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Delta Opioid Pharmacology in Relation to Alcohol Behaviors

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Abstract

Delta opioid receptors (DORs) are heavily involved in alcohol-mediated processes in the brain. In this chapter we provide an overview of studies investigating how alcohol directly impacts DOR pharmacology and of early studies indicating DOR modulation of alcohol behavior. We will offer a brief summary of the different animal species used in alcohol studies investigating DORs followed by a broader overview of the types of alcohol behaviors modulated by DORs. We will highlight a small set of studies investigating the relationship between alcohol and DORs in analgesia. We will then provide an anatomical overview linking DOR expression in specific brain regions to different alcohol behaviors. In this section, we will provide two models that try to explain how endogenous opioids acting at DORs may influence alcohol behaviors. Next, we will provide an overview of studies investigating certain new aspects of DOR pharmacology, including the formation of heteromers and biased signaling. Finally, we provide a short overview of the genetics of the DORs in relation to alcohol use disorders (AUDs) and a short statement on the potential of using DOR-based therapeutics for treatment of AUDs.

Keywords

Alcohol use disorder; Delta opioid receptor; Pharmacology; Behavioral models; Genetics; Medication development; Enkephalin

1 Direct Impact of Alcohol on Delta Opioid Receptor Pharmacology

Acute and chronic alcohol exposure can impact DOR pharmacology on several different levels: (1) by changes to endogenous opioid levels, (2) changes in DOR expression level, or (3) modifying affinity or potency of endogenous and exogenous ligands for DORs in particular brain regions. Acute alcohol exposure has been shown to reduce the affinity of DOR by various mechanisms. Hiller and Hoffman have demonstrated that alcohol and other aliphatic alcohols selectively inhibit the binding of enkephalins, the DOR preferring endogenous opioids, to DOR binding sites as observed by a reduction in the affinity or by an increase in the ligand's dissociation rate (Hiller et al. 1984; Hoffman et al. 1984). This reversible inhibition may result from the cell membrane perturbation by alcohols since the potency of inhibitory effect and the degree of membrane disorganization are correlated with the alcohol chain length (Hiller et al. 1984). Acute alcohol treatment also decreases the

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binding of the DOR agonist [^{3}H]DPDPE, agonist-stimulated [^{35}S]GTPγS binding, and rate of receptor internalization in brain tissue or in N18TG2 cells expressing mouse DOR (Khatami et al. 1987; Gomes et al. 2000; Tabakoff and Hoffman 1983). However, the effects of acute alcohol on DOR pharmacology may be more pronounced when directly administered to the tissue as brains from rats with prior exposure to a single dose of alcohol did not exhibit changes in DOR affinity (Jorgensen and Hole 1986).

While the effects of acute alcohol exposure may be detectable only in vitro, chronic alcohol exposure has been reported to modify DOR affinity and expression both in cell lines and in animal tissue. Chronic alcohol exposure in neuronal cell lines endogenously expressing DORs has been reported to increase DOR levels (Charness et al. 1983, 1986, 1993) in part due to increasing DOR mRNA levels (Charness et al. 1993; Jenab and Inturrisi 1994). Ex vivo, functional studies on brain tissue from chronic alcohol-exposed rats found decreased DOR agonist-stimulated [^{35}S]GTPγS binding in the alcohol-exposed rats compared to controls, possibly as a consequence of receptor internalization and phosphorylation (Saland et al. 2004). A small number of studies have reported minor changes in DOR affinity, expression, and/or functionality with chronic alcohol exposure (Lucchi et al. 1984, 1985; Sim-Selley et al. 2002). On the other hand, several studies found that chronic alcohol exposure increased DOR expression levels, either without affecting affinity (Rossi et al. 1988) or while slightly decreasing affinity (Hynes et al. 1983). In vivo experiments have also found evidence for increased expression of DORs after chronic alcohol exposure (van Rijn et al. 2012a; Bie et al. 2009). Some of the differential DOR expression in response to chronic alcohol exposure may be ascribed to different species, strains, or age of animals, specific brain regions studied, and alcohol intake paradigms (e.g., duration, dose/concentration used). Previous studies have shown that young rats express higher levels of DORs than older rats (Rossi et al. 1988; Nielsen et al. 2012a). The influence of stress, for example, stress induced by alcohol withdrawal (Becker 2012), may be another factor that can impact DOR expression in some of the animal models. It has been shown that stressful events can increase DOR expression (Margolis et al. 2011; Commons 2003; Nielsen et al. 2012b), whereas stress prior to alcohol consumption may prevent an increase in DOR affinity for DPDPE (Przewlocka and Lason 1990).

2 Initial Behavioral Evidence for a Role of Delta Opioid Receptors in Alcohol Use

Initial behavioral evidence for an interventional role of opioid receptors in alcohol use came from studies using the nonselective opioid receptor antagonists naloxone (Froehlich et al. 1991) and naltrexone (Le et al. 1993). In order to identify which of the opioid receptor subtypes is involved in alcohol consumption, various groups have tested antagonists selective for different subtypes of opioid receptor. Beta-funaltrexamine, an irreversible mu-opioid receptor (MOR) antagonist, did not decrease alcohol consumption at a dose previously shown to antagonize various effects of morphine (Le et al. 1993). On the other hand, selective DOR antagonists, ICI 174,864 and naltrindole, did reduce voluntary alcohol consumption (Le et al. 1993). ICI 174,864 is a peptide and thus susceptible to endogenous proteases (Cotton et al. 1984), whereas naltrindole is a nonpeptide small molecule, which

has a longer period of effectiveness in vivo (Portoghese et al. 1988, 1990). Naltrindole also has greater potency, selectivity, and binding affinity for DOR than ICI 174,864 (Portoghese et al. 1990) and is therefore more commonly used as a tool to study DOR pharmacology. However, naltrindole has been reported to decrease saccharin intake as well as alcohol consumption, suggesting that intake of sweet solutions may also release endogenous opioids (Krishnan-Sarin et al. 1995a). Studies using the enkephalinase inhibitor thiorphan provided another line of support for a role of DORs in alcohol intake. Thiorphan, by enhancing endogenous activation of DORS through their ability to increase enkephalin tone, can elevate alcohol intake in rats (Froehlich et al. 1991). To better understand the mechanism of action behind the opioid modulation of alcohol intake, Widdowson and Holman looked at alcohol's effect on dopamine release in the brain. Basal dopamine release from striatal slices is dose-dependently increased in the presence of DOR agonist. Bath application of alcohol onto the striatal slices raised the dopamine level in a dose-dependent manner. This effect is reversible by the use of the DOR antagonist ICI 174,864, linking this response to DORs (Widdowson and Holman 1992).

Additional data supporting a role for DORs in alcohol consumption came from studies performed by de Waele et al. (1996, 1997) using a portacaval anastomosis (PCA) model in rats. In this model, a cirrhosis-like state was induced using portal-systemic shunts causing portal-systemic encephalopathy (de Waele et al. 1996). PCA rats exhibited enhanced voluntary alcohol consumption compared to sham controls, and PCA rats also had a reported increased density of DORs in the nucleus accumbens (de Waele et al. 1996). These increases in alcohol consumption due to PCA are also reversible by the use of naloxone (de Waele et al. 1997).

3 Use of Preclinical Animal Models to Study the Role of Delta Opioid Receptors in Alcohol Use Disorders

Delta opioid receptors form a novel target to treat AUDs. In order to develop novel DOR therapeutics, DOR-selective ligands need to be tested in preclinical animal models. To properly interpret results of DOR modulation of alcohol behaviors in animal models, it is important to understand pharmacological differences and similarities between the animal species used. The species most commonly used in preclinical studies are mice, rats, and primates. Reports have identified modulation of alcohol behaviors in all three species by DOR-selective drugs. Additionally, certain strains of mice and rats are known to prefer alcohol more than other substrains (Belknap et al. 1993; Yoneyama et al. 2008; Simms et al. 2008). Several research groups have selectively bred mice and rats to either prefer or not prefer alcohol including high- and low-alcohol-preferring (HAP, LAP) mice (Grahame et al. 1999), Finnish Alko alcohol and non-alcohol (AA, ANA) rats (Eriksson 1968), high- and low-alcohol-drinking (HAD, LAD) rats (Li et al. 1993), and Sardinian alcohol-preferring and alcohol-non-preferring (sP, sNP) rats (Fadda et al. 1989). Opioid and enkephalin expressions can differ within these species (Nylander et al. 1994). Alcohol-preferring C57BL/6 mice show higher DOR expression in brain regions mediating drug reward compared to low-alcohol-preferring DBA/2 mice (de Waele and Gianoulakis 1997). The more alcohol-preferring C57BL/6J mice expressed met-enkephalin at lower levels than the

less alcohol-preferring C57BL/N mice (Blum et al. 1982). This may in part be due to increased enkephalinase activity in C57BL/6 mice (George et al. 1991). It is important to note that several studies using selectively bred alcohol-preferring AA rats did not find DOR antagonists (naltrindole, Me2-Dmt-Tic-OH, and ICI 174,864) to decrease alcohol intake (Hyytia 1993; Honkanen et al. 1996; Ingman et al. 2003). Only two studies were identified that have investigated DOR modulation of alcohol behaviors in primates. A study in rhesus monkeys (Williams and Woods 1998) did not find that naltrindole modulated alcohol intake. In squirrel monkeys MOR agonists were found to be more effective than DOR agonists in attenuating the discriminative stimulus of alcohol, although the DOR agonist SNC80 was able to increase the discriminative stimulus effects of low-to-intermediate doses of alcohol (Platt and Bano 2011).

4 Delta Opioid Receptor Modulation of Alcohol Behaviors

There are many facets to what constitutes as well as what causes AUDs. In order to understand the therapeutic potential of a drug target in the treatment of AUDs, it is important to model these different aspects of alcohol use. The therapeutic potential of DORs has been studied in a diverse set of alcohol paradigms, which we will try to summarize here.

4.1 Volitional Alcohol Intake

Alcohol use in rodents is frequently studied using a two-bottle choice paradigm, in which mice or rats are given a choice between water and alcohol with a certain percentage, usually in the range of 1–20%, for a specified period of time per day. Frequently these studies are performed under a reversed light cycle to enable the animals to drink the alcohol during their active cycle (drink in the dark, DiD paradigm). It has been shown that DOR antagonists like ICI 174,864, naltrindole and naltriben, and SoRI-9409 can reduce voluntary alcohol intake in these models (Krishnan-Sarin et al. 1995a, b; Franck et al. 1998; Nielsen et al. 2008; Henderson-Redmond and Czachowski 2014). In a similar mouse model, the DOR agonist TAN-67 has also been reported to decrease alcohol intake (van Rijn and Whistler 2009), whereas the DOR agonist SNC80 increased alcohol consumption (van Rijn et al. 2010). Some studies however report not finding that naltrindole significantly decreases volitional alcohol intake in rodents (van Rijn and Whistler 2009; Stromberg et al. 1998). This may be due to differences in endogenous opioid tone based on the age, genetic background, and alcohol history of the animals tested. For example, naltrindole was found to decrease alcohol intake when, during alcohol exposure, no water is available (Kim et al. 2000).

4.2 Taste Aversion

The bitter taste of alcohol can serve as a deterrent for alcohol use. Behavioral models exist that measure palatability of alcohol using a taste-reactivity test in which animals are monitored for their physical response when they come in contact with alcohol. Relatively high dose of naltrindole can cause alcohol taste aversion and reduce alcohol intake in rats (Higley and Kiefer 2006; Froehlich et al. 1998). However, it remains to be seen whether naltrindole-induced taste aversion would be a viable strategy to promote alcohol cessation considering the high dose necessary to accomplish this effect.

4.3 Alcohol Uptake and Metabolism

Delta opioid receptor agonists were not shown to interfere with alcohol uptake from the stomach or modify alcohol metabolism (van Rijn and Whistler 2009; Chiang et al. 2016).

4.4 Loss of Righting Reflex

High doses of alcohol will cause sedation. In rats microinjections of the DOR antagonist ICI 174,864 in the periaqueductal gray (PAG), nucleus accumbens (NAcc), and septum decreased alcohol-induced loss of righting reflex, suggesting a role for endogenous opioids in alcohol-induced sedation (Widdowson 1987).

4.5 Behavioral Sensitization

Repeated use of drugs of abuse and alcohol can cause behavioral sensitization, i.e., a stronger behavioral response compared with that observed during the first exposure. Repeated alcohol exposure can lead to sensitized alcohol-induced locomotion. Several studies have shown that this type of behavioral sensitization can be blocked by a MOR but not a DOR antagonist (Arias et al. 2010; Pastor and Aragon 2006; Pastor et al. 2005).

4.6 Motivated Responding for Alcohol

In animals trained to lever press for alcohol, naltrindole did not reduce responding on the alcohol-paired lever in mice (Middaugh et al. 2000), rats (Spanagel 1996), or monkeys (Williams and Woods 1998). However, in infant rats or alcohol-preferring rats, the DOR antagonists (naltrindole or naltriben) can decrease alcohol responding (Henderson-Redmond and Czachowski 2014; Hyytia and Kiianmaa 2001; June et al. 1999; Miranda-Morales et al. 2012). These results again highlight how experimental factors can affect the ability to observe DOR modulation of alcohol behaviors.

4.7 Conditioned Place Preference

Alcohol, at nonsedating doses, can cause release of dopamine from dopaminergic ventral tegmental area (VTA) neurons. This dopamine is thought to valuate alcohol as a pleasurable and rewarding substance worth seeking (Mirenowicz and Schultz 1996; Brodie et al. 1999; Bromberg-Martin et al. 2010). A commonly used paradigm to study the rewarding properties of drugs is the conditioned place preference (CPP) test (Tzschentke 1998). In rats the expression of alcohol-induced CPP could also be blocked by naltrindole (Gibula-Bruzda et al. 2015). In C57BL/6 mice the expression of alcohol CPP can be blocked by the DOR agonist SNC80 but can be slightly enhanced by another DOR agonist TAN-67 (van Rijn et al. 2012b). This corresponds with earlier findings showing that SNC80 increases but TAN-67 decreases alcohol consumption (van Rijn and Whistler 2009; van Rijn et al. 2010). Van Rijn et al. (2010) proposed that, by reducing the rewarding effects of alcohol, mice treated with SNC80 will need to drink more alcohol to obtain the same rewarding effects they would normally obtain when drinking alcohol. Not only can DOR agonists modulate alcohol CPP, alcohol exposure can also impact CPP of DOR agonists. Mitchell et al. found that rats exposed to alcohol, but not alcohol-naïve rats, displayed conditioned place preference to the DOR2 agonist deltorphin II (2014). It has been shown that stress (induced by foot shock) increases the rewarding properties of alcohol, which can be blocked by

naltrindole, suggesting the involvement of endogenous enkephalins. In this paradigm TAN-67 enhanced stress-induced alcohol place preference (Matsuzawa et al. 1998, 1999), consistent with the finding that TAN-67 enhances alcohol CPP (van Rijn et al. 2012b).

4.8 Reinstatement of Alcohol-Seeking Behavior

Like other types of drug addiction, alcoholism is characterized as a chronic relapsing condition. One method of studying alcohol relapse is to train mice to self-administer alcohol followed by a period of abstinence and then use either drugs, stress, or contextual cues to reinstate alcohol-seeking behavior. In this paradigm the DOR antagonists naltrindole and SoRI-9409 were able to inhibit drug seeking in rats (Nielsen et al. 2012b; Ciccocioppo et al. 2002; Marinelli et al. 2009). Reinstatement can also be measured in a CPP paradigm. A study by Gibula-Bruzda et al. found that the enkephalin derivative cUENK6 (cyclo[Nε, Nbeta-carbonyl-D-Lys2,Dap5] enkephalinamide) could reinstate alcohol CPP in a naltrindole reversible manner (2015).

4.9 Alcohol Withdrawal-Induced Seizures

One of the well-known consequences of alcohol withdrawal is the occurrence of potentially life-threatening seizures (Becker et al. 1997; McKeon et al. 2008). Even though both DOR agonists (van Rijn and Whistler 2009; van Rijn et al. 2010, 2012b, 2013) and DOR antagonists (Nielsen et al. 2008, 2012b; Krishnan-Sarin et al. 1995a, b; June et al. 1999) are considered possible options for reducing alcohol use, a potential limiting side effect of some DOR agonists is that they can produce seizures in naïve animals (Broom et al. 2002a, b; Dykstra et al. 1993; Jutkiewicz et al. 2006; Negus et al. 1998; Yajima et al. 2000). However, this is not the case for all DOR agonists (Naidu et al. 2007; Saitoh et al. 2011). It is thus more encouraging than surprising that certain DOR agonists are able to reduce alcohol withdrawal-induced audiogenic seizures (Kotlinska and Langwinski 1986). Given that enkephalin levels are decreased during alcohol withdrawal (Borg et al. 1982), the use of DOR agonists to prevent alcohol withdrawal-induced seizures can be considered a form of replacement therapy.

5 Impact of Alcohol Use and Withdrawal on Delta Opioid Receptor-Mediated Analgesia

Certain doses of alcohol produce analgesia (Woodrow and Eltherington 1988), potentially through the release of endogenous opioids. Indeed alcohol-induced thermal analgesia can be blocked by opioid receptor subtype-selective antagonists (Campbell et al. 2007). Additionally, alcohol exposure can modulate opioid-induced antinociception. For example, chronic but not acute alcohol consumption decreases thermal analgesic potency of MOR (morphine) and DOR (DSLET) agonists without changes in opioid receptor expression or affinity in both brain and spinal cord (Shah et al. 1997).

Recent studies have revealed that, under naïve conditions, DORs are selectively expressed in nonpeptidergic pain circuits that regulate mechanical sensitivity, whereas MORs are localized in peptidergic pain circuits that process thermal nociception (Scherrer et al. 2009). Van Rijn and coworkers have illustrated that chronic alcohol may increase DOR cell surface

expression in the spinal cord neurons modulating thermal pain (van Rijn et al. 2012a). The newly translocated DORs could potentially modulate MOR analgesia by forming a DOR-MOR heteromeric complex (van Rijn et al. 2012a; Milan-Lobo et al. 2013; He et al. 2011) or potentially by competing for downstream mediators or by synergistic cross talk (Overland et al. 2009; Rowan et al. 2014). Given that alcohol dependence and alcohol withdrawal can induce a state of hyperalgesia (Egli et al. 2012; Dina et al. 2008; Gatch 2009; Jochum et al. 2010) and upregulate DOR cell surface expressions, DORs may serve as a promising target to treat hyperalgesia caused by alcoholic neuropathy or alcohol withdrawal. Yet, surprisingly few studies have investigated the role of opioid receptors in the mechanism by which alcohol dependence modulates analgesia. Further investigations are thus needed to understand how DORs and other opioid receptor subtypes impact the dynamic process of alcohol modulation of pain states.

6 Neuroanatomical Analysis of Delta Opioid Receptor-Induced Modulation of Alcohol Behaviors

The dopaminergic neurons in the VTA play a central role in the mechanism of action of drugs of abuse and alcohol (Pierce and Kumaresan 2006; Koob and Volkow 2010). VTA dopaminergic neurons project to the NAcc, striatum, prefrontal cortex, hypothalamus, amygdala, and hippocampus (Fields et al. 2007). Studies using autoradiography and in situ hybridization or using a transgenic DOR receptor linked to a green fluorescent protein (DOR-eGFP) have provided evidence that DORs are expressed in these important brain areas (de Waele and Gianoulakis 1997; Dilts and Kalivas 1990; Goodman et al. 1980; Codd et al. 2010; Kitchen et al. 1995; Mansour et al. 1987; Blackburn et al. 1988; Shivers et al. 1986; Harlan et al. 1987; Le Moine et al. 1994; Mansour et al. 1994; Erbs et al. 2015). Different studies have investigated the role of DORs on alcohol behaviors in each of these brain regions. Here we summarize the unique functions of DORs in these brain regions in relation to alcohol behaviors (Fig. 1).

6.1 Ventral Tegmental Area

Opioid receptors located on presynaptic GABA terminals in the VTA are well known for their ability to disinhibit dopaminergic neurons upon activation (Fields et al. 2007; Fields and Margolis 2015). It is known that rats will lever press to receive intra-VTA infusions of not only morphine and other MOR agonists but also DOR agonists (Devine and Wise 1994). This indicates that DORs, like MORs, play a role in drug reinforcement of opioid self-administration. Interesting evidence of DOR function modulating dopamine release from VTA neurons came from a study investigating the use of acupuncture in alcohol withdrawal. Alcohol withdrawal increases the excitability of the VTA GABA neurons (Zhao 2008), which can be reduced by acupuncture in rats in a naltrindole reversible manner (Yang et al. 2010), suggesting that acupuncture releases DOR-selective endogenous opioids in the VTA. Studies by the Fields group have provided important insight into the role of DORs in alcohol consumption. Margolis et al. found that low-alcohol-drinking rats exhibited stronger DOR inhibition of $GABA_A$ signaling in VTA slices. In these low-alcohol-drinking rats, intra-VTA injection of a DOR agonist decreased alcohol intake, whereas injection of the DOR antagonist TIPP-ψ significantly increased alcohol intake in low but not in high-alcohol-

drinking rats (Margolis et al. 2008). This result could explain how microinjection of naltrindole in the VTA of alcohol-preferring rats and high-alcohol-drinking Wistar rats did not affect alcohol intake (Hyytia and Kiianmaa 2001). It appears that rats that are more anxious, more stressed, and/or more intoxicated by alcohol express higher levels of DORs in the VTA (Margolis et al. 2011; Mitchell et al. 2012). It remains uncertain how translatable the findings of an association between DOR expression and stress levels in alcohol-consuming rodents are to humans as results from PET study using the DOR radiotracer in alcohol-dependent patients found no correlation between [^{11}C] methyl-naltrindole-binding potential and cortisol or adrenocorticotropin (Wand et al. 2013).

6.2 Nucleus Accumbens

The nucleus accumbens plays a critical role in processes of drug reinforcement and stress (Marinelli et al. 2005). Mesolimbic dopamine projections connecting the VTA with the NAcc also play a facilitatory role in alcohol self-administration. The DOR agonist deltorphin II directly infused into the NAcc has been shown to mimic the effect of alcohol-induced dopamine release (Acquas et al. 1993). This effect can be inhibited by using naltrindole, suggesting that endogenous opioids are involved and that DORs are locally expressed on the terminals of dopaminergic neurons, as previously suggested by Borg and Taylor (Borg and Taylor 1997). Microinjection of naltrindole into the NAcc also decreases alcohol responding in alcohol-preferring Wistar rats (Hyytia and Kiianmaa 2001). Several studies have reported that DOR and enkephalin expressions are lower in the NAcc of alcohol-preferring animals compared to alcohol-non-preferring subjects (Soini et al. 1998; Fadda et al. 1999; Strother et al. 2001). However, alcohol exposure can increase pro-enkephalin (Mendez and Morales-Mulia 2006) and enkephalin mRNA levels in the NAcc of the alcohol-preferring but not of the alcohol-non-preferring animals (Nylander et al. 1994; Marinelli et al. 2005; Mendez et al. 2010; Li et al. 1998). Despite release of endogenous opioids upon alcohol use, Turchan found no changes in DOR expression in the NAcc and striatum after access to 1–6% alcohol over a 1-month period (Turchan et al. 1999). It seems that genotype has a substantial influence on whether or not alcohol exposure increases endogenous opioid levels in the NAcc and whether those endogenous opioids will impact DOR expression levels or can be effectively blocked by a DOR antagonist to modulate alcohol responding.

6.3 Striatum

Already early on, DORs in the striatum were identified to modulate dopamine release (Dourmap et al. 1990; Petit et al. 1986). These striatal DORS are involved in the dynamic interplay between alcohol and the delta opioidergic system. For example, acute alcohol can increase met-enkephalin levels in the striatum (Seizinger et al. 1983; Schulz et al. 1980). Prolonged alcohol exposure on the other hand decreases met-enkephalin levels in the striatum of rats (Seizinger et al. 1983; Schulz et al. 1980), but will return to baseline after withdrawal (Schulz et al. 1980). However, in mice, relatively short access to 7% alcohol did not have a large effect on DOR expression or activity in the striatum (Shen et al. 1997). Still, in rats, endogenous opioids acting on DORs in the striatum are suggested to increase alcohol intake. For example, microinfusions of naltrindole into the dorsal striatum inhibit alcohol intake in Long-Evans rats, whereas microinjection of the DOR agonist SNC80 increases alcohol intake (Nielsen et al. 2012a). While striatopallidal neurons are known to contain

enkephalins, naltrindole injection into the ventral pallidum did not affect alcohol intake in AA rats (Kemppainen et al. 2012).

6.4 Hypothalamus

The paraventricular nucleus (PVN) of the hypothalamus plays a coordinating role with regard to neuroendocrine responses. The PVN neurons are involved in stress management and appetitive behavior and are innervated by enkephalinergic fibers (Beaulieu et al. 1996). It has been shown that dietary fat releases endogenous opioids in the PVN (Chang et al. 2007a). Alcohol similarly increases enkephalin levels in the PVN (Chang et al. 2007b). In an apparent positive feedback loop, direct microinjection of the DOR agonist DALA in the PVN increases alcohol intake (Barson et al. 2010). The actions of this feedback loop were also apparent by findings showing that ingestion of a fatty meal can increase alcohol intake (Carrillo et al. 2004). Interestingly, microinjection of DALA in the perifornical lateral hypothalamus decreases alcohol intake. This may be caused by local inhibition of orexin function in the perifornical lateral hypothalamus that indirectly controls opioid action in other brain areas (Chen et al. 2013).

6.5 Amygdala

The amygdala is important for processing fearful as well as rewarding stimuli (Koob and Volkow 2010; Janak and Tye 2015). Studies have revealed that in the absence of DORs, alcohol increases $GABA_A$ inhibitory postsynaptic currents (IPSCs) in the central amygdala. This effect could also be mimicked using a DOR antagonist (Kang-Park et al. 2007). These results suggest that in wild-type mice, alcohol causes release of endogenous enkephalins in the central amygdala that block GABA release by acting on inhibitory coupled DORs. On the other hand, the DOR agonist DPDPE could decrease GABA IPSCs (Kang-Park et al. 2007). Interestingly, functional DORs in the central amygdala are only detectable in alcohol-exposed, but not naı¨ve, rats (Bie et al. 2009). This may be an underlying reason why microinjection of naltrindole in the amygdala of alcohol-preferring Wistar rats can decrease alcohol responding (Hyytia and Kiianmaa 2001). Micro-injection of naltrindole into the central amygdala could also decrease alcohol-conditioned place preference in rats (Bie et al. 2009), highlighting the important role of DORs in reward processing in the amygdala of alcohol-dependent subjects.

7 Role of Enkephalins and Endogenous Opioids on Delta Opioid Receptor Modulation of Alcohol Use

Endogenous opioids are thought to play an important role in the development of AUDs. Two hypotheses exist describe the association between endogenous opioids and alcohol use. The “opioid compensation hypothesis of alcoholism” presumes that subsequent alcohol intake can compensate a lack of endorphinergic activity during alcohol withdrawal (Ulm et al. 1995). The second hypothesis which we will call the “opioid reward hypothesis of alcoholism” proposes that alcohol-increased release of endogenous opioids in response to alcohol can enhance dopamine release in the NAcc by disinhibiting dopaminergic neurons (Cowen and Lawrence 1999).

7.1 The "Opioid Compensation Hypothesis of Alcoholism"

This hypothesis is supported by evidence showing that intracerebroventricular injection of met-enkephalin into rat brains decreases alcohol consumption (Ho and Rossi 1982). Additionally, increased enkephalinase activity is associated with increased alcohol consumption (George et al. 1991). Chronic alcohol consumption seems to decrease levels of met-enkephalin in the striatum of Sprague-Dawley rats (Lucchi et al. 1984; Nylander et al. 1994; Cowen and Lawrence 1999). Lower levels of met-enkephalin in the nucleus accumbens (NAcc) and lower levels of leu-enkephalin in the VTA have been observed in alcohol-preferring AA rats and C57BL/6J mice relative to alcohol-avoiding ANA rats and C57BL/6N mice (Nylander et al. 1994; Blum et al. 1982). Alcohol has been shown to elevate levels of met-enkephalin in these rats, which may, in turn, regulate its reinforcement (Nylander et al. 1994). The mRNA expression of preproenkephalin in the striatum and NAcc of alcohol-preferring FH rats has also been demonstrated to be lower than that of alcohol-non-preferring WKY rats (Cowen et al. 1998).

7.2 The "Opioid Reward Hypothesis of Alcoholism"

This hypothesis is supported by the fact that medications used to manage alcohol dependence such as the nonselective opioid antagonist Revia® (naltrexone) block the effects of endogenous opioids released by alcohol intake (Benjamin et al. 1993; Gonzales and Weiss 1998; Zalewska-Kaszubska et al. 2006; Zalewska-Kaszubska et al. 2008). The selective DOR antagonists naltrindole and naltriben, which block endogenous opioids binding to DORs, have been reported to decrease alcohol consumption (Krishnan-Sarin et al. 1995a, b; van Rijn and Whistler 2009). Concor-dantly, elevated endogenous enkephalin tone using the enkephalinase inhibitor thiorphan (Froehlich et al. 1991), microinjection of enkephalin analogues into mesolimbic and hypothalamic regions (Barson et al. 2009, 2010), or microinjection of SNC80 in rat striatum (Nielsen et al. 2012a) increases alcohol consumption. It has been suggested that alcohol-induced endogenous opioid peptide release may counteract the aversive effects of alcohol and ultimately lead to high alcohol drinking (Froehlich et al. 1991).

7.3 Potential Reasons for the Bidirectional Effect of Enkephalins on Alcohol Behaviors

It appears that the role of the endogenous opioid system in alcohol reward is still not unequivocally understood. Interpretation of studies investigating the role of the endogenous opioid system in alcohol behaviors may be complicated by anxiety (Mitchell et al. 2012; Roberts et al. 2001) or stress (Pohorecky et al. 1999) mechanisms, dissimilar distribution patterns of enkephalins in the brain (Lugo et al. 2006), or a joint action of enkephalins and beta-endorphin (Tseng et al. 2013). The DORs have been implicated in modulating anxiety-like behavior; for example, DOR KO mice are reported to have enhanced anxiety-like behavior relative to wild-type mice (Filliol et al. 2000), and DOR agonists can reduce anxiety-like behavior (van Rijn et al. 2010; Saitoh et al. 2013). The anxiety-like response in DOR KO mice can be reversed by the self-administered alcohol (Roberts et al. 2001). The increased anxiety-like state of the DOR KO mice could be a major reason why DOR KO mice show increased alcohol intake and alcohol self-administration (van Rijn and Whistler 2009; Roberts et al. 2001), a result which would not have been predicted based on the

observed decrease in alcohol intake by several DOR antagonists. In addition to anxiety, stress may also modulate DOR responses by potentiating the effect of DOR agonists (Pohorecky et al. 1999). Despite no changes in alcohol consumption or alcohol place preference between preproenkephalin knockout and wild-type mice (Koenig and Olive 2002), stress-induced alcohol intake was decreased in preproenkephalin knockout mice, suggesting the importance of stress in the interpretation of these results (Racz et al. 2008). Thus it may be difficult to dissociate the individual contribution of opioids, anxiety, stress, and dopamine from each other for their effect on the reinforcing effects of alcohol (Cowen and Lawrence 1999; Herz 1997). Furthermore, alcohol exposure does not unidirectionally alter enkephalin levels throughout the brain. Lugo et al. found that alcohol exposure increased met-enkephalin levels in the VTA, but decreased them in the central nucleus of the amygdala (2006). Moreover, even though the single enkephalin or endorphin knockout mice did not show altered alcohol CPP, mice lacking both enkephalins and beta-endorphin exhibited a decrease in alcohol-induced CPP when compared to wild-type controls, suggesting that alcohol may at least exert its rewarding action through a joint action of enkephalins and beta-endorphin (Tseng et al. 2013). These results are supported by data showing that only a high dose of naloxone that blocks both DORs and MORs attenuates alcohol CPP (Tseng et al. 2013).

8 Impact of Heteromerization and Biased Signaling of the Delta Opioid Receptor on Alcohol Use

Before the DOR was cloned, suggestions of the existence of two DOR subtypes had appeared based on differential behavioral responses of a set of DOR agonists and DOR antagonists. Responses that were induced by DPDPE and blocked by 7-benzylidenenaltrexone were labeled DOR1, whereas effects stemming from deltorphin II activation that could be blocked by naltriben were labeled DOR2. However, the pharmacology of these DOR subtypes has been difficult to reproduce in vitro and remains unclear (van Rijn et al. 2013). Still that hasn’t prevented researchers from investigating how these DOR subtype-selective compounds modulate alcohol behaviors. Initial studies showed that the DOR2-selective antagonist naltriben could reduce alcohol intake in rats (Krishnan-Sarin et al. 1995b) and in mice (van Rijn and Whistler 2009). Interestingly, there appears to be a dichotomy between DOR subtype-selective ligands and their ability to modulate alcohol intake as the DOR1 agonist reduces alcohol intake in mice (van Rijn and Whistler 2009). DOR1 and DOR2 modulate alcohol intake through different mechanisms as coadministration of naltriben and TAN-67 synergistically decreased alcohol intake (van Rijn and Whistler 2009). Margolis and coworkers found that the DOR1 agonist DPDPE when injected into the VTA decreased alcohol intake in rats (Margolis et al. 2008). Later, van Rijn et al. reported that the DOR-selective agonist SNC80 increased alcohol intake in mice and labeled this as a DOR2 response (van Rijn et al. 2010). This was confirmed by data showing that intra-striatal microinjection of SNC80 in rats led to an increase in alcohol consumption (Nielsen et al. 2012a). The opposing alcohol modulatory responses of TAN-67 and SNC80 were confirmed in alcohol CPP studies (van Rijn et al. 2012b). A similar distinction in DOR1 and DOR2 modulation of alcohol behavior came from a CPP study by Mitchell et al. showing that alcohol-exposed rats displayed CPP for the DOR2 agonist deltorphin II CPP,

but not the DOR1 agonist DPDPE when the drugs were injected directly into the VTA (Mitchell et al. 2014).

Three hypotheses, which are not necessarily mutually exclusive, have been proposed to explain the DOR subtypes: the “location hypothesis,” the “receptor hypothesis,” and the “drug hypothesis.” The “location hypothesis” originates from findings that in the VTA DOR1 actions are primarily presynaptic, whereas DOR2 effects are most likely both pre- and postsynaptic (Margolis et al. 2011). Moreover, Mitchell et al. have proposed that alcohol exposure can change expression and function of the presynaptic DORs with time (Mitchell et al. 2012).

The “receptor hypothesis” suggests that the existence of the DOR subtypes arises through receptor dimerization. More precisely DOR1 is a DOR-MOR heteromer, whereas DOR2 are DOR homomers. Transgenic studies using knockout animals revealed that the effects of TAN-67 on alcohol intake, but not those of naltriben, were abolished in MOR KO mice (van Rijn and Whistler 2009). Both compounds were ineffectual in DOR KO mice (van Rijn and Whistler 2009).

The “drug hypothesis” proposes that differences in ligand-induced signal trans-duction pathways underlie the differential responses of DOR agonists and antagonists. This hypothesis is based on the notion of biased G protein-coupled receptor signaling, where certain drugs may only activate G-proteins, while other drugs solely signal by recruiting beta-arrestins (McDonald et al. 2000; Miller and Lefkowitz 2001). A very recent publication has shown that there is a very strong correlation between the degree of beta-arrestin 2 recruitment and the ability of a DOR-selective drug to decrease or increase alcohol intake (Chiang et al. 2016). Chiang et al. proposed that SNC80 and drugs with similar chemical structures increase alcohol intake in mice because of their strong degree of beta-arrestin 2 recruitment. On the other hand, TAN-67 is a very weak recruiter of beta-arrestin 2 and decreases alcohol intake in a mechanism that is not beta-arrestin 2 dependent (Chiang et al. 2016), most likely G-protein mediated.

9 Genetic Variations in the Delta Opioid Receptor and Its Association with Alcohol Dependence

It has been well documented that certain mice strains consume more alcohol than others (Belknap et al. 1993; Yoneyama et al. 2008). Scientists have performed genetic studies aimed at finding genes that are associated with increased alcohol intake in hopes of translating these findings to human studies. For example, C57BL/ 6 mice more readily consume alcohol than DBA/2J mice (Belknap et al. 1993; Yoneyama et al. 2008). A study performing quantitative trait locus (QTL) analysis on these two strains of mice found that a QTL for taste aversion was, among several other genes on multiple chromosomes, in close proximity of the DOR gene (Risinger and Cunningham 1998). However, to our knowledge no studies have investigated if the DOR gene of C57BL/6 mice contains different single nucleotide polymorphisms (SNPs) than those found in DBA/2J mice. The rise of CRISPR technology would make it easier to change a C57BL/6 DOR SNP, if it were to exist, into the DBA/2J counterpart and vice versa and observe alcohol behaviors. Another study in mice

found that the C320T polymorphism (Ala107Val) in exon 2 of the DOR gene conferred higher alcohol preference to CT heterozygous mice compared to homozygous CC mice (Sacharczuk et al. 2014). The C320T SNP was more prevalent in mice selectively bred to experience limited swim stress-induced analgesia that tend to have lower opioid receptor system activity, but enhanced basal and stress-induced alcohol drinking (Sacharczuk et al. 2008), suggesting that the C320T SNP may be partially responsible for these phenotypical changes in behavior. Interestingly the Ala107Val mutation in the DOR changes the analgesic potency of the DOR agonist SNC80 (Sacharczuk et al. 2010). In humans a relatively common point mutation in the MOR gene (A118G/Asn40Asp) has been linked with affecting the effectiveness of Revia® (naltrexone) in treatment-seeking patients suffering from AUDs, although clinical evidence is not uniform (Gelernter et al. 2007; Oslin et al. 2003). Therefore, a number of genetic studies have investigated SNPs in the DOR and their relation to naltrexone efficacy, as well as their correlation with alcohol and substance use disorders. One study found a significant interaction between the DOR SNP (rs4654327) and naltrexone-induced reduction in alcohol craving and stimulatory effects (Ashenhurst et al. 2012). However other studies reported that alcohol-dependent males carrying one of three DOR SNPs (rs1042114, rs2234918, rs678849) did not significantly impact naltrexone therapeutic efficacy (Gelernter et al. 2007). Two of those SNPs (rs2234918, rs678849) also did not alter the therapeutic efficacy of the opioid antagonist nalmefene in heavy drinkers (Arias et al. 2008). A linkage study identified the DOR gene as a candidate gene for heavy alcohol use (Hansell et al. 2009). Indeed a couple of studies identified a specific haplotype (G/C/A/A/ C/T), consisting of six alleles (rs1042114, rs678849, rs2298896, rs12749204, rs2234918, rs204076) to be a potential risk factor for AUDs (Zhang et al. 2008) as well as haplotypes of DOR SNPs (rs2298896, rs12749204, rs2236857, rs421300) with MOR SNPs to associate with AUDs in European Americans (Li and Zhang 2013). However, most studies investigating SNPs in the DOR gene have not found significant associations with AUD. For example, the rs2234918 SNP which is a silent mutation (C921T/Gly307Gly) in the DOR gene was shown by two research groups not to be associated with increased alcohol dependence (Franke et al. 1999; el Loh et al. 2004). Another study investigating a population of European Americans found no positive association between 11 individual DOR SNPs and AUD (Zhang et al. 2008). Further studies that included several more DOR SNPs, as well as single-point mutations in the preproenkephalin gene, did not find genetic association with AUDs in large cohort of alcohol-dependent European Americans (Xuei et al. 2007). Despite the limited association between human DOR SNPs and AUDs, DOR SNPs (rs1042114, rs678849, rs2236857, and rs581111) and preproenkephalin SNPs (rs1437277, rs1975285, and rs2609997) have been associated with opioid/heroin and cocaine use disorders (Zhang et al. 2008; Xuei et al. 2007; Crist et al. 2013; Nelson et al. 2014).

10 Therapeutic Potential of DOR Agonists for Treatment of Alcohol Use Disorders

Alcohol, enkephalins, and DORs are dynamically linked making drugs that target DORs interesting therapeutics for treatment of AUDs. Interestingly both DOR antagonists and agonists are capable of decreasing alcohol intake. Yet, we hypothesize that “DOR1”-selective agonists like TAN-67 are the most suitable option for developing efficacious

therapy for alcohol dependence (van Rijn et al. 2013). In particular DOR agonists have anxiolytic-like, antidepressive-like, and antinociceptive properties (van Rijn et al. 2013; Pradhan et al. 2011), which would help reduce alcohol relapse (George et al. 2008; Heilig et al. 2010; Sinha and Li 2007). Whether TAN-67 is particularly effective because it has limited beta-arrestin2 efficacy (Chiang et al. 2016) or it can preferentially engage DOR-MOR heteromers (van Rijn and Whistler 2009), or both, remains under investigation. While certain DOR agonists may decrease seizure threshold (Broom et al. 2002a, b; Dykstra et al. 1993; Jutkiewicz et al. 2006; Negus et al. 1998; Yajima et al. 2000), several DOR agonists are available that have limited to no observable seizure activity at therapeutic dose (Naidu et al. 2007; Saitoh et al. 2011). Moreover, DOR agonists may have less abuse potential, based on several reports showing absence or limited place preference (van Rijn et al. 2012b; Mitchell et al. 2014; Suzuki et al. 1996).

The variability in alcohol behaviors observed with DOR agonists and antagonists is most likely due to the dynamic nature of the relationship between alcohol and the delta opioid system. In mouse and rat models, there appears to be important differences in DOR functionality depending on age, genotype, environmental factors (e.g., stress), and history of alcohol exposure. We believe there is a great potential for DOR-selective drugs to be beneficial in the treatment of AUDs. However, at this point in time, only a handful of studies have modulated DORs in primates to investigate the impact on alcohol behavior. Given the weak association of DOR SNPs with alcohol-dependent patients, it is crucial to perform more primate studies to obtain a better sense of the translatability of the rodent findings. In particular studies using primates with a history of alcohol use and/or in a subset of high-alcohol-drinking primates will be valuable additions to the current knowledge on DOR modulation of alcohol behavior.

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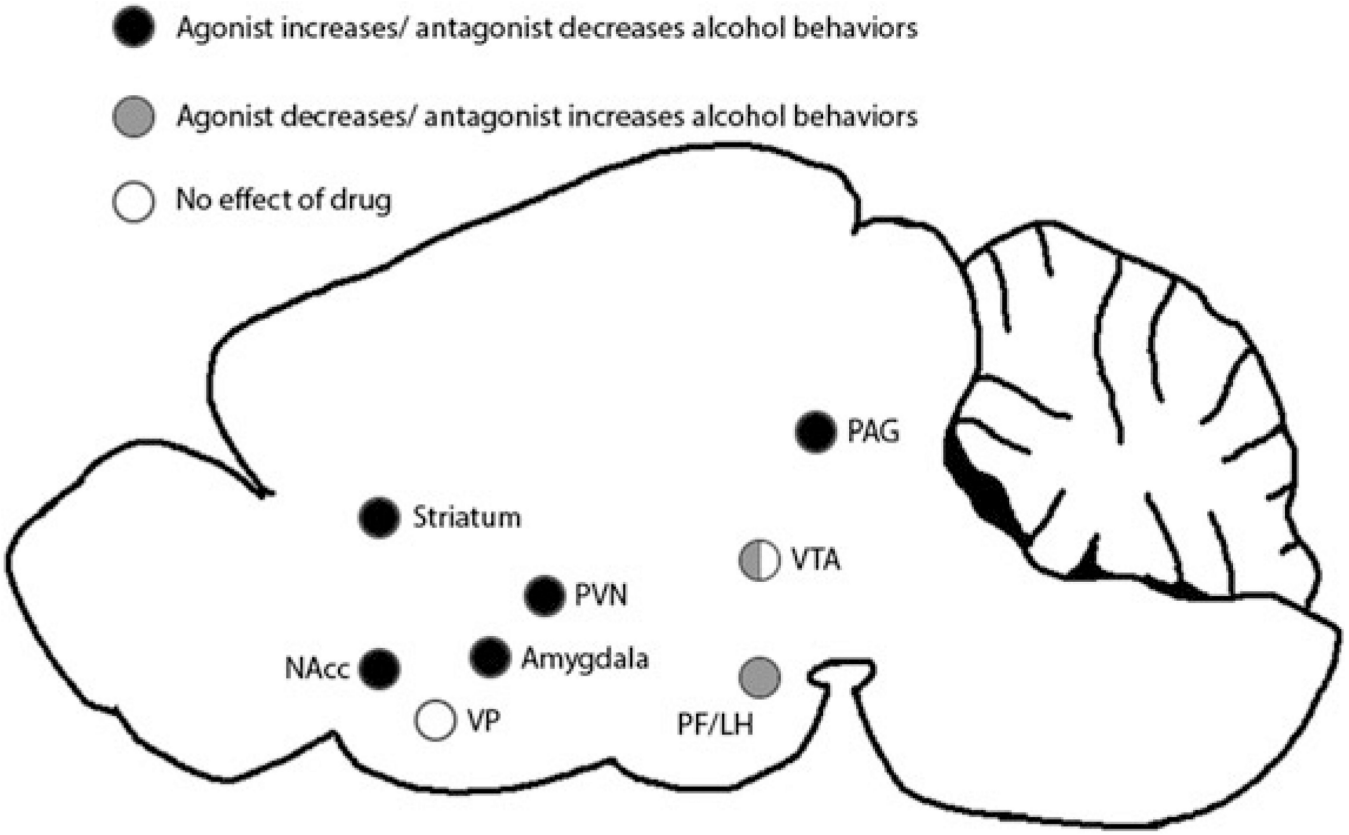

Fig. 1.

Impact of local modulation of DORs on alcohol behaviors. In the ventral tegmental area (VTA), the DOR agonist DPDPE decreases and the DOR antagonist TIPPψ increases alcohol intake (Margolis et al. 2008), although naltrindole reportedly had no effect (Hyytia and Kiianmaa 2001). The DOR agonist SNC80 increases and the DOR antagonist naltrindole decreases alcohol intake in the dorsal striatum (Nielsen et al. 2012a). In the nucleus accumbens (NAcc), the DOR agonist DALA increases alcohol intake (Barson et al. 2009) and naltrindole decreases alcohol intake (Hyytia and Kiianmaa 2001) and alcohol-induced dopamine release (Acquas et al. 1993), whereas the DOR antagonist ICI 174,864 attenuates alcohol-induced loss of righting reflex (Widdowson 1987). Naltrindole decreases alcohol intake (Hyytia and Kiianmaa 2001) and alcohol place preference (Bie et al. 2009) in the amygdala. The DOR agonist DALA increases alcohol intake (Barson et al. 2010) in the paraventricular nucleus (PVN) but decreases alcohol intake (Chen et al. 2013) in the perifornical lateral hypothalamus (PF/LH). Naltrindole injection in the ventral pallidum (VP) does not modulate alcohol intake (Kemppainen et al. 2012)