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REVIEW

The μ-Opioid Receptor and Treatment Response to Naltrexone
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Abstract — Aims: To evaluate the pharmacogenetic evidence relating to the use of opioid antagonists (in particular naltrexone) in treating patients with alcohol abuse problems. Methods: Narrative review of pre-clinical and clinical published research regarding genetic modulation of psychotropes produced by alcohol and the therapeutic effects of opioid antagonists. Results: Alcohol activates brain reward pathways, leading to positive reinforcement of alcohol seeking and consumption. Thus, the underlying biological mechanisms may be targets for treatment, particularly in the early stages of addiction development. Alcohol reward is in part mediated by endogenous opioids. A single-nucleotide polymorphism (SNP) within the OPRM1 gene, A118G, leading to an amino acid change (Asn40Asp) in the extracellular portion of the receptor, has been implicated in alcoholism as well as in drug addiction, pain sensitivity and stress response, and in animal and human studies relates to the alcohol-dependent phenotype as well as to the treatment response to the μ-opioid antagonist naltrexone. Conclusion: The effect size reported in naltrexone clinical studies is often small, which may be due to heterogeneity among patients. Pharmacogenetic approaches may help guide us in the search for the appropriate treatment optimal for one patient’s need.

INTRODUCTION

Despite alcohol use being a major contributor to the global disease burden and a major cause of disability worldwide (Murray and Lopez, 1997a,b; Rehm et al., 2009), available treatments are limited in number and have limited efficacy (Bouza et al., 2004). In the USA, alcohol addiction or alcoholism affects >12% of the population at some point in their lifetime (Hasin et al., 2007), and in the UK harm to self and others as a result of alcohol abuse is far more common than that caused by drugs of abuse such as cocaine or heroin (Nutt et al., 2010). With this in mind, development of novel, effective pharmacotherapies for treating alcohol use disorders is an important avenue. However, compared with many other drugs of abuse, alcohol has a complex pharmacology that needs to be considered. GABAergic and glutamatergic signaling mediate the sedative, ataxic and anxiolytic effects of alcohol, while the rewarding properties involve the endogenous opioids and mesolimbic dopamine (Di Chiara and Imperato, 1985; Imperato and Di Chiara, 1986; Koob et al., 1998; Cowen and Lawrence, 1999; Hendler et al., 2013).

The clinical diagnosis of alcohol use disorders is based on standardized diagnostic criteria. While this provides some foundation for reliability across clinics and between clinicians, there is also evidence that patients diagnosed with alcohol use disorders constitute a markedly heterogeneous group. This is presumably partly because this is a chronic, relapsing disorder with significant environmental influences and individual influences, some of which reflect variations in genetic susceptibility components. Periods of withdrawal may be interspersed with periods of alcohol use, compounding a cyclic process of gene x environment interactions. Twin studies of the interaction of genetic and environmental influences on alcohol use disorders have obtained relatively consistent findings, with the genetic risk being ameliorated or exacerbated by the environmental factors. Family, twin and adoption studies indicate that with regard to environmental influences and expectancies, a family history of alcoholism has been shown to be a consistent environmental risk factor in the intergenerational transference of alcohol problems. However, the genetic component is strong too: twin studies have shown that the heritability of common drug addictions ranges from about 0.4 (hallucinogens) to 0.7 (cocaine), with alcohol use disorders having a heritability of 0.5–0.6 (Goldman et al., 2005; Ducci and Goldman, 2012), with genes influencing each stage from initiation to addiction. It is believed that multiple genetic variants with small individual effects contribute to the risk of alcohol dependence (i.e. it is polygenic (Agrawal and Lynskey, 2008; Du and Wan, 2009; Biernacka et al., 2013)). Children of parents with alcoholism have a 2- to 9-fold increased risk of alcohol-related problems, partly due to their genetic disposition (McGue, 1997). On average, a genetic contribution of ~50–60% to the disease risk in alcoholism has been reported, but multiple risk alleles may contribute to the individual genetic risk (Du and Wan, 2009; Bjork et al., 2010; Miranda et al., 2013; Yan et al., 2013).

A genetic risk component may contribute to the development of alcoholism by ‘pre-kindling’ an individual. Specifically, in individuals with low genetic risk, a significant environmental influence, often severe adverse events, is required to trigger an episode of compulsive alcohol intake. However, in ‘pre-kindled’ individuals with a high genetic risk, a limited exposure to adverse, environmental influences may be enough to trigger the episode of compulsive intake.

One candidate gene, and gene-product, that has been shown to contribute to risk of drug-abuse and to addiction-related phenotypes is the μ-opioid receptor (MOR; gene OPRM1). The MOR has an endogenous ligand, beta-endorphin, and was first shown to be involved in analgesia (Matthes et al., 1996). Since its characterization, MOR has been further implicated in reward-related behaviors as well as regulation of anxiety and arousal. With regards to alcoholism and drug addiction, MOR-antagonists have been developed as pharmacological treatments for these conditions. Here, we will examine the therapeutic effect of such antagonists and attempt to relate the treatment effect to the concept of pharmacogenetics.

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GENE AND FUNCTION OF THE MOR

There are three main classes of opioid receptors: delta (DOR), kappa (KOR) and mu (MOR), all belonging to the 7-transmembrane domain, G-protein coupled receptor family. MOR interacts with Gi/Go and activation at the receptor leads to the opening of G-protein gated inwardly rectifying K+ (GIRK) channels, inhibition of voltage-gated Ca2+ channels and a reduction of intracellular adenylyl-cyclase-mediated cAMP production, all of which serve to decrease membrane potential, neuronal excitability and neurotransmitter release, in addition to affecting downstream effects on second-messenger systems and gene expression. The regulation of MOR is dependent on the particular agonist acting on the receptor (Groer et al., 2011). Beta-endorphin, encoded by the proopiomelanocortin (POMC) gene, is the main endogenous ligand. In addition, analgesic compounds such as morphine, codeine and oxycodone bind to the MOR.

The human MOR gene, OPRM1 [chromosome 6q24-q25], consists of at least nine exons and spans over 200 kb (Bergen et al., 1997). A number of different splice variants exist that are under the control of multiple promoters (Shabalina et al., 2009). The most studied and most abundant variant, MOR-1, spans about 80 kb and contains four exons. Within the gene locus for OPRM1 multiple sites for single-nucleotide polymorphisms (SNPs) exist. One functional SNP, rs1799971, occurs at position 118 within exon 1 of the OPRM1 gene. Here, an adenine-to-guanosine substitution (thus, A118G) leads to an exchange of an asparagine for an aspartic acid at a putative glycosylation site (N40D) in the extracellular loop of the receptor.

The A118G SNP is common in individuals of European (15–30%) and Asian ancestry (40–50%), while rare in individuals with African or Hispanic heritage (1–3%) (Gelernter et al., 1999; Tan et al., 2003). The frequencies may indicate a recent positive selection for the minor allele (Pang et al., 2009).

Upon initial identification and characterization (Bond et al., 1998) the A118G SNP within exon 1 of the OPRM1 gene was determined to result in greater G-protein binding and subsequent G-protein activation in stably transfected cells expressing the MOPR and in Xenopus oocytes. However, this has not been replicated (Befort et al., 2001; Beyer et al., 2004; Ramchandani et al., 2011). In rat sympathetic superior ganglion neurons, the potency of both DAMGO and morphine-mediated calcium current inhibition was enhanced in neurons expressing the 118G allele (Margas et al., 2007). With regards to gene expression, there is a report of decreased mRNA expression level for the minor G-allele both in cell-culture and in human post-mortem tissue (Zhang et al., 2005).

THE MOR IN REWARD AND ALCOHOL DEPENDENCE

The rewarding and reinforcing properties of alcohol have been shown to be, in part, mediated by dopaminergic pathways originating in the ventral tegmental area (VTA) and mainly projecting to the nucleus accumbens (NAcc) and the frontal cortex (Nestler et al., 1993; Koob et al., 1998). It has been demonstrated in experimental animal models as well as in humans that alcohol induces mesolimbic dopamine release (Di Chiara and Imperato, 1988a,b; Weiss et al., 1993; Boileau et al., 2003; Gilman et al., 2008).

The MOR modulates dopamine transmission within the corticomesolimbic system. Activation of MOR via ligand-binding (e.g. endogenous beta-endorphin or administered exogenous ligand such as morphine) on GABAergic interneurons removes the inhibitory tone on these interneurons in the VTA leading to increased dopamine release in the terminal areas in the ventral striatum (Shippenberg et al., 1992; Spanagel et al., 1992). Reward and reinforcement are associated with this dopamine influx and underlie in part the development of drug dependence (Di Chiara and Imperato, 1985; Imperato and Di Chiara, 1986). The exact mechanism by which alcohol interacts with this circuitry is unknown. However, it has been shown that alcohol administration to laboratory animals induces release of endogenous opioids (Marinelli et al., 2003, 2005, 2006). Volpicelli and others proposed an endorphin compensation model for the opioids in addiction (Volpicelli, 1987; Volpicelli and Ulm, 1990; Kreek, 1996). Endorphin levels decrease after stress, and alcohol consumption or administration increases beta-endorphin release in regions such as the hypothalamus and NAcc (Rasmussen et al., 1998). In addition, in patients undergoing alcohol withdrawal decreased plasma levels of beta-endorphin were detected (Aguirre et al., 1990). Therefore, alcohol may be the most rewarding at times when endorphins are low, as occurs following experience of an adverse, stressful life event.

Transgenic mice deficient for the MOR have been generated in multiple laboratories. Matthes et al. (1996) showed that inactivation of the MOR gene led to a loss of morphine-induced analgesia as well as morphine-dependence related measures. However, the effect of the gene-inactivation is dependent on whether the generated animals are exon-1 and/or exon-2 deficient (Fuchs et al., 1999; Schuller et al., 1999). With regard to alcohol dependence, mice lacking the MOR do not readily self-administer alcohol. They lack the anxiolytic response seen in wild-type mice to a low dose of alcohol, but they display signs of alcohol withdrawal earlier than wild-type controls (Ghozland et al., 2005).

Blockade of MOR within the VTA to a large extent prevents dopamine release in the NAcc following alcohol intake. This indirectly demonstrates that alcohol leads to release of endogenous opioids within this structure and thus drives dopamine release (Tanda and Di Chiara, 1998). Additionally, expression of alcohol-induced place preference in mice is at least in part mediated via opioid action within the VTA (Bechtholt and Cunningham, 2005).

OPIOID ANTAGONISTS IN TREATING ALCOHOL DEPENDENCE

Naltrexone was approved as a treatment for alcohol dependence by the U.S. Food and Drug Administration in 1994. The indication has significant experimental support with preclinical and animal studies showing that opioid-receptor antagonists reduce alcohol intake in animals with heavy consumption (Froehlich et al., 1990; Mitchell et al., 2009) and alcohol preference (Hubbell et al., 1986; Kornet et al., 1991; Sabino et al., 2012). In addition, opioid-receptor antagonists block reinstatement of alcohol-seeking in rats, an animal
model mirroring relapse to drug-taking in humans (Ciccocioppo et al., 2002; Burattini et al., 2006). In relation to reward-related behaviors, it was demonstrated quite early that naltrexone can reverse dopamine release in the NAcc induced by alcohol (Benjamin et al., 1993). Here, locally applied alcohol induced a dopamine release which was dose-dependently suppressed by concomitant naltrexone administration.

The prescription of naltrexone as a treatment for alcohol abuse is not widely accepted in the USA despite it having been approved (ReVia) for almost 20 years. In 2003 Mark et al. (2003) reported that prescribing physicians’ perception of effectiveness and safety was significantly correlated with will to prescribe naltrexone. It is recommended that patients use naltrexone daily for 3–6 months, possibly up to 24 months, based on the patient’s preference, compliance and response to treatment. However, it is found that the medication tends to be used for a much shorter time (average 30–45 days (Harris et al., 2004)). Low patient compliance and perceived ineffectiveness (Kranzler et al., 2000; Mark et al., 2003; Bouza et al., 2004), as well as unwanted side-effects, may have contributed to this. And, despite having a confirmed efficacy in alcoholism treatment studies, the average effect size is small (Cohen’s D of ~0.2 (Bouza et al., 2004)).

With regard to treatment effects, naltrexone does reduce the number of heavy drinking days (e.g. Anton et al., 1999; Heinala et al., 2001; Monti et al., 2001; Guardia et al., 2002; Baldin et al., 2003; Gueorguieva et al., 2007, 2010) and craving for alcohol (Davidson et al., 1999; Chick et al., 2000). Naltrexone reduces the pleasurable and reinforcing effects of alcohol in social drinkers (Swift et al., 1994) and in alcoholics who relapse (O’Malley et al., 1992, 1996; Volpicelli et al., 1992). Other studies did not confirm a treatment effect (Krystal et al., 2001). However, while having small to moderate efficacy on measures at a group level, there is significant variability in the response to naltrexone treatment on an individual level, presumably reflecting heterogeneity in the patient population.

THE OPRM1 A118G SNP AND TREATMENT RESPONSE TO NALTREXONE

A family history of alcohol dependence predicts a patient’s clinical improvement following naltrexone treatment (Monterosso et al., 2001; Rubio et al., 2005). Furthermore, it has been found that naltrexone treatment leads to differential subjective responses after alcohol consumption in individuals defined as ‘high risk’ (HR) and ‘low risk’ (LR) based on family history (King et al., 1997). Specifically, naltrexone blunts the experience of ‘high’ or subjective stimulation following alcohol consumption in HR individuals, as well as the level of alcohol self-administration (Krishnan-Sarin et al., 2007). A family history of alcoholism may result from genetic and/or environmental factors; however, it seems that pharmacogenetics may be crucial in determining individual response to naltrexone treatment. While the actual functional consequences of the N40D substitution introduced by the minor 118G-allele remain largely unclear and its contribution to the genetic risk of addiction disorders is being debated, studies have been presented establishing a link between the A118G SNP and treatment response to naltrexone (Bart et al., 2005; Arias et al., 2006; Oslin et al., 2006; Chamorro et al., 2012), while other studies do not confirm such a moderate effect of the A118G SNP on the treatment effect of naltrexone (Gelernter et al., 2007; Tidey et al., 2008). The contradictory results obtained in these studies warrant the question whether or not the OPRM1-A118G has any effect on complex behaviors in polygenic disorders such as alcohol use disorders. The complexity of the genetics of alcoholism with multiple genetic variants having a small influence on complex traits can be analyzed using pathway techniques. Biernacka et al. (2013) demonstrated the usefulness of this technique and presented SNPs with significant contributions to alcohol use disorders. Another approach is to isolate the SNP of interest in genetically modified mice or use the existence of naturally occurring orthologous variants in order to examine the influence of the SNP on behaviors in established models. The contribution of the A118G SNP has been examined using mouse-models and a corresponding SNP found in the rhesus macaque has also been evaluated with regard to contribution to addiction-disorder risk and naltrexone treatment.

The functional equivalent of the human A118G OPRM1 SNP identified in rhesus macaques is at position 77 in the OPRM1 gene (Miller et al., 2004). The C77G SNP results in a proline to arginine exchange at position 26 of the receptor protein. Male carriers of the rhesus OPRM1 77G allele display increased alcohol preference, increased drinking to intoxication and increased psychomotor stimulation in response to alcohol (Barr et al., 2007, 2010), as well as an increased HPA axis response (Schwandt et al., 2011). Psychomotor stimulation may be related to mesolimbic dopamine activity, and therefore, the OPRM1 77G carriers may be sensitive suppression of alcohol preference by naltrexone, which has also been demonstrated (Barr et al., 2010; Vallender et al., 2010).

In order to be able to study the contribution of the human A118G OPRM1 SNP to addiction disorders, we created two mouse lines carrying the human exon 1 sequence with either the major 118A or the minor 118G-SNP. Following administration of alcohol, microdialysis within the NAcc revealed a 4-fold higher dopamine release in the 118G animals compared with the 118A. This indicates that the A118G SNP is sufficient to cause elevated dopamine release following alcohol administration (Ramchandani et al., 2011). The OPRM1 118G carriers also show a decreased sensitivity to morphine, a finding replicated in another mouse line where an amino acid substitution functionally equivalent to the human N40D was introduced directly into the genetic background of C57Bl6 mice (N38D, A112G SNP (Mague et al., 2009; Mahmoud et al., 2011)). The decreased sensitivity to morphine can also be seen in human 118G carriers (Lotsch et al., 2002).

In both humans and mice, it was demonstrated that the OPRM1 118G allele confers a more vigorous dopamine response to alcohol in the ventral striatum, compared with that seen in homozygous OPRM1 118A carriers (Ramchandani et al., 2011). Additionally, carriers of the 118G allele showed signs of rapid acute tolerance, similar to that previously seen in men at genetic risk of alcoholism. The excessive reward-related dopamine response seen in these individuals may be of pharmacogenetic importance when determining treatment of an alcohol-dependence disorder.
However, in this study there was also a noted discrepancy between the objective measures of alcohol-induced dopamine release and the subjective measure of alcohol effects as reported by the participants. In another study examining treatment seeking heavy drinkers, individuals with at least one OPRM1-118G copy reported higher alcohol-induced ‘high’ and lower alcohol craving (Ray and Hutchison, 2007). This may argue against a simplistic view of alcohol-induced dopamine release as an immediate mediator of drug reward. The study showed that the 118G allele confers a higher dopamine release in response to alcohol administration regardless of whether it occurs in the context of other markers within its haplotype block or not.

The impact of the OPRM1 A118G on treatment response to naltrexone was demonstrated by Oslin and colleagues (Oslin et al., 2003) in a meta-analysis of three previously reported clinical trials. The minor 118G allele was strongly associated with the therapeutic effect of naltrexone with the 118G carriers being more responsive to treatment and showing a prolonged period of time prior to first relapse compared to controls. The major 118A-allele homozygote did not differ from placebo for this measure. ACTH and cortisol response to opioid antagonist treatment is significantly elevated in OPRM1 118G carriers in a Caucasian population (Wand et al., 2002). A recent meta-analysis study provided support for the finding that carriers of the minor OPRM1 118G allele have lower rates of relapse to heavy drinking compared with 118A subjects, but similar total abstinence rates (Chamorro et al., 2012).

The complexity of alcohol use disorders is mirrored in the varying contributions of the OPRM1-A118G SNP to alcohol- and treatment-related measures in different populations. This may be related to differential genetics in selected patient groups affecting physiological and psychological effects of alcohol intake, and response to naltrexone treatment. In polygenic disorders such as alcohol use disorders SNPs (as well as other (epi-) genetic contributors) act in concert to generate the end-phenotype (Anton et al., 2012). In different patient-populations, SNPs may display different expression-frequencies and thus have a differential impact. In addition to selection by ethnicity, which influences SNP frequency, gender has been shown to be of importance in treatment outcome (Pettinati et al., 2008). Here, high-dose treatment with naltrexone decreased cocaine and alcohol use in men, but not in women with co-occurring alcohol and cocaine abuse disorders. In the COMBINE study, however, women with alcohol use disorder responded to naltrexone treatment in a manner similar to male patients (Greenfield et al., 2010).

CONCLUSION

We have considered the MOR and treatment response to naltrexone in relation to alcoholism. A pharmacogenetic perspective reveals that consideration of genetic variants is important when determining treatment options for different individuals, and possibly crucial in determining which patients will be most likely to respond to naltrexone treatment. Benefits of such an approach, in addition to increasing treatment response and health, may be an increased cost-effectiveness in health care, as well as a decreased risk of exposing individuals to medication that is ineffective. However, the advent of pharmacogenetics has introduced additional ethical considerations that need to be remembered in the search for better care (Shields, 2011). The benefits of individualized medicine are great if we can maintain a professional and respectful attitude in the management and handling of individuals as well as information obtained.

With regards to the OPRM1 A118G SNP, significant differential contributions of the alleles are emerging for alcohol or drug taking, as well as in treatment response to naltrexone (and perhaps other opioid antagonists). Thus, it may be concluded that these differences can be attributed, at least in part, to different genetics. Treatment effects that on a group level are modest may result in significant clinical improvement for subpopulations of patients. Opioid antagonist treatment may be the right choice for individuals with the right genetic make-up who are in the early stages when consumption of alcohol or drug is primarily reward driven. The pharmacogenetic approach may provide the tools and theories for optimizing the treatment response to naltrexone. However, the complexity of a polygenic disorder such as alcohol use disorders is clearly displayed in the studies presented here. Further exploration of pharmacogenetics may give us tools to better identify individuals that have a higher probability of benefiting from treatment with opioid antagonists.

Conflict of interest statement: None declared

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