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The potential role of oxytocin in addiction: What is the target process?

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Abstract

Oxytocin regulates a variety of centrally-mediated functions, ranging from socio-sexual behavior, maternal care, and affiliation to fear, stress, anxiety. In the past years, both clinical and preclinical studies characterized oxytocin for its modulatory role on reward-related neural substrates mainly involving the interplay with the mesolimbic and mesocortical dopaminergic pathways. This suggests a role of this nonapeptide on the neurobiology of addiction raising the possibility of its therapeutic use. Although far from a precise knowledge of the underlying mechanisms, the putative role of the bed nucleus of the stria terminalis as a key structure where oxytocin may rebalance altered neurochemical processes and neuroplasticity involved in dependence and relapse has been highlighted. This view opens new opportunities to address the health problems related to drug misuse.

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Oxytocin, Addiction, Relapse, BNST, CRF, Stress, Dopamine, Mesolimbic pathway.

Introduction

The nonapeptide oxytocin (OXT) is synthesized by parvocellular and magnocellular neurons allocated in the paraventricular (PVN) and supraoptic nucleus (SON) of the hypothalamus and it has been traditionally known for its well-established peripheral effects on gestation, lactation, and parturition. However, more recently, it has been implicated in a broad array of centrally-mediated functions ranging from sexual behavior and feeding to social interaction, maternal care and affiliative behaviors, motor activity, fear, stress, anxiety, yawning, as well as (social) memory and reward processes [1–9] reflected by the distribution of extrahypothalamic oxytocin projections and oxytocin receptors (OXTRs) in the Central Nervous System (CNS). Accordingly, several mapping studies evidenced oxytocin and OXTRs expression in limbic brain areas such as the ventral tegmental area (VTA), amygdala, bed nucleus of the stria terminalis (BNST), hippocampus (HPC), nucleus accumbens (NAc), prefrontal cortex (mPFC) [10], that are part of a complex circuit playing a key role in the regulation of motivated behavior (i.e., goal-directed behavior) [11]. Here, oxytocin interacts locally with other neurotransmitters and neuropeptides to modulate the emotional/motivational aspects of the above-mentioned functions by both direct excitatory influences and indirect regulation on core pathways of the reward circuit such as the mesolimbic dopamine (DA) pathways and their projection areas [2,3,12–16] and these interactions are thought to be the neurochemical link between the motivational and consummatory aspects of rewarding behaviors [17–19]. The broad modulatory function exerted by oxytocin on reward-related neural substrates and behaviors has attracted in recent years the attention of scientists on a possible role of this peptide on addiction-related neural substrates and mechanisms. In this regard, the development of pharmaceutical approaches based on intranasal delivery poses a real possibility to utilize the neuropeptide as a therapeutic agent for the treatment of addiction-related conditions. However, the current knowledge is still far away from a precise characterization of the brain sites and mechanisms of action of the potential positive effects of oxytocin-based treatments for addiction. This review tries to briefly summarize the most recent advances in the field with the final aim to propose directions for future research and strategic applicative development.

Oxytocin efficacy in substance use disorders

Preclinical studies have shown that oxytocin can influence addictive behaviors and might interact with the DArgic system, which is a pivotal component of addictive behaviors (see Table 1 for a summary of the more recent preclinical studies on oxytocin actions in addiction models). Although oxytocin chemical instability and fast pharmacokinetics, its intranasal administration

Table 1

Preclinical studies on oxytocin effect on different classes of drugs of abuse (2015–2020).

Substance	Species, Gender	Oxytocin Dosage Regimen	Main findings	References
Alcohol	OxtR KO, female	N/A	Oxytocin receptors are involved in the conditioned effects of an ethanol-associated social stimulus.	[81]
	C57BL/6 mice, male	N/A	Pharmacological and genetic modulation of the oxytocin receptor can modulate the acquisition, extinction, and reinstatement of conditioned reinforcing effects of ethanol.	[82]
	Sprague–Dawley rats, male	0.05–0.5 mg/kg IP	Decrease of ethanol intake.	[83]
	Prairie Voles, male and female	1-10 mg/kg IP	Reduction of alcohol consumption.	[84]
	Wistar rats, male	1 μg ICV	Blockade of Ethanol-induced dopamine release and reduced EtOH self-administration.	[85]
	C57BL/6J mice, male	0.3–3 or 10 mg/kg IP	Reduction of EtOH Self-Administration in different models, at doses not effective on sucrose SA.	[86]
	Wistar rats, male	10 nM ICV	Reduction of cue-induced reinstatement of alcohol-seeking in dependent rats, but not in non-dependent rats.	[38]
	C57BL/6J mice, male and female	0.1–1 mg/kg, IP	Attenuation of stress-induced reinstatement of alcohol seeking.	[87]
	Wistar and SD rats, male	0.125–1 mg/kg IP 0.25–1 mg/kg/20 μl IN 3–30 μg ICV	Decrease of enhanced motivation for alcohol in alcohol dependence; blockade of alcohol effects on GABAergic transmission in the central amygdala.	[88]
	OF1 mice, male	1 mg/kg IP	Reduction of the negative effects of social stress on ethanol consumption and the neuroinflammatory process.	[89]
	Prairie Voles, male and female	3 mg/kg, IP	Temporarily reduction of alcohol consumption but not alcohol preference in the presence of peers that are not receiving similar treatment; assessment by radio frequency tracking.	[90]
	OxtR KO Mice, male and female	N/A	In females, disruptions in oxytocin signaling may contribute to increased voluntary alcohol consumption.	[91]
Methamphetamine	SD rats, male	0.5–4.5 pmol/NAc core	Decrease of METH-primed reinstatement in a dose-dependent manner.	[92]
	SD rats, female	1 mg/kg IP daily during adolescence	Adolescent exposure inhibits responsiveness for METH under a PR reinforcement schedule, and reduces METH-primed reinstatement.	[93]
	SD rats, male	1 mg/kg IP	Acute treatment suppresses METH-seeking exacerbated by stress.	[94]
	SD rats, male and female	1 mg/kg IP 0.6 nmol/0.25 μl/NAc core	Systemic injection or infusion into the NAc core decreased responding to meth-associated cues.	[95]
	SD rats, male and female	1 mg/kg IP 0.6 μg/NAc core	Attenuation of METH demand and seeking in both sexes, by oxytocin signaling in the NAc core.	[96]
	Long Evans rats, female	0.3 mg/kg IP prior to SA session	Chronic treatment can reduce motivation for METH.	[97]
	SD rats, male	1 μg/PrL	Reduction of both cue-induced and METH-primed relapse to METH-seeking behaviors.	[98]
	SD rats, male and female	1.0 mg/kg i.p.	Attenuation of incubation and METH-primed reinstatement in both sex and reduction of anxiety phenotype.	[99]
Cocaine	C57BL/6J mice, male	N/A	Brain region-specific neuroadaptations of the oxytocin system after cocaine abstinence may contribute to an abstinence-induced negative emotional state.	[100]

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Table 1. (*continued*)

Substance	Species, Gender	Oxytocin Dosage Regimen	Main findings	References
	Sprague Dawley rats, male and female	0.1–3 mg/kg IP	Sex similarities in oxytocin's decrease of cocaine seeking; sex differences in cocaine-induced locomotor activity.	[101]
	Sprague Dawley rats, male and female	1 mg/kg, IP 3 μg/0.5 μL/side ICV	Attenuation of cocaine-seeking behavior and region-specific increase of cFos in males and females.	[60]
	Sprague Dawley rats, male and female	0.3 or 1.0 mg/kg, IP	Reduction of cocaine-seeking during initial drug abstinence and cue-induced reinstatement.	[102]
Morphine	Wistar rats, male	0.2 μg ICV	Activation of oxytocin receptors within the NAc Sh enhances the expression of morphine-induced CPP and robust firing rate increase of medial NAc Sh neuron; this effect is not present in morphine-treated rats.	[103]
Nicotine	C57BL6J mice, male	N/A	Neuroadaptation of the oxytocinergic system after nicotine.	[104]
	G72 transgenic CD-1 mice, female	N/A	Nicotine administration normalizes the dysregulated central oxytocinergic system in a mouse model of schizophrenia.	[105]
Oxycodone	SD rats, male	2.5 μg, ICV	Block of oxycodone CCP, and inhibition of oxycodone addiction. Attenuation of rewarding effects induced by oxycodone through the reversal of Hipp DNA hypomethylation induced by oxytocin.	[80]
Methylphenidate	SD rats, male	0.1–2 mg/kg IP	Downward shift in the dose-response of MP-maintained self-administration behavior in rats and increase of NAc shell DA levels.	[16]

allows its direct transport from the nose to the brain across the blood–brain-barrier and rapid onset of the therapeutic effects. However, the putative central actions of peripherally administered oxytocin have been long time debated [20] and represent a nodal point on the effective possibilities to develop strategies for the use of oxytocin as a centrally acting therapeutical agent [21]. Recent preclinical studies employing innovative approaches such as knock-out mice for oxytocin [22] or labeled (i.e., deuterated) oxytocin in rhesus macaques that allows a reliable assessment of brain oxytocin penetrance and distribution [23,24] seem to convincingly confirm that intravenous or intranasal exogenous oxytocin is able to cross or bypass the blood–brain-barrier and enter the brain where the interaction with its own receptors in specific brain areas, can affect a wide range of behaviors. Moreover, the specific formulation used (e.g., nanoparticle encapsulation) can significantly influence the entity and duration of the behavioral effects induced [25]. A large number of clinical trials are currently investigating the potential use of oxytocin as a therapeutical agent for the treatment of addictions (see for instance https://www.clinicaltrials.gov/; NCT04306354, NCT01573273, NCT01827332) and a growing number of research papers have already shown the potential benefits of oxytocin for different CNS disorders, including substance use disorders. In particular, selected papers from 2015 to 2020 suggest that oxytocin signaling is directly involved in heroin, alcohol, cocaine, methamphetamine, nicotine, ketamine, and poly-drug dependence and concomitant affective disorders, as illustrated in Table 2. Among opioid users, blunted plasma oxytocin levels were associated with higher craving scores [26] and novelty-seeking [27]. However, other studies revealed increased oxytocin plasma levels among abstinent heroin users and a direct correlation with their aggressiveness, anti-social emotions, and mood disorders [28]. Notably, oxytocin levels were higher in those patients who cease the heroin detoxification program than in those who accomplished it [29]. A weak oxytocinergic functioning (i.e., A allele homozygous in OXTR rs53576 polymorphism) is associated with alcohol use and prevalence of alcohol use disorders in a small group of males at ages 15, 18, and 25 [30] and, although based on self-reports measurements, these findings are in line with the clinical interviews. oxytocin system deregulations have been observed after chronic ketamine abuse, and notably, this seems to be associated with severe anxiety [31]. On the other hand, Woolley and coll (2016) [32] showed that a single dose of intranasal oxytocin did not reduce addiction-related assessments while Moeini and coll (2019) [33] reported reduced craving score and withdrawal symptoms in heroin users during the abstinence. Contrasting results are also provided after methamphetamine [34] and nicotine studies. oxytocin decreased cue-induced cravings in daily cigarette smokers [35], but did not alter stress-induced cigarette smoking [36]. The small

Table 2

Clinical studies on oxytocin role on addiction (2015–2020).

Subjects	Number and Gender	Route of administration	Main conclusion	References
Opioid users	77, male and female	N/A	Negative association between the blood level of plasma oxytocin and novelty seeking.	[26]
	18, male	N/A	Increased oxytocin levels among abstinent heroin addicts and direct association with aggressive behavior and mood disorders. Possible role of oxytocin during defensive and "anti-social' emotions and behaviors often characterizing the clinical history of addicted patients.	[28]
	57, male	N/A	Plasma oxytocin levels were significantly higher in those individuals who dropped out than in those who completed the detoxification program.	[29]
	77, male and female	N/A	Negative association between plasma oxytocin level and heroin craving score in patients under methadone treatment, stronger effect among patients with a lower level of novelty-seeking.	[27]
	37, male	Intranasal (40 IU)	A single dose of oxytocin is well tolerated by patients on opioid replacement therapy; no significant improvement in craving or Implicit Association Task scores after oxytocin and evidence that social perception was worsened.	[32]
	58, male	Intranasal (40 IU)	Attenuation of craving and withdrawal symptom in heroin-dependent patients; reduction of cortisol level and improvement of cortisol/DHEAS ratio during abstinence after a single dose of oxytocin.	[33]
Alcohol users	593, male and female	N/A	Oxytocin receptor gene (OXTR rs53576 polymorphism) is associated with alcohol use and the prevalence of alcohol use disorders in males.	[30]
	32, male and female	Intranasal (40 IU)	Improvement of social perception, reduction of cue-induced alcohol craving, and reduction of appetitive approach bias in subjects with alcohol abuse.	[106]
	27, male	N/A	Oxytocin peptide mRNA was significantly elevated in the prefrontal cortex of subjects with alcohol use disorder compared to controls. A significant positive correlation between the fold change in oxytocin peptide mRNA in the prefrontal cortex and both daily alcohol intake and drinks per week was observed.	[107]
	15, male	Intranasal (24 IU)	oxytocin reduces alcohol cue-reactivity in alcoholics; potential anticraving medication.	[38]
	40, male and female	Intranasal (24 IU)	Intranasal oxytocin did not significantly reduce the oxazepam dose needed to complete a 3-day course of alcohol detoxification and withdrawal treatment.	[108]
	13, male	Intranasal (24 IU)	Reduction of NAc connectivity during an alcohol cue-reactivity task, which is related to changes in subjective craving for alcohol.	[39]
	40, male	Intranasal (24 IU)	Intranasal oxytocin did not affect actigraphy-recorded motor activity nor sleep in patients with acute alcohol withdrawal.	[109]
Cocaine users	67, male and female	Intranasal (40 IU)	Reduction of cue reactivity in cocaine dependence, effect modified by sex and childhood trauma history.	[110]
	112, male and female	Intranasal (40 IU)	Different effects in men and women with Cocaine use disorder (CUD). Women may be at greater risk for relapse in response to social stressors, but ovarian hormones may attenuate this effect.	[111]
Methamphetamine users	50, male	Intranasal (40 IU)	Oxytocin may safely increase treatment attendance by means of modulation of the autonomic nervous system.	[112]
	48, male	Intranasal (40 IU)	Small effect of oxytocin on group cohesion, but not effect on anxiety or craving.	[113]
Nicotine users	35, male and female	Intranasal (40 IU)	Oxytocin decreases some indices of smoking desire and consumption, providing modest support for the idea that OT might be effective for reducing cigarette smoking.	[114]

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Table 2. (*continued*)

Subjects	Number and Gender	Route of administration	Main conclusion	References
	48, male and female	Intranasal (40 IU)	Oxytocin did not alter responses to stress, whether it was administered before or after the stressful task, on measures of cigarette craving, anxiety, heart rate, blood pressure, and cortisol levels.	[36]
	19, male and female	N/A	Significant positive correlations for saliva cotinine and serum oxytocin, β-endorphin, and orexin, but not for either γ-glutamyl transferase (GGT) or self-reported smoking or alcohol drinking in individuals with both alcohol and nicotine use disorders.	[115]
Cocaine and Opioid users	22, male and female	Intranasal (40 IU)	Reduction of cocaine and heroin craving and use over time.	[43]
Drug user or hazardous drinkers	66, male and female (33 couples)	Intranasal (40 IU)	Attenuation of cortisol response following the task, an increase of Distress Maintaining Attributions and decrease of Relationship Enhancing Attributions among women. Decrease of Distress Maintaining Attributions and decline of Relationship Enhancing Attributions among men.	[116]
Ketamine users	65, male and female	N/A	Oxytocin system dysregulation following chronic ketamine abuse. Reduction in oxytocin level that does not normalize after early abstinence. Lower oxytocin might be associated with the anxious phenotype of ketamine dependence.	[31]

number of subjects of each of the studies described together with differences in the experimental protocols can account for this discrepancy. Indeed, other studies showed that the same treatment attenuates alcohol withdrawal and craving [37–40], decreases stress-induced craving in marijuana-dependent individuals [41], mitigates the effect of state anger on cocaine cue-reactivity [42] or cocaine craving [43] in dependent individuals. Thus, although OT may exert a common action on reward processes shared amongst substances of abuse, there are subtle differences in efficacy based on the drug, the context of drug use, as well as positive reinforcement, such as anxiolysis and stress relief contributing to negative drug-associated reinforcement.

Oxytocin and the brain reward system: interaction with dopamine

The mesolimbic DA pathway, connecting the VTA to the NAc, particularly the shell region, is crucially involved in natural and drug-mediated reward and motivational processes [44]. Nevertheless, several studies indicate an association between oxytocin and the DA system in the regulation of the same rewarding processes [17]. This is most likely due to the PVN oxytocin projections onto VTA DA cell bodies whose optogenetic manipulation affects social reward [14], and on NAc DA terminals [13], but also to the amygdala [6] and medial PFC [45] that interact directly with the VTA and NAc DA neurons. These evidences clearly explain why a direct injection of oxytocin in the VTA of rats stimulates DA release in NAc [12] and modulates the reinforcing properties of social interactions [46] and intracerebroventricular oxytocin *per se* may be rewarding [47]. This aspect is of particular interest for the common peculiarity of the different classes of drugs of abuse that, independently from their pharmacological profile and mechanism of action, are able to preferentially stimulate the release of extracellular DA in the NAc shell [44]; however, the issue of the effect of oxytocin on DA transmission in response to drugs of abuse in brain areas where oxytocin and DA interact to increase motivated behaviors for natural reward is still open, as shown by recent preclinical studies on oxytocin actions in models of addiction (Table 1). On one hand, oxytocin was shown to be able to antagonize behavioral changes (i.e. locomotion, self-administration, tolerance, conditioned place preference, cue-induced drug-seeking) induced by opiates, alcohol, cannabinoids, and psychostimulants such as cocaine or methamphetamine [48,49]; in addition, when administered directly into the NAc, oxytocin has been shown to inhibit the increase of DA induced by cocaine and the DA turnover induced by methamphetamine in the same area [50]. On the other hand, a recent, nicely designed microdialysis study from the lab of G. Tanda showed that both systemic and locally applied oxytocin robustly potentiated the methylphenidate-induced DA release in the

NAc shell but not in the core [16]. Notably, oxytocin *per se* had no effect on NAc shell DA levels confirming that it has been administered at not reinforcing doses. The study is also completed by the intriguing downward shift of the dose–response curve for intravenous self-administration of methylphenidate subsequent to the systemic administration of oxytocin in rats. Microdialysis data underscore the context-dependent effect of oxytocin on DA signaling selectively in the NAc shell. The facilitation of NAc shell DA release, possibly by local OTXRs activation, could also account for an enhancement of morphine-induced CPP [51]. All these evidences clearly implicate that oxytocin regulation of reward circuitry is more complex than a direct linear action on DA neurotransmission. In fact, OXTRs are expressed also by GABA and glutamate neurons in the mesencephalon [3,13,15]. This has been well characterized for the effects of ethanol where both these neuronal populations modulate in an opposite manner the activity of VTA DA neurons locally, and alternatively, through projections to other brain regions, including the NAc, adjusting either aversion or positive reinforcement [40].

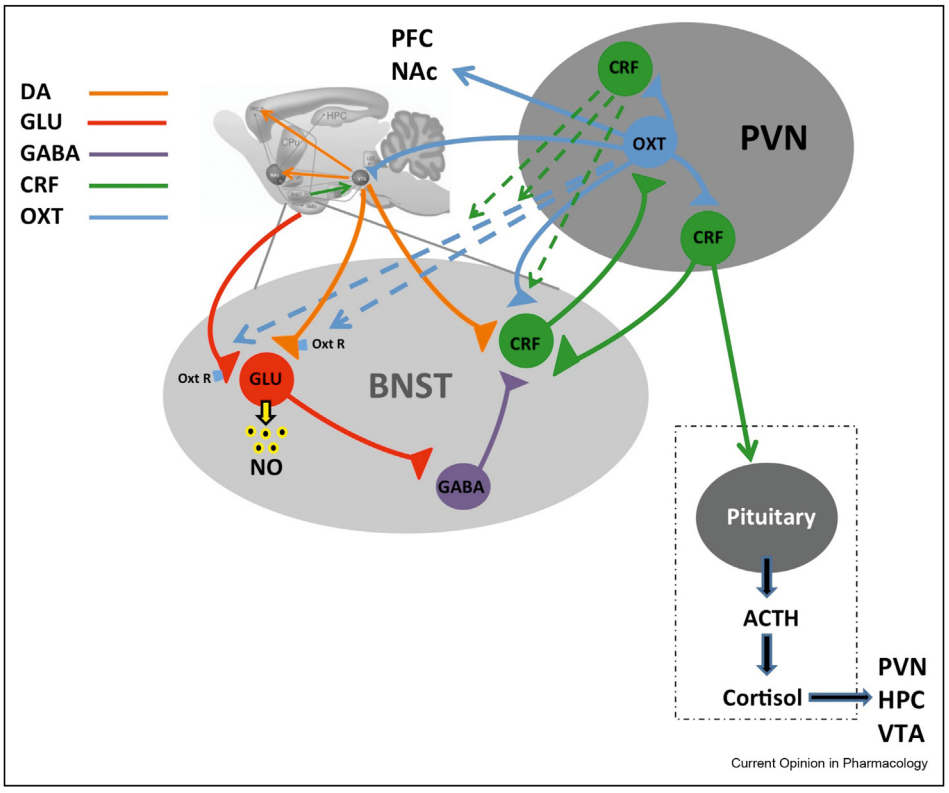
Differential roles of oxytocin in addiction

Preclinical studies (see Table 1) suggest that the brain oxytocin system can modulate neuronal systems underlying the different stages of addiction (i.e. binge and intoxication, negative affect and withdrawal, preoccupation and anticipation) at the basis of its development, maintenance, and further relapse [52]. In this regard, the ability of oxytocin to regulate the activity of limbic structures and the hypothalamic–pituitary–adrenal axis has been proposed as a potential mechanism for the ability of oxytocin to inhibit ethanol-induced negative reinforcement since long-term alcohol intake can down-regulate oxytocin signaling [53]. According to a postulated role of oxytocin in promoting allostasis [54], an intriguing hypothesis recently proposed is that oxytocin can act at the system level as a regulator of impaired neurochemical signals within these circuits [37,55,56]. What clearly emerges from these studies is that the potential therapeutical effects of oxytocin on addiction can be mainly due to its ability to: (i) modulate/recover altered rewarding processes by promoting the positive and reinforcing effects of natural rewards (such as social interactions) by a direct or indirect recovering of an altered DA mesolimbic and mesocortical functioning; (ii) modulate/recover altered stress and anxiety processes related to dysphoria and negative feelings due to withdrawal and abstinence by interfering with CRFergic neurotransmission at the level of the BNST/CeA. Yet, a general hypothesis postulating oxytocin interference on NAc DA function seems not to be sufficient *per se* for the explanation of its potential therapeutical effects on addiction and addiction-like states. It should be recalled in this regard that DA mesolimbic activation codes for salient stimuli [57] and is a common feature of several physiological conditions such as feeding, sexual behavior, coping to stress, aversion, learning, and social interactions [46,58,59], as well as pathological ones such as compulsions and addiction [52]; hence, it appears clear that there should be something else/more – we are just now starting to characterize the specificity of the dopamine neural pathways activated by drug or natural rewards – that enables the system to recognize different neurochemical and molecular signals thus redirecting the behavior towards more adaptive choices in substitution of the abused substance and its rewarding effects. Moreover, this leading hypothesis, although convincingly supported by data from both animal and human studies still lacks knowledge about the precise molecular mechanisms at the basis of these oxytocin effects. In a recent study oxytocin decreased the reinstatement of cocaine seeking, increased Fos activation in the PVN and central amygdala, but normalized cue-induced Fos activation in the mPFC, NAc core, and subthalamic nucleus, thereby demonstrating regionally specific activation patterns [60]. These and similar results point out the intriguing possibility that the target of the oxytocin actions in its ability to recover from addiction is more complex than previously hypothesized, involving several structures of the emotional/motivational limbic system, as well as the stress HPA axis as acting in concert both in physiological and pathological (altered) conditions. In this regard, an area that deserves particular attention and that can play a key role in the neurochemical and behavioral mechanisms at the basis of the potential therapeutical action of oxytocin in addiction is the bed nucleus of the stria terminalis (BNST).

Possible role of the BNST for oxytocin action in preventing addiction relapse

The BNST is a part of the so-called "extended amygdala" and serves as a key relay connecting limbic forebrain structures to hypothalamic and brainstem regions involved in autonomic and neuroendocrine functions, as well as in several behavioral responses, such as sociosexual and ingestive behaviors, as well as adaptive responses to stress, fear, and drugs of abuse in laboratory animals [61–65] and even in humans [66]. The BNST receives oxytocin innervations from the PVN [67] and here oxytocin modulates the activity of several neurotransmitters such as dopamine, glutamic acid, and nitric oxide (NO) [63] involved in sexual responses, as well as CRF neurotransmission involved in maternal behavior [68] and adaptive fear and anxiety responses [69] (Figure 1). Long-term neuroplastic adaptations induced by the addiction process in the BNST and related structures such as the CeA have been consistently involved in negative feelings, dysphoria, and stress due to alcohol, opioids, and cocaine abstinence [70]. Synaptic rearrangements in the BLA-CeA-BNST circuit

Figure 1



Schematic representation of the pathways in the rat brain involved in the interplay between oxytocin and CRF at the level of the PVN-BNST-mesolimbic circuit and at the basis of the possible therapeutical effects of oxytocin in preventing drug relapse. Paraventricular oxytocinergic neurons project to several extrahypothalamic brain areas such as the VTA, PFC, NAc, BNST, HPC, and AMG where oxytocin modulates motivated behavior by interacting with DA, GLU, and GABA. In addition, oxytocin interacts bidirectionally with CRF in the PVN and BNST to regulate rewarding and aversive behaviors through modulation of the activity of the dopamine mesolimbic pathway and peripheral responses to stress through activation of the HPA axis. References are reported in the main text where appropriate. NAc : nucleus accumbens; AMG : amygdala; BNST : bed nucleus of the stria terminalis; HPC : hippocampus; PFC : prefrontal cortex; PVN : paraventricular nucleus of the hypothalamus; VTA : ventral tegmental area; CRF : corticotropin releasing factor; DA : dopamine; GABA : gamma-aminobutyric acid; GLU : glutamic acid; NO : nitric oxide; OXY : oxytocin.

during long-term abstinence [71–73], may exacerbate the emotional impact of drug-related cues, increasing proneness to reinstatement and relapse, which provides support to the view of addiction as an allostatic state with predominant feelings of anxiety and dysphoria, together with a generalized hedonic deficit, that can lead to relapse, even after long-term abstinence [74]. A major candidate in mediating these effects is the neuropeptide CRF. The BNST is the most abundant CFR brain area and here CRF interacts with several neurotransmitters to alter/modulate the connectivity and responsiveness to stress [75,76]. Notably, chronic activation of the CRF system in the BNST is thought to be part of the complex neuroplastic processes at the basis of stress and anxiety due to abstinence and the main leading precipitating factor of drug relapse [74]. Hence, the modulating effects of oxytocin on the addicted behavior and in particular in its ability to prevent relapse (see Tables 1 and 2) can be due to its ability to interfere with BNST CRFergic mediated distress, negative feelings, and anxiety linked to both early withdrawal and long-term abstinence and at the basis of an increased risk of relapse itself. In this regard, it has been shown that between oxytocin and CRF there are reciprocal PVN-BNST interactions, with type 2 CRF receptors located on paraventricular oxytocinergic terminals in the BNST and cell bodies in the PVN and OXTr mRNA expressed on BNST CRF neurons suggesting the existence of a feedback loop where oxytocin can be able to directly modulate the excitability of the CRFergic neurons [77]. Moreover, in keeping with the strict anatomical and functional connections between the BNST and the PVN with the dopaminergic mesocorticolimbic system [74] it could be postulated that oxytocin positively interferes with the above-mentioned mechanisms: (i) by promoting abstinence distress and anxiety reduction through its direct action on BNST CRFergic activity and (ii) by contributing to recover adaptive motivational processes through direct PVN and/or indirect (e.g., glutamatergic) vHPC/BNST/CeA

action on the mesocorticolimbic system (see Figure 1). As regards the molecular mechanisms involved, it can be suggested that oxytocin-related recovering of the physiological function and prevention of relapse is achieved by promoting/rearranging (neuro)plastic processes in all these areas through modifications in LTP and/or LDP processes, MAPK/ERK pathway activations and modulation of IEGs and gene expression and (epi)genetic modifications [10,60,78–80].

Concluding remarks

In recent years is becoming clear that oxytocin can represent a valid and promising agent for the treatment of several psychopathological conditions, including addiction. In this regard, oxytocin intranasal spray delivery opened a real possibility for its clinical use as a therapeutic agent. An appreciable effort has been recently done in the attempt to shed light on the links between the molecular, behavioral, and clinical layers of oxytocin actions. However, although we are now starting to obtain more precise information about the putative neural substrates where oxytocin can modulate altered/dysfunctional circuits in the addicted brain, the molecular mechanisms at the basis of the oxytocin differential effects on these systems are almost completely unknown. This mini-review of the literature highlights that oxytocin modulation of addiction depends on the specific drug, the sex/gender, and the study design with particular importance of drug-associated stressors. However, and in keeping with possible nonspecific actions of oxytocin on the treatment of addiction, targeting stress-activated pathways directly involved in the risk of relapse even after long-term abstinence may lead to therapeutic advancements in the treatment of substance use disorders, conditions for which in the past have been already found several, although ephemeral, panaceas.

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Conflict of interest statement

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