Scholar Publishing Group
International Journal of Public Health and Preventive Medicine
https://doi.org/10.38007/IJPHPM.2023.040105
ISSN 2789-8377 Vol. 4, Issue 1: 37-48

Effects of Oxytocin on Drug Addiction and Its Relationship to Prosocial Behavior

Shuna Peng*

Department of Psychology, Jiaying University, Meizhou, Guangdong, China

psnath@139.com
**corresponding author*

Keywords: Oxytocin, Drug Addiction, Prosocial Behaviour, Neural Mechanisms

Abstract: The use of oxytocin may bring a new dawn to the treatment of drug addiction. This study first summarizes the neural mechanism of oxytocin affecting drug addiction from two aspects: synaptic plasticity and neural circuits. Furthermore, the theoretical hypothesis of oxytocin on addiction is reviewed, and strong evidence is made for the therapeutic effect of individual adolescent oxytocin pretreatment on drug addiction. The efficacy of oxytocin may be influenced by the effects of drug addiction on prosocial behavior. Models of prosocial behavior in rodents were also introduced to clarify the relationship between drug addiction and oxytocin and prosocial behavior. It is hoped that the review of this paper can do what can be done for researchers to understand the impact of oxytocin on drug addiction and its relationship with prosocial behavior.

1. Introduction

Substance use disorder (also known as substance addiction) is a chronic recurrent brain disease(Koob & Volkow, 2016). A World Health Organization survey of attitudes towards 18 disabilities in 14 countries found that substance addiction was almost at the top of social disapproval. The use of psychoactive substances can lead to dependence syndrome, that is, a group of physiological, behavioral and cognitive phenomena. The use of certain active substances takes precedence over other once important behaviors for specific individuals, and patients gradually transition from accidental behaviors to compulsive behaviors. The core feature of addiction is that patients clearly know that their behaviors are harmful but cannot control themselves(Zhang et al., 2021). With the prevalence of new drugs, the number and harm of addiction may increase year by year, so it is urgent to find effective pharmacological and psychosocial intervention measures with low side effects and high compliance.

The application of oxytocin (OXT) may bring a new breakthrough to this problem (Bowen & Neumann, 2017b). OXT is a cyclic neuropeptide composed of 9 amino acids, which is mainly

synthesized in hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON)(Numan & Young, 2016). Neuropeptide OXT can not only influence the changes of neural adaptability in the process of drug addiction (Mobasher et al., 2021), but also regulate prosocial effects and anti-anxiety and depression (Yoon & Kim, 2022), and play a central role in stimulating social interaction(Dölen, 2015). Interest for the use of oxytocin as a treatment for prescription begin over 40years ago. Better known for its roles in partition, lactation and pair bonding, oxytocin also has anxiolytic properties, reduces immune and inflammatory responses, and has a role in learning and memory.(Leong et al., 2018). We sum up oxytocin's impact on drug taking, seeking, and relapse by highlighting research findings that have used oxytocin with current models of addiction, relapse, or cravs A graphic presentation of results is show in Table 1.

Table 1. Oxytocin Effects on Predictive Models of Addiction

Drug	Procedures	roles
Methamphetamine/ Cocaine/Heroin/Alcohol	Acquisition and Maintenance	Impaired acquisition
	Motivation to Seek	Decreases motivation
	Extinction	Enhanced the extinction
	Reinstated	Reduced reinststatement

2. Effect of oxytocin on drug addiction

Drug addiction is a process of neural adaptation to repeated drug exposure, so it is also considered as a form of "learning". Repeated use of addictive drugs such as opioids, psychostimulants, ethanol and nicotine leads to physical and mental dependence on drugs. Tolerance, sensitivity and withdrawal are the phenomena of pharmacological effects in different stages of addiction, which together constitute the main characteristics leading to forced use and recurrence. Brain OXT system is gradually becoming one of the most exciting new targets for the treatment of drug addiction(Bowen & Neumann, 2017a).

2.1. The role of the Endogenous Oxytocin System

At present, most studies support that endogenous OXT system can inhibit drug addiction better. Sarnyai (1992) argues that endogenous OXT may play an important regulatory role in the development of behavioral changes caused by repeated cocaine administration, and the effect of microinjection targeting hippocampus and basal nucleus (including nucleus accumbens and the posterior olfactory nucleus) is obviously better than that of peripheral administration(Sarnyai et al., 1992). OXT alleviated naloxone-induced withdrawal symptoms in morphine-addicted mice, and OXT receptor antagonists promoted morphine tolerance after intracerebral administration, which indicated that endogenous OXT might participate in the physiological feedback process of morphine addiction. This conclusion was further verified by the changes of OXT content in hippocampus of acute and chronic morphine addiction and after withdrawal. The researchers used electrophysiological techniques to explore the cellular mechanism of neuronal excitability during morphine withdrawal, and revealed that the initial acute opioid administration inhibited OXT neurons in hypothalamic giant cells, but the rebound hyperexcitation occurred after withdrawal, which may be due to the change of intracellular membrane potential(Brown et al., 2005). These results provide cellular mechanism support for previous behavioral studies, that is, endogenous

brain OXT system may play a role in regulating neural adaptation during addiction.

2.2. Oxytocin Affects the Neural Mechanism of Addiction

2.2.1. Effects of Oxytocin on Synaptic Plasticity

Neuropeptides can regulate learning and memory processes in rodents and other species (including birds and mollusks). The memory process involves retrieving and integrating the acquired information, and integration is an unstable stage, which is the key period for drug-affected information storage. The second sensitive stage in the learning process is information extraction, that is, testing is carried out shortly after administration to understand how drugs affect this learning process. To be continued

Early OXT studies suggested that the tolerance induced by opioids and ethanol was a result of "learning". These early research results have been verified by a large number of molecules and behaviors, which provide direct evidence for studying the common neurobiological mechanism between learning and addiction(Hyman et al., 2005). Addictive drugs affect synaptic plasticity, which is the neural basis of learning and memory, and also plays an important role in the development of drug addiction(Hyman et al., 2006). Drug abuse can directly induce or regulate long-term potentiation (LTP), which is a synaptic plasticity and reflects the enhancement of functional connections between neurons(Kenney & Gould, 2008). In addition, repeated cocaine uptake affects a large number of signal cascades, growth factors and earlier physiological processes of neurodevelopment involved in normal learning and memory, including the signaling pathway of extracellular signal-regulated kinase (ERK, brain-derived neurotrophic factor (BDNF), glutamate transport and synaptic plasticity, and generally mainly affects the formation of LTP and LTD (long-term depression, LTD) . The rapid generation, destruction and shape change of dendritic spines of neurons are the basis of short-term and long-term plasticity of excitatory synapses of vertebral neurons in cerebral cortex, which indicates that dendritic spine dynamics is an important cytological basis for cognition and memory(Kasai et al., 2010). Addictive drugs lead to the continuous recombination of several neurons. For example, the change of dendritic spin density in midbrain limbic dendrites is considered to be the cause of learning-like and long-term behavioral plasticity in addictive situations. In addition, hippocampus is also involved in learning and memory in the long-term neural plasticity process and drug addiction. Hippocampus is a key brain region for memory consolidation and can promote the cognitive process of addiction by providing conditional cues for learning. As early as 1984, Mühlethaler(1984) found that OXT increased the firing rate of inhibitory hippocampal neurons(Mühlethaler et al., 1984). While in 2013, Tsien et al., showed that OXT-specific rapid target stimulation of hippocampal inhibitory interneurons could fine-tune and shape different forms of inhibition(Tsien et al., 2013). Therefore, OXT-induced changes in hippocampal excitability may in turn affect the terminal regions of dopamine system in midbrain margin, such as nucleus accumbens and prefrontal cortex, to change neural plasticity related to addiction.

In a word, there is enough evidence to show that: first, learning, memory and addiction have a common neural basis; Secondly, the learning mechanism constitutes the performance of addiction in different stages; Third, neurobiological processes that regulate learning and memory may affect drug addiction. Therefore, to study the effect of neuropeptide OXT on addiction, we can start with exploring how OXT affects the learning and memory processes involved in maintaining the control mechanism of addictive drugs on behavior.

2.2.2. Effects of Oxytocin on the Neural Circuits of Addiction

The midbrain marginal dopamine reward circuit is the most typical neural circuit of addiction, which projects from ventral tegmental area (VTA) to nucleus accumbens (NAC) (Dessoki et al., 2023). Oxytocin interacts directly with dopamine, glutamate, and GABA neurotransmission, and oxytocin projects neurons in PVN synapses on dopaminergic cells in NAC. Oxytocin receptor is ubiquitous in addiction circuit. Peris (2017) shows that oxytocin receptor exists on dopaminergic neurons projected from VTA to NAC and MPFC(Peris et al., 2017). Intracerebral injection of oxytocin can inhibit the dopamine production of METH(Qi et al., 2008) and prevent the dopamine release caused by NAC alcohol administration, which corresponds to the decrease of drug-seeking behavior(Peters et al., 2016). Other studies have proved that oxytocin dopamine receptor complex (OXT-D2R) exists in NAC, and oxytocin may reduce drug-seeking behavior by interacting with D2R in NAC: oxytocin as an allosteric agonist in this complex can improve D2R affinity(Tarakanov et al., 2016). Interestingly, the activation of D2R reduces drug-seeking behavior, and this receptor subtype decreases after chronic administration (Dessoki et al., 2023).

Oxytocin can also affect drug-seeking behavior and dopaminergic signaling through GAGBergic interneurons. It is found that excitatory GQ-coupled oxytocin receptors are located in NAC, hippocampus and PFC. Oxytocin signals in these neurons can increase the inhibitory effect of GABAergic interneurons in hippocampal CA1 layer on the discharge of hippocampal pyramidal cells . Oxytocin receptor in NAC exists in GABA interneurons containing small albumin, which can regulate the expression of behavioral adaptation induced by psychoactive substances(Wang et al., 2018). Oxytocin directly affects drug-seeking behavior by interacting with its own GABAergic interneuron receptor.

2.3. Theoretical Hypothesis of Oxytocin Affecting Addiction

(1) Sarnyai put forward a theoretical hypothesis that OXT can weaken addiction-related neural plasticity by regulating and integrating stress and stress-related projection, learning and memory, and prosocial behavior(Sarnyai & Kovács, 2014).

(2) Leong(2018) thinks that oxytocin interacts with other neurotransmitter systems in addiction circuit and puts forward a theoretical hypothesis, that is, oxytocin weakens drug-seeking behavior through its anti-anxiety and prosocial characteristics(Leong et al., 2018).

(3) The addiction cycle includes the periodic cycle pattern of "maintaining drug use-detoxification-relapse", which is supported by severe interruption and imbalance of neural circuits involving reward, learning, motivation, stress, social emotion regulation and higher-order cognitive abilities (such as inhibition control) (Koob et al., 2016). Oxytocin can break the cycle pattern of behavior. Specifically, they hypothesized that excessive dopaminergic signal transduction in the neural circuit of basal ganglia caused by long-term excessive use of psychoactive substances leads to behavioral preference of material reward (food, drug, alcohol) effect, and the final execution of behavioral cycle is drug seeking. As a drug for treating addiction, oxytocin may reduce relapse by diverting attention, that is, drug-seeking behavior shifts to social interaction, which directly interferes with behavioral preference of material reward. At the same time, oxytocin may increase the tendency of social reward, thus strengthening social ties, which may be very important for maintaining drug rehabilitation effect. In short, OXT not only reduces the dosage and drug reward, but also restores the normal response to some natural enhancers, reduces the mood and stress during withdrawal and withdrawal, and prevents relapse(Bowen & Neumann, 2017a).

Along this line, Tops et al. hypothesized that oxytocin is involved in the circulatory mechanism between attachment formation and stress, by transferring preference from new experience to

another family, and by promoting the ventral to dorsal movement of cortical striatum activation(Tops et al., 2014). This hypothesis is consistent with the ventral to dorsal displacement of striatum control behavior during addiction. That is to say, in the early stage of drug use, behavior is driven by dopamine release in ventral striatum mediated by acute reward effect of drug (Levis et al., 2021). With the repeated use of drugs, the habitual reaction is controlled by the dorsal striatum. Perhaps oxytocin as an adjuvant to addiction increases a preference for familiarity, thereby strengthening social connections that help to endure the detoxification effect. This biological shift during learning appeals to reflect a progressive increment via the corticostrial loops of, highly, ventral/limbic (the "ventral control path"), dorsal/associate (the "dorsal control path") and dorsal/motor systems (see Figure 1).

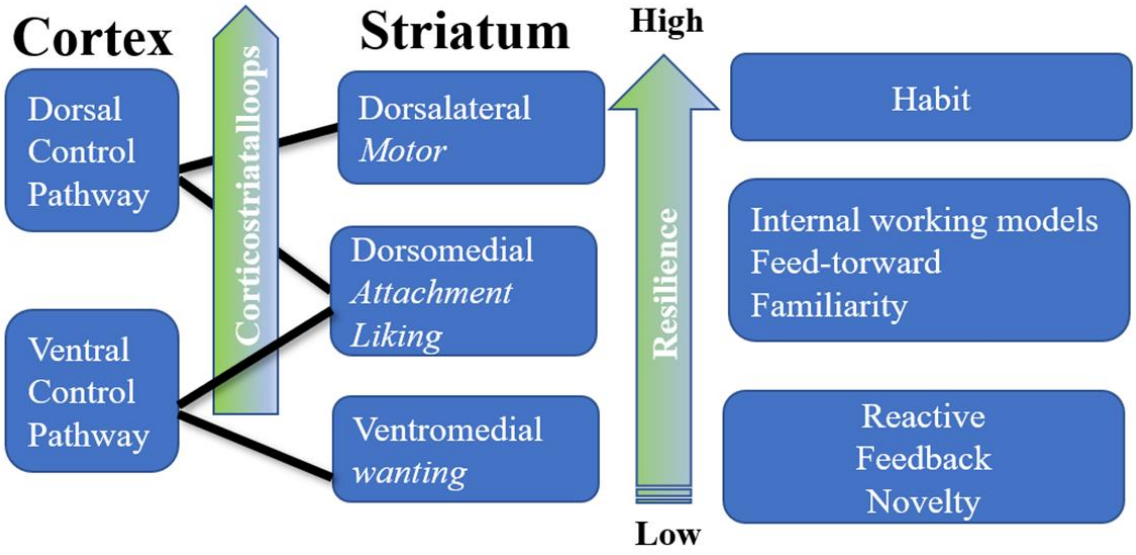

Figure 1. Corticostrial interactions(Levis et al., 2021).

2.4. Effect of Oxytocin Preconditioning on Drug Addiction in Adolescence

Cognitive neuroscience holds that adolescence is a period that is highly sensitive to social and cultural signals in the environment, a key period for the formation of biological and social transformation, and helps to establish long-term patterns of brain function and behavior. The brain plays an important role in shaping adaptive social behavior to the maximum extent. Adolescence is the most sensitive to social reward learning clues, and this sensitivity decreases in adulthood. Studies even show that this critical period of mice is on the 40th day after birth, and the selective regulation of synaptic plasticity mediated by OXT in NAc is at least one of the foundations for establishing the critical period of social reward learning(Nardou et al., 2019). There have been many experimental results that oxytocin can become a potential drug for treating addiction (King et al., 2017).

During puberty, when the OXT neural circuit is developmentally programmed, the OXT system may be particularly unstable. Studies have shown that pretreatment of OXT in adolescent rodents can produce positive "characteristic change" effect, improve social ability and reduce anxiety, which is far beyond the administration in adulthood (Suraev et al., 2014). Bowen et al. 's research preliminarily proves that the effect of chronic OXT administration to adolescent rats can last until adulthood, which not only has significant effects on reducing anxiety, increasing social skills and increasing OXT concentration in plasma, but also reduces alcohol intake of adult rats. The study

verified that OT pretreatment in young age can effectively reduce the self-administration of METH (methamphetamine); The results also show that chronic OXT treatment in adolescence can continuously increase plasma OXT concentration, which may indicate that oxytocin pretreatment in adolescence can prevent drug-seeking behavior in adult female rats, and play a role in up-regulating the feedforward upregulation of OT systems in OXT system. The increase of endogenous OXT can still be detected more than 12 weeks after pretreatment, and plasma OXT has nothing to do with METH intake(Hicks et al., 2016). Therefore, Hicks believes that the increase of plasma OXT is not the result of METH intake, but may be caused by pretreatment effect, which at least indicates that puberty OXT pretreatment may trigger long-term up-regulation of endogenous OXT system(Hicks et al., 2014). In the above studies of oxytocin pretreatment, self-administration is adopted for addictive drugs. Some studies believe that once rats establish self-administration mode, peripheral OT pretreatment can still inhibit METH addiction and reduce the possibility of relapse. This result is similar to that after chronic OXT treatment in adolescence. The endogenous OXT system may undergo neuroadaptive changes due to repeated administration of addictive drugs, which at least indicates that the neuroplasticity of endogenous OXT system development is related to addictive behavior, and the long-term social defects of forced drug addicts may involve the long-term adaptation of brain OXT system. The increase of endogenous OXT level induced by OXT preconditioning affects METH-related neural adaptation in central OXT substrate, which may be related to some behavioral and social damage caused by repeated administration of METH(Clemens et al., 2007) (Clemens et al. 2007).

3. Effect of Drug Addiction on Prosocial Behavior

The diagnostic criteria of substance use disorder in Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) clearly point out that "individuals continue to use substances even though it is clear that their effects cause or aggravate persistent or repeated social or interpersonal communication problems" (APA), and these social and interpersonal communication problems are the focus of current research(Tomek et al., 2019), one of the important influences of substance use disorder on others may be the lack of social behavior, including "prosocial behavior" (Shahini et al., 2021). Researchers at Duke University in the United States not only confirmed that OXT intranasal administration can penetrate the central nervous system, but more importantly, it enhanced rhesus monkeys' attention to rewarding others and promoted rhesus monkeys to make prosocial choices, such as letting another monkey get juice, even if doing so would make them have nothing to drink. Researchers say that if it is used to treat autism, schizophrenia and other diseases, it seems to make patients have better social skills and enhance their trust, but the specific mechanism is unclear, and it is not known whether it can achieve long-term results(Shahini et al., 2021)

3.1. Prosocial Behavior Model

Prosocial behavior, also known as social behavior, refers to the behavior that conforms to the social hope and has no obvious benefit to the actor himself, but the actor voluntarily brings benefits to the object of the behavior, including rescue, cooperation, child-rearing, donation and other behaviors. Previous studies have also shown that animal models of prosocial behavior can be established with laboratory rodents (Tomek et al., 2019), and the establishment of prosocial behavior models plays an important role in exploring the psychological and biological mechanisms of prosocial behavior. The research established a set of prosocial behavior rescue model (hereinafter referred to as Bartal rescue model)(Bartal et al., 2011). SD rats were used as experimental objects. After being raised in pairs for 14 days, they were divided into four groups, one of which was randomly selected as a trapped rat and the other as a free rat. Four groups were set up in the study.

The first group was the "trapped group". The trapped rats were trapped in a restraint that could open the door from the door. They were trained for 12 days and recorded the incubation period of free rats. It was found that free rats rescued their companions in 6.9 ± 2.9 days, and the incubation period showed a downward trend, which proved that free rats could learn to open the door. The experiment also set up three other control groups: "object group" (there is an object in the binding device), "empty binding device group" (there is nothing in the binding device), and "2 + empty binding device group" (an empty binding device and an untrapped rat). The results of these three groups showed that the free rats were neither willing to approach the binding device nor open the door, which indicated that the free rats in the first group had the motivation to open the door. To further explain the motivation of free rats, the study also excluded the motivation of social interaction and food reward. The study thought that empathy, that is, empathy for the pain of another trapped rat and intention to stop this pain, was the motivation of prosocial behavior. After a lapse of three years, the team used SD rats raised in different cages as experimental subjects to eliminate the familiarity of genes, and the rats still showed rescue behavior, further verifying that previous social experience played a regulatory role in prosocial behavior(Bartal et al., 2014).

In order to further test whether free rats release trapped rats out of emotional needs, midazolam (MDZ) was used to treat rats. The free rats treated with MDZ could open the door of the restrainer to obtain food, but did not open the door of the restrainer, that is, no rescue behavior occurred. The results show that empathy is necessary for rescue behavior. This study suggests that MDZ specifically interferes with the social emotional processing function, and this emotional processing is necessary to motivate free mice to help trapped mice (Bartal et al., 2014). In a study, using a water-based rescue model, free rats can rescue rats of the same breed soaked in water, and show that rats soaked in water learn to open doors and make rescue behaviors faster than those not soaked before(Nobuya et al., 2015). It combines the aversion awakening experimental paradigm with Bartal rescue model, so that free rats can escape the aversion environment(Joana et al., 2019). However, rats still choose to open the door of the restrainer to rescue trapped rats. The latest research results show that adolescent rats will show prosocial behavior even if they can escape, and certain pain and stress promote prosocial behavior, and think that there is an inverted U-shaped curve relationship between stress and rescue behavior.

3.2. Relationship between Drug Addiction and Prosocial Behavior

The Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) points out that part of the characteristics of substance use disorder is the damage of social function (First et al., 2021). Substance dependence causes a major burden on the society; It effects the quality of life in patients causing a significant reduction in their production in mandatory and social fields (El-Shinnawy et al., 2021).

Tomek et al. Used Bartal rescue model to understand the neural mechanism of social function impairment in opioid addiction. First, establish the baseline level: through the training of rescue model lasting 14 days, record the rescue rate and the latent period of free rats opening the door, and determine the baseline level of rescue behavior; Then, heroin self-administration: half of rats were randomly selected to self-administer heroin and the other half sucrose granules (orally) for 14 consecutive days; Finally, post-test comparison: the rescue behavior of free rats was recorded for 3 days. During the post-test, rats chose between self-administration and rescuing trapped rats. The results showed that the rats who took sucrose orally continued to save the trapped rats, while the heroin-addicted rats chose heroin for self-administration. It can be seen that heroin-addicted rats show prosocial behavior defects, which is consistent with the diagnostic criteria of substance use disorders in Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition). Tomek believes

that the behavioral paradigm of choosing between prosocial behavior and continuing drug use may help to establish prosocial behavior model and play an important role in investigating the neural basis of social dysfunction in drug addiction (Tomek et al., 2018).

4. Relationship between Oxytocin and Prosocial Behavior

Emotion regulation is a mediator for SUDs especially with long duration of illnesses, presence of certain personality traits and disorders, and high impulsiveness (Okasha et al., 2021). Oxytocin, which enhances social interaction and social reward, plays a key role in the regulation of social behavior and emotion(Baracz et al., 2018), and is increasingly famous for its prosocial effect and potential to treat a series of mental diseases. Researchers have verified that OXT can regulate social interaction, social preference and maternal behavior through different animal models. When OXT is released in the brain, it can promote the formation of prosocial relations and thus produce positive effects. Social reward in the process of social interaction This trait requires the coordinated activity of oxytocin and 5-HT in nucleus accumbens (NACC). Social factors are one of the important causes of addiction (Ramsewak et al., 2020).

Prosocial behavior includes comforting behavior. Comforting behavior is based on empathy, and it will be mediated by conservative neurobiological and neurochemical mechanisms related to empathy. Comfort behavior was tested after ventricular injection of oxytocin antagonist (OTA) in prairie voles. The data showed that comfort behavior was significantly reduced, indicating that activation of OTR in brain was a necessary condition for comfort behavior. The anterior cingulate cortex (ACC), adjacent anterior cingulate cortex (PLC) and nucleus accumbens shell (NACS) of prairie voles all expressed high density OTR; In humans, ACC and homologous medial prefrontal cortex (MPFC) are related to empathy, while NAC is usually related to social and non-social rewards. Immunoassay was used to identify ACC (but not PLC or NACS) with different activity by targeting the immediate early gene (IEG) protein FOS. This study hypothesizes that oxytocin may play a specific role in OTR in ACC, thus causing comfort behavior. In order to verify this point, OTA injection directly into ACC can eliminate comfort reaction, while injection into adjacent PLC has no elimination effect; this suggests that OTR signals in ACC may regulate comfort behavior by disturbing physiological, emotional or behavioral responses. This evidence shows that ACC is a node, and ACC activity increases under the interaction of peer stress, and OTR activation is necessary to express comforting behavior. These nerve matrices provide a conservative biological mechanism for comfort behavior between prairie voles and humans, and are of great significance in understanding the social behavior defects in many mental diseases. The answer may not be simple, straightforward, or easy to find, but it is well worth the fight (Dator, 2020).

5. Conclusions

Addiction treatment should be a five-in-one comprehensive psychological disease treatment model, which integrates drug treatment, psychotherapy, behavior correction, gratitude education and social support. Future steps may include focusing on educational schemes to mitigate this higher risk of developing OUD in at-risk talents (Tasmim et al., 2022).

Funding

This research supported by the Guangdong Province Key Platform and Scientific Research Project, Young Innovative Talents Program (Natural Science) Nos. 2018KQNCX240; Guangdong Province Philosophy and Social Sciences Planning 2023 Year, Special Research Project on Northeast and West Guangdong Nos. GD23YDXZXL01.

Data Availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The author states that this article has no conflict of interest.

References

[1] Baracz, S. J., Everett, N. A., & Cornish, J. L. (2018). The impact of early life stress on the central oxytocin system and susceptibility for drug addiction: Applicability of oxytocin as a pharmacotherapy. Neuroence & Biobehavioral Reviews, 110, S0149763418302768-. https://doi.org/10.1016/j.neubiorev.2018.08.014.

[2] Bartal, B. A., Decety, J., & Mason, P. (2011). Empathy and Pro-Social Behavior in Rats. Science. https://xueshu.baidu.com/usercenter/paper/show?paperid=04a84e129d2af12ea9a19132884f0f53&site=xueshu_se&hitarticle=1.

[3] Bartal, B. A., Rodgers, D. A., Sarria, M. S. B., Decety, J., & Mason, P. (2014). Pro-social behavior in rats is modulated by social experience. ELife Sciences, 3. https://doi.org/10.7554/eLife.01385#.dpuf.

[4] Bowen, M. T., & Neumann, I. D. (2017a). Rebalancing the Addicted Brain: Oxytocin Interference with the Neural Substrates of Addiction. Trends in Neurosciences, 40(12), 691–708. https://doi.org/10.1016/j.tins.2017.10.003.

[5] Bowen, M. T., & Neumann, I. D. (2017b). The Multidimensional Therapeutic Potential of Targeting the Brain Oxytocin System for the Treatment of Substance Use Disorders. R. Hurlemann & V. Grinevich, Behavioral Pharmacology of Neuropeptides: Oxytocin, 35, 269–287. Springer International Publishing. https://doi.org/10.1007/7854_2017_17.

[6] Brown, C. H., Stern, J. E., Jackson, K. L. M., Bull, P. M., Leng, G., & Russell, J. A. (2005). Morphine withdrawal increases intrinsic excitability of oxytocin neurons in morphine-dependent rats. European Journal of Neuroscience, 21(2), 501–512. https://doi.org/10.1111/j.1460-9568.2005.03885.x.

[7] Clemens, K. J., Cornish, J. L., Hunt, G. E., & Mcgregor, I. S. (2007). Repeated weekly exposure to MDMA, methamphetamine or their combination: Long-term behavioural and neurochemical effects in rats. Drug & Alcohol Dependence, 86(2–3), 183–190. https://doi.org/10.1016/j.drugalcdep.2006.06.004.

[8] Dator DM (2020) Exploring the Relationship between Oxytocin, Risktaking, and Childhood Maltreatment. East Carolina University ProQuest Dissertations Publishing. 2020. 28400112. Retrieved from the Scholarship. http://hdl.handle.net/10342/8628.

[9] Dessoki, H. H., Abedlrasoul, H. A., Dawoud, M. E., Mohamed, A. M., & Soltan, M. R. (2023). Oxytocin level among patients with opioid use disorder and its correlation with personality traits and perceived childhood trauma. Middle East Current Psychiatry, 30(1), 20. https://doi.org/10.1186/s43045-023-00289-2.

[10] Dölen, G. (2015). Autism: Oxytocin, serotonin, and social reward. Social Neuroscience, 10(5), 450–465. https://doi.org/10.1080/17470919.2015.1087875

[11] El-Shinnawy, H., Sayed, R. H., Khalil, M. A., & Ayoub, D. R. (2021). Substance Dependence Comorbidity with Mental Disorders in Egyptian Young Adults. Addictive Disorders & Their Treatment, 20(1), 33–42. https://doi.org/10.1097/ADT.0000000000000208.

[12] First, M. B., Gaebel, W., Maj, M., Stein, D. J., Kogan, C. S., Saunders, J. B., Poznyak, V. B., Gureje, O., Lewis‐Fernández, R., Maercker, A., Brewin, C. R., Cloitre, M., Claudino, A., Pike, K. M., Baird, G., Skuse, D., Krueger, R. B., Briken, P., Burke, J. D., … Reed, G. M. (2021). An organization‐ and category‐level comparison of diagnostic requirements for mental disorders in ICD‐11 and DSM‐5. World Psychiatry, 20(1), 34–51. https://doi.org/10.1002/wps.20825.

[13] Hicks, C., Cornish, J. L., Baracz, S. J., Suraev, A., & Mcgregor, I. S. (2014). Adolescent pre-treatment with oxytocin protects against adult methamphetamine-seeking behavior in female rats. Addiction Biology. https://doi.org/10.1111/adb.12197.

[14] Hicks, C., Ramos, L., Dampney, B., Baracz, S. J., Mcgregor, I. S., & Hunt, G. E. (2016). Regional c-Fos expression induced by peripheral oxytocin administration is prevented by the vasopressin 1A receptor antagonist SR49059. Brain Research Bulletin, 127, 208–218. https://doi.org/10.1016/j.brainresbull.2016.10.005.

[15] Hyman, S. E., Malenka, R. C., & Nestler, E. J. (2006). Neural mechanisms of addiction: The role of reward-related learning and memory. Annual Review of Neuroscience, 29(1), 565. https://doi.org/10.1146/annurev.neuro.29.051605.113009.

[16] Hyman, Steven, & E. (2005). Addiction: A Disease of Learning and Memory. American Journal of Psychiatry. https://xueshu.baidu.com/usercenter/paper/show?paperid=0cfa8f6e5f6241ab3d2f2f2cc45aa55a&site=xueshu_se.

[17] Joana, Carvalheiro, Ana, Seara-Cardoso, Ana, Raquel, Mesquita, Liliana, de, & and, S. (2019). Helping behavior in rats (Rattus norvegicus) when an escape alternative is present. Journal of Comparative Psychology (Washington, D.C. : 1983). https://doi.org/10.1037/com0000178.

[18] Kasai, H., Fukuda, M., Watanabe, S., Hayashi-Takagi, A., & Noguchi, J. (2010). Structural dynamics of dendritic spines in memory and cognition. Trends in Neurosciences, 33(3), 121–129. https://doi.org/10.1016/j.tins.2010.01.001.

[19] Kenney, J. W., & Gould, T. J. (2008). Modulation of Hippocampus-Dependent Learning and Synaptic Plasticity by Nicotine. Molecular Neurobiology, 38(1), 101–121. https://doi.org/10.1007/s12035-008-8037-9.

[20] King, C. E., Griffin, W. C., Luderman, L. N., Kates, M. M., Mcginty, J. F., & Becker, H. C. (2017). Oxytocin Reduces Ethanol Self-Administration in Mice. Alcoholism Clinical & Experimental Research, 41(5), 955–964. https://doi.org/10.1111/acer.13359.

[21] Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. The Lancet Psychiatry, 3(8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8.

[22] Leong, K.-C., Cox, S., King, C., Becker, H., & Reichel, C. M. (2018). Oxytocin and Rodent Models of Addiction. International Review of Neurobiology.140, 201-247. https://doi.org/10.1016/bs.irn.2018.07.007.

[23] Levis, S. C., Mahler, S. V., & Baram, T. Z. (2021). The Developmental Origins of Opioid Use Disorder and Its Comorbidities. Frontiers in Human Neuroscience, 15, 601905. https://doi.org/10.3389/fnhum.2021.601905.

[24] Mobasher, M. W., Eid, H. F., Soliman, A. M., El-Hanafi, H. M., & El-Makawi, S. M. (2021). Serum Oxytocin Level among Male Patients with Opioid Dependence and Its Relation to Craving. Addictive Disorders & Their Treatment, 20(2), 132–140. https://doi.org/10.1097/ADT.0000000000000231.

[25] Mühlethaler, M., Charpak, S., & Dreifuss, J. J. (1984). Contrasting effects of neurohypophysial peptides on pyramidal and non-pyramidal neurones in the rat hippocampus. Brain Research, 308(1), 97–107. https://doi.org/10.1016/0006-8993(84)90921-1.

[26] Nardou, R., Lewis, E. M., Rothhaas, R., Xu, R., Yang, A., Boyden, E., & Dolen, G. (2019). Oxytocin-dependent reopening of a social reward learning critical period with MDMA. Nature, 569(7754), 1–5. https://doi.org/10.1038/s41586-019-1075-9.

[27] Nobuya, Sato, Ling, Tan, Kazushi, Tate, Maya, & Okada. (2015). Erratum to: Rats demonstrate helping behavior toward a soaked conspecific. Animal Cognition. https://doi.org/10.1007/s10071-015-0906-9.

[28] Numan, M., & Young, L. J. (2016). Neural mechanisms of mother–infant bonding and pair bonding: Similarities, differences, and broader implications. Hormones and Behavior, 77, 98–112. https://doi.org/10.1016/j.yhbeh.2015.05.015.

[29] Okasha, T., Abd Elsamie, A., Azzam, H., Elserafi, D., Morsy, M., & Shorub, E. (2021). Emotional Regulation as a Mediating Factor in Substance Use Disorders. Addictive Disorders & Their Treatment, 20(3), 202–210. https://doi.org/10.1097/ADT.0000000000000241.

[30] Peris, J., Macfadyen, K., Smith, J. A., De Kloet, A. D., Wang, L., & Krause, E. G. (2017). Oxytocin receptors are expressed on dopamine and glutamate neurons in the mouse ventral tegmental area that project to nucleus accumbens and other mesolimbic targets. Journal of Comparative Neurology. https://doi.org/10.1002/cne.24116.

[31] Peters, S. T., Bowen, M. T., Bohrer, K., Mcgregor, I. S., & Neumann, I. D. (2016). Oxytocin inhibits ethanol consumption and ethanol-induced dopamine release in the nucleus accumbens. Addiction Biology, 702–711. https://doi.org/10.1111/adb.12362.

[32] Qi, J., Yang, J. Y., Song, M., Li, Y., Wang, F., & Wu, C. F. (2008). Inhibition by oxytocin of methamphetamine-induced hyperactivity related to dopamine turnover in the mesolimbic region in mice. Naunyn-Schmiedeberg's Archives of Pharmacology, 376(6), 441–448. https://doi.org/10.1007/s00210-007-0245-8.

[33] Ramsewak, S., Putteeraj, M., & Somanah, J. (2020). Exploring substance use disorders and relapse in Mauritian male addicts. Heliyon, 6(8), e04731. https://doi.org/10.1016/j.heliyon.2020.e04731.

[34] Sarnyai, Z., Biro, E., Babarczy, E., Vecsernyes, M., Laczi, F., Szabo, G., Krivan, M., Kovacs, G., & Telegdy, G. (1992). Oxytocin modulates behavioural adaptation to repeated treatment with cocaine in rats. Neuropharmacology, 31(6), 593–598. https://doi.org/10.1016/0028-3908(92)90192-R.

[35] Sarnyai, Z., & Kovács, G. L. (2014). Oxytocin in learning and addiction: From early discoveries to the present. Pharmacology Biochemistry and Behavior, 119, 3–9. https://doi.org/10.1016/j.pbb.2013.11.019.

[36] Shahini, N., Talaei, A., Salimi, Z., Adinepour Sarab, M., Gholamzad, S., Teimouri, A., Hajebi Khaniki, S., & Kamkar, M. (2021). Temperament and character traits in substance use disorder in Iran: A case control study. BMC Psychology, 9(1), 138. https://doi.org/10.1186/s40359-021-00647-x.

[37] Suraev, A. S., Bowen, M. T., Ali, S. O., Hicks, C., Ramos, L., & Mcgregor, I. S. (2014). Adolescent exposure to oxytocin, but not the selective oxytocin receptor agonist TGOT, increases social behavior and plasma oxytocin in adulthood. Hormones & Behavior, 65(5), 488–496. https://doi.org/10.1016/j.yhbeh.2014.03.002

[38] Tarakanov, Alexander, Fuxe, Kjell, Borroto-Escuela, Dasiel, O., Mora, P. D. L., Miguel, Perez-Carrera, & Diana. (2016). Signaling in dopamine D2 receptor-oxytocin receptor heterocomplexes and its relevance for the anxiolytic effects of dopamine and oxytocin interactions in the amygdala of the rat. Biochimica et Biophysica Acta. Molecular Basis of Disease: BBA. https://xueshu.baidu.com/usercenter/paper/show?paperid=370388320e11b7533f984579e88e7d8d &site=xueshu_se

[39] Tasmim, S., Le Foll, B., & Hassan, A. N. (2022). Moderators for the Relationship between Post-Traumatic Stress Disorder and Opioid Use Disorder. Journal of Dual Diagnosis, 18(1), 3–10. https://doi.org/10.1080/15504263.2021.2016341

[40] Tomek, S. E., Stegmann, G. M., & Olive, M. F. (2019). Effects of heroin on rat prosocial behavior. John Wiley & Sons, Ltd, 4. https://doi.org/10.1111/adb.12633

[41] Tops, M., Koole, S. L., IJzerman, H., & Buisman-Pijlman, F. T. A. (2014). Why social attachment and oxytocin protect against addiction and stress: Insights from the dynamics between ventral and dorsal corticostriatal systems. Pharmacology Biochemistry and Behavior, 119, 39–48. https://doi.org/10.1016/j.pbb.2013.07.015

[42] Tsien, R. W., Owen, S. F., Tuncdemir, S. N., Bader, P. L., Tirko, N. N., & Fishell, G. (2013). Oxytocin enhances hippocampal spike transmission by modulating fast-spiking interneurons. Nature. https://xueshu.baidu.com/usercenter/paper/show?paperid=8c55eae9f3f62d2fb0061ad24c0cceba&site=xueshu_se&hitarticle=1

[43] Wang, Xiaoting, Gallegos, David, A., Pogorelov, Vladimir, M., O'Hare, & Justin. (2018). Parvalbumin Interneurons of the Mouse Nucleus Accumbens are Required For Amphetamine-Induced Locomotor Sensitization and Conditioned Place Preference. Neuropsychopharmacology Official Publication of the American College of Neuropsychopharmacology. https://xueshu.baidu.com/usercenter/paper/show?paperid=f95faf1f2dfe319277d681b7d55735bf&site=xueshu_se&hitarticle=1

[44] Yoon, S., & Kim, Y.-K. (2022). Possible oxytocin-related biomarkers in anxiety and mood disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 116, 110531. https://doi.org/10.1016/j.pnpbp.2022.110531

[45] Zhang, M., Liu, S., Wang, S., Xu, Y., Chen, L., Shao, Z., Wen, X., Yang, W., Liu, J., & Yuan, K. (2021). Reduced thalamic resting‐state functional connectivity and impaired cognition in acute abstinent heroin users. Human Brain Mapping, 42(7), 2077–2088. https://doi.org/10.1002/hbm.25346