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Alcohol addiction and the mu-opioid receptor

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ABSTRACT

Alcohol addiction is one of the most common and devastating diseases in the world. Given the tremendous heterogeneity of alcohol addicted individuals, it is unlikely that one medication will help nearly all patients. Thus, there is a clear need to develop predictors of response to existing medications. Naltrexone is a mu-opioid receptor antagonist which has been approved in the United States for treatment of alcohol addiction since 1994. It has limited efficacy, in part due to noncompliance, but many patients do not respond despite high levels of compliance. There are reports that a mis-sense single nucleotide polymorphism (rs179919 or A118G) in the mu-opioid receptor gene predicts a favorable response to naltrexone if an individual carries a 'G' allele. This chapter will review the evidence for this hypothesis. The data are promising that the 'G' allele predisposes to a beneficial naltrexone response among alcohol addicted persons, but additional research is needed to prove this hypothesis in prospective clinical trials.

1. Introduction: the role of opioids in alcohol reward

Ventral tegmental neurons release dopamine at nerve terminals in ventral striatum and medial prefrontal cortex. Activation of this circuit is a common element of abused drugs, including alcohol (e.g., Di Chiara and Imperato, 1988; for review see Koob and Volkow, 2010). Thus, alcohol shares in common with nicotine, cocaine, amphetamine, morphine, etc., this property of enhancing dopaminergic transmission in ventral striatum and medial prefrontal cortex. Both animal model and human studies are in agreement on this point (Boileau et al., 2003; Gilman et al., 2008; Spanagel, 2009). This release of dopamine in the ventral striatum and medial prefrontal cortex is partially enhanced by stimulation of mu-opioid receptors (for which endorphin is the primary endogenous ligand) located on inhibitory GABAergic interneurons in the ventral tegmental area. The GABAergic interneurons inhibit the dopaminergic ventral tegmental neurons, whose activation signals immanent reward. Thus, mu-opioid receptor agonists enhance the likelihood of ventral tegmental dopaminergic neuron activation (and the experience of reward) by lessening the tonic inhibition of the associated GABAergic interneurons (Johnson and North, 1992; Spanagel et al., 1992; Tanda and Di Chiara, 1998).

Given this circuitry, it has been consistently shown that endogenous opioids play a role in ethanol reinforcement in various animal paradigms. Endorphin elevations after alcohol are seen in discrete reward regions of the hypothalamus (Popp and Erickson, 1998), ventral tegmentum and ventral striatum (Rasmussen et al., 1998). It is important to note that endorphin deficient rats continue to self-administer alcohol, indicating that endorphin is not the sole mechanism of alcohol reward (Grahame et al., 1998). The importance of mu-opioid receptor activation as a mechanism for alcohol reward is underscored by the fact that alcohol consumption in alcohol-preferring rats is persistently reduced after inactivating mu-opioid receptors in the ventral striatum (Myers and Robinson, 1999). Similarly, decreased alcohol-self administration is observed in primates after pre-treatment with opioid antagonists (Altshuler et al., 1980). C57Bl/6 J mice, an inbred strain which prefers alcohol, has increased endorphin release in the hypothalamus after alcohol administration (De Waele et al., 1992). Alcohol preferring rats have high levels of opioid gene mRNA species in the hypothalamus, prefrontal cortex, and mediodorsal nucleus of the thalamus (Marinelli et al., 2000), as well as increased mu-opioid receptor density in the ventral striatum and medial prefrontal cortex.

2. Clinical studies of naltrexone in alcoholism

The development of a substantial body of evidence, in the 1980s, that naltrexone (an orally-active mu-opioid receptor antagonist) diminished alcohol self-administration in animal models (Altshuler et al., 1980; Kiianmaa et al., 1983; Myers et al., 1986; Volpicelli et al., 1986) led to the first use of naltrexone in alcohol addicted populations in a controlled clinical trial (Volpicelli et al., 1992), the promising outcome of which was immediately confirmed in a second controlled clinical trial (O'Malley et al., 1992). Naltrexone was found to reduce alcohol craving and relapse to heavy drinking (operationally defined as 5 or more drinks/day for a man, 4 or more for a woman), but did not increase abstinence rates. On the basis of these two controlled trials, naltrexone was approval by the FDA.

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In the intervening twenty years, there have been more than 30 clinical trials of naltrexone in alcohol addiction (for review see Bouza et al., 2004; Srisurapanont and Jarusuraisin, 2005; Pettinati et al., 2006). While the majority of these clinical trials demonstrate efficacy of naltrexone in reducing risk for relapse to heavy drinking, the effect size is small, with many patients having no benefit. This has resulted in multiple reports in which the naltrexone arm outcomes are not significantly better than the placebo arm outcomes (e.g., Krystal et al., 2001). This is an expected outcome, given the tremendous heterogeneity of clinical alcohol addiction. It is likely that important clinical characteristics, such as compliance, severity and duration of alcohol addiction, comorbidity (both medical and psychiatric) and/or attendance at psychosocial treatment, may influence outcomes.

In this situation, multiple investigators have attempted to define clinical characteristics which might enhance the probability of naltrexone response. Some clinical measures have shown promise in characterizing a naltrexone responder: high alcohol craving (Chick et al., 2000; Monterosso et al., 2001; O'Malley et al., 2002) and strong family history of alcohol addiction (Monterosso et al., 2001), but family history of alcohol addiction did not predict response to naltrexone in the COMBINE multi-center trial (Capone et al., 2011). Alcohol addicts who experience greater euphoria after alcohol may have a better response to naltrexone (Volpicelli et al., 1995).

3. A118G OPRM1 mis-sense single nucleotide polymorphism: molecular and cellular effects

A common mis-sense single nucleotide polymorphism (rs 1799971) in the first exon of the mu-opioid receptor gene, OPRM1, was described by Bergen et al. (1997), A118G, or N40G, reflecting the fact that the A allele encodes asparagine, while the minor G allele encodes aspartate. The A (asparagine) allele is thought to be N-glycosylated (Huang et al., 2012), whereas this is not possible for the G (aspartate) allele, as there is no free amino group. Subsequent study (e.g., Crowley et al., 2003; Gelernter et al., 1999; Szeto et al., 2001; Tan et al., 2003) revealed large ethnic differences in allele frequencies (see Table 1). The G allele is rare (~1% allele frequency) in Africans, common among Asians (30–40% allele frequency) and intermediate (~15%) among peoples of European origin.

This allele has been the subject of multiple molecular investigations to determine its functional consequences, in terms of gene expression, protein translation, receptor signaling and receptor density. Initially, Bond et al. (1998) reported that the minor "G" allele mu-opioid receptor resulted in decreased affinity for binding to beta-endorphin, compared to the common "A" allele receptor. There was no change in binding affinity for alkaloid ligands. This result has not been confirmed in subsequent investigations (Beyer et al., 2004; Ramchandani et al., 2011). In one such study transfected HEK293 cells (a fibroblastoid cell type) were used (Beyer et al., 2004), but the 118G allele did not differ in binding affinity for beta-endorphin, compared to 118A. Beyer et al. (2004) also reported that the 118G allele was not different from the 118A allele in rate of desensitization, internalization or resensitization, but 118G had decreased transcription, compared to 118A. Ramchandani et al. (2011) also did not report differences in kinetics of binding of beta-endorphin to the 118G, compared to 118A. Mahmoud et al. (2011), using a whole cell patch clamp technique in acutely dissociated trigeminal ganglion neurons, reported that morphine was 5 fold less active at the 'G' allele receptor form in activating a Ca++ channel. There was no such difference for fentanyl. Zhang et al. (2005) conducted allelic imbalance studies in post-mortem human brain, revealing a marked decrease in 118G allele mRNA (see Fig. 1). In a second experiment, they showed *in vitro* evidence of a marked decreased translation of the 118G mRNA (see Fig. 4; Zhang et al., 2005).

Table 1
Frequency of G allele for A118G SNP in ethnic groups.

Ethnic group	Freq G	Ethnic group	Freq G
African	1%	Korean	31%
African–American	3%	Chinese	35%
Swedish	11%	Malaysian	43%
European–American	15%	Indian	47%

4. A118G OPRM1 mis-sense single nucleotide polymorphism: animal model studies

In the murine OPRM1 gene, there is no equivalent of the A118G naturally-occurring variation. A homologous variation (A112G, with the A allele encoding asparagines and the G allele encoding aspartate, as in the human OPRM1 gene) was created by bacterial artificial chromosome engineering and murine transgenic techniques by Mague et al. (2009). They reported decreased transcription and translation of the G allele in transgenic C57Bl/6 mouse brain (see Fig. 2), a result congruous with the human post-mortem brain *ex vivo* results of Zhang et al. (2005), as well as the *in vitro* results of Beyer et al. (2004). There was a blunted locomotor response to morphine in the 112G mice, as well as decreased morphine conditioned place preference (CPP) in 112G female mice, the latter being a sexually dimorphic response, with 112G males showing the expected CPP response to morphine.

Two other forms of transgenic mice were produced, using homologous recombination to replace the murine OPRM1 exon 1 with one of the two forms (118A and 118G) of human OPRM1 exon 1 (Ramchandani et al., 2011). These investigators conducted *in vivo* microdialysis experiments in the ventral striatum, demonstrating that the 118G mice had the expected elevations in dopamine release after alcohol, while the 118A mice had no significant increase over baseline (see Fig. 6). These data suggest that the 'G' allele conveys an increased rewarding valence to alcohol, compared to the 'A' allele.

There have been several studies of a similar single nucleotide polymorphism (SNP) in the rhesus monkey, the C77G, which results in a homologous amino acid change, asparagine to aspartate (Barr et al., 2007, 2010; Vallender et al., 2010). Both groups report that the G allele monkeys consume significantly more alcohol than the CC monkeys. Further, both groups note that naltrexone significantly decreases alcohol intake in the GG monkeys.

These reports, taken together, are consistent with the hypothesis that the 118G allele (or its equivalent in mouse and primate) (Fig. 3) conveys a greater rewarding effect of alcohol, a difference which is inhibited by naltrexone. These studies are remarkably consistent, given the species, paradigm, technical and molecular engineering differences among these studies.

5. A118G OPRM1 mis-sense single nucleotide polymorphism: human pharmacogenetic studies of alcohol

There have been several pharmacogenetic reports of the A118G SNP in human laboratory experiments involving alcohol (Ramchandani et al., 2011; Ray and Hutchison, 2004, 2007, 2010; Setiawan et al., 2011). In a laboratory investigation of the A118G pharmacogenetics of alcohol reward, Ray and Hutchison (2004, 2007) demonstrated that the G allele carriers experienced significantly greater euphoria after standard oral doses of alcohol (while controlling for breath alcohol concentration), compared to homozygous AA persons. Further, naltrexone significantly blunted the euphoria in the G allele carriers and was without effect in the AA group (see Fig. 5).

In agreement with this result, Ramchandani reported that G allele carriers had a greater striatal release of dopamine after alcohol (using a raclopride PET scan technique), compared to AA participants (see Fig. 6). In a more naturalistic approach, Ray et al. (2010) studied drinking habits of social drinkers over a 5 day period, analyzing subjective responses to alcohol by A118G genotype. G allele carriers reported significantly more 'vigor' less negative mood after drinking, compared to the AA group. Similarly, Setiawan et al.