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# The Role of Delta Opioid Receptors in Ethanol Consumption and Seeking: Implications for New Treatments for Alcohol Use Disorders

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## 1. Introduction

There are few effective medications available for the treatment of alcohol use disorders (AUDs). To date, the opioid antagonist, naltrexone, is the most effective in reducing alcohol consumption in combination with behavioral therapy. Naltrexone has high affinity for the mu opioid peptide receptor (MOP-R) with moderate activity at the delta opioid peptide receptor (DOP-R) and kappa opioid peptide receptor (KOP-R). Preclinical studies suggest that the MOP-R plays a significant role in ethanol-mediated behaviors, however, there is evidence suggesting the DOP-R may be a better therapeutic target for treating AUDs. This chapter will review studies investigating the role of the opioid receptors in ethanol-mediated behaviors with the view of identifying improved therapeutics for the treatment of AUDs.

### 1.1 Current therapeutics for the treatment of alcohol use disorders

AUDs are a major public health problem; currently the National Institute on Alcohol Abuse and Alcoholism, reports there are 17.6 million people in the United States either abuse alcohol or are alcohol dependent. There have been three medications approved by the U.S. Food and Drug Administration: disulfiram (Antabuse), acamprosate (Campral), and naltrexone (ReVia, Vivitrol) - all of which suffer from limited effectiveness due to side-effects and compliance issues (Bouza et al., 2004; Mark et al., 2003a; Mark et al., 2003b; Pettinati et al., 2000). The aldehyde dehydrogenase blocker, disulfiram has not been very effective for treating AUDs (Johnson, 2008; O'Shea, 2000) primarily because of patient compliance (Johnson, 2008; O'Shea, 2000). Disulfiram is reportedly only clinically effective in patients who were fully compliant with taking their medication and were under supervision (Fuller et al., 1986). Acamprosate has been shown to be effective for alcohol dependence in European trials, but not in U.S. trials, and has a low incidence of side-effects (Anton et al., 2006; Bouza et al., 2004; Whitworth et al., 1996). To date, the opioid antagonist, naltrexone, appears to be the most effective medication for alcohol dependence (Anton et al., 2006; O'Malley et al., 1992; Volpicelli et al., 1992).

## 1.2 Preclinical studies with naltrexone

Naltrexone has been shown to effectively reduce ethanol consumption and seeking in a large number of studies (Ciccocioppo et al., 2002a; Critcher et al., 1983; Franck et al., 1998; Gardell et al., 1996; Le et al., 1999; Nielsen et al., 2008; Simms et al., 2008; Stromberg et al., 1998a; Walker & Koob, 2008). Furthermore, intramuscular injections of naltrexone reduce intravenous (i.v.) or oral self-administration of ethanol in rhesus monkeys (Altshuler et al., 1980; Williams et al., 2001). Naltrexone reduces ethanol consumption in both low ethanol consuming rats (Stromberg et al., 1998a) and high ethanol consuming rats (Nielsen et al., 2008; Simms et al., 2008). However, the effects of naltrexone on ethanol consumption are non-selective as fat, sucrose and water intake are also reduced (Corwin & Wojnicki, 2009; Nielsen et al., 2008; Rao et al., 2008; Simms et al., 2008; Wong et al., 2009). Also, naltrexone reduces alcohol- and cue-induced reinstatement, but not foot-shock stress-induced reinstatement of ethanol-seeking in rodents (Ciccocioppo et al., 2002a; Le et al., 1999; Liu & Weiss, 2002).

## 1.3 Clinical studies with naltrexone

A number of clinical studies have reported that naltrexone effectively reduces relapse in a subset of alcohol-dependent humans (Anton et al., 1999; Anton et al., 2006; O'Malley et al., 1992; Volpicelli et al., 1992) and is more effective at reducing heavy drinking (Pettinati et al., 2006). Alcohol-dependent patients that have a polymorphism in the OPRM1 gene encoding the mu opioid peptide receptor (MOP-R) with a mutation at A118G (Asn40Asp) have greater euphoric responses to alcohol, increased pain thresholds, greater susceptibility to AUDs and greater responses treatment with naltrexone (Anton et al., 2008; Bart et al., 2005; Oroszi et al., 2009; Oslin et al., 2003). More recently, the use of naltrexone in an extended-release intra-muscular (i.m.) depot formulation (Vivitrol<sup>®</sup>) is more effective in patients who are able to abstain from drinking prior to treatment (O'Malley et al., 2007; Pettinati et al., 2009). Taken together, treatment with naltrexone appears to have the most consistent effects on drinking outcomes in subjects with A118G mutation.

## 1.4 Pharmacological activity of naltrexone in reducing ethanol-mediated behaviors

Naltrexone has the highest affinity for the MOP-R, moderate activity at the delta (DOP-R) and kappa (KOP-R) opioid peptide receptors, but without activity at nociceptin (NOP-R) and the sigma (SIG-R) receptors (Ananthan et al., 1999; Goldstein & Naidu, 1989; Takemori & Portoghese, 1984). There is a large body of evidence that suggests that the MOP-R plays a significant role in ethanol-mediated reward behavior (Becker et al., 2002; Ciccocioppo et al., 2002a; Gardell et al., 1996; Hall et al., 2001; Le et al., 1999; Reid & Hunter, 1984; Roberts et al., 2000) (Table 1). Ethanol has been reported to stimulate the activity of the endogenous opioids which target the MOP-R leading to increased basal dopamine release in the mesolimbic pathway (Herz, 1997). Naltrexone's mechanism of action has been proposed to result from inhibition of ethanol-induced activity of endogenous opioid peptides and dopamine release *in vivo* (Benjamin et al., 1993; Gonzales & Weiss, 1998; Zalewska-Kaszubska et al., 2006; Zalewska-Kaszubska et al., 2008). In comparison, the roles of the other opioid subtypes on ethanol-mediated behaviors, such as the DOP-R (Krishnan-Sarin et al., 1995a; Roberts et al., 2001; Stromberg et al., 1998a) and KOP-R (Kovacs et al., 2005; Lindholm et al., 2001; Mitchell et al., 2005) are less well-defined.

## **2. The role of the Mu Opioid Peptide Receptor (MOP-R) in ethanol consumption and seeking**

### **2.1 Ethanol consumption in MOP-R knockout mice**

Mice with a genetic deletion of the MOP-R have reduced levels of ethanol intake and seeking in comparison to wild-type mice with a mixed C57/129sv background (Becker et al., 2002; Hall et al., 2001; Roberts et al., 2001; Roberts et al., 2000) (Table 1). Although one study using purebred C57BL/6 mice failed to show any difference in ethanol intake (van Rijn & Whistler, 2009), the differences in these studies may reflect the varying degrees of ethanol intake in mice with different genetic backgrounds (Yoneyama et al., 2008) and also the models of ethanol consumption employed.

### **2.2 MOP-R activation and ethanol consumption**

The opioid receptor agonist, morphine increases ethanol (3-26%) intake in solutions containing sucrose (Hubbell et al., 1986; Reid & Hunter, 1984) suggesting an involvement of the opioid system in the reinforcing properties of ethanol (Table 1). Furthermore, microinjections of morphine into the rat nucleus accumbens (NAc), a brain region involved in the reinforcement pathway, increases ethanol and food intake (Barson et al., 2009). The selective MOP-R agonist, DAMGO, into the NAc increases intake of saccharin, salt, fat and ethanol (de Wet et al., 2001). Since morphine has the highest affinity for the MOP-R but also activity at KOP-R and DOP-R (Goldstein & Naidu, 1989), this may explain some of the non-selective effects on consummatory behavior. It cannot be ruled out that the effects of morphine on food and ethanol consumption may be related to morphine's rewarding effects (Gaiardi et al., 1991; Shippenberg et al., 2009; Shippenberg et al., 1996). Taken together, this data suggests that the MOP-R plays a more general role in ingestive behaviors.

### **2.3 MOP-R antagonists and ethanol consumption and seeking**

The MOP-R has been proposed to be primarily responsible for the action of naltrexone in reducing ethanol consumption and seeking (Stromberg et al., 1998a). Although naltrexone has consistently been shown to reduce ethanol consumption and seeking, the effects of opioid antagonists with higher selectivity for the MOP-R have been shown to produce mixed results (Ciccocioppo et al., 2002a; Hyytia & Kiianmaa, 2001; Marinelli et al., 2009) (Table 1). The selective MOP-R antagonist, CTOP (D-Pen-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH<sub>2</sub>), reduces operant ethanol responding in rats when administered into either the cerebroventricles or into the amygdala, but not when administered into the NAc or ventral tegmental area (VTA) (Hyytia & Kiianmaa, 2001). In rats trained to self-administer ethanol and subsequently extinguished from responding, CTOP had no effect of light/tone cue-induced reinstatement and only short-lasting reductions on context-induced reinstatement of ethanol-seeking (Marinelli et al., 2009). Furthermore, in a model of cue-induced reinstatement using visual and olfactory discriminative stimuli, the MOP-R1-selective antagonist, naloxonazine, reduced reinstatement but also produced some nonselective behavioral suppression (Ciccocioppo et al., 2002a). In the same study, naltrexone selectively inhibited cue-induced reinstatement of ethanol-seeking (Ciccocioppo et al., 2002a). The irreversible MOP-R-selective antagonist, clocinnamox, did not reduce responding for oral

ethanol in rhesus monkeys, except when it was co-administered with naltrexone (Williams & Woods, 1998). These studies suggest that naltrexone's ability to reduce ethanol consumption and seeking may be mediated via a non-MOP-R.

### **3. The role of the Delta Opioid Peptide Receptor (DOP-R) in ethanol consumption and seeking**

#### **3.1 Ethanol consumption in DOP-R knockout mice**

Studies in mice with a genetic deletion of the DOP-R (C57BL/6 or mixed C57/129sv background) have increased levels of ethanol intake when compared to wild-type mice (Roberts et al., 2001; van Rijn & Whistler, 2009) (Table 1). This suggests that decreased DOP-R activity is associated with high ethanol consumption. This may be related to the increased anxiety levels in DOP-R knockout mice as anxiety-like responses were reversed by the consumption of ethanol in the DOP-R knockout mice (Roberts et al., 2001).

#### **3.2 DOP-R activation and ethanol consumption**

Ethanol has been shown to stimulate the activity of the endogenous opioids,  $\beta$ -endorphins and enkephalins, which target the MOP-R and DOP-R, respectively, to increase basal dopamine release in the mesolimbic pathway (Herz, 1997). Activation of the enkephalinergic system and occupation of DOP-Rs has been proposed to be important for the maintenance of high voluntary ethanol intake (Froehlich et al., 1991). The enkephalinase inhibitor, thiorphan, which potentiates the actions of the endogenous opioids for the DOP-R by protecting the enkephalins from degradation, increased ethanol, but not water, intake in alcohol-preferring rats (Froehlich et al., 1991).

Recently, further studies have examined the effects of activation of the DOP-R on ethanol consumption using various DOP-R agonists (Barson et al., 2009; Barson et al., 2010; van Rijn et al., 2010) (Table 1). In support of the earlier studies, systemic administration of the DOP-R agonist, SNC80, in mice and microinjections of the DOP-R agonist, DALA (7-14 nM), into the NAc and hypothalamic paraventricular nucleus (HPN) of rats lead to increased ethanol consumption (Barson et al., 2009; Barson et al., 2010; van Rijn et al., 2010). In mice trained using the 10% ethanol 4 hr limited access paradigm, SNC80 increased ethanol consumption (van Rijn et al., 2010). In rats trained to consume up to 7% ethanol for 12 h each day with incremental increases in the concentration of ethanol every four days, the administration of DALA into the NAc selectively increased ethanol consumption over food and water (Barson et al., 2009). Similarly, the effects of DALA administered into the HPN were selective for ethanol over food and water consumption (Barson et al., 2010). DOP-R agonists have also been shown to reduce ethanol consumption in rats (Margolis et al., 2008) and mice (van Rijn & Whistler, 2009). Systemic administration of the selective DOP-R agonist, TAN67, reduced voluntary ethanol intake in mice using a 4 hr limited ethanol access paradigm (van Rijn & Whistler, 2009). Following administration of the DOP-R agonist, DPDPE (10 mM), into the ventral tegmental area (VTA) of rats using continuous access to 10% ethanol paradigm, ethanol intake was reduced in low but not high ethanol consuming rats (Margolis et al., 2008). It is hypothesized that DOP-Rs in the VTA play a protective role against elevated ethanol consumption (Margolis et al., 2008).

### 3.3 Ethanol consumption and seeking with DOP-R antagonists

The administration of DOP-R antagonists decreases ethanol consumption and seeking in rats (Franck et al., 1998; Hyytia & Kiianmaa, 2001; June et al., 1999; Krishnan-Sarin et al., 1995b; Marinelli et al., 2009; Nielsen et al., 2011; Nielsen et al., 2008). However, DOP-R antagonists also have been shown to not affect (Ingman et al., 2003; Stromberg et al., 1998a) or increase ethanol intake (Margolis et al., 2008) (Table 1). Factors likely contributing to these disparities include the length of ethanol exposure, the route of drug administration, different types of drinking models that induce low, moderate and high ethanol consumption, the rodent strains used (such as alcohol-preferring rats) and potential different roles of subtypes of the DOP-R on ethanol-mediated behaviors.

Opioid Receptor	Effects on Ethanol Consumption and Seeking ↓ Decreased, ↑ Increased, or No Effect (Reference)						
	Voluntary ethanol consumption			Operant responding for ethanol		Reinstatement of ethanol-seeking	
	Knock-out mice	Antagonists	Agonists	Antagonists	Agonists	Antagonists	Agonists
MOP-R	↓ (1,2,3)	↓ (6,7,8,10,20,18,3,6,47,48) No Effect (10)	↓ (6) ↑ (18,33) No Effect (22,23)	↓ (9,27,30,32)	-	↓ (11,30) No Effect (28)	↓ (32)
DOP-R	↑ (4,24)	↓ (10,14,15,20,24) ↑ (21) No Effect (7,13)	↓ (21,24) ↑ (22,23,25)	↓ (9, 12)	-	↓ (11,28,29)	-
KOP-R	↓ (5)	↓ (46) ↑ (16)	↓ (19,23) No Effect (22)	↓ (26, 27)	-	No Effect (17)	↑ (17)
NOP-R	↓ (42)	No Effect (33,38)	↑ (35, 45) ↓ (33,34,35,37,38,40,45)	-	↓ (32,37,41) No Effect (37)	-	↓ (32, 34, 39, 41)
SIG-R	-	↓ (44)	-	↓ (43)	↑ (31)	↓ (44)	-

Table 1. The roles of opioid receptors in ethanol consumption and seeking in rats and mice. 1. Roberts et al., 2000; 2. Hall et al., 2001; 3. Becker et al., 2002; 4. Roberts et al., 2001; 5. Kovacs et al., 2005; 6. Critcher et al., 1983; 7. Stromberg et al., 1998a; 8. Gardell et al., 1996; 9. Hyytia & Kiianmaa, 2001; 10. Franck et al., 1998; 11. Ciccocioppo et al., 2002a; 12. June et al., 1999; 13. Ingman et al., 2003; 14. Krishnan-Sarin et al., 1995a; 15. Krishnan-Sarin et al., 1995b; 16. Mitchell et al., 2005; 17. Holter et al., 2000; 18. Reid & Hunter, 1984; 19. Lindholm et al., 2001. 20. Nielsen et al., 2008; 21. Margolis et al., 2008; 22. Barson et al., 2009; 23. Barson et al., 2010; 24. van Rijn & Whistler, 2009; 25. van Rijn et al., 2010; 26. Walker et al., 2011 ; 27. Walker & Koob, 2008; 28. Marinelli et al., 2009; 29. Nielsen et al., 2011; 30. Le et al., 1999; 31. Sabino et al., 2011; 32. Kuzmin et al., 2007; 33. Ciccocioppo et al., 2007; 34. Ciccocioppo et al., 2003; 35. Ciccocioppo et al., 1999; 36. Simms et al., 2008; 37. Economidou et al., 2008; 38. Ciccocioppo et al., 2002b. 39. Martin-Fardon et al., 2000; 40. Cifani et al., 2006 41. Ciccocioppo et al., 2004; 42. Sakoori & Murphy, 2008; 43. Sabino et al., 2009a; 44. Sabino et al., 2009b; 45. Economidou et al., 2006; 46. Sandi et al., 1990.; 47. Stromberg et al., 2002; 48. Stromberg et al., 1998b.

### 3.4 DOP-R antagonists in high drinking rats

DOP-R antagonists reduce ethanol consumption in high-ethanol consuming or alcohol-preferring strains of rats (Hyytia & Kiianmaa, 2001; Krishnan-Sarin et al., 1995a; Krishnan-Sarin et al., 1995b; Nielsen et al., 2008). In studies using alcohol-preferring (P) rats, the DOP-R antagonists naltrindole, ICI 174864 and naltriben all effectively reduced ethanol consumption using the two-bottle choice 10% ethanol paradigm (Krishnan-Sarin et al., 1995a; Krishnan-Sarin et al., 1995b). Naltrindole given systemically in the maximally effective dose (15 mg/kg) produced a long-lasting reduction in ethanol intake for at least 8 h following a single dose and for at least 28 h following a second dose given 4 h later (Krishnan-Sarin et al., 1995a). Although the effects of naltrindole were selective for ethanol over water intake, naltrindole also suppressed the intake of saccharin solutions either with or without ethanol (Krishnan-Sarin et al., 1995a). In comparison, another study by the same group showed that systemic administration of the DOP-R2-selective antagonist, naltriben, (6 mg/kg in two doses) reduced ethanol consumption but not water consumption (Krishnan-Sarin et al., 1995b). Furthermore, it was shown that naltriben reduced the intake of solutions containing ethanol with saccharin and ethanol with quinine but did not affect the intake of either saccharin or quinine solutions alone. Taken together, this suggests that the suppressive effects of naltriben are selective for ethanol. In high-drinking AA (Alko, Alcohol) rats trained to operantly respond for 10% ethanol, intracerebroventricular (i.c.v.) administration of naltrindole, but not the MOP-R antagonist, CTOP, produced a significant and dose-dependent suppression of responding for ethanol (Hyytia & Kiianmaa, 2001). Furthermore, both naltrindole and CTOP suppressed responding in non-ethanol preferring Wistar rats suggesting that the DOP-R may play a greater role than the MOP-R in suppressing responding in high drinking rats, regardless of strain. This is further supported by other studies using models of low to moderate ethanol or limited access paradigms in which DOP-R antagonists do not reduce ethanol consumption (Ingman et al., 2003; Margolis et al., 2008; Stromberg et al., 1998a).

The recent recharacterization of a rat model of voluntary high ethanol intake using intermittent access to 20% ethanol without the use of any initiation procedures (Simms et al., 2008; Wise, 1973) has led to the investigation of the roles of opioid receptors and effects of opioid ligands in high-ethanol consuming, albeit non-ethanol preferring, rats. Using this model of high ethanol intake, the naltrexone-derived DOP-R antagonist, SoRI-9409, was shown to be threefold more effective and selective in reducing ethanol intake than naltrexone in Long-Evans rats (Nielsen et al., 2008). SoRI-9409 more potently reduced high ethanol intake using the model of intermittent access to 20% ethanol compared to less potent reductions in moderate ethanol intake using a model of continuous access to 10% ethanol. The effects of single doses of SoRI-9409 were long-lasting such that reductions in high ethanol intake were observed after 24 h of access, in comparison to naltrexone which was only effective after short access periods (30 min). The effects of SoRI-9409, unlike naltrexone, were also selective for ethanol such that water intake was not reduced. Furthermore, SoRI-9409 did not reduce sucrose intake at doses that effectively reduced ethanol intake. Using the high drinking model of intermittent access to 20% ethanol, daily systemic administrations of SoRI-9409 to Long Evans rats for 28 days selectively reduced the onset and escalation of ethanol intake and continued to selectively reduce ethanol intake by > 50%

for up to 28 days compared with vehicle-treated rats (Nielsen et al., 2008). When the daily administrations of SoRI-9409 were ceased after 28 days, ethanol consumption was maintained at approximately one-half of the baseline drinking levels of post-vehicle-treated rats, for a further 28 days. Cessation of SoRI-9409 treatment did not result in any significant escalation in ethanol consumption suggesting that multiple administrations of SoRI-9409 produce long-lasting and permanent effects on the modulation of ethanol consumption. This further suggests that inhibition of DOP-Rs directly reduces ethanol intake during the escalation and maintenance of drinking in high-ethanol-consuming rats.

### 3.5 DOP-R antagonists in models of relapse to ethanol-seeking

A major problem in treating AUDs is the high rate of relapse, which can be triggered by re-exposure to cues or an environment previously associated with alcohol use and also by stress. An effective pharmacological treatment for AUDs would ideally prevent relapse of alcohol-seeking in addition to reducing consumption of ethanol. Naltrexone reduces alcohol- and cue-induced reinstatement, but not foot-shock stress-induced reinstatement of ethanol-seeking in rodents (Ciccocioppo et al., 2002a; Le et al., 1999; Liu & Weiss, 2002). It has been shown that DOP-Rs, rather than MOP-Rs, are important for cue-induced reinstatement of ethanol-seeking, as the DOP-R antagonist, naltrindole, reduces cue-induced reinstatement of ethanol-seeking behavior in rodents more effectively than the MOP-R selective antagonists, naloxonazine or CTOP (Ciccocioppo et al., 2002a; Marinelli et al., 2009). Furthermore, recent studies show that the DOP-R antagonist, SoRI-9409, effectively and dose-dependently reduces yohimbine stress-induced reinstatement of ethanol-seeking in rats (Nielsen et al., 2011). This study further demonstrated that the DOP-R plays a greater role than MOP-R or KOP-R in yohimbine stress-induced reinstatement of ethanol-seeking in rats as TAN67- and Deltorphin II-mediated DOP-R activity, using the [<sup>35</sup>S]GTP $\gamma$ S coupling assay in midbrain membranes, were increased in membranes of yohimbine-treated ethanol-extinguished rats compared to vehicle-treated rats. Moreover, the increase in DOP-R-mediated [<sup>35</sup>S] GTP $\gamma$ S stimulation observed in yohimbine-treated ethanol-trained rats was absent in naive (non ethanol-trained) rats, suggesting that a history of ethanol self-administration plays an important role in the regulation of DOP-R signaling. In contrast with DOP-R activity, there were no changes in DAMGO-mediated MOP-R or (-)U50488-mediated KOP-R activity in ethanol-trained rats, further supporting studies showing DOP-Rs rather than MOP-Rs are important for reinstatement of ethanol-seeking (Ciccocioppo et al., 2002a; Marinelli et al., 2009).

### 3.6 DOP-R subtypes in ethanol consumption and seeking

Although one DOP-R gene has been cloned (Evans et al., 1992; Kieffer et al., 1992), two DOP-R subtypes, DOP-R1 and DOP-R2, have been pharmacologically identified *in vivo* and in binding studies in rodent brain membranes (Buzas et al., 1994; Mattia et al., 1991; Negri et al., 1991; Sofuoglu et al., 1991; Zaki et al., 1996). However, the roles of DOP-R subtypes in ethanol-mediated behaviors are not well defined. Studies in mice suggest DOP-R1 and DOP-R2 may have opposing effects on voluntary ethanol intake (van Rijn & Whistler, 2009) such that the DOP-R1 agonist, TAN67, and the DOP-R2 antagonist, naltriben, both reduce ethanol consumption. These different roles of DOP-R1 and DOP-R2 on ethanol intake are



hypothesized as DOP-R1 existing as a MOP-R/DOP-R heterodimer which opposes the actions of DOP-R2, which may exist as a DOP-R homomer (van Rijn & Whistler, 2009). Another recent study showed that DOP-R1 inhibition appears more important than DOP-R2 inhibition in yohimbine stress-induced reinstatement of ethanol-seeking in rats (Nielsen et al., 2011). Using the [<sup>35</sup>S]GTP $\gamma$ S signaling assay in midbrain membranes prepared from yohimbine-treated rats previously responding for ethanol and subsequently extinguished, there was higher TAN67-mediated DOP-R1 activity (> 700-fold) than deltorphin II-mediated DOP-R2 activity ( $\geq$  4-fold) compared to vehicle-treated rats (Nielsen et al., 2011). Pre-treatment with the DOP-R antagonist, SoRI-9409, in yohimbine-treated rats reduced DOP-R1 activity by 37-fold, but did not change DOP-R2, MOP-R or KOP-R activity. The potent inhibition of TAN67-stimulated DOP-R1 activity in yohimbine-treated rat membranes by SoRI-9409, naltrindole and the DOP-R1 antagonist, 7-Benzylidenenaltrexone (BNTX) (Sofuoglu et al., 1993), further suggests that DOP-R1 inhibition is important for reducing yohimbine-induced ethanol-seeking (Nielsen et al., 2011). As SoRI-9409 effectively reduces ethanol consumption in rats and potently reduces DOP-R1 activity in brain membranes of high-ethanol consuming rats (Nielsen et al., 2008), DOP-R1 inhibition appears to play a role in both reducing reinstatement of ethanol-seeking and voluntary ethanol intake in rats. However, as SoRI-9409 inhibits both deltorphin II-mediated DOP-R2 analgesia and DPDPE-mediated DOP-R1 analgesia in mice (Wells et al., 2001), it appears that the subtypes of the DOP-R have different roles in different behaviors and species.

### 3.7 The role of the DOP-R in the rewarding effects of ethanol

The DOP-R has been shown to play a role in the reinforcing effects of ethanol (Borg & Taylor, 1997; Froehlich et al., 1998; Froehlich et al., 1991; Shippenberg et al., 2008). Activation of DOP-Rs in the NAc and VTA leads to increased basal dopamine release (Borg & Taylor, 1997; Devine et al., 1993b; Herz, 1997; Vetulani, 2001). Dopamine release in the striatum is stimulated by ethanol, DOP-R agonists and enkephalinase inhibitors (Dourmap et al., 1990; Petit et al., 1986; Spanagel et al., 1990) and ethanol-induced release of dopamine in the striatum is blocked by DOP-R antagonists (Acquas et al., 1993; Widdowson & Holman, 1992). DOP-R agonists increase and DOP-R antagonists decrease, respectively, ethanol-induced place preference in rats (Bie et al., 2009; Matsuzawa et al., 1999a; Matsuzawa et al., 1999b) and DOP-R antagonists can make a nonaversive dose of alcohol aversive (Froehlich et al., 1998). A series of studies demonstrated that the DOP-R plays a role in conditioned place preference (CPP) to ethanol using a model of conditioned fear stress (Matsuzawa et al., 1998; Matsuzawa et al., 1999a; Matsuzawa et al., 1999b). In this model, ethanol produced a significant CPP only in rats that were exposed to an environment previously paired with an electric foot shock (Matsuzawa et al., 1998; Matsuzawa et al., 1999a; Matsuzawa et al., 1999b). Significant CPP to ethanol (300 mg/kg, intraperitoneal (i.p.) in rats was attenuated following systemic administration of the non-selective opioid receptor antagonist naloxone (1-3 mg/kg, subcutaneous (s.c.)), the MOP-R antagonist beta-funaltrexamine (3-10 mg/kg, i.p.), the DOP-R antagonist naltrindole (1-3 mg/kg, s.c.) and the KOP-R agonist, U50488 (0.3-1 mg/kg, s.c.) (Matsuzawa et al., 1998; Matsuzawa et al., 1999a). This is in contrast to enhanced place preference to ethanol following systemic administration of the KOP-R antagonist, nor-binaltorphimine (nor-BNI; 3 mg/kg, i.p.) (Matsuzawa et al., 1999a).

Conversely, when ethanol (75-150 mg/kg) was combined with the MOP-R-preferring agonist, morphine (0.1 mg/kg), or the selective DOP-R agonist, TAN-67 (20 mg/kg, s.c.), at doses below the threshold to produce place preference on their own, there was an enhancement of place preference to ethanol (Matsuzawa et al., 1998; Matsuzawa et al., 1999a). Furthermore, naltrindole (3 mg/kg, s.c.) significantly attenuated the enhancement of the ethanol-induced (75 mg/kg, i.p) place preference produced by TAN67 (20 mg/kg, s.c.) suggesting DOP-R receptors may be involved in the rewarding mechanism of ethanol under psychological stress (Matsuzawa et al., 1999b). The attenuation of CPP to ethanol and increased conditioned taste aversion to ethanol by the DOP-R antagonist, naltrindole (Froehlich et al., 1998; Matsuzawa et al., 1998; Matsuzawa et al., 1999a; Matsuzawa et al., 1999b) may contribute, at least in part, to the reductions in ethanol consumption following administration of DOP-R antagonists (Hyytia & Kiianmaa, 2001; Krishnan-Sarin et al., 1995a; Krishnan-Sarin et al., 1995b; Nielsen et al., 2008). However, whether enhanced CPP to ethanol following treatment with TAN67 would explain the effects of DOP-R agonists on ethanol consumption and seeking is unclear. An increase in the rewarding actions of ethanol by TAN67 may subsequently lead to reduced consumption (van Rijn & Whistler, 2009) as less ethanol may be required to produce ethanol's effects. Conversely, activation of DOP-Rs and the subsequent increased rewarding effects of ethanol may have contributed to further increased levels of ethanol consumption following treatment with DOP-R agonists (Barson et al., 2009; Barson et al., 2010; van Rijn et al., 2010). Collectively, these studies suggest that activation and inhibition of DOP-R activity may modulate ethanol consumption via different mechanisms in the central nervous system.

#### **4. The role of the Kappa Opioid Peptide Receptor (KOP-R) in ethanol consumption and seeking**

##### **4.1 Ethanol consumption in KOP-R knockout mice**

Mice with a genetic deletion of the KOP-R (mixed C57BL/6-129SvJ background) have reduced levels of ethanol intake in animals consuming 12% ethanol and saccharin using a two-bottle choice paradigm (Kovacs et al., 2005) (Table 1). In contrast to the MOP-R and DOP-R, stimulation of the KOP-R is associated with dysphoria, suppression of reward, induced states of aversion, reduced dopamine release in the NAc, inhibition of dopaminergic neurons in the VTA and promotion of negative reinforcement (Bruijnzeel, 2009; Ebner et al., 2010; Margolis et al., 2003; Shippenberg & Herz, 1986).

##### **4.2 KOP-R activation and ethanol consumption**

Systemic administration of the KOP-R agonist, U50488, reduces intake of 10% ethanol using two-bottle choice paradigms (Lindholm et al., 2001; Nestby et al., 1999) (Table 1). Furthermore, administration of the KOP-R agonists, dynorphin1-17 or MR-2266-BS, prior to the first free-choice session following a period of forced ethanol exposure reduced preference for ethanol (Sandi et al., 1988; Sandi et al., 1990). The long-acting benzomorphan opioid compound, bremazocine, which acts as an antagonist at MOP-R and DOP-R and an agonist at KOP-R, was shown to more potently reduce 10% ethanol intake than the non-selective opioid antagonist, naltrexone (Nestby et al., 1999). However, as KOP-R agonists

produce aversion, this may lead to reductions in ethanol consumption but this remains to be studied. The KOP-R agonist, U69593, produces conditioned place aversion (CPA) in animals (Shippenberg & Herz, 1986) and KOP-R agonists induce dysphoria in humans (Kumor et al., 1986; Pfeiffer et al., 1986; Rimoy et al., 1994). In contrast, the KOP-R agonist, enadoline (or CI-977), when delivered via mini-osmotic subcutaneous pumps increased 10 and 20% ethanol consumption (Holter et al., 2000). However, in rats responding for ethanol for long periods, the lever pressing for ethanol was either decreased or increased following acute systemic administration of higher or lower doses of enadoline, respectively (Holter et al., 2000). As lever pressing for water was also reduced with enadoline treatment, these reductions in responding for ethanol may have been due to sedative effects of this treatment at higher doses.

### **4.3 KOP-R antagonists and ethanol consumption and seeking**

A number of studies have shown mixed results for the selective KOP-R antagonist, nor-BNI using a variety of models of ethanol consumption and seeking (Table 1). In rats given continuous access to 10% ethanol using the two-bottle choice paradigm, a single systemic injection of nor-BNI induced a long-lasting increase in ethanol consumption, particularly in higher drinking rats without inducing CPP (Mitchell et al., 2005). However, nor-BNI has been shown to increase ethanol-induced place preference in rats (Matsuzawa et al., 1999a). In rhesus monkeys responding for solutions of 1-2% ethanol, nor-BNI reduced responding for ethanol on the day of the systemic injection (Williams & Woods, 1998). nor-BNI has low affinity for the MOP-R at 2 h post-injection time point and high affinity for the KOP-R up to 24 h post-injection (Broadbear et al., 1994; Endoh et al., 1992; Horan et al., 1992) suggesting the reductions in ethanol responding on the day of nor-BNI dosing may be MOP-R mediated. In Wistar rats responding for 10% ethanol, nor-BNI has been shown to be more effective in a rat model of ethanol-dependence, using a 4-week intermittent vapor exposure paradigm, compared to non-ethanol dependent rats (Walker & Koob, 2008). Although i.c.v. administration of nor-BNI given immediately before the testing session reduced responding for ethanol in dependent rats (Walker & Koob, 2008), further studies performed with systemically administered nor-BNI given 24 h before the test session similarly reduced responding in ethanol-dependent rats but not in non-dependent rats (Walker et al., 2011). These studies suggest that the dynorphin/KOP-R systems are dysregulated in dependence and contribute to the increased consumption observed during acute withdrawal in dependent rats. Systemic administration of nalmefene, which has similar affinity for MOP-R but higher affinity for KOP-R and DOP-R, compared to naltrexone (Michel et al., 1985), was found to more effectively reduce responding for ethanol in dependent rats than naltrexone (Walker and Koob, 2008). As nalmefene and naltrexone had similar effects on reducing responding in non-dependent rats, this further supports a specific role of the KOP-R in ethanol-dependence (Walker & Koob, 2008).

### **5. Nociceptin/Orphanin FQ Receptors (NOP-R) and ethanol consumption and seeking**

A number of studies have investigated the role of the nociceptin receptor (NOP-R), also known as the opioid receptor-like 1 receptor (ORL1), using the endogenous ligand for the NOP-R, nociceptin/orphanin FQ. Although nociceptin has structural homology with opioid peptides, it does not bind to MOP-R, DOP-R or KOP-R (Reinscheid et al., 1996;

Reinscheid et al., 1998) and appears to possess anti-opioid functional activity (Mogil et al., 1996a; Mogil et al., 1996b; Mogil & Pasternak, 2001). Opioid antagonists, such as naloxone and naltrexone, are not reported to have activity at the NOP-R (Ciccocioppo et al., 2007; Darland et al., 1998; Henderson & McKnight, 1997), although indirect interactions between NOP-R and the classical opioid receptors have been suggested (Yu et al., 2002). In mice with a genetic deletion of the NOP-R ethanol consumption was reduced and ethanol-induced CPP was increased compared to wild-type mice (Koster et al., 1999; Sakoori & Murphy, 2008). However, activation of the NOP-R, using NOP-R agonists including nociceptin and R0-64-6198, have consistently shown reductions in ethanol intake and ethanol CPP (Ciccocioppo et al., 2003; Ciccocioppo et al., 2007; Ciccocioppo et al., 1999; Ciccocioppo et al., 2002b; Economidou et al., 2006; Kuzmin et al., 2007). In addition, NOP-R agonists have been shown to increase food intake (Cifani et al., 2006). In contrast, the effects of NOP-R antagonists administered alone to rats have not resulted in altered ethanol consumption and seeking. The results of these studies are summarized in Table 1 and have been previously reviewed (Ciccocioppo et al., 2000; Ciccocioppo et al., 2003).

## 6. Sigma Receptors and ethanol consumption

Sigma receptors (SIG-R) were originally categorized as members of the opioid receptor family (Quirion et al., 1992) although more recent studies suggested SIG-Rs are unique binding sites including phencyclidine binding sites (Gundlach et al., 1985; Gundlach et al., 1986; Martin et al., 1976; Walker et al., 1990). Furthermore, the opioid antagonist, naltrexone, is not reported to have activity at the SIG-R (Holtzman, 1989; Vaupel, 1983).

The SIG-Rs antagonist, BD1047, reduces ethanol-induced locomotion, ethanol-induced place preference and taste conditioning in Swiss mice (Maurice et al., 2003). Conversely, the SIG-R agonist, PRE-084, increased ethanol CPP without effects on ethanol-induced locomotion (Maurice et al., 2003). A series of studies have shown the SIG-R to play a role in ethanol consumption and seeking in Sardinian alcohol-preferring (sP) rats (Sabino et al., 2011; Sabino et al., 2009a; Sabino et al., 2009b) (Table 1). Administration of the SIG-R antagonists, BD1063 NE-100, selectively reduces ethanol consumption, responding for ethanol and also prevents the increase in ethanol intake after an ethanol-deprivation period in rats (Sabino et al., 2009b). Chronic administration of the SIG-R agonist, DTG, increased responding for ethanol in rats, an effect that was blocked with BD-1063 pretreatment (Sabino et al., 2011). However, DTG treatment also increased responding for saccharin and sucrose (Sabino et al., 2011). Chronic administration of DTG to naive rats resulted in increased mRNA expression of MOP-R and DOP-R, but not KOP-R, in the VTA (Sabino et al., 2011). This increased opioid mRNA expression was suggested to be responsible for the excessive alcohol intake following DTG treatment, in agreement with previous studies reporting the importance of DOP-R activity in maintaining high ethanol intake in alcohol-preferring rats (Froehlich et al., 1991) and the roles of MOP-R and DOP-R activation on VTA-mediated dopamine release (Devine et al., 1993b).

## 7. Brain-region specific roles of opioid receptors in ethanol consumption and seeking

The mesolimbic dopamine system plays a key role in mediating the reinforcing properties of ethanol and other drugs of abuse (Herz, 1997). Moreover, ethanol reinforcement and high

alcohol drinking behavior have been suggested to involve the ethanol-induced activation of endogenous opioid systems (Froehlich et al., 1991). Ethanol may alter opioidergic transmission at different levels, including opioid peptide biosynthesis and release, as well as binding to opioid receptors. Ethanol stimulates the activity of the endogenous opioids for MOP-R ( $\beta$ -endorphins) and DOP-R (enkephalins) leading to an enhanced release of dopamine in the mesolimbic pathway (Herz, 1997). Activation of MOP-R in the VTA leads to dopamine release in the NAc (Leone et al., 1991; Spanagel et al., 1992), however modulation of dopamine terminal activity is also reported to involve DOP-R (Borg & Taylor, 1997; Widdowson & Holman, 1992).

### **7.1 Brain-region specific activity of DOP-R with ethanol consumption**

Studies have shown that ethanol differentially alters opioid receptor binding in brain tissue and neuroblastoma cell lines depending on the conditions of study (Charness et al., 1993; Charness et al., 1986). Rat brain membranes treated with ethanol show inhibited enkephalin and DOP-R binding (Hiller et al., 1981). However, treatment of DOP-R-expressing neuroblastoma x glioma NG108-15 hybrid cells with ethanol (200 mM for 4 days or 25 mM for 2 weeks) results in increased DOP-R gene expression and increases in DOP-R binding sites (Charness et al., 1993; Charness et al., 1986), which was hypothesized to be due to a neuronal adaption to ethanol involving changes in receptor density. The discrepancies in ethanol responses in these studies may be explained by differences in ethanol doses and route of administration, time of exposure to the drug, time elapsed after ethanol administration at the moment the experiment was carried out, and receptor ligand used. A series of studies have demonstrated that an acute injection of ethanol given to rats results in altered DOP-R binding affinity, mRNA expression and release of enkephalins (Mendez et al., 2010; Mendez & Morales-Mulia, 2006; Mendez et al., 2004)(Table 2). The most consistent changes in DOP-R activity following acute ethanol treatment have been increased binding and met-enkephalin release, but not content, in mesocorticolimbic and nigrostriatal pathways (Mendez et al., 2010; Mendez et al., 2004). A number of studies have shown that rats given chronic or long-term access to ethanol have altered DOP-R activity in mesocorticolimbic and nigrostriatal pathways (Table 3). Long-term ethanol exposure in rats has been shown to increase DOP-R binding and supersensitivity of striatal DOP-Rs which has been suggested to be due to decreased endogenous peptide release (Lucchi et al., 1985; Lucchi et al., 1984). In comparison, the effects of long-term ethanol treatment in mice have been less consistent. CF-1 mice given ethanol for 5 days had an intermediate DOP-R binding site compared to a high and a low affinity DOP-R binding site in control mice (Hynes et al., 1983). Higher enkephalin degrading enzyme activity was detected in the striatum of alcohol preferring C57/BL6 mice compared to the alcohol-avoiding DBA/2 mice (Winkler et al., 1998). However, enkephalin degrading enzyme activity was reduced in the hypothalamus, but not the striatum, following long-term ethanol treatment and ethanol withdrawal (Winkler et al., 1998). Furthermore, a higher density of DOP-Rs was found in the VTA and NAc of C57/BL6 mice compared to DBA/2 mice (Moller et al., 2002).

### **7.2 Brain region-specific effects on ethanol consumption by DOP-R ligands**

The different effects on ethanol consumption by cerebral injections of the DOP-R agonists, DPDPE and DALA, (Barson et al., 2009; Barson et al., 2010; Margolis et al., 2008) suggest that

DOP-Rs in specific brain regions have different roles in ethanol consumption and seeking. This is further supported by the increased ethanol consumption observed following administration of the DOP-R antagonist, TIPP-Ψ, into the VTA (Margolis et al., 2008) compared to reduced responding for ethanol following administration of naltrindole, given either systemically (Krishnan-Sarin et al., 1995a) or microinjected into the cerebroventricles, the NAc and basolateral amygdala (BLA), but not into the VTA (Hyytia & Kiiänmaa, 2001). Furthermore, the reductions in ethanol consumption following administration of DOP-R antagonists into the cerebroventricles, the NAc and BLA are consistent with the reductions in ethanol consumption following systemic administration of DOP-R antagonists (Franck et al., 1998; Hyytia & Kiiänmaa, 2001; June et al., 1999; Krishnan-Sarin et al., 1995b; Marinelli et al., 2009; Nielsen et al., 2008).

Strain	Model	Assay	Brain tissue	Effect on DOP-R	Reference
Wistar rats	Acute ethanol 2.5 g/kg, i.p.	[3H]DPDPE autoradiography	Substantia nigra, Frontal cortex Prefrontal cortex Nucleus accumbens shell Nucleus accumbens core caudate putamen (anterior-medial) caudate putamen (medial-posterior) caudate putamen (posterior)	Increased Increased Increased Increased Increased Increased Reduced	Mendez et al., 2004
Wistar rats	Acute ethanol 2.5 g/kg, i.p.	Pro-enkephalin mRNA expression by in situ hybridization and densitometry	VTA Prefrontal cortex Nucleus accumbens shell Nucleus accumbens core	Reduced Increased Increased Increased	Mendez & Morales-Mulia, 2006
Wistar rats	Acute ethanol treatment 0.5, 1, 2.5 g/kg i.p.	Microdialysis/radioimmunoassay of Met-enkephalin release and content	Nucleus accumbens Caudate Putamen Prefrontal cortex	Increased release Reduced content; Reduced content No change	Mendez et al., 2010

Table 2. Table of DOP-R activity in brain regions following acute ethanol treatment in rats.

### 8. Preclinical considerations of targeting the DOP-R for the treatment of AUDs

In view of the potential development of opioid-receptor selectively acting compounds for the treatment of AUDs, it is important to consider adverse effects associated with opioid receptor activity. A number of adverse effects have been reported with the use of the non-

Species/strain	Model	Assay	Brain tissue	Effect on DOP-R	Effect on MOP-R	Reference
Sprague-Dawley rats	6.5% ethanol (v/v) for 3 weeks	[ <sup>3</sup> H]DADLE and [ <sup>3</sup> H]dihydromorphine binding	Whole minus cerebellum	Increased	Increased	Sommer et al., 2001
Wistar rats	1-6% ethanol for 4 weeks	[ <sup>3</sup> H]H-Tyr-Tic psi[CH <sub>2</sub> -NH]Phe-Phe-OH and [ <sup>3</sup> H]ile5,6deltorphin b [ <sup>3</sup> H]Tyr-D-Ala-Gly-MePhe-Gly-ol binding	Striatum Nucleus Accumbens	No change No change	Reduced Reduced	Turchan et al., 1999
Sprague-Dawley rats	1-6.7% ethanol (v/v) for 16 days	[ <sup>35</sup> S]GTPγS binding	Hippocampal Dentate gyrus Hippocampal CA1 Inferior colliculus Cerebellum Superior colliculus Medial frontal cortex Caudate nucleus Nucleus accumbens	Reduced Reduced Reduced Reduced No change No change No change No change	Reduced Reduced Reduced No change Reduced No change No change No change	Saland et al., 2004
Sprague-Dawley rats	1-6.7% ethanol (v/v) for 16 days	Immunohistochemical staining	Hippocampal CA1 Hippocampal CA3 Hippocampal Dentate gyrus Cerebral cortex Midbrain colliculi Inferior colliculi Striatum Nucleus accumbens	Increased No change No change No change No change No change No change No change	No change Reduced No change Reduced Reduced Reduced Reduced Reduced	Saland et al., 2005
Sprague-Dawley rats	6% ethanol for 6 weeks	[ <sup>3</sup> H]DADLE [ <sup>3</sup> H]etorphin [ <sup>3</sup> H]met-enkephalin [ <sup>3</sup> H]dihydromorphine binding	Striatum	Increased	Reduced	Lucchi et al., 1985; Lucchi et al., 1984
Sprague-Dawley rats	6% ethanol for 6 weeks	Enkephalin release	Striatum	Reduced	-	Lucchi et al., 1984
Fisher 344 rats	1-5% ethanol for 70 days and 24 h withdrawal	[ <sup>35</sup> S]GTPγS binding	Spinal cord	No change	Reduced	Morley et al., 1985
Sprague-Dawley rats	3 weeks of access to 15% ethanol (forced)	[ <sup>3</sup> H]DADLE, [ <sup>3</sup> H]dihydromorphine binding	Forebrain containing striatum	Increase	No change	Moller et al., 1999

Table 3. Table of DOP-R and MOP-R activity in brain regions following long-term ethanol consumption in rats.

selective opioid antagonists (naloxone, naltrexone and methylnaltrexone) in both preclinical (Brown & Holtzman, 1979; Holtzman, 1979; Yuan et al., 2009a; Yuan et al., 2009b) and clinical studies (Bertino et al., 1991; Spiegel et al., 1987; Sternbach et al., 1982; Yeomans & Gray, 1996; Yeomans & Gray, 1997). In humans, naltrexone has neuropsychiatric side effects including anxiety, chills, dizziness, drowsiness, depression, headache, irritability, nervousness and insomnia (Oncken et al., 2001). Furthermore, gastrointestinal side effects associated with naltrexone treatment include appetite loss, constipation, diarrhea, nausea, vomiting and stomach pain/cramps (Oncken et al., 2001). High doses of naltrexone are also associated with hepatotoxicity (Mitchell et al., 1987). Preclinical testing of compounds utilize a number of animal behavioral models to test for adverse effects including effects on nonselective consummatory behavior (self-administration of sugar solutions, food, fat, water), anxiety (elevated plus maze), pain perception (tail-flick, hotplate, paw pressure, von Frey tests), abuse potential (conditioned place preference/aversion), depression (forced swim, learned helplessness), seizure thresholds, (scored observations of clonic movements and catalepsy-like behaviors), and sedation (rotarod and righting reflex tests). Using both opioid receptor knockout mice and opioid receptor subtypes-selective compounds, the roles of opioid receptors in the development of these adverse effects have been investigated in a number of studies. Compounds with affinity for the DOP-R have been tested for adverse effects using a number of these behavioral methods.

### 8.1 Selective effects on ethanol and general consummatory behaviors

A pharmacotherapeutic for the treatment of AUDs would ideally have selective activity on alcohol consumption and seeking over general consummatory behaviors such as food and fluid intake. Preclinical studies show that naltrexone reduces fat, sucrose and water consumption (Corwin & Wojnicki, 2009; Nielsen et al., 2008; Rao et al., 2008; Wong et al., 2009). Similarly, preclinical studies have shown reduced food intake and weight loss with the opioid antagonists, naloxone (Brown & Holtzman, 1979; Holtzman, 1979; Yuan et al., 2009a; Yuan et al., 2009b) and methylnaltrexone (Yuan et al., 2009a; Yuan et al., 2009b). Conversely, preclinical studies have shown that the MOP-R agonist, morphine, increases both ethanol and food intake (Barson et al., 2009) and the selective MOP-R agonist, DAMGO, increases intake of saccharin, salt, fat and ethanol (de Wet et al., 2001; Tatsuo et al., 1999). Clinical studies have reported that naltrexone treatment leads to reduced food intake and weight loss (Atkinson et al., 1985; Bertino et al., 1991; Spiegel et al., 1987; Sternbach et al., 1982; Yeomans & Gray, 1996; Yeomans & Gray, 1997), although the effects of naltrexone on the eating behavior of obese subjects have been less consistent with reports of either reductions (Spiegel et al., 1987) or no effects on food intake and body weight (Atkinson, 1987; Atkinson et al., 1985; Maggio et al., 1985; Malcolm et al., 1985). Conversely, studies in humans have found that treatment with an opioid agonist with highest affinity for the MOP-R, such as methadone and butorphanol, results in increased food intake and weight gain (Atkinson, 1987; Levine & Atkinson, 1987). Taken together, these studies suggest that the MOP-R plays a more general role in ingestive behaviors.

Activation of the KOP-R has been suggested to affect taste responses due to a non-selective aversive action which could explain changes in levels of ethanol intake (Kovacs et al., 2005). KOP-R knockout mice have a reduced preference for saccharin solutions and a greater



preference for quinine solutions (Kovacs et al., 2005). Unlike ligands with highest activity for the MOP-R (such as naltrexone), KOP-R, NOP-R and SIG-R, the ligands which have selective for DOP-R appear to have greater selectivity for ethanol consumption with reduced activity on general consummatory behavior, such as food, sugar or water consumption (Barson et al., 2009; Barson et al., 2010; Froehlich et al., 1991; Krishnan-Sarin et al., 1995b). Central administration of naltrexone, nor-BNI and  $\beta$ -funaltrexamine, but not naltrindole, reduces intake of sucrose solutions in rats (Beczowska et al., 1992; Koch et al., 1995). Furthermore, central administration of naltrexone, naloxonazine and nor-BNI, but not naltrindole or the DOP-R agonist DALCE, reduces fat intake in food-deprived rats (Koch & Bodnar, 1994). The enkephalinase inhibitor, thiorphan, increased ethanol, but not water, intake in alcohol-preferring rats (Froehlich et al., 1991). Central administration of the DOP-R agonist, DALA, to rats selectively increased ethanol consumption over food and water in comparison to non-selective actions on ethanol intake by the MOP-R agonists, DAMGO and morphine (Barson et al., 2009; Barson et al., 2010). The naltrexone-derived DOP-R antagonist, SoRI-9409, was shown to be much more effective and selective in reducing ethanol consumption than naltrexone such that, unlike naltrexone, SoRI-9409 did not reduce water intake and did not reduce sucrose intake in doses that effectively reduced ethanol intake (Nielsen et al., 2008). Although one study found that the DOP-R antagonist, naltrindole, reduced ethanol and saccharin, but not water, consumption in rats (Krishnan-Sarin et al., 1995a), further studies by these same researchers showed that the DOP-R antagonist, naltriben, reduced the intake of solutions containing ethanol with saccharin and ethanol with quinine but no effects on the intake of either saccharin or quinine solutions alone (Krishnan-Sarin et al., 1995b). Taken together, these studies suggest that compounds with activity at the DOP-R selectively alter ethanol intake over general consummatory behavior.

## 8.2 Anxiety and stress

A major problem in treating AUDs is the high rate of relapse which is usually triggered by stress and anxiety (Sinha, 2007; Sinha & Li, 2007). Recent preclinical studies have suggested that potential new pharmacotherapies for AUDs act by reducing anxiety and cravings in alcohol-dependent subjects (George et al., 2008; Heilig et al., 2010). Treatment options to control stress and anxiety disorders include benzodiazepines, which carry the risk of abuse potential, and antidepressants, which demonstrate a relative large interindividual variability in terms of drug response (O'Brien, 2005; Tiwari et al., 2009). Studies investigating the roles of opioid receptors in anxiety and stress indicate that the DOP-R plays a significant role. DOP-R knockout mice have increased anxiety (Filliol et al., 2000). In comparison, rats administered the DOP-R agonist, SNC80 have increased anxiolytic activity, an effect that is reversed by naltrindole (Perrine et al., 2006; Saitoh et al., 2004). Naltrindole was found to have anxiogenic activity when given in higher, but not lower doses (Perrine et al., 2006; Saitoh et al., 2004) although the DOP-R antagonist, SoRI-9409 has neither anxiogenic nor anxiolytic activity (Nielsen et al., 2008). In contrast,  $\beta$ -funaltrexamine and nor-BNI did not produce any anxiogenic or anxiolytic effects, suggesting the MOP-R and KOP-R do not play a role in anxiety states (Saitoh et al., 2004). Following the forced swim test, plasma levels of the stress hormone, corticosterone are the same, in triple opioid receptor knockout (MOP-R, DOP-R, KOP-R) knockout and wild-type mice (Contet et al., 2006). This suggests that opioid

receptors are not involved in the hormonal stress response. However, other studies have shown that rats housed in a stressful environment were more sensitive to the sedative effects of the DOP-R agonist, SNC80, compared to stimulant effects by SNC80 in rats that were not stressed (Pohorecky et al., 1999). In contrast, plasma corticosterone levels were increased in rats following acute intracerebral administration of the DOP-R agonists DPDPE and DADLE (Gonzalvez et al., 1991; Iyengar et al., 1987). Increased plasma corticosterone levels were found in rats administered naltrindole but not in rats co-administered naltrindole and SNC80 (Saitoh et al., 2005) or rats administered SoRI-9409 (Nielsen et al., 2008). Furthermore, pre-treatment with SoRI-9409 decreased yohimbine stress-induced reinstatement of ethanol-seeking in rats but did not affect yohimbine-induced increases in plasma corticosterone (Nielsen et al., 2011).

### 8.3 Abuse potential

An issue with the use of pharmacotherapeutics for the treatment of addiction is the incidence of potential abuse of the therapeutic itself. For example, the MOP-R agonist methadone, which is used to treat heroin addiction, has been reported to be widely abused (Li et al., 2011; Simonsen et al., 2011a; Simonsen et al., 2011b; Tormoehlen et al., 2011). Although the use of “substitution” therapy with opioid agonists has been effective for some patients, it has remained controversial (Gerra et al., 2009; Ling et al., 1994; Rhodes & Grossman, 1997). However, as naltrexone induces aversive side-effects in humans and conditioned place aversion in rats (Mitchell et al., 2009), it does not appear to be rewarding itself. Furthermore, naltrexone attenuates the expression of ethanol place conditioning in mice (Middaugh & Bandy, 2000). MOP-R agonists increase and MOP-R antagonists decrease, respectively, ethanol-induced CPP in rats (Matsuzawa et al., 1998; Matsuzawa et al., 1999a; Matsuzawa et al., 1999b). In comparison, activation of the KOP-R is associated with general aversive activity in rats (Shippenberg & Herz, 1986) and induces dysphoria in humans (Kumor et al., 1986; Pfeiffer et al., 1986; Rimoy et al., 1994). The KOP-R agonist, U50488, attenuates ethanol-induced CPP in rats (Matsuzawa et al., 1999a). KOP-R agonists, therefore, do not appear to carry the risk of abuse potential. In comparison, KOP-R antagonists, such as nor-BNI do not produce CPP or CPA (Mitchell et al., 2005; Sante et al., 2000) although nor-BNI did increase ethanol-induced CPP in one study (Matsuzawa et al., 1999a).

As described earlier, DOP-R agonists increase and DOP-R antagonists attenuate, respectively, ethanol-induced CPP in rats (Bie et al., 2009; Matsuzawa et al., 1998; Matsuzawa et al., 1999a; Matsuzawa et al., 1999b) and DOP-R antagonists can make a nonaversive dose of alcohol aversive (Froehlich et al., 1998). DOP-R antagonists administered alone do not induce CPP or CPA (Nielsen et al., 2008) suggesting they are not rewarding themselves. The increase in the rewarding actions of ethanol by DOP-R agonists may contribute to the altered levels of ethanol consumption following treatment with DOP-R agonists, as described above (Barson et al., 2009; Barson et al., 2010; Margolis et al., 2008; van Rijn et al., 2010; van Rijn & Whistler, 2009). Furthermore, DOP-R (and MOP-R) agonists have been shown to be rewarding themselves such that DPDPE is self-administered into the VTA of rats (Devine & Wise, 1994; McBride et al., 1999). Activation of DOP-R (and MOP-R) leads to increased basal dopamine release in brain regions involved in the reward pathway

(Borg & Taylor, 1997; Devine et al., 1993a; Devine et al., 1993b; Herz, 1997; Vetulani, 2001). The DOP-R agonists, BW373U86 and SNC80, induce significant CPP in rats, effects of which are reversed by pretreatment with naltrindole given in doses which does not modify preference when given alone (Ehlers et al., 1999). Collectively, as DOP-R antagonists inhibit the actions of ethanol-induced endogenous opioids and subsequent dopamine release, and also reduce the rewarding effects of ethanol without being rewarding themselves, these compounds do not appear to be prone to potential abuse.

#### **8.4 Pain perception**

Hyperalgesia has been commonly noted following alcohol withdrawal in alcohol-dependent patients (Dina et al., 2008; Gatch, 2009; Jochum et al., 2010) and so analgesic medications may be prescribed to provide pain relief in the early stages of withdrawal (Gillman & Lichtigfeld, 1990). As naltrexone has been shown to block morphine-mediated analgesia in mice (Yan et al., 2003) and in rats (Nielsen et al., 2008), naltrexone treatment may therefore interfere with pain-relieving medications. Furthermore, as naltrexone can precipitate withdrawal symptoms in opioid-dependent rats (Adams & Holtzman, 1990) and monkeys (Paronis & Bergman, 2011), naltrexone treatment may potentially lead to exacerbation of withdrawal-induced hyperalgesia in alcohol-withdrawn patients. Although opioid receptor agonists with highest affinity for the MOP-R, such as morphine and methadone, have been widely used in the clinic for the treatment of pain (Nissen et al., 2001; Peng et al., 2008), preclinical studies have also demonstrated that KOP-R and DOP-R both play roles in analgesia. The administration of opioid agonists acting at the KOP-R (Leighton et al., 1988; Nielsen et al., 2007; Ross & Smith, 1997; Tiseo et al., 1988) and DOP-R (Kamei et al., 1994; Kamei et al., 1997; Scherrer et al., 2004) produce analgesia and anti-allodynia in rats and mice. Furthermore, co-administration of morphine with a KOP-R or a DOP-R agonist results in enhanced analgesia (Ross et al., 2000; Suzuki et al., 1995). A recent study showed that the DOP-R antagonist, SoRI-9409, does not reduce morphine-mediated tail-flick analgesia compared to the significant reduction in morphine-mediated analgesia by naltrexone (Nielsen et al., 2008). When administered alone, SoRI-9409, did not produce tail-flick analgesia or hyperalgesia (Nielsen et al., 2008) but did produce analgesia in the acetic acid writhing test in mice (Wells et al., 2001). Although DOP-R antagonists attenuate DOP-R agonist-mediated analgesia in mice (Kamei et al., 1995; Tseng et al., 1997), they do not block the analgesic effects of clinically used opioid analgesics (Nielsen et al., 2008).

#### **8.5 Seizure thresholds**

Seizures have commonly been observed following alcohol withdrawal in alcohol-dependent patients (Amato et al., 2011; Eyer et al., 2011a; Eyer et al., 2011b; Kim et al., 2011). Treatment options to control alcohol-withdrawal convulsions include carbamazepine, valproate and benzodiazepines (Amato et al., 2011; Eyer et al., 2011a) which all have a number of undesirable side-effects. A number of studies have indicated that activation of the DOP-R is associated with an increased incidence of convulsive activity. The DOP-R agonists, SNC80 and BW373U86, induce convulsions in mice (Broom et al., 2002b; Comer et al., 1993), rats (Broom et al., 2002a) and monkeys (Dykstra et al., 1993; Negus et al., 1994). The BW373U86-induced convulsant activity was reduced by

naltrindole, naltriben and 7-benzylidenenaltrexone, suggesting the convulsive activity by BW373U86 is DOP-R-mediated (Broom et al., 2002a; Broom et al., 2002b; Comer et al., 1993). Furthermore, the BW373U86-induced convulsive effects were reduced by naltrexone given in very high doses (10-100 mg/kg), doses of which would presumably block DOP-R (Comer et al., 1993). However, recent studies in the pursuit of the development of DOP-R agonists for the treatment of pain and depression have discovered new DOP-R agonists, such as KNT-127, which are devoid of convulsant activity, while still retaining analgesic and antidepressant activity (Saitoh et al., 2011). However, since inhibition of the DOP-R reduces the incidence of DOP-R agonist-induced convulsive activity, the use of DOP-R antagonists may also provide an additional benefit for alcohol-dependent patients to prevent seizures in the early stages of withdrawal.

## 9. Conclusions

Although naltrexone has the most consistent effects in reducing alcohol consumption, it only effectively prevents relapse in a subset of alcohol-dependent patients. Preclinical studies suggest that potential new therapeutics that target the DOP-R may offer advantages in the treatment and prevention of relapse compared with agents that have activity for the other opioid receptor subtypes. DOP-R agonists may offer advantages for the relief of ethanol withdrawal-induced anxiety and hyperalgesia. DOP-R antagonists appear to effectively and selectively reduce ethanol consumption and seeking with limited effects on general consummatory behavior. The particular effectiveness of DOP-R antagonists in models of high ethanol consumption and relapse to ethanol-seeking may represent an alternative therapeutic strategy for reducing heavy drinking and relapse to alcohol abuse. Furthermore, DOP-R antagonists do not appear to have any abuse potential, effects on pain perception or inductions of convulsive activity. Taken together, the DOP-R represents a very promising candidate therapeutic target for the treatment of alcohol use disorders.

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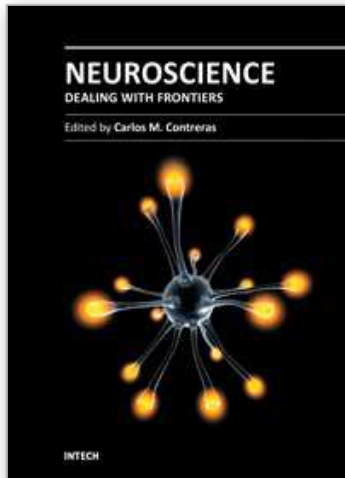
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## **Neuroscience - Dealing With Frontiers**

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The Neuronal Doctrine recently reached its 100th year and together with the development of psychopharmacology by the middle of 20th century promoted spectacular developments in the knowledge of the biological bases of behavior. The overwhelming amount of data accumulated, forced the division of neuroscience into several subdisciplines, but this division needs to dissolve in the 21st century and focus on specific processes that involve diverse methodological and theoretical approaches. The chapters contained in this book illustrate that neuroscience converges in the search for sound answers to several questions, including the pathways followed by cells, how individuals communicate with each other, inflammation, learning and memory, the development of drug dependence, and approaches to explaining the processes that underlie two highly incapacitating chronic degenerative illnesses.

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