous system [5].

The current article by Everett and colleagues demonstrates that the central effects of peripheral oxytocin may be mediated by peripheral vagal nerve stimulation (VNS) via oxytocin receptors on vagal abdominal fibers. VNS has been evaluated as a potential treatment for multiple neuropsychiatric disorders for which oxytocin is also a proposed treatment, including depression, anxiety, post-traumatic stress disorder, and addiction. As such, this finding is exciting to both clinicians and pre-clinical animal researchers. Further, identification of this mechanism is important and timely given the number of clinical trials approved for the use of oxytocin in multiple neuropsychiatric disorders; all with limited knowledge about oxytocin's therapeutic mechanisms.

Everett and others have previously shown that systemic administration of oxytocin deceased methamphetamine seeking in response to various relapse precipitants, including stress, drug cues and a methamphetamine priming injection (reviewed in [2]). To determine whether the vagus nerve is involved in oxytocin's inhibition of drug seeking, Everett and colleagues surgically disconnected the subdiaphragmatic vagus nerve in male and female rats before methamphetamine self-administration and reinstatement testing. The subdiaphragmatic vagotomy (SDV) was performed by removing a section of each nerve from the diaphragm to the stomach before implantation of jugular cannula.

First, Everett and colleagues showed that SDV did not impact acquisition or maintenance of methamphetamine self-administration, indexed as the number of nose pokes and infusions earned during the sessions. However, oxytocin administration during this phase of the addiction cycle provided the initial support for oxytocin's impact on VNS. As expected, oxytocin decreased methamphetamine infusions in both male and female sham (control) rats, an effect that was blocked in SDV rats after a low dose of oxytocin. Interestingly, the blockade was only partial, as a higher dose of oxytocin still decreased infusions in SDV rats. The authors suggest that SDV may not be able to surmount the effects of this high dose, as increased circulating oxytocin stimulates other peripheral structures such as the BBB-deficient area postrema or the nodose ganglion. Both of these mechanisms modulate the ability of the nucleus solitary tract to stimulate oxytocin release from the paraventricular nucleus [6, 7]. Alternatively, the higher dose of oxytocin may also bind vasopressin V1A receptors located on peripheral vagal fibers [8], as the two peptides display significant homology.

Subsequently, a complex interplay emerged during reinstatement testing between male and female rats, as SDV blocked the inhibitory effect of oxytocin to both relapse precipitants (drug cue and prime) in males only. As this study is among the first to study the effects of VNS using females in an addiction model, the divergent interactions between SDV, oxytocin, and sex are difficult to interpret. This finding provides a basis for future investigations using female-targeted models to determine sex-specific treatment approaches for the use of oxytocin. The endogenous oxytocin system is sexually dimorphic and this study demonstrates convergent sex differences exist [9]. Convergent sex differences occur when males and females exhibit the same behavior, but the underlying processes that mediate the trait are different [9]. Specifically, in this study, oxytocin decreases drug seeking in male and female rats (i.e., similar behavioral output) but SDV was only effective in male rats during reinstatement (i.e., different mechanisms).

Everett and colleagues suggest that some altering mechanisms may be non-identical patterns of oxytocin receptor expression in the brain and/or organic or methamphetamine-associated sex-specific effects on the ability of oxytocin to cross the BBB. They ruled out altered vagal regeneration through functional vagotomy testing with administration of the satiety-signaling peptide CCK-8, which inhibits feeding through subdiaphragmatic vagal signaling. Indicative of successful SDV, CCK-8 injections reduced food intake in both male and female SDV rats relative to sham.

In conclusion, Everett and colleague's demonstration of SDV blockade of oxytocin's impact on methamphetamine seeking is well-timed given the current interest in using oxytocin to treat

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multiple neuropsychiatric disorders. This research group has helped advance our understanding of how systemic oxytocin can impact centrally mediated behavior in light of the small amounts of the peptide that cross the BBB. Future work by this group will be exciting to review as we learn more about the covert sex differences that emerged and the mechanisms by which higher doses of oxytocin can surmount SDV. The relevance of these findings extends beyond methamphetamine self-administration and addiction models by defining basic mechanisms between peripheral and central oxytocin interactions. Finally, a more complete understanding of oxytocin's mechanisms will propel oxytocin's journey across the bridge of translational relevance.

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ADDITIONAL INFORMATION

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