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Can We Bottle Psychosocial Treatments for Addiction? The Role of Oxytocin

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> The literature on the hedonic properties of drugs of abuse has been our major source of information about the neurobiology of reward. … It seems likely that these pathways and genes evolved not for drug abuse but for mediating the motivational aspects of social interaction.
>
> —Thomas R. Insel, Director of the National Institute of Mental Health[1]

> Is my love your drug? Because your love, your love, your love is my drug.
>
> —Ke$ha, “Your Love Is My Drug”

Many parallels exist between love and addiction, and the two have often been compared in art, philosophy, and science throughout history. Although the mechanisms are not completely elucidated, we will briefly identify some of the key neurobiological parallels that exist between social attachment and addiction. We will also outline the advancement of knowledge related to the novel antiaddiction properties of oxytocin and future directions for its development as a potential adjunct to addiction treatment.

Neurobiology of Love

Love is a broad, often elusive term. However, *attachment* is defined as an evolved, biologically rooted motivation system that dictates the organization of behaviors in young children to promote proximity to one or more discriminated attachment figures.[2] This system translates into relationships with adult romantic partners as well.[3] The basic tenets of attachment theory are (1) the attachment motivation system is activated by stress or threat, (2) “securely attached” individuals are able to utilize social support to buffer the stress response, and (3) the relationship acts as a “secure base” from which to independently explore and gain a sense of mastery over the environment.[2] Attachment theory has been extensively studied for over 50 years, and a large body of research demonstrates consistent, predictable patterns that can be utilized in clinical settings.[4]

On a neurobiological level, it can be hypothesized that the attachment system is another hypothalamic regulatory system, modulating social proximity[5] in the same way we regulate water balance and thirst, feeding behavior, temperature, and sleep-wake cycles using

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feedback systems within the hypothalamic-pituitary-adrenal axis to maintain homeostasis in response to stressors. According to the well-studied opioid hypothesis of social attachment, low activation of opioid receptors induces a drive to seek social rewards[6]; thus, separation distress may reflect a state of endogenous opioid withdrawal. In addition to a low opioid state, oxytocin is released in response to stress, promoting close social proximity with trusted individuals and reducing cortisol.[7,8] This important mechanism also factors into oxytocin's prominent role in birth, breastfeeding, and sex,[9] all instances requiring enhanced social proximity and restricted stress response. Endorphins are released upon reunion with the attachment figure, activating opioid receptors and feeding back to inhibit both the stress response and hypothalamic oxytocin release.[10] High activation of opioid receptors within specific limbic structures signals a reward state.[11] Within a social context with a trusted individual, this reward state may contribute to the creation of a secure base. Mesolimbic dopamine signaling controls incentive salience and reward motivation[11] and likely plays a large role in the independent exploratory behavior and attainment of nonsocial "object-orientated rewards"[12] that complement a secure attachment base. Oxytocin co-opts mesolimbic dopaminergic cells to uniquely assign social salience to motivation and reward.[6,9,10] In fact, without oxytocin, affiliative behaviors may be lost altogether, as seen in conditional oxytocin receptor knockout mice.[13] Therefore, endogenous opioids and dopamine, key players within the reward system that are known to be involved in addiction, along with oxytocin, homeostatically regulate social proximity in response to the presence or absence of stressors. The role of these neuromodulators in social attachment may be the evolutionary root of their interactions in addiction.

Neurobiology of Love and Addiction

Addiction has been conceptualized as a process that hijacks the brain's learning and reward circuitry through hyperphysiologic activation of dopamine and opioid receptors within the mesolimbic reward system.[10] This process results in psychological and physical dependence on exogenous substances of abuse at the expense of other forms of reward, including social reward. By the same token, chronic substance dependence has been correlated with low hypothalamic oxytocin.[10,12] Addiction "rewires" the attachment system, leading to neglect of social motivation and reward and, instead, reliance on drugs to fulfill attachment needs. In other words, heroin, for example, becomes mother and/or partner to the dependent individual. A well-balanced secure attachment, or the ability to utilize social support to buffer the effects of stress and maintain independence, is protective against substance use disorders (SUDs).[14] On the other hand, insecure attachment styles, such as avoidant attachment, described as avoidance of social intimacy and overvalued independence, are associated with higher risk of developing SUDs.[15] Therefore, social deficits are both a risk factor for and a result of SUDs.

Furthermore, attachment avoidance within SUD populations may impair engagement in SUD treatment, which heavily involves psycho social interventions. For example, only the first of the 12 steps of Alcoholics Anonymous addresses alcohol directly; the other steps essentially involve the reparation and maintenance of supportive social networks. A large meta-analysis[16] recently found that the adaptive social factors of Alcoholics Anonymous, such as increasing recovery-supportive social networks, are by far the most important for

sustained sobriety. Despite the significance of psychosocial interventions for SUDs (such as intensive counseling; individual, group, and family therapy; and vocational rehabilitation), these treatment components can be challenging, time-consuming, and costly. Pharmacologic replacement for SUDs, such as methadone maintenance therapy, the gold standard in treating heroin addiction, effectively treats withdrawal and craving.[17] However, physiologic dependence on opioids persists, and social deficits[18] and relapse rates[19] remain stubbornly high. Many substances of abuse, such as psychostimulants, currently have no approved pharmacologic treatments. Furthermore, there is no approved prosocial pharmacologic agent that may help facilitate psychosocial aspects of treatment.

The Role of Oxytocin in Addiction Treatment

In the 1970s, prior to the discovery of oxytocin's major role in social behavior, its effects on learning and memory were being investigated. In one series of studies, laboratory mice were taught to avoid a particular section of floor coupled with an electric shock. Oxytocin was found to facilitate the extinction of this learned avoidance. Thus, oxytocin seemed to "reset" the adaptive fear association with the otherwise neutral floor space. Hungarian researchers Sarnyai and Kovács[10] hypothesized that similar learning and extinction processes were underlying tolerance and withdrawal to substances of abuse, both major components of substance dependence, and moved on to investigate the effects of oxytocin on these processes.

By the mid-1990s, preclinical studies using animal models of addiction for myriad substances of abuse had found parabolic dose-dependent effects of oxytocin administration on tolerance and withdrawal. For example, oxytocin attenuates tolerance to morphine, alcohol, and cocaine and mitigates naloxone-induced morphine withdrawal and alcohol withdrawal.[10,12] Furthermore, oxytocin interacts with psychostimulants to reduce cocaine- and methamphetamine-induced stereotyped movements.[12] Perhaps administration of exogenous oxytocin is counter-regulating a homeostatic system thrown off balance by substances of abuse. If this were the case, would this "resetting" phenomenon affect addiction-related *behavior*? Aside from attenuation of tolerance and withdrawal, oxytocin administration decreases heroin, alcohol, cocaine, and methamphetamine self-administration in dependent animals.[10,12] Decreased self-administration, seemingly secondary to a reduction in craving, is an important behavioral outcome that we hope to see translated in human research.

It was not until the mid-2000s that intranasal oxytocin became a popular intervention in social neuroscience research. In addition to demonstrating virtually no reliable side effects and no detectable subjective changes for subjects,[20] investigations using oxytocin in healthy populations have provided much insight into human social behavior over the past decade. For example, oxytocin levels are positively correlated with trust, ideal parenting behavior, spousal support, and increased physical contact with a romantic partner.[8,13] In one study, participants receiving a single dose of intranasal oxytocin, in addition to social support from their best friend, had the lowest levels of anxiety and showed the lowest cortisol elevation in response to a social stress test compared with those receiving only oxytocin or social support alone or with neither intervention.[13] Furthermore, administration of intranasal oxytocin

increases perceptions of trustworthiness and approachability and may particularly enhance trust and cooperation in individuals with high attachment avoidance.[21,22] In more recent years, researchers have been investigating intranasal oxytocin's potential as a therapeutic intervention for various psychopathologies. Oxytocin administration may attenuate the symptoms of autism,[23] schizophrenia,[24] and social anxiety[13]—all disorders involving difficulty seeking and utilizing social support to mitigate stress.

Few investigators have studied the effects of oxytocin on SUDs in human subjects. Thus far, published findings have come from underpowered pilot studies. For example, one randomized, double-blind clinical trial of 11 subjects experiencing acute alcohol detoxification (7 receiving oxytocin) demonstrated that intranasal oxytocin administration resulted in significantly reduced lorazepam dosage required to complete detoxification, lower Clinical Institute Withdrawal Assessment for Alcohol scores, and lower self-reported alcohol craving compared to placebo.[24] In another pilot study of 16 marijuana-dependent individuals (8 receiving oxytocin), administration of a single dose of intranasal oxytocin significantly reduced social stress–induced marijuana craving compared to placebo.[25] We are actively furthering this work through pilot studies investigating the role of oxytocin in the treatment of patients with SUDs including opioid dependence, cocaine dependence, and alcohol abuse (C.S.S., J.D.W., manuscript in preparation). Despite the preliminary nature of these studies, results are quite promising.

Conclusions and Future Research

Over the past few decades, data have been steadily accruing in support of the use of oxytocin in the treatment of SUDs.[7,26] The age-old link between love and addiction, and their shared neurobiology, may be the key to unlocking the development of crucial improvements in current SUD treatments. Large individual differences in basal oxytocin levels and reactivity of the oxytocin system exist[27] and can influence SUD risk and may dictate susceptibility to different treatments. Research suggests that the mitigating effect of oxytocin on SUDs involves shifting attentional bias toward adaptive social reward at the expense of conditioned drug-related reward. Decades ago, medical professionals translated knowledge of hypothalamic homeostasis into clinical treatment for central diabetes insipidus using desmopressin to prompt renal water retention. Perhaps someday we will prompt and strengthen the utilization of vital social support of patients with SUDs through the clinical use of oxytocin.

Many questions remain about the pharmacokinetics of intranasal oxytocin,[8,20] the precise neural mechanisms of the effects of oxytocin on addiction, and the translatability of preclinical findings to human populations with SUDs. The relative importance of the role of oxytocin in aiding patients through withdrawal, "resetting" drug tolerance, abating stress-induced craving, or facilitating engagement in psychosocial components of treatment remains unknown. Additionally, more research is needed on optimal oxytocin administration and dosing. U-shaped dose response curves in animal studies[10] demonstrate the need for clinical studies involving tiered dosing. Chronic dosing, as opposed to the single-dose data that currently exist, should also be explored. Among other measures, future studies should include validated measures of attachment style, which may help identify subpopulations

with differing responses to oxytocin as a treatment option (Bartz[22] and C.S.S., J.D.W., manuscript in preparation). With much yet to learn about oxytocin's role in the treatment of SUDs, clinicians should, nonetheless, be aware of its promising potential.

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