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REVIEW

The role of δ-opioid receptors in learning and memory underlying the development of addiction

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Opioids are important endogenous ligands that exist in both invertebrates and vertebrates and signal by activation of opioid receptors to produce analgesia and reward or pleasure. The μ-opioid receptor is the best known of the opioid receptors and mediates the acute analgesic effects of opiates, while the δ-opioid receptor (DOR) has been less well studied and has been linked to effects that follow from chronic use of opiates such as stress, inflammation and anxiety. Recently, DORs have been shown to play an essential role in emotions and increasing evidence points to a role in learning actions and outcomes. The process of learning and memory in addiction has been proposed to involve strengthening of specific brain circuits when a drug is paired with a context or environment. The DOR is highly expressed in the hippocampus, amygdala, striatum and other basal ganglia structures known to participate in learning and memory. In this review, we will focus on the role of the DOR and its potential role in learning and memory underlying the development of addiction.

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Abbreviations
BLA, basolateral amygdala; CeA, central nucleus of the amygdala; CPA, conditioned place aversion; CPP, conditioned place preference; DLS, dorsolateral striatum; DMS, dorsomedial striatum; DOR, δ-opioid receptor; DPDE, D-penicillamine(2,5)-enkephalin; KOR, κ-opioid receptor; LTP, long-term potentiation; MOR, μ-opioid receptor; MSN, medium-sized spiny neuron; NAc, nucleus accumbens; PVN, paraventricular nucleus; TIPPψ, H-Tyr-Tic[CH2NH]-Phe-Phe-OH; VS, ventral striatum; VTA, ventral tegmental area

Introduction

Opioid receptors are members of the class A GPCR subfamily and include the δ-(DOR), μ-(MOR) and κ-(KOR) opioid receptor subtypes (see Rachinger-Adam *et al.*, 2011; Feng *et al.*, 2012; Pradhan *et al.*, 2012; Lamberts and Traynor, 2013; nomenclature follows Alexander *et al.*, 2013). The endogenous ligands that bind DORs are the enkephalins (Leu and Met). DOR activation leads to the activation and dissociation of G_i/G_o-associated subunits and has subsequent effects on a number of effectors, including inhibition of cAMP production (Law and Loh, 1993), stimulation of signalling kinases such as ERK and src (Gutstein *et al.*, 1997; Kramer *et al.*, 2000), induction of β-arrestin (Cheng *et al.*, 1998), inhibition of voltage-gated Ca2+ channels (Piros *et al.*, 1996), the opening of inward rectifying K+ channels (North *et al.*, 1987), and ultimately inhibition of neuronal cell activation through reduced firing or neurotransmitter release. After activation, DORs are internalized and degraded in lysosomes, desensitizing the cell to further activation by an agonist (Pradhan *et al.*, 2009). This is unlike the MORs, which upon activation are also internalized but then recycled to the cell surface (Sternini *et al.*, 1996; Whistler *et al.*, 1999).

There is a significant debate about DOR pharmacology (see Table 1 for a list of DOR compounds discussed in this review) as DOR agonists have differential behavioural effects in *in vivo* experiments and, *in vitro*, DOR pharmacology changes when the receptor is co-expressed with either MOR

Table 1

Affinity estimates of opioid ligands at MORs, DORs and KORs

Compound	Species	Tissue/recombinant	pK_i MOR	pK_i DOR	pK_i KOR	Reference
ADL5747	Human	Recombinant	n/a	8.57	n/a	Le Bourdonnec *et al.* (2009)
BW373U86	Rat	Brain	7.82	8.74	7.47	Chang *et al.* (1993)
CTAP	Rat	Brain	2.1[a]	5314[a]	n/a	Kazmierski *et al.* (1988)
CTOP	Rat	Recombinant	9.74			Raynor *et al.* (1994)
	Mouse	Recombinant		<6.00	<6.00	Raynor *et al.* (1994)
DALA	Rat	Brain	8.30	8.80	8.92	Maruyama *et al.* (1987)
DAMGO	Rat	Brain	8.97	7.19		Amiche *et al.* (1989)
	Guinea pig	Cerebellum			<4.70	Amiche *et al.* (1989)
Deltorphin	Rat	Brain	5.79	8.62	<4.60	Kreil *et al.* (1989)
DPDPE	Guinea pig	Brain	6.61	9.02	4.92	Mosberg *et al.* (1987)
Naltrexone	Rat	Vas deferens	9.11			Carroll *et al.* (1988)
	Mouse	Recombinant		6.63		Raynor *et al.* (1994)
	Guinea pig	Cerebral cortex			9.08	Smith *et al.* (1989)
Naltriben	Rat	Recombinant	7.92			Raynor *et al.* (1994)
	Mouse	Recombinant		10.89	7.89	Raynor *et al.* (1994)
Naltrindole	Rat	Recombinant	7.20			Raynor *et al.* (1994)
	Mouse	Recombinant		10.70	7.18	Raynor *et al.* (1994)
NIH11082	Rat	Recombinant	7.99	6.85	7.54	Traynor *et al.* (2005)
SB-235863	Human	Recombinant	6.04	8.32	6.60	Petrillo *et al.* (2003)
SCN80	Rat	Brain	5.12	9.38	n/a	Codd *et al.* (2006)
SDM25N	Rat	Brain	5.10	8.33	5.42	McLamore *et al.* (2001)
SoRI9409	Rat	Brain	7.29	8.66		Ananthan *et al.* (1999)
	Guinea pig	Brain			7.70	Ananthan *et al.* (1999)
TAN67	Guinea pig	Brain	5.63	8.95	5.75	Nagase *et al.* (1998)
TIPPψ	Rat	Brain	5.49	9.51		Schiller *et al.* (1993)
					<5	Nevin *et al.* (1995)

Affinity estimates from rodent and guinea pig tissue or recombinant receptors expressed in transfected cell lines are shown as pK_i for MOR, DOR and KOR, except for CTAP, which is reported as IC_{50} denoted by [a].

(Sofuoglu *et al.*, 1993; Stewart and Hammond, 1993; Jordan and Devi, 1999; Decaillot *et al.*, 2008; van Rijn and Whistler, 2009; van Rijn *et al.*, 2010b; 2012; Dietis *et al.*, 2011) or KOR (Jordan and Devi, 1999; Gomes *et al.*, 2000). Although only one gene has been cloned for DOR (Evans *et al.*, 1992; Kieffer *et al.*, 1992), it has been proposed that there are two DOR subtypes, DOR1 and DOR2, based on the inability of some DOR antagonists to block the effect of DOR agonists. In animal models of ethanol dependence, the DOR subtypes have opposing effects, where the administration of the DOR1 agonist, D-penicillamine(2,5)-enkephalin (DPDPE), and the DOR2 antagonist, naltriben, decreased ethanol consumption in rats and mice, while the DOR2 agonist SNC80 increased ethanol consumption (Krishnan-Sarin *et al.*, 1995b; van Rijn and Whistler, 2009; van Rijn *et al.*, 2010a; Nielsen *et al.*, 2012b). Administration of the DOR1 agonist TAN-67 to either $MOR^{-/-}$ or $DOR^{-/-}$, but not $KOR^{-/-}$ mice, did not change the level of ethanol consumption, providing evidence that functional MORs were required for DOR1 activity (see van Rijn *et al.*, 2013). In addition, DORs are primarily located intracellularly (Arvidsson *et al.*, 1995; Kalyuzhny *et al.*, 1996; Kalyuzhny and Wessendorf, 1998; Cahill *et al.*, 2001a; Commons *et al.*, 2001) and are translocated to the plasma membrane of neurons in the dorsal spinal cord cell following chronic morphine treatment (Cahill *et al.*, 2001b; Morinville *et al.*, 2003). This increases DOR activity and produces DOR-mediated analgesia (Hack *et al.*, 2005). It has been argued that DORs become functional upon translocation to the plasma membrane, as they are primarily localized to dense-core vesicles in axon terminals (Kalyuzhny *et al.*, 1996; Commons *et al.*, 2001). This review will predominantly focus on the DOR however, in some cases we will discuss experiments that involve MORs when they are related to DORs.

DORs in addiction

The DOR contributes to the rewarding/reinforcing properties of drugs of abuse by modulating presynaptic release of dopamine in the ventral tegmental area (VTA) (Pentney

and Gratton, 1991) and the nucleus accumbens (NAc) (Broekkamp *et al.*, 1979; Latimer *et al.*, 1987; Di Chiara and Imperato, 1988a,b; Spanagel *et al.*, 1990; 1992; Leone *et al.*, 1991; Longoni *et al.*, 1991; Pentney and Gratton, 1991; Devine *et al.*, 1993; Pontieri *et al.*, 1995; Yoshida *et al.*, 1999; Hirose *et al.*, 2005), two key brain regions associated with the development of addiction. While morphine operant self-administration is not directly modulated by DOR, shown using transgenic $DOR^{-/-}$ mice (Le Merrer *et al.*, 2011), DORs in the VTA and NAc play a role in cocaine self-administration, where inhibiting DORs with naltrindole 5′-isothiocyanate in the NAc reduces, and in the VTA increases, cocaine self-administration (Ward and Roberts, 2007). Furthermore, $DOR^{-/-}$ mice have decreased morphine and nicotine-induced conditioned place preference (CPP) and lithium-induced conditioned place aversion (CPA) compared with wild-type mice, but unchanged cannabinoid CPP (Ghozland *et al.*, 2002; Chefer and Shippenberg, 2009; Le Merrer *et al.*, 2011; Berrendero *et al.*, 2012). Furthermore, β-endorphin and pro-enkephalin double knockout mice have reduced CPP for ethanol, indicating that this form of learning may involve an interaction between the MORs and DORs (Tseng *et al.*, 2013). This suggests that the DOR contributes to the acute rewarding properties of morphine, cocaine and nicotine, and that DOR plays an important role in learning paired cue associations (see Figure 1). For a review of the role of opioid receptors in models of drug abuse, see Charbogne *et al.* (2014).

There have been many studies showing that DORs contribute to the reinforcing properties of ethanol (see Nielsen and Bartlett, 2012) and these studies have contrasting results. However, it has been shown that the administration of non-selective DOR antagonists naltriben and naltrindole reduced ethanol intake in rodents (Froehlich *et al.*, 1991; Le *et al.*, 1993; Krishnan-Sarin *et al.*, 1995a,b; June *et al.*, 1999; Nielsen *et al.*, 2012b). The brain regions responsible for the effect of DOR on ethanol consumption have been shown to be the basolateral amygdala (BLA) (Hyytia and Kiianmaa, 2001), NAc (Hyytia and Kiianmaa, 2001; Barson *et al.*, 2009), paraventricular nucleus (PVN) (Barson *et al.*, 2010) and dorsal striatum (Nielsen *et al.*, 2012b). Additionally, activation of the DOR in both the perifornical lateral hypothalamus by [D-Ala2]-methionine enkephalinamide and the VTA with DPDPE results in a decrease in ethanol consumption (Margolis *et al.*, 2008; Chen *et al.*, 2013). Microinfusion of a DOR selective antagonist H-Tyr-Tic[CH2NH]-Phe-Phe-OH (TIPPψ), into the VTA increases ethanol consumption in low-drinking animals, an effect blocked by the $GABA_A$ antagonist bicuculline. This suggests that activation of DOR causes inhibition of GABAergic neurons (Margolis *et al.*, 2008). This effect is likely to be mediated by DOR1, as microinfusion of the selective DOR2 agonist deltorphin had no effect on GABAergic activity or ethanol consumption (Margolis *et al.*, 2008; Mitchell *et al.*, 2014).

In relapse, the DOR plays an important role in both cue and stress-induced reinstatement (Ciccocioppo *et al.*, 2002; Marinelli *et al.*, 2009; Nielsen *et al.*, 2012a). Yohimbine-induced stress and long-term ethanol consumption cause increased GTPγS activity at the cell membrane, indicating a possible increase in trafficking of DOR to the cell membrane (Nielsen *et al.*, 2012a). Brain slices taken from the yohimbine-treated rats had greater activity with TAN-67, a DOR1 selective agonist, over deltorphin, a DOR2 agonist, indicating DOR1 plays a greater role in stress-induced reinstatement (Nielsen *et al.*, 2012a). Furthermore, systemic administration of TAN-67 and naltriben, a DOR2 selective antagonist, both reduced ethanol consumption in mice, suggesting that DOR1

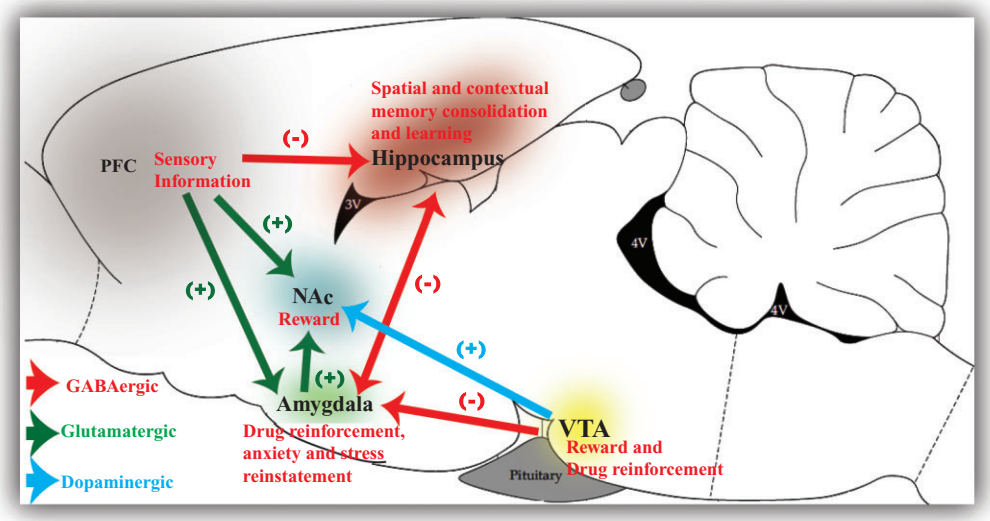

Figure 1

Activity of DORs in brain regions associated with learning and memory in addiction including the prefrontal cortex (PFC), hippocampus, NAc, amygdala and the VTA. Arrows indicate sites of neurotransmitter modulation by DORs, which have been shown to be important for drug reward and reinforcement, cue and contextual learning associated with drug use, and negative emotions such as stress and anxiety that contribute to drug relapse.

and DOR2 may exert opposing effects on ethanol consumption (van Rijn and Whistler, 2009). Visualization of DOR in DOR-eGFP transgenic mice showed that DORs were located both intracellularly and at the cell surface (Scherrer *et al.*, 2006). Long-term ethanol consumption increased DOR activity in the dorsal striatum of rats (Nielsen *et al.*, 2012a,b), suggesting that long-term ethanol consumption facilitated increased DOR expression at the cell membrane and that the DORs were dynamically regulated by drugs of abuse such as morphine and ethanol. Together, these data indicate that DORs strengthen the association between the drug and the cue or context in which the drug is taken.

It is known that DOR plays a role in reward/reinforcement, and in addition may play a role in the regulation of negative emotions such as anxiety (see Chu Sin Chung and Kieffer, 2013). $DOR^{-/-}$ mice have higher ethanol consumption and anxiety levels than the corresponding wild-type mice (Filliol *et al.*, 2000; Roberts *et al.*, 2001) and alcohol-preferring rats exhibit a 10–20% decrease in DOR binding in the BLA and posterior hippocampus (Strother *et al.*, 2001). Additionally, after 14 days of binge cocaine administration followed by withdrawal, DORs uncouple from their G-protein causing receptor desensitization, leading to greater anxiety and depressive behaviour (Perrine *et al.*, 2008). These results suggest that DOR activation may provide a protective mechanism against the exacerbation of anxious behaviour. Conversely, during states of stress, including opioid withdrawal, repeated immobilization, novel stress such as a single immobilization event, intraperitoneal injection of hypotonic saline or a puff of air, increased enkephalin gene expression is observed in the PVN (Lightman and Young, 1987; Dumont *et al.*, 2000). Furthermore, DOR-stimulated [^{35}S]GTPγS binding is increased in the midbrain of stressed rats (Nielsen *et al.*, 2012a). This is reversed by the DOR antagonist SoRI-9409, which also prevents stress-induced reinstatement of ethanol seeking (Xu *et al.*, 2001; Nielsen *et al.*, 2008; 2012a; Ananthan *et al.*, 2012). Together, this suggests that the DOR modulates negative emotions that reinforce drug seeking in rats (Nielsen *et al.*, 2012a). The DOR-mediated reductions in ethanol consumption appear to result from two possible mechanisms: (i) DOR activation that produces decreased anxiety and (ii) reduced stress caused by inhibition of DOR activity in brain regions associated with stress responses including the PVN and amygdala.

Learning and memory associated with drug addiction

'Alcoholism is an excellent example of the transition from an easily modulated behavior to a habit of drunkenness' (Edwards, 2010). The process of learning and memory when a drug is paired with a specific context or environment relies on neural connections among cortical structures, the hippocampus and the amygdala (Pennartz *et al.*, 2011). Furthermore, additional connections between these structures, the striatum and other basal ganglia structures appear to contribute to the formation and storage of procedural memories including skill and habit learning (Pennartz *et al.*, 2011). These brain circuits also encode memories of emotional and reward value to internal and external stimuli, which contributes to predictive and evaluative learning and drives motivational behaviours (Koob and Volkow, 2010). Because DORs are highly expressed within these brain circuits, studies are beginning to uncover their role in memory and learning (Paden *et al.*, 1987; Blackburn *et al.*, 1988; Erbs *et al.*, 2012). This review will discuss how DORs and other opioid receptor subtypes affect neuronal function in learning and memory processes associated with addiction by examining the function of opioid receptor activity in the brain regions and circuits associated with learning and memory.

DORs in the hippocampus in memory formation and retrieval of spatial and contextual associations

Studies with learning protocols such as CPP, cross-maze tasks and a novel object recognition task have demonstrated that the hippocampus plays an important role in memory formation and retrieval of spatial and contextual associations (Ammassari-Teule *et al.*, 1991; Kim and Fanselow, 1992; Packard and McGaugh, 1996; Frankland *et al.*, 1998; Anagnostaras *et al.*, 1999; Bast *et al.*, 2001; Rossato *et al.*, 2004). The expression of DORs in the hippocampus is predominantly in GABAergic neurons, shown using GFP-tagged DOR transgenic mice (Erbs *et al.*, 2012). DORs are mainly localized presynaptically in interneurons that form afferent connections to glutamatergic principal cells (Rezai *et al.*, 2012) and DOR-containing interneurons have been shown to project to the pyramidal neuronal dendritic layers (Svoboda *et al.*, 1999). This suggests that activation of DORs inhibits glutamatergic pyramidal cell firing, and in doing so increases afferent signalling to the pyramidal neuronal dendrites (Svoboda *et al.*, 1999).

Pharmacological and electrophysiological characterization of DORs has been performed in brain regions involved in learning and memory formation including the hippocampus, amygdala and striatum (Jiang and North, 1992; Simmons and Chavkin, 1996; Kang-Park *et al.*, 2007). The physiological effects of DORs within the hippocampus are well defined. These include inhibition of presynaptic neurotransmitter release and increased excitation of pyramidal cells in CA1, CA3 and dentate gyrus regions (Masukawa and Prince, 1982; Duggan and North, 1983; Gruol *et al.*, 1983; Wiesner *et al.*, 1986; Wiesner and Henriksen, 1987; Neumaier *et al.*, 1988; Pang and Rose, 1989), leading to a reduction in evoked and spontaneous GABA-mediated IPSPs (Cohen *et al.*, 1992; Lupica *et al.*, 1992; Lupica, 1995). Because increased pyramidal cell excitability in the hippocampus is thought to facilitate long-term potentiation (LTP), it is conceivable that DOR activation contributes to hippocampal LTP. This is supported by studies showing that the release of enkephalins in nerve fibres of the lateral perforant path and DOR induced LTP in this region (Chavkin *et al.*, 1985; Bramham *et al.*, 1991; Bramham and Sarvey, 1996).

DOR-mediated inhibition of hippocampal GABA release disrupts memory retrieval associated with these learning paradigms and activation of $GABA_A$ receptors in the hippocampus impairs memory acquisition and consolidation in

contextual learning tasks (Ammassari-Teule *et al.*, 1991; Kim and Fanselow, 1992; Frankland *et al.*, 1998; Anagnostaras *et al.*, 1999; Bast *et al.*, 2001). It has been shown that re-exposure to a context previously paired with morphine stimulates DOR internalization in the CA1, CA3 and dentate gyrus regions of GFP-tagged DOR mice, possibly due to the release of enkephalin (Faget *et al.*, 2012). Additionally, $DOR^{-/-}$ mice display impaired performance in contextual and spatial learning tasks (Le Merrer *et al.*, 2013). One possibility is that DOR-mediated LTP in the hippocampus may be associated with the acquisition and consolidation of this form of declarative memory.

DORs in the amygdala during incentive learning and motivation

The amygdala plays an important role in emotional states including stress, anxiety and depression that contribute to addiction and drug-seeking behaviour (Koob, 2009; Koob and Volkow, 2010). Furthermore, strong evidence implicates the amygdala in incentive learning and motivational behaviours associated with the rewarding effects of addictive substances (Everitt *et al.*, 1999; Robbins and Everitt, 2002). Input and output connections of the BLA appear to play a role in the formation of memories that encode incentive value associated with rewarding stimulus (Everitt *et al.*, 1999; Robbins and Everitt, 2002). The greatest levels of DORs in the amygdala are located in the BLA (Paden *et al.*, 1987). DORs are localized in MOR expressing fibres in the central nucleus of the amygdala (CeA) (Chieng *et al.*, 2006) and are absent from glutamatergic and GABAergic synapses. Following chronic morphine and ethanol dependence, it has been shown that functional DORs are recruited to the synapse leading to inhibition of glutamatergic synaptic currents (Bie *et al.*, 2009a,b). The recruitment of functional DORs in the CeA results from morphine-induced up-regulation of nerve growth factor (Bie *et al.*, 2012). The predominant enkephalinergic afferents extending to the medial CeA emanate from the bed nucleus of the stria terminalis along with other regions of the amygdala (Poulin *et al.*, 2006).

Opiate-dependent enhancement of excitatory input to the BLA involves increased dopaminergic signalling onto pyramidal cells (Li *et al.*, 2011). This mechanism is thought to involve an up-regulation of presynaptic dopamine D_1 receptors caused by chronic morphine treatment, which facilitates the excitatory effect of dopamine leading to enhanced glutamate release (Li *et al.*, 2011). Activation of dopamine D_1 and D_2 receptors within the BLA also increased the activity of neurons within the NAc shell and enhanced the rewarding effects of opiates (Lintas *et al.*, 2012).

Opioid receptor activation also modulates GABAergic transmission in the amygdala (Ford *et al.*, 2006; 2007; Kang-Park *et al.*, 2007; 2009; 2013). All three opioid receptor subtypes have been shown to produce inhibition of GABAergic transmission in dopamine neurons projecting from the VTA to the BLA and reduce GABAergic IPSCs in CeA (Ford *et al.*, 2006; 2007; Kang-Park *et al.*, 2007; 2009; 2013). It is proposed that the inhibitory effects of opioid receptor activation on GABA in the CeA cause a sensitization to the anxiolytic effects of ethanol and contribute to increased ethanol reinforcement (Kang-Park *et al.*, 2007; 2009; 2013).

It has become increasingly recognized that exposure to environmental contexts associated with drug use can lead to relapse. The cortical-hippocampus-amygdala brain circuit is thought to be critical for the development of associations formed between a particular context or environment and a conditioned stimulus (Gruber and McDonald, 2012). The DOR antagonist naltrindole inhibits cue-induced ethanol seeking when administered centrally and reduces ethanol and morphine-induced CPP when microinfused into the CeA (Marinelli *et al.*, 2009). This suggests that DOR activity within the CeA plays an important role in learned associations that are formed during drug-context conditioning paradigms.

Opioid receptors in the striatum in motor and habit learning

The striatum and associated basal ganglia circuitry have key roles in motor learning, controlling instrumental outcome/actions (operant learning) and the development of habitual performance of these learned behaviours (see Graybiel, 2008). In addition to the connections among the ventral striatum (VS), BLA and hippocampus that contribute to declarative memory formation (Parkinson *et al.*, 2000; Corbit *et al.*, 2001; Roitman *et al.*, 2005; Balleine *et al.*, 2007; Ito *et al.*, 2008), results from recent neuropharmacological gene-targeted and electrophysiology studies are beginning to uncover important contributions of the striatum to procedural learning (Yin and Knowlton, 2006; Wickens *et al.*, 2007; Yin *et al.*, 2008; 2009; Grahn *et al.*, 2009; Lovinger, 2010). Further, there are two subregions in the dorsal striatum: the dorsolateral striatum (DLS) and the dorsomedial striatum (DMS). The DLS is involved in habits and integrates sensorimotor information and utilizes a reinforcement process during their acquisition, while the DMS is involved in non-habitual (or goal-directed) actions and more like the executive system is involved in both cognitive and emotional or reward-related processes (Cui *et al.*, 2013). Mechanisms that mediate long-lasting changes in synaptic plasticity over time are critical for the development of motor skill and habit learning.

DORs in the ventral striatum

The VS includes the NAc core and NAc shell and plays a key role in the rewarding effects of abused substances and goal-directed behaviours (Wise and Bozarth, 1985; Koob, 2006). Furthermore, limbic and cortical inputs to the VS contribute to motivational learning and processes that reinforce drug-seeking behaviour (Wise, 2004; Everitt and Robbins, 2005; Day *et al.*, 2007; Da Cunha *et al.*, 2012). The NAc has been recognized for its role in motivational learning associated with goal-directed actions and decision making that involves reward outcome (Wise, 2004; Everitt and Robbins, 2005; Day *et al.*, 2007; Da Cunha *et al.*, 2012). Rather than memory encoding of reward value, recent evidence suggests that the role of the NAc in these behaviours is primarily facilitated by changes in motor output that determine the motivational

drive and influence instrumental performance (Stuber *et al.*, 2011). These changes are derived from the processing of sensory input of the rewarding experience within limbic brain regions including the BLA (Mogenson *et al.*, 1980; Shiflett and Balleine, 2010) which then project to the NAc. A shift in motivation or reward incentive is produced when the 'predicted' reward value is different from the 'expected' value of the reward, determined by internal motivation conditions and prior learning (Schultz *et al.*, 1997; Stuber *et al.*, 2008).

Predominately, the expression of DORs within the rat NAc is presynaptic, suggesting that their contribution to these behaviours primarily involves effects on inhibitory and dopaminergic input into the NAc (Svingos *et al.*, 1998; 1999; Cahill *et al.*, 2001a). Recently, however, studies with GFP-tagged DOR mice have confirmed postsynaptic expression of DORs in GABergic projection neurons and cholinergic interneurons within the NAc shell (Scherrer *et al.*, 2006; Bertran-Gonzalez *et al.*, 2013). The MORs are expressed mainly at the extrasynaptic membrane of dendrites of cholinergic cells and GABAergic medium-sized spiny neurons (MSNs), which form synapses that receive excitatory and GABAergic input to modulate the activity of NAc neurons (Gracy *et al.*, 1997; Svingos *et al.*, 1997; Wang and Pickel, 1998; Ma *et al.*, 2012). The expression of MORs in GABA terminals of NAc cells suggests that these receptors may also modulate the presynaptic release of GABA (Svingos *et al.*, 1997).

Recent work has shown that the MOR agonist, (D-Ala2-MePhe4-Gly(ol)5)enkephalin (DAMGO), produced inhibition of spontaneous EPSCs (sEPSCs) and spontaneous IPSCs (sIPSCs) in MSNs of the VS containing dopamine D_1 and D_2 receptors. These effects persisted in the presence of tetrodotoxin, and produced depolarization and enhanced intrinsic cell excitability (Ma *et al.*, 2012).

Studies have also demonstrated the ability of MORs and DORs within the VS to modulate drug-seeking behaviour. Infusions of DOR and MOR agonists into the NAc restored cocaine seeking in rats (Simmons and Self, 2009). Also, abstinence from chronic cocaine use in animals leads to an increase in MOR expression within the NAc core, suggesting that opioid receptor signalling is dynamically regulated within the VS and may contribute to drug reward-related learning (Simmons and Self, 2009).

Recent studies have begun to investigate the effects of MORs and DORs in the NAc on learning using Pavlovian instrumental transfer and outcome devaluation tests (Laurent *et al.*, 2012; Bertran-Gonzalez *et al.*, 2013). These tests rely on a form of predictive learning, which is required to assign a value or validity to a stimulus which is paired with a reward. This work suggests that MORs within the NAc core contribute to motivational drive in reward seeking, as observed by reduced sensitivity to outcome devaluation tasks following infusion of the selective MOR antagonist D-Phe-Cys-Tyr-d-Trp-Arg-Thr-Pen-Thr-NH_2 (CTAP) (Laurent *et al.*, 2012). Inhibition of DORs in the NAc shell or core did not affect outcome devaluation but did reduce performance during instrumental transfer (Laurent *et al.*, 2012). As previous studies have shown that DOR and MOR agonists promote feeding behaviour in rodents when infused into the NAc shell (Zhang and Kelley, 2000; Zhang *et al.*, 2003; Smith and Berridge, 2007; Ambroggi *et al.*, 2009; Katsuura and Taha, 2010) and also enhance motor reflexes associated with palatable tastes such as sucrose (Pecina and Berridge, 2005; Smith and Berridge, 2007), it was proposed that the observed MOR effects were caused by changes in evaluative learning that alters incentive value, motor output and motivational drive in reward seeking (Laurent *et al.*, 2012). The reduction in performance mediated by DOR antagonism during instrumental transfer was attributed to a deficit in predictive learning required to guide choice based on paired stimulus-reward outcomes. This is also supported by recent work showing that Pavlovian conditioning in mice increases DOR expression within the somatic membrane of cholinergic interneurons in the NAc shell (Bertran-Gonzalez *et al.*, 2013). This effect persisted well after the initial training phase and correlated with the level of conditioned responding. Furthermore, increased DOR expression was accompanied by higher irregular/burst firing in these neurons but no change in action potential frequency (Bertran-Gonzalez *et al.*, 2013). Increased burst firing variability has previously been shown to produce changes in the pattern release of acetylcholine at target MSNs resulting in disinhibition (Ding *et al.*, 2010). This mechanism of DOR-mediated synaptic plasticity may contribute to future actions that guide choice based on stimulus-reward outcomes (Bertran-Gonzalez *et al.*, 2013).

DORs and MORs in the dorsal striatum

The striatum is the largest nucleus of the basal ganglia that is involved in motor control, reinforcement learning and action selection (Alexander and Crutcher, 1990; Graybiel *et al.*, 1994; Redgrave and Gurney, 2006; Wickens *et al.*, 2007). There are two subregions in the dorsal striatum: the DLS and the DMS. The DLS integrates sensorimotor information and the DMS is involved in motivation and reward (Cui *et al.*, 2013). Furthermore, excitatory inputs to the striatum arise from cortical and thalamic structures and inhibitory outputs project to the basal ganglia output neurons (striatonigral or direct pathway) or to the striatopallidal neurons (indirect pathway) (Cui *et al.*, 2013). There has been considerable debate about the precise roles of these two pathways in action selection, with recent evidence suggesting there is coordinated rather than separate activation of the direct and the indirect pathways (Graybiel, 2008).

The striatum plays an important role in learning and memory. Within the striatum, MSNs constitute approximately 95% of all neurons and receive convergent glutamatergic afferents from the cortex and thalamus, as well as dopaminergic afferents from the substantia nigra (reviewed in Graybiel, 2008). As the only output from the striatum, MSNs link these nuclei to the rest of the basal ganglia. The dorsal striatum also plays a role in signalling proximity and value of distant rewards, where it was shown that dopamine transients in the DLS and DMS appeared as rats navigated mazes seeking for rewards (Howe *et al.*, 2013). It is known that endogenous opioids are widely expressed and are present in the striatum in MSNs that are grouped into two populations based on differential expression of dopamine D_1 and D_2 receptors and the opioid peptides they contain (Blomeley and

Bracci, 2011). For example, the D_1 receptor MSNs define the direct pathway and express dynorphins, and the D_2 receptor MSNs contribute to the indirect pathway and express enkephalins (Gerfen, 1992; Britt and McGehee, 2008; Gertler *et al.*, 2008). The current thinking is that the D_1 pathway mediates action initiation and the D_2 pathway inhibits alternative actions (Cui *et al.*, 2013). In the mouse striatum, DOR mRNA is predominantly found in cholinergic neurons (Le Moine *et al.*, 1994) and receptor expression is confined to the soma and proximal dendrites (Scherrer *et al.*, 2006; Bertran-Gonzalez *et al.*, 2013). In the rat, DORs were found in the somatodendritic profiles, axon terminals, in the cytoplasm of dendrites and at the nerve terminals of striatal neurons (Wang *et al.*, 2003). A subset of DOR-expressing dendrites also expressed the D_1 receptor, indicating that these dopamine receptors may mediate DOR function (Ambrose *et al.*, 2006).

Recent work is beginning to uncover the potential for opioid receptor activity to affect local processing within the dorsal striatum in order to determine the functional consequences on striatal output. Experiments using antidromic stimulation of MSNs or paired recordings to facilitate the presynaptic release of endogenous opioids revealed negative effects on evoked EPSCs stimulated from cortical inputs (Blomeley and Bracci, 2011). The majority of the current studies have been on the MORs. It is hoped that these studies focused will reveal the role of the DORs in these circuits. The opioid-mediated reduction in evoked EPSC amplitude was blocked by the MOR antagonist CTAP but continued in the presence of the DOR antagonist SDM25N, suggesting that these effects are caused by activation of presynaptic MORs (Blomeley and Bracci, 2011). Postsynaptic MOR activation within cholinergic interneurons in the striatum has also been shown to cause inhibition of spontaneous cell firing (Ponterio *et al.*, 2013).

These studies demonstrate the ability of opioids to modulate the activity between neurons within the striatum. The ability of MORs to inhibit the cortical-induced excitation of neighbouring MSNs is thought to involve the release of enkephalin from striatopallidal MSNs (Blomeley and Bracci, 2011). Local inhibition may also involve MOR-mediated reductions in cholinergic interneuron excitability (Ponterio *et al.*, 2013). The consequence of this activity on output nuclei remains to be determined. Although the dorsal striatum is not implicated in the reinforcing effects of abused substances, the recent work has demonstrated the importance of corticostriatal circuits in the shift between goal-directed and habitual learning (Gremel and Costa, 2013). The contribution of these processes to drug addiction is receiving greater attention considering that addicts exhibit compulsive drug-seeking habits (Everitt *et al.*, 2008). The shift between goal-directed and habitual actions is thought to depend on the transfer of information from the DMS to the DLS. Increased activation of striatal presynaptic MORs in opioid addicts and other substance abusers that modulate endogenous opioid activity (i.e. cocaine) produce changes in receptor density and presumably effect receptor efficacy and signalling. This may alter dynamic processes between MSNs and disrupt striatal information processing and/or transfer, resulting in enhanced storage of procedural and contextual memories associated with drug use.

Pharmacotherapeutics

The early DOR agonists were the peptides DPDPE and deltorphin (Mosberg *et al.*, 1983; Kreil *et al.*, 1989; Kramer *et al.*, 1993). The non-peptide compounds BW373U86 and SNC80, followed by TAN-67, were synthesized later and shown to be highly selective for DOR (Calderon *et al.*, 1994; 1997; Fujii *et al.*, 2001). DOR agonists are thought to be effective analgesics with reduced side effects such as addiction liability and respiratory depression, at least in preclinical animal models (Ling *et al.*, 1985; O'Neill *et al.*, 1997; Gallantine and Meert, 2005). A number of other DOR agonists, including but not limited to ADL5747, SB-235863 and NIH 1108, have undergone preclinical testing, largely focused on the treatment of chronic pain, anxiolytic and antidepressant effects (Petrillo *et al.*, 2003; Aceto *et al.*, 2007; Saitoh *et al.*, 2011; 2013; Nozaki *et al.*, 2012). The DOR antagonist naltrindole has been shown to reduce the behavioural and biochemical signs of morphine withdrawal following chronic morphine administration and reduce ethanol self-administration in animals (Krishnan-Sarin *et al.*, 1995b; Suzuki *et al.*, 1995; Hyytia and Kiianmaa, 2001; Aceto *et al.*, 2007; Nielsen *et al.*, 2008). Although there have been no DOR-targeted drugs approved by the FDA to date, the drug class is still at an early stage in their development, and a number of compounds hold promise for further development (Fujii *et al.*, 2013).

Conclusions

DORs have been known for many decades and have been extensively reviewed; however, their role in regulating emotions and learning has put these receptors into a new light for developing novel pharmacotherapeutics. It may be possible that activation of these receptors plays a role in the storage of reward-related memories during drug taking. The data suggest that developing DOR compounds may be useful for reducing the drug cue and/or context learning during the development of addiction. The ability of drugs that modulate DOR activity to reduce the rewarding properties of addictive substances, alleviate symptoms associated with drug withdrawal and attenuate relapse to drug seeking may represent a novel therapeutic strategy for the management of drug addiction.

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Conflict of interest

None.

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