British Journal of Pharmacology

British Journal of Pharmacology (2018) **175** 2809–2824 2809

Themed Section: Emerging Areas of Opioid Pharmacology

REVIEW ARTICLE

Oxytocin and opioid addiction revisited: old drug, new applications

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Received 11 December 2016; **Revised** 1 February 2017; **Accepted** 13 February 2017

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Opioid addiction has devastating health and socio-economic consequences, and current pharmacotherapy is limited and often accompanied by side effects, thus novel treatment is warranted. Traditionally, the neurohypophyseal peptide oxytocin (OT) is known for its effects on mediating reward, social affiliation and bonding, stress and learning and memory. There is now strong evidence that OT is a possible candidate for the treatment of drug addiction and depression-addiction co-morbidities. This review summarizes and critically discusses the preclinical evidence surrounding the consequences of pharmacological manipulation of the oxytocinergic system on opioid addiction-related processes, as well as the effects of opioids on the OT system at different stages of the addiction cycle. The mechanisms underlying the effects of OT on opioid addiction, including OT' interaction with the monoaminergic, glutamatergic, opioidergic systems and its effect on the amygdala, the hypothalamic–pituitary–adrenal axis and on memory consolidation of traumatic memories, are also reviewed. We also review clinical evidence on the effects of intranasal OT administration on opioid-dependent individuals and discuss the therapeutic potential along with the limitations that accompany OT-based pharmacotherapies. Review of these studies clearly indicates that the OT system is profoundly affected by opioid use and abstinence and points towards the OT system as an important target for developing pharmacotherapies for the treatment of opioid addiction and co-existing affective disorders, thereby preventing relapse. Therefore, there is a clear need for clinical studies assessing the efficacy of OT-based pharmacotherapies in opioid addiction.

LINKED ARTICLES

This article is part of a themed section on Emerging Areas of Opioid Pharmacology. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v175.14/issuetoc

Abbreviations

5-HT, serotonin; ACTH, adenocorticotropic hormone; CPP, conditioned-place preference; ARC, arcuate nucleus; CRF, corticotropin-releasing factor; GPCR, G protein-coupled receptor; HPA, hypothalamic-pituitary adrenal; i.c.v., intracerebroventricular; OT, oxytocin; PVN, paraventricular nucleus; SON, supraoptic nucleus

DOI:10.1111/bph.13757

Tables of Links

TARGETS	
GPCRs[a]	**Ligand-gated ion channels**[b]
μ receptor	$GABA_A$ receptor δ subunit
D_2 receptor	
OT receptor	
V_{1A} receptor	

LIGANDS	
5-HT	Noradrenaline
CRF, corticotrophin-releasing hormone	Oxytocin
Dopamine	Vasopressin
Glutamate	

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b]Alexander *et al.*, 2015a,b).

The oxytocin system

Oxytocin (OT), a nine amino acid peptide, was discovered by Sir Henry Dale in 1906 (Dale, 1906) and was the first peptide hormone to be sequenced and synthesized by Du Vigneaud (Du Vigneaud *et al.*, 1953; Tuppy, 1953;Du Vigneaud *et al.*, 1954). OT is synthesized in the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus. Besides the well-described peripheral function of OT to stimulate uterine contraction and milk ejection, its role as a neurotransmitter and neuromodulator in the brain has recently received increasing attention. OT-producing neurons located in the hypothalamus innervate brain regions associated with stress, reward, mood, fear, emotionality and drug-seeking behaviour, such as the amygdala, septum, nucleus accumbens and the bed nucleus of stria terminalis, where OT receptors are expressed (see Gimpl and Fahrenholz, 2001). Following release from nerve terminals, OT binds to OT receptors, but also to vasopressin receptors, as the latter exhibit >85% homology with OT receptors (Busnelli *et al.*, 2013). The OT receptors are G protein-coupled receptors (GPCRs) (Kimura *et al.*, 1992), but the molecular mechanism(s) of receptor activation and the intracellular signalling events following receptor activation are only partly understood. Activation of the central OT receptors is involved in the modulation of several behaviours including autonomic function, social, sexual, pair-bonding, maternal, anxiety-, depressive- and psychotic-like behaviours (see Gimpl and Fahrenholz, 2001; Hashimoto *et al.*, 2012). Recent advances in the field, both from preclinical and clinical studies, have revealed the potential of OT as a possible therapeutic target for the treatment of mental disorders characterized by social dysfunction such as autism, social anxiety disorders, depression, borderline personality disorders and schizophrenia (see Meyer-Lindenberg *et al.*, 2011).

Based on the key role of OT in social reward and stress regulation, there has been significant interest in the role of OT in addiction. The present review focuses on new and old, preclinical and clinical evidence, suggesting a central involvement of the oxytocinergic system in opioid addiction and addictive-related behaviours and discusses the potential of OT-based pharmacotherapies for the treatment of opioid addiction and prevention of relapse. Underlying neurobiological mechanisms and limitations of OT use as a pharmacotherapeutic agent are also discussed.

Oxytocin and the reward system

Increasing interest in the involvement of the oxytocinergic system in drug addiction came from findings suggesting that the brain systems involved in drug reward interact with those involved in natural rewards, such as sexual behaviour and social bonding. Early findings from Carmichael *et al.* (1987) outlined the ability of sexual self-stimulation (mediated by the mesolimbic dopaminergic system) to increase plasma OT levels in humans. These findings were recently replicated by de Jong *et al.* (2015), who showed enhanced salivary OT concentrations due to sexual self-stimulation. Preclinical findings also showed that partner bonds of prairie voles (a well-characterized monogamous species) are greatly influenced and regulated by the OT neurotransmission in the brain (Insel and Shapiro, 1992; Insel *et al.*, 1994; Young, 2003). Oxytocinergic interactions with the dopaminergic system in the brain were shown to underlie this pair bonding (Liu and Wang, 2003), indicating possible association between the oxytocinergic and dopaminergic systems to regulate behaviour. Kovacs *et al.* (1990) showed that both central and peripheral administration of OT acutely increases dopamine utilization within the nucleus accumbens, while chronic systemic administration of OT decreases dopamine utilization within the basal forebrain of mice (Kovacs *et al.*, 1986).

These interactions of the oxytocinergic with the dopaminergic system suggest that OT might have a critical role in the treatment of several dopamine-related disorders including drug addiction, and its beneficial effects might in fact be mediated by its interactions with several dopaminergic pathways in the brain.

Drug addiction cycle

Addiction is often characterized as a cycle of neurochemical and psychological changes that bring about a shift from an impulsive use of a drug to the compulsive use (see Koob and Le Moal, 2008). Acute administration of drugs of abuse

activates the mesolimbic dopaminergic reward pathway in the brain, thus inducing hedonic effects that positively reinforce the user to repeat drug administration. Upon repeated use of the drug, neuroadaptive tolerance to the rewarding effects of the drug is developed and an escalation of the dose is needed in order to achieve the same initial pleasurable effects (see Koob and Le Moal, 2001). During this period, positive reinforcement associated with acute drug administration is gradually replaced with a negative reinforcement, where the drug is taken to prevent the emergence of a negative withdrawal syndrome upon drug cessation. Acute withdrawal from drug use causes aversive drug-specific physical symptoms that are usually short-lived, and for some drugs of abuse, including opioids, protracted withdrawal could cause long-term emotional impairment (see below). In fact, drug users who have abstained from drug administration over a long period of time are still vulnerable to relapse to drug-seeking, particularly during re-exposure to the drug itself, to drug-associated environmental cues or following stress (see Koob and Le Moal, 2008).

Comorbid drug addiction and mood disorders

Chronic exposure to drugs of abuse, as well as prolonged abstinence from these drugs, is associated with lowered mood, increased anxiety, irritability and social withdrawal and isolation. It has been estimated that 45% of the drug-dependent population has a comorbid psychiatric disorder, compared with 12% of the non-dependent population (Farrell *et al.*, 2003). More specifically, according to epidemiological studies, there is a marked comorbidity (50–60%) between drug addiction and depression (Guest and Holland, 2011), which is a major issue in psychiatry as it is accompanied by more severe symptoms, longer illness duration, higher service utilization and higher relapse rates (Kosten *et al.*, 1986; Alterman *et al.*, 1996; Brooner *et al.*, 1997). Therefore, considering that antidepressants (see Riggs, 2003) and current addiction pharmacotherapies (see Kampman *et al.*, 2005) have limited efficacy and are frequently accompanied by side effects in people suffering from this comorbidity, understanding the neurobiological mechanisms underlying comorbid depression and addiction disorders will have important therapeutic implications in improving mental health care.

Effects of opioid addiction on the oxytocinergic system

The effects of opioid addiction on the oxytocinergic system and the effect of OT treatment in modulating addiction-related behaviours are summarized in Tables 1 and 2 respectively.

Acute opioid administration

Studies showing a clear role of the oxytocinergic system in the acute reinforcing effects of the opiate morphine were among the first evidence pointing towards the involvement of OT in drug addiction. In particular, acute morphine administration was shown to decrease hypothalamic OT release in female rodents (Clarke *et al.*, 1979; Haldar and Sawyer, 1978). However, Kovacs *et al.* (1987a) observed increased OT immunoreactivity in extra-hypothalamic regions including the hippocampus, amygdala and basal forebrain of male mice, suggesting either differential effects of acute opioid administration on OT neurotransmission in different areas of the brain or a sex-dependent regulation of the oxytocinergic system upon an acute challenge with opioids.

Chronic opioid administration

Chronic administration of morphine induced a significant decrease in OT immunoreactivity in the hippocampus, decreased OT mRNA levels within the SON, median eminence and arcuate nucleus of the hypothalamus (ARC) and reduced brain OT synthesis and plasma OT levels (Kovacs *et al.*, 1987a; Laorden *et al.*, 1998; You *et al.*, 2000; Zanos *et al.*, 2014a). This general down-regulation of the oxytocinergic system following chronic opioid administration, in comparison with the acute stimulatory effects of opioid administration in different brain regions, may be a result of several neuroadaptive changes in the oxytocinergic system caused by chronic exposure to opioids. We showed that this hypo-oxytocinergic tone following chronic administration of opioids is linked with a marked increase in OT receptor binding within the olfactory nuclei and amygdala of mice (Zanos *et al.*, 2014a). This effect might comprise a neuroadaptive/compensatory mechanism to counteract the decreased oxytocinergic signalling in the brain. Increased OT receptor binding in the brain following chronic opioid administration might also indicate a hypersensitivity of the oxytocinergic system during this period and should be taken into consideration when choosing the right OT dosing regimen. In fact, while acute administration of low doses of OT lacks deleterious side effects in humans (see MacDonald *et al.*, 2011), there is uncertainty on the effects of chronic administration of OT at both low and higher doses. Importantly, Peters *et al.* (2014) demonstrated that chronic (15 day) intracerebroventricular (i.c.v.) infusion of OT, at a high dose (10 $ng{\cdot}h^{-1}$), induced a paradoxical anxiogenic phenotype in mice. This is particularly important in the case of opioid addiction, where the OT receptor system may be more sensitive based on findings from Zanos *et al.* (2014a) showing an up-regulation of OT receptors in an animal model of chronic opioid use. Therefore, high doses of OT could be proven deleterious and even worsen the treatment prognosis in this population. Nonetheless, chronic administration of low doses of OT (1 $ng{\cdot}h^{-1}$; 19 days; i.c.v.) prevented psychosocial stress-induced anxiety (Peters *et al.*, 2014), indicating a dose-dependent effect of OT. These findings highlight that it may be important for future clinical studies assessing the effects of OT on opioid-dependent individuals, to use low doses of OT, in order to avoid potential undesirable side effects.

Opioid conditioning/self-administration

Interestingly and in contrast with the hypothesis that OT might be a potential target for the treatment of drug

Table 1

Effects of OT on opioid-induced, addiction-related, behaviours

Addictive substance	Administration paradigm	Animal model	Oxytocin administration paradigm	Effect of oxytocin	Reference
Morphine	Morphine tolerance: 37.5 mg morphine.HCl pellet, s.c. 48 h^{-1}	Male CFLP mice (25 ± 5 g) housed in groups	OT: 50 μg and 100 μg per animal, s.c. (2 h prior to morphine pellet implantation)	↓development of tolerance	(Kovacs *et al.*, 1985c)
	Morphine tolerance: 30 mg·kg^{-1} morphine.HCl, s.c. and 5 h later 5 mg·kg^{-1} morphine.HCl, s.c.	Male albino inbred mice (25 ± 5 g) housed in groups	OT: 1 μg i.c.v. or intra-CPu (1 h prior the tolerance-inducing dose of morphine)	↔ development of tolerance	(Sarnyai *et al.*, 1988)
	Morphine tolerance: 30 mg·kg^{-1} morphine.HCl, s.c. and 5 h later 5 mg·kg^{-1} morphine.HCl, s.c.	Male albino inbred mice (25 ± 5 g) housed in groups	OT: 1 μg microinjection into: posterior olfactory nucleus, Central nucleus of the amygdala, ventral hipoccampus (1 h prior the tolerance-inducing dose of morphine)	↓ development of tolerance	(Sarnyai *et al.*, 1988)
	Morphine tolerance: 60 mg·kg^{-1} morphine.HCl, s.c. and 5 h later 1 mg·kg^{-1} morphine.HCl, s.c.	Male CFLP mice (25 ± 5 g) housed in groups	OT: 2 μg·kg^{-1}, s.c. (1 h prior the tolerance-inducing dose of morphine)	↓ development of tolerance	(Kovacs *et al.*, 1987b)
	Morphine tolerance: 100 mg·kg^{-1} morphine.HCl, s.c. and 5 h later 1 mg·kg^{-1} morphine. HCl, s.c.	Male CFLP mice (25 ± 5 g) in groups	OT: 2 μg ·kg^{-1}, s.c. (1 h prior the tolerance-inducing dose of morphine)	↓ development of tolerance	(Kovacs *et al.*, 1987b)
	Morphine tolerance: 37.5 mg morphine.HCl pellet, s.c. 48 h^{-1} then, morphine.HCl (5 mg·kg^{-1}, s.c.)	Male CFLP mice, housed in groups	OT: 50 μg, s.c. (24 h prior to pellet implantation)	↓ development of tolerance	(Kovacs *et al.*, 1984)
	Morphine tolerance: 37.5 mg per morphine.HCl pellet, s.c. 48 h^{-1} then, morphine.HCl (5 mg·kg^{-1}, s.c.)	Male CFLP mice, housed in groups	OT: 5 ng or 0.5 μg·in 1 μL, i.c.v. (24 h prior to pellet implantation)	↓ development of tolerance	(Kovacs *et al.*, 1984)
	Morphine tolerance: 37.5 mg morphine.HCl pellet, s.c. 48 h^{-1} then, morphine.HCl (5 mg·kg^{-1}, s.c.)	Male CFLP mice, housed in groups	OT: 0.5 ng in 1 μL into the dorsal Hip or the Acb (24 h prior to pellet implantation)	↓ development of tolerance	(Kovacs *et al.*, 1984)
	Morphine tolerance: 37.5 mg morphine.HCl pellet, s.c. 48 h^{-1} then, morphine.HCl (5 mg·kg^{-1}, s.c.)	Male CFLP mice, housed in groups	OT: 0.5 ng in·1 μL, into the CPu, VTA or external cortical surface (24 h prior to pellet implantation)	↔ development of tolerance	(Kovacs *et al.*, 1984)
	Morphine-induced conditioned-place preference: Acquisition: 3 conditioning days (morphine. HCl, 5 mg·kg^{-1}·day^{-1}, s.c.)	Male Wistar rats (250–300 g), housed in groups	OT: 0.2 μg, i.c.v., 5 min prior to each conditioning session (both prior to morphine and prior to saline injections)	↔ acquisition of morphine CPP	(Moaddab *et al.*, 2015)
	Morphine-induced conditioned-place preference: Expression: 3	Male Wistar rats (250–300 g), housed in groups	OT: 0.2 μg, i.c.v., 5 min prior to the post-conditioning session	↑ expression of morphine CPP	(Moaddab *et al.*, 2015)

continues

Table 1 (Continued)

Addictive substance	Administration paradigm	Animal model	Oxytocin administration paradigm	Effect of oxytocin	Reference
	conditioning days (morphine. HCl, 5 mg·kg^{-1}·day^{-1}, s.c.)				
	Physical signs following precipitated withdrawal: Day 1: 2 x 20 mg·kg^{-1}, i.p. Days 2–4: 2 x 40 mg·kg^{-1} i.p. (morning and afternoon injections) Naloxone: 4 mg·kg^{-1}, i.p. (1 h after the morning morphine injection daily)	Female Wistar rats (130–150 g) housed individually	OT: 1.0 μg per animal, s.c. (1 h prior to each morphine injection daily)	↑ physical dependence (decreased body weight)	(van Ree and de Wied, 1976)
	Naloxone-precipitated withdrawal: 37.5 mg morphine.HCl pellet, s.c. 74 h^{-1} Naloxone (74 h after pellet implantation): 1 mg·kg^{-1}, i.p.	Male CFLP mice, housed in groups	OT: 50 μg, s.c., (24 h prior to pellet implantation)	↑ latency of naloxone-precipitated withdrawal	(Kovacs *et al.*, 1984)
	Naloxone-precipitated withdrawal: 37.5 mg morphine.HCl pellet, s.c. 74 h^{-1} Naloxone (74 h after pellet implantation): 1 mg·kg^{-1}, i.p.	Male CFLP mice, housed in groups	OT: 5 ng or 0.5 μg·in 1 μL, i.c.v. (24 h prior to pellet implantation)	↑ latency of naloxone-precipitated withdrawal	(Kovacs *et al.*, 1984)
	Naloxone-precipitated withdrawal: 37.5 mg morphine.HCl pellet, s.c. 74 h^{-1} Naloxone (74 h after pellet implantation): 1 mg·kg^{-1}, i.p.	Male CFLP mice, housed in groups	OT: 0.5 ng in·1 μL into the dorsal Hip or the mesolimbic Acb (24 h prior to pellet implantation)	↑ latency of naloxone-precipitated withdrawal	(Kovacs *et al.*, 1984)
	Naloxone-precipitated withdrawal: 37.5 mg morphine.HCl pellet, s.c. 74 h^{-1} Naloxone (74 h after pellet implantation): 1 mg·kg^{-1}, i.p.	Male CFLP mice, housed in groups	OT: 0.5 ng·in 1 μL into the CPu, VTA or external cortical surface (24 h prior to pellet implantation)	↔ latency of naloxone-precipitated withdrawal	(Kovacs *et al.*, 1984)
	Naloxone-precipitated withdrawal: 37.5 mg morphine.HCl pellet, s.c. 72 h^{-1} Naloxone (72 h after pellet implantation): 1 mg·kg^{-1}, i.p.	Male CFLP mice (25 ± 5 g) housed in groups	OT: 50 μg and 100 μg per animal, s.c. (2 h prior to morphine pellet implantation)	↓ withdrawal symptoms	(Kovacs *et al.*, 1985c)
	Spontaneous withdrawal: 20–100 mg·kg^{-1}·day^{-1}, for 7 days, i.p. morphine sulphate Withdrawal: 7 days in home cage without injections	Male C57BL/6 J mice (20–25 g), housed individually	Carbetocin: 6.4 mg·kg^{-1}, i.p. (15 min prior to FST, EPM 5 min^{-1} prior to 3-CB test/	↓ withdrawal-induced depressive-, anxiety-like behaviours, sociability deficits	(Zanos *et al.*, 2014a)
	Stress-induced reinstatement morphine CPP: 10 mg·kg^{-1}, s.c., for 4 conditioning days (morphine sulphate in the afternoon) Stress: forced-swim stress (6-min total)	Male C57BL/6 J mice (20–25 g), housed individually	Carbetocin: 6.4 mg·kg^{-1}, i.p. (5 min prior to swim stressor for reinstatement)	↓ stress-induced reinstatement of morphine conditioned place preference	(Zanos *et al.*, 2014a)
	Priming-induced reinstatement of morphine CPP: 10 mg·kg^{-1}, s.c., for 4 conditioning days (morphine	Male C57BL/6 J mice (20–25 g), housed individually	Carbetocin: 6.4 mg·kg^{-1}, i.p. (5 min prior to morphine priming injection)	↓ morphine-primed induced reinstatement of morphine conditioned place preference	(Georgiou *et al.*, 2015b)

continues

Table 1 (Continued)

Addictive substance	Administration paradigm	Animal model	Oxytocin administration paradigm	Effect of oxytocin	Reference
	sulphate in the afternoon) Priming: 2 mg·kg^{-1}, i.p. (morphine sulphate)				
Heroin	Self-administration: 5 days of fixed ratio schedule of reinformcement: 0.25 mL of heroin solution (0.125 mg·mL^{-1} per infusion), i.v.; experimenter delivered two initial heroin injections by pressing the lever	Male Wistar rats (200–230 g) housed individually	OT: 1.0 μg per animal, s.c. (1 h prior to experimentation daily)	↑ self-administration (slightly)	(Van Ree and De Wied, 1977)
	Self administration: 0.05 mg·kg^{-1}·s^{-1}.c., 2 × daily·4 days^{-1} +0.4 mg·kg^{-1}, s.c., 2 × daily·3 days^{-1} Followed by 7 days of progressive ratio schedule of reinforcement: 0.25 mL of heroin solution (0.125 mg·mL^{-1} per infusion), i.v.	Male Wistar rats (200–220 g) housed individually	OT: 1.0 μg per animal, s.c. (1 h prior to self-administration session on the day 7)	↓ self-administration	(Kovacs and Van Ree, 1985)
	Development of heroin tolerance (escalating-dose): 2 x daily i.p. injections (100, 200, 400, 800, 800, 800 μg·kg^{-1}) Self-administration: On day 7 of heroin injections, rats were placed in self-administration chambers; fixed-ratio reinforcement: 50 μL of heroin solution (0.4 g·L^{-1}) – flow rate 5 μL s; schedule terminated upon stable level of responding for 3 consecutive days (usually 7–8 days)	Male Sprague–Dawley rats (250 ± 30 g) housed individually	OT: intra-accumbal or injections directly into the ventral Hip; 2 ng; treatment block of saline/OT/saline/OT 1.0 μg per animal, s.c. (1 h prior to self-administration session daily)	↓ self-administration	(Ibragimov *et al.*, 1987)

A detailed summary of the effects of OT or OT-based drugs administration on the behavioural effects of opioids in rodents. ↑ increase; ↓ decrease; ↔ no effect. Acb, nucleus accumbens; CPu, caudate-putamen; Hip, hippocampus; VTA, ventral tegmental area.

Table 2

Effects of opioids on the oxytocinergic system

Treatment	Addiction phase	Administration paradigm	Animal model	Effect on oxytocin	Reference
Morphine	Acute	4 μg, i.v.	Lactating Wistar rats	↓ hypothalamic OT release	(Clarke *et al.*, 1979)
		10 mg·kg^{-1}, s.c.	Swiss Webster mice between the 11th and 22nd day of lactation	↓ OT release during suckling	(Haldar and Sawyer *et al.* 1978)
		5 mg·kg^{-1}, s.c.	Male CFLP mice (25 ± 5 g) housed in groups	↑ OT immunoreactivity in Hip, Amy and basal forebrain	(Kovacs *et al.* 1987a)
		5 mg·kg^{-1}, i.v.	Virgin Sprague–Dawley female rats (~270 g)	↓ spontaneous activity of SON OT neurons ↓ plasma OT levels	(Pumford *et al.*, 1991)
		0.1–1.5 μg·μL^{-1}, i.c.v.	Virgin Sprague–Dawley female rats (~300 g)	↓ spontaneous activity of SON OT neurons	(Pumford *et al.*, 1991)
	Chronic	Morphine pellet (37.5 mg morphine.HCl), s.c.	Male CFLP mice (25 ± 5 g), housed in groups	↔ OT immunoreactivity in Amy and basal forebrain	(Kovacs *et al.* 1987a)
		Osmotic mini-pump (75 mg), s.c., 1 on day 0, 2 on day 2 and 3 on day 4. On day 8 morphine.HCl (30 mg·kg^{-1}.i.p.)	Male Sprague–Dawley rats (230–270 g) housed in groups	↓ OT immunoreactivity in the Hip, SON, ME and ARC ↓ OT peptide levels in SON and ME ↔ OT peptide levels in PVN	(Laorden *et al.*, 1997; Laorden *et al.*, 1998)
		Osmotic mini-pump, s.c., 10 μg·h^{-1}·40 h^{-1} then 20 μg h^{-1}·40 h^{-1} and then 50 μg h^{-1}·40 h^{-1}	Lactating, primiparous Sprague–Dawley female rats (2–4 days post-partum)	↔ plasma OT levels	(Bicknell *et al.*, 1988)
		Osmotic mini-pump, s.c., 10 μg h^{-1}·40 h^{-1} then 20 μg h^{-1}·40 h^{-1} and then 50 μg h^{-1}·40 h^{-1}	Virgin Sprague–Dawley female rats (~270 g)	↔ firing rate of active non-phasic OT neurons	(Pumford *et al.*, 1991)
		20–100 mg·kg^{-1}·day^{-1}, for 7 days, i.p. morphine sulphate	Male C57BL/6 J mice (20–25 g), housed individually	↑ OT receptor levels in the olfactory nuclei, PirCx and Amy ↓ hypothalamic OT levels	(Zanos *et al.*, 2014a)
	Naloxone - Precipitated withdrawal	Morphine: osmotic mini-pump, s.c., 10 μg h^{-1}·40 h^{-1} then 20 μg h^{-1}·40 h^{-1} and then 50 μg h^{-1}·40 h^{-1} Naloxone (day 5; following morphine administration): 5 mg·kg^{-1}, i.v.	Lactating, primiparous Sprague–Dawley female rats	↑ plasma OT levels; ↑ firing rate of OT neurons (SON)	(Bicknell *et al.*, 1988)
		Morphine sulphate (20–40 mg·kg^{-1}) x 5 days, i.c.v (1 μL·h^{-1})	Virgin Sprague–Dawley female rats (243–287 g) housed individually	↑ plasma OT levels; ↑ OT levels in CSF	(Coombes *et al.*, 1991)

continues

Table 2 (Continued)

Treatment	Addiction phase	Administration paradigm	Animal model	Effect on oxytocin	Reference
		Naloxone (day 5; after i.c.v. morphine): 5 mg·kg^{-1}, i.v.			
		Osmotic mini-pump (75 mg), s.c., 1 on day 0, 2 on day 2, 3 on day 4. Naloxone.HCl 1 mg·kg^{-1}, s.c. (on day 7)	Male Sprague–Dawley rats (200–210 g) housed in groups	↑ OT mRNA levels in the ME and PVN	(Laorden *et al.*, 1998)
		Morphine: osmotic mini-pump, s.c., 10 μg h^{-1}·40 h^{-1}, then 20 μg h^{-1}·40 h^{-1}, then 50 μg h^{-1}·40 h^{-1} Naloxone (day 5; after last morphine infusion): 5 mg·kg^{-1}, i.v.	Virgin Sprague–Dawley female rats (~250 g) housed individually	↑ plasma OT levels ↑ OT peptide levels in the mediolateral septum ↔ OT levels in the dorsal Hip ↔ OT levels in the nucleus of tractus solitarius	(Russell *et al.*, 1992)
		Morphine: osmotic mini-pump, s.c., 10 μg h^{-1}·40 h^{-1}, then 20 μg h^{-1}·40 h^{-1}, then 50 μg h^{-1}·40 h^{-1} Naloxone (day 5 after last morphine infusion): 5 mg·kg^{-1}, i.v.	Virgin Sprague–Dawley female rats housed individually	↑ OT SON neuron post-spike excitability in morphine-dependent rats and to a lesser extend in morphine-naïve rats	(Brown *et al.*, 2005)
	Spontaneous withdrawal	20–100 mg·kg^{-1}·day^{-1}, for 7 days, i.p. morphine sulphate Withdrawal: 7 days in home cage without injections	Male C57BL/6 J mice (20–25 g), housed individually	↑ OT receptor levels in the olfactory nuclei, MS, VDB, LS, PirCx and Amy	(Zanos *et al.*, 2014a)

A detailed summary of the effects of opioid drugs on the oxytocinergic system. ↑ increase; ↓ decrease; ↔ no effect.

Abbreviations: Amy, amygdala; ARC, arcuate nucleus; Hip, hippocampus; LS, lateral septum; ME, median eminence; MS, medial septum; SON; supraoptic nucleus of the hypothalamus; PirCx, piriform cortex; PVN, paraventricular nucleus of the hypothalamus; VDB, ventral limb of the diagonal band of Broca.

addiction, central administration of OT did not prevent the acquisition of morphine-conditioning and it even increased the expression of morphine place-preference when it was administered prior to the post-conditioning test in a conditioned place-preference (CPP) study in rats (Moaddab *et al.*, 2015). In line with this finding, Van Ree and De Wied (1977) showed that peripherally administered OT slightly facilitated heroin self-administration in rats. These paradoxical effects of OT might be related to the direct actions of OT stimulation on the dopaminergic system (see Section 'Oxytocin and the reward system'). The fact that activation of the central OT receptors directly increases striatal dopaminergic content (Georgiou *et al.*, 2015b) and OT facilitates the effects of dopamine (Insel, 2003), which is directly involved in the reinforcing properties of the drugs of abuse (Volkow *et al.*, 2006; Wong *et al.*, 2006), indicates that OT administration might cause an enhanced morphine-induced CPP and/or heroin self-administration via mimicking and thus augmenting the hedonic effects of morphine. Indeed, similar to morphine (Lintas *et al.*, 2011), OT administration was shown to increase the firing rate of accumbal neurons (Moaddab *et al.*, 2015), indicating that there might be a possible additive effect of morphine and OT on the hyperexcitability of the mesolimbic dopaminergic neurons, which might have driven the enhanced morphine-induced conditioning. However, the choice of OT dose seems to be critical in determining the beneficial effects of the drug. Indeed, in the morphine CPP study (Moaddab *et al.*, 2015), the authors used a dose of 0.2 μg (i.c.v.), whereas Ibragimov *et al.* (1987) using a dose of 0.2 ng microinjected into the nucleus accumbens or ventral hippocampus demonstrated that OT was able to abolish heroin self-administration in heroin-dependent rats, an effect that was prevented by OT receptor blockade. These controversies highlight the importance for choosing the correct dose for OT to exert its beneficial effect, especially as OT is known to also bind to vasopressin receptors at higher doses (Busnelli *et al.*, 2013), which could cause the exactly opposite behavioural effects (Neumann and Landgraf, 2012). In support of this, Peters *et al.* (2014) showed dose-dependent differential effects of chronic central administration of OT on anxiety, stress-related behaviours and OT receptor binding in different brain regions.

Opioid tolerance

OT was also shown to modulate short- and long-term opioid tolerance. In particular, both peripheral and central OT administration dose-dependently attenuated the development of analgesic morphine and heroin tolerance in rodents, and a single OT injection also blocked the expression of heroin tolerance following repeated heroin administration (Kovacs *et al.*, 1985b; Kovacs *et al.*, 1984; Kovacs *et al.*, 1998; Kovacs and Telegdy, 1987). These results strongly suggest that OT can rapidly modulate both the early development, as well as the expression of an already developed opioid tolerance. Interestingly, OT treatment reduced heroin self-administration in heroin-tolerant (Kovacs *et al.*, 1985a), but not in non-tolerant rats (Kovacs *et al.*, 1998), although it inhibited the development of tolerance to morphine-induced hyper-locomotion in mice (Kovacs and Telegdy, 1987), which might indicate differential effect of OT on the adaptive *versus* acute opioid tolerance processes. Importantly, the lateral septum was shown to mediate the inhibitory effect of OT on heroin self-administration as direct microinjection of OT within this brain region abolished heroin self-administration in heroin-tolerant rats (Ibragimov and Kovacs, 1987). While the effect of OT on reducing opioid tolerance may be desirable in increasing the therapeutic efficacy of opioid replacement therapy, it may also be dangerous as it could lead to opioid toxicity in patients receiving opioid replacement therapy, especially in cases of accidental opioid overdose. In addition, if tolerance to the respiratory depressant effects of opioids is also reduced by OT, this effect could lead to a higher risk of opioid overdose, which has been also suggested to be the case with the effects of ethanol on tolerance to the respiratory depressant effects of opioids (Hill *et al.*, 2016).

Opioid withdrawal/relapse

The first evidence for a role of OT on the regulation of opioid withdrawal came from Kovacs *et al.* (1985c) who showed that peripheral OT administration decreases naloxone-precipitated morphine withdrawal symptoms in rodents. To unravel the mechanism underlying the inhibitory effect of OT on opioid withdrawal symptoms, later studies investigated the effect of pharmacologically induced opioid withdrawal on OT neurotransmission. In particular, Bicknell *et al.* (1988) demonstrated that naloxone-precipitated morphine withdrawal, a protocol that is widely used to precipitate acute physical opioid withdrawal symptoms, increases plasma OT levels, as well as the firing rate of oxytocinergic neurons in the SON of chronically morphine-treated, lactating rats. Additionally, naloxone administration also produced a large increase in OT levels within the CSF of opioid-dependent rats (Coombes *et al.*, 1991). Finally, naloxone-precipitated morphine withdrawal increased expression of *Fos* protein within the SON (Murphy *et al.*, 1997; Johnstone *et al.*, 2000) and OT mRNA levels within the median eminence and PVN (Laorden *et al.*, 1998), which may illustrate an increase in the biosynthesis of OT. These findings are somewhat unexpected as OT treatment prevents naloxone-precipitated withdrawal symptoms at a time when OT neurotransmission is already enhanced. Taken together, these results might indicate a possible OT receptor-independent mechanism of action of exogenously administered OT on the regulation of opioid withdrawal physical symptoms. Indeed, it has been demonstrated that OT might exert an OT receptor-independent action at $GABA_A$ receptor δ subunits, to regulated addiction-related processes (Bowen *et al.*, 2015).

In contrast to the pharmacologically induced morphine withdrawal findings, recent studies have demonstrated a differential regulation of the oxytocinergic system following non-precipitated, long-term spontaneous withdrawal from opioid treatment in mice. Zanos *et al.* (2014a) found decreased hypothalamic OT levels and increased OT receptor binding in the olfactory nuclei, piriform cortex, septum and amygdala following spontaneous (non-precipitated) withdrawal from chronic escalating-dose morphine administration in mice. These neuroadaptive alterations of the oxytocinergic system were concomitant with the emergence of emotional deficits including depressive-,

anxiety-like behaviours and social impairment, at least in an animal model. We also demonstrated that carbetocin, an OT analogue, was able to prevent morphine withdrawal-induced emotional impairment, as well as stress- and priming-induced reinstatement of morphine conditioned preference in mice (Zanos *et al.*, 2014a; Georgiou *et al.*, 2015b). These findings demonstrate the ability of OT treatment to reduce the physical and emotional symptoms of opioid abstinence, suggesting a promising pharmacotherapy for comorbid mood and substance abuse disorders, as well as relapse prevention, thus warranting a clinical investigation in opioid abusers and abstinent individuals undergoing detoxification.

Mechanisms underlying the effect of OT on opioid addiction

The mechanism/s by which OT exerts its effect on drug-related behaviours are complex and not fully understood. Here, we outline some of the main suggested mechanisms based on preclinical and clinical evidence.

Interactions with the monoaminergic system

Dopamine. The most characterized link between the oxytocinergic and the dopaminergic systems stems from the fact that OT-mediated social affiliative behaviours are also linked to key alterations in the dopaminergic reward system (Young and Wang, 2004; Skuse and Gallagher, 2009). OT is known to modulate dopamine turnover, and OT receptors have been shown to functionally interact with the dopamine D_2 receptors in the nucleus accumbens (Romero-Fernandez *et al.*, 2012). Thus, it is perhaps not surprising that the dopaminergic system is involved in the mechanism(s) underlying the effect of OT in modulating addictive-related behaviours. For instance, Qi *et al.* (2008) demonstrated that OT administration prevents methamphetamine-induced hyperlocomotion via decreasing methamphetamine-associated reduction on dopamine turnover in the mesolimbic system of the brain. In addition, intra-prefrontal cortex administration of OT prevented amphetamine-induced impairment of pair-bond formation, via blocking amphetamine-induced increases in dopamine levels in the nucleus accumbens (Young *et al.*, 2014). With regards to opioid addiction, Georgiou *et al.* (2015b) showed that administration of the OT analogue carbetocin increases dopamine turnover in the striatum of mice, which was associated with the ability of the drug to prevent both priming- and stress-induced reinstatement to opioid CPP.

Noradrenaline. Some preliminary evidence for an interaction between the oxytocinergic and noradrenergic systems exists. OT administration enhances noradrenaline release in the SON nucleus of the hypothalamus, which then activates hypothalamic OT neurons (Onaka *et al.*, 2003). Importantly, we have recently shown that the prevention of morphine primed-reinstatement of opioid-seeking behaviour following administration of OT is directly associated with the ability of OT to suppress striatal noradrenaline turnover in mice (Georgiou *et al.*, 2015b), thus suggesting the presence of a noradrenergic mechanism underlying the beneficial effect of OT on opioid relapse prevention. Nonetheless, this was not the case with stress-induced reinstatement indicating differential regulation of OT-noradrenaline interactions in mediating diverse reinstatement triggers.

5-HT (serotonin). Preliminary data suggest possible interactions between the oxytocinergic and serotonergic systems, which might be implicated in the modulation of several neuropsychiatric disorders. For example, serotonergic terminals originating from the dorsal and median raphe nuclei were shown to project to the PVN magnocellular neurons (Sawchenko *et al.*, 1983; Larsen *et al.*, 1996), where they possibly regulate OT release via an interaction with the 5-HT receptors (Jorgensen *et al.*, 2003; Ho *et al.*, 2007). In addition, administration of a 5-HT receptor agonist to healthy individuals increased plasma OT levels (Lee *et al.*, 2003). Although the involvement of the serotonergic system in the mechanisms underlying the effects of OT on opioid addiction-related behaviours has not been investigated to date, it is important to pursue research aiming to understand whether OT-based pharmacotherapies, via interacting with the serotonergic system, are effective in treating opioid addiction-mood disorder comorbidities, considering the evidence that serotonin reuptake inhibitor antidepressant drugs, such as citalopram and fluvoxamine, may exert their antidepressant effects partly via interacting with the oxytocinergic system (Uvnas-Moberg *et al.*, 1999; Swaab *et al.*, 2000; de Jong *et al.*, 2007).

Interactions with the glutamatergic system. While the role of glutamatergic neurotransmission in opioid addiction has not yet been identified, there is evidence to suggest a key involvement of the glutamatergic system in the pharmacological effects of OT on modulating addictive-related behaviours. In particular, Qi *et al.* (2009) showed that OT treatment abolished stress-induced, but not methamphetamine-priming, increases in glutamate levels in the medial prefrontal cortex of mice undergoing reinstatement of methamphetamine CPP. Interestingly, this effect was associated with the ability of OT to prevent stress-induced, but not drug-primed, reinstatement to methamphetamine place-preference.

Role of the amygdala. Intranasal OT has been shown to decrease anxiety via reducing amygdala reactivity in response to threat (Kirsch *et al.*, 2005; Domes *et al.*, 2007; Baumgartner *et al.*, 2008; Labuschagne *et al.*, 2010). As there is high comorbidity between drug addiction and anxiety disorders, it is plausible that OT may act within this precise brain network to induce its restorative effect on recovering emotional impairment in drug-dependent individuals. Indeed, we have shown that chronic administration of morphine (Zanos *et al.*, 2014a), cocaine (Georgiou *et al.*, 2015a; Georgiou *et al.*, 2016b), methamphetamine (Zanos *et al.*, 2014b; Georgiou *et al.*, 2016a) and nicotine (Zanos *et al.*, 2015) induces an up-regulation of the OT receptor binding in the amygdala of mice, indicating a possible common neuroadaptation of the oxytocinergic system in response to different classes of drugs of abuse. Although the

exact mechanisms underlying these neuroadaptations need further investigation, it is likely that these changes of the OT receptor system in the amygdala are involved in the modulation of drug/emotional impairment comorbidity. Given the anxiolytic, antidepressant and social-enhancing effects of OT administration on humans when administered via an intranasal spray (Kirsch *et al.*, 2005; Baumgartner *et al.*, 2008; Di Simplicio *et al.*, 2009) or on animal models when administered centrally or peripherally (Windle *et al.*, 2004; Dabrowska *et al.*, 2011), this dysregulation (up-regulation) of the OT receptor system in the amygdala may constitute a common neurobiological mechanism to counteract the negative emotional state induced by chronic drug administration. Therefore, the use of an OT-based pharmacotherapy to preferably jump-start the amygdala to attenuate emotional distress, including anxiety, and activate stress-coping mechanisms could be an important area for research and further our understanding of the role of the oxytocinergic system in the amygdala, in controlling substance abuse.

Hypothalamic–pituitary–adrenal (HPA) axis activity. There is evidence to support a regulatory role of the HPA axis on the anxiolytic and antidepressant effects of OT. Specifically, i.c.v. administration of OT decreased stress-induced corticosterone release in rats (Windle *et al.*, 1997). Moreover, intra-PVN administration of an OT receptor antagonist increased basal adenocorticotropic hormone (ACTH) levels, while it reduced ACTH release in response to a forced-swim stress in male rats (Neumann *et al.*, 2000a, b). These findings indicate a possible tonic inhibition of the HPA axis by OT and an enhancing action under stress conditions. With regards to opioid addiction, we have shown that the effect of carbetocin on preventing stress- (Zanos *et al.*, 2014a) and priming-induced (Georgiou *et al.*, 2015b) reinstatement of morphine-seeking does not depend on changes in activity of the HPA axis, as we did not observe any effects of carbetocin on plasma corticosterone levels following either priming- or stress-induced reinstatement in mice. However, the effects of OT or OT-based drug administration on the central corticotropin-releasing factor (CRF) system cannot be precluded since there is evidence for a direct regulation of the CRF neurotransmission by OT (Bulbul *et al.*, 2011; Jurek *et al.*, 2015; Pati *et al.*, 2015).

Extinction of traumatic memories. Although not tested in the context of drug addiction, there is compelling evidence to suggest that OT facilitates extinction of memories associated with fear. For instance, i.c.v. administration of OT prior to fear conditioning does not appear to have any effect on fear learning; however, later fear extinction is facilitated by OT, while OT receptor antagonists administration impairs extinction learning and retrieval (Singewald *et al.*, 2015). Therefore, it is conceivable that OT may be able to alleviate the affective emotional consequences of drug addiction and prevent relapse by interfering with the consolidation of fear memories, making these memories weaker and more susceptible to extinction (Singewald *et al.*, 2015). This hypothesis warrants further exploration.

Interactions with the endogenous opioid system. Opioid peptide regulation of the OT system has been suggested to at least partly underlie the effects of opioid drugs on the OT system. In fact, opioid peptide neuronal fibres and terminals are located in close proximity with OT neurons within the hypothalamus (Bicknell *et al.*, 1988). Moreover, μ-opioid receptors are highly expressed in the hypothalamus, and particularly within the SON and PVN nuclei, where oxytocinergic neurons project from (Atweh and Kuhar, 1983). These studies indicate possible interactions between the opioid and oxytocinergic systems. Indeed, it was recently demonstrated with the use of receptor autoradiographic binding in μ receptor knockout mice, the presence of brain region-specific interactions between the μ receptor and OT receptor systems (Gigliucci *et al.*, 2014; Georgiou *et al.*, 2015b), which may be involved in the effects of OT on the modulation of opioid-associated behaviours discussed in this review. Furthermore, a remarkable decrease in OT gene expression was observed in the nucleus accumbens of mice lacking the μ receptor gene (Becker *et al.*, 2014), further supporting a close interaction between the opioidergic and oxytocinergic systems.

OT as a potential pharmacotherapy for opioid addiction: from bench to bedside

Clinical studies. There is currently a limited number of clinical trials investigating the efficacy of OT in the treatment of drug addiction. With regards to opioid addiction, there have been only two clinical studies to-date that assessed the effects of intranasal OT on opioid-dependent patients (Stauffer *et al.*, 2016; Woolley *et al.*, 2016). The main outcome of both studies demonstrates a safe and good tolerability profile of OT administration in opioid-dependent individuals, even after repeated administration for 2 weeks. In a randomized, double-blind, placebo-controlled, crossover study, Woolley *et al.* (2016) reported that intranasal OT administration (40 IU) did not improve cue-induced craving in opioid-dependent subjects receiving opioid replacement therapy. In contrast, in a placebo-controlled trial of individuals undergoing methadone replacement treatment for opioid and co-occurring cocaine use disorder, placebo-treated patients reported an increase for heroin craving, while individuals who received intranasal OT treatment (40 IU; two times daily × 2 weeks) did not exhibit increased craving response (Stauffer *et al.*, 2016), providing some promise for the treatment of this population. No evidence of a reduction of opioid tolerance following OT administration was observed in these trials. This is especially important considering the findings of OT-induced opioid tolerance observed in animals, which could have potentially led to fatal overdose

Therapeutic potential of OT in opioid addiction treatment and addiction-emotional impairment comorbidities. In light of the literature reviewed here, OT has unambiguously a key role in mediating several opioid addiction-related behavioural and neurochemical processes and can be considered a promising target for the treatment of opioid dependence and emotional impairment comorbidity. One important factor that distinguishes OT from currently available

medications is that it does not show abuse or addiction potential. In fact, the doses used in the preclinical studies, which revealed that OT induces CPP, are much higher than the doses used in the clinical trials (Liberzon *et al.*, 1997). Evidence also suggests that patients treated with OT could not discriminate between placebo or the actual drug (MacDonald *et al.*, 2011), further supporting the lack of rewarding properties of OT at least at doses ranging from 18 - 40 IU. However, future studies should assess the possibility of any rewarding effects following chronic administration of OT in humans.

Another unique property of OT that is particularly important for the treatment of opioid addiction and/or comorbid mood disorders is related to its prosocial effects (Churchland and Winkielman, 2012). Prolonged use of drugs of abuse results in disintegration of the social lives of drug addicts and may lead to social isolation and poor decision-making in their social domain at the expense of compulsive pre-occupation with the drug and its related cues (Dawe *et al.*, 2009; Volkow *et al.*, 2011). Impaired social behaviours have been linked with the propensity of addicts to relapse after long-term abstinence (Tokar *et al.*, 1975). Therefore, considering the therapeutic effects of social support programs (e.g. Alcoholics Anonymous, Narcotics Anonymous) and the benefits of social rehabilitation and social reintegration in keeping addicts abstinent from the drug (Koerner, 2010; McGregor and Bowen, 2012), the current findings for the pro-social effects of OT may suggest its use as an adjunct to cognitive behavioural therapy as a novel effective 'psycho-biological therapy' for the prevention of relapse to drug-seeking. In support of this, OT and social support have been shown to interact and exert a stress-buffering effect following a psychosocial stress challenge in humans (Heinrichs *et al.*, 2003). Moreover, there is clinical evidence for a beneficial role of OT in the treatment of other disorders characterized by social cognitive impairment including autistic spectrum disorders and schizophrenia (Carter, 2007; Heinrichs and Gaab, 2007).

Limitations. One concern for studies looking at effects of exogenously administered OT is that it has a very short plasma (3–5 min) and central (30 min) half-life (Uvnas-Moberg, 1998; Ludwig and Leng, 2006). However, intranasal administration of OT has been shown to induce more prolonged release of at least 80 min (Burri *et al.*, 2008) and has extended biological (endocrine and sexual) activity, even after a single dose in humans (Uvanas-Moberg *et al.*, 2005). Intranasally administered OT has been shown to cross the blood-brain barrier and to exert central effects (Born *et al.*, 2002; Chang *et al.*, 2012; Pedersen *et al.*, 2013). Nonetheless, the development of smaller non-peptide OT agonists with high specificity for central OT receptors is undoubtedly desirable.

Although the outcome from the many clinical trials using intranasal OT treatment points towards a safe profile of the drug (MacDonald *et al.*, 2011), there are some unanswered questions related to its safety following chronic use in drug-dependent individuals. In fact, high doses of intravenous OT have been associated with cardiovascular side effects including hypotension and myocardial ischaemia (Dyer *et al.*, 2011) or electrolyte imbalances due to its structural similarity to arginine vasopressin and its effects on the kidneys (Rasmussen *et al.*, 2004). Importantly, OT administration at high doses could also activate the vasopressin V_{1A} receptors in the brain, which may actually lead to opposing behavioural responses (Neumann and Landgraf, 2012). Concerns also include the safety of OT administration in females at different reproductive phases due to the peripheral effects of OT (i.e. milk ejection, labour induction), as well as the regulation of OT by the gonadal hormones (Zhang *et al.*, 1991; McCarthy, 1995).

Moreover, caution needs to be applied when choosing the dose of OT for chronic intranasal administration. Peters *et al.* (2014) showed that chronic i.c.v. infusion of OT (15 days) at a high dose (10 $ng{\cdot}h^{-1}$) induced an anxiogenic phenotype whereas low doses of OT(1 $ng{\cdot}h^{-1}$ for 19 days) prevented psychological stress-induced hyper-anxiety in rats. These findings highlight the need for a deeper understanding of chronic treatment and dose-dependent effects of OT before we consider OT for long-term therapeutic use for the treatment of psychiatric conditions such as addiction.

Concluding remarks

Preclinical and clinical evidence clearly indicates the potential of OT as an effective next-generation treatment (possibly as an *ad hoc* medication) for opioid addiction and comorbid mood disorders, as well as prevention of relapse. Therefore, there is a need for future clinical studies to directly assess the effect of OT-based pharmacotherapies on the different stages of opioid addiction and to determine doses that would avoid any detrimental side effects.

Conflict of interest

The authors declare no conflicts of interest.

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