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OPRM1 SNP (A118G): Involvement in disease development, treatment response, and animal models

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Abstract

Endogenous opioids acting at μ-opioid receptors mediate many biological functions. Pharmacological intervention at these receptors has greatly aided in the treatment of acute and chronic pain, in addition to other uses. However, the development of tolerance and dependence has made it difficult to adequately prescribe these therapeutics. A common single nucleotide polymorphism (SNP), A118G, in the μ-opioid receptor gene can affect opioid function and, consequently, has been suggested to contribute to individual variability in pain management and drug addiction. Investigation into the role of A118G in human disease and treatment response has generated a large number of association studies across various disease states as well as physiological responses. However, characterizing the functional consequences of this SNP and establishing if it causes or contributes to disease phenotypes have been significant challenges. In this manuscript, we will review a number of association studies as well as investigations of the functional impact of this gene variant. In addition, we will describe a novel mouse model that was generated to recapitulate this SNP in mice. Evaluation of models that incorporate known human genetic variants into a tractable system, like the mouse, will facilitate the understanding of discrete contributions of SNPs to human disease.

Keywords

alcohol; morphine; analgesia; dependence; pain; stress

1. Introduction

The opioid system plays a role in diverse biological functions, including reward, analgesia, and stress responsivity (Kreek and Koob, 1998; Vaccarino and Kastin, 2000). Therapeutically, opioids are commonly prescribed for their effective analgesic properties. However, the response to treatments varies widely between individuals leaving many people taking the wrong dose, experiencing unbearable side effects, or receiving inadequate therapy. Additionally, chronic use is marred by habituation, tolerance, and the development of

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Terms:
Human SNP: A118G = Asn40Asp = N40D
Mouse SNP: A112G = Asn38Asp = N38D
Rhesus Macaque SNP: C77G = Pro26Arg = P26R

dependence, which occur in varying degrees depending on the individual. The ability to better predict clinical outcomes based on individual differences to opioid therapeutics would greatly reduce the trial and error of finding suitable drugs and doses, and could reduce the number of patients developing drug dependence.

Individual variability results from a complex interaction of genetic and environmental factors. However, linkage disequilibrium, genome-wide association, case-controlled, and family-controlled studies have demonstrated the heritability of complex behaviors and response to drug treatments, suggesting that specific genes or alterations in genes may be responsible for the differences in behavior. Common genetic variations among individuals include single nucleotide polymorphisms (SNPs), in which a single nucleotide of the genome is altered. SNPs occur every 100-300 base pairs and account for approximately 90% of human genetic variation. The nature of the change produced by the SNP greatly depends on which nucleotide is being altered and where this change occurs in the gene. For instance, synonymous SNPs will alter the nucleotide without changing the resulting amino acid (also called a “silent mutation”). Non-synonymous SNPs are produced when the nucleotide substitution alters the resulting amino acid. Additionally, these alterations can occur in promotor, exonic, or intergenic regions and, consequently, may differentially affect transcription, processing, stability, translation, folding, transportation, and ultimately, function of the corresponding gene product.

In human populations, a commonly investigated SNP (rs1799971) occurs in exon 1 of the μ-opioid receptor gene (*OPRM1*), in which an adenine to guanine substitution (A118G) exchanges an asparagine for an aspartic acid at a putative N-glycosylation site (N40D). It is common in persons of European (15–30%) and Asian ancestry (40–50%), with lower prevalence in African American and Hispanic populations (1-3%) (Bergen et al., 1997; Gelernter et al., 1999; Tan et al., 2003). Despite the vast number of papers investigating the role of this SNP in human disease and drug responses, a consensus has yet to be reached on its functional consequences. The A118G SNP has been implicated in a wide variety of disorders, such as drug addiction and stress responsivity, and in treatment responses, including dependence and pain reduction; however, the mechanisms that mediate these alterations have not been determined. In this manuscript, we will review the relevant literature investigating the role of this SNP in human disease and treatment response, molecular and cellular function, and animal models that may help explain these effects. Indeed, several comprehensive reviews describe the role of pharmacogenetics, including *OPRM1* and other genes, in specific disease states and treatment responses, such as alcoholism/addiction (Dick and Foroud, 2003; Enoch, 2003; Haile et al., 2008; LaForge et al., 2000; Oroszi and Goldman, 2004; Oslin et al., 2006) and pain (Kosarac et al., 2009; Lotsch et al., 2004; Skorpen et al., 2008); therefore, in this review we focus on the elucidation of the functional significance of the A118G SNP in disease states both in humans and animal models.

2. The μ-opioid receptor (MOPR)

2.1. MOPR form and function

Early investigation of the endogenous targets of opioid drugs identified three main classes of opioid receptors: μ, δ, and κ. The cloning and characterization of the opioid receptors have impacted our understanding of their gene and protein structures. The MOPR is a member of the G-protein-coupled receptor (GPCR) family and interacts with (G_i/G_o) heterotrimeric G-proteins. Activation of the receptor and subsequent dissociation of the G-proteins results in the opening of G-protein-gated inwardly-rectifying K^+ (GIRK) channels, inhibition of voltage-gated Ca^{2+} channels, and reduction of adenylyl cyclase-mediated cAMP production, all of which serve to decrease membrane potential, neuronal excitability, and neurotransmitter release in addition to affecting second-messenger systems and gene expression.

Receptor activation is achieved through binding of endogenous or exogenous ligands. β-endorphin, the peptide encoded by proopiomelanocortin (*POMC*), has high affinity and selectivity for the MOPR and is considered the endogenous MOPR ligand. In addition, a separate class of peptides has been proposed as μ-selective: the endomorphins (Zadina et al., 1997). The preproenkephalin gene encodes enkephalin, the endogenous ligands for the δ receptor, which has modest affinity for the MOPR as well (Raynor et al., 1994). A large number of opioids and non-opioid ligands exist for this receptor; however, those most commonly prescribed for their effective analgesic properties include morphine, codeine and oxycodone.

2.2. Genetic Variation in Human OPRM1

The human MOPR gene, *OPRM1*, [chromosome 6q24-q25] spans over 200kb with at least 9 exons and 19 different splice variants under the control of multiple promoters (Shabalina et al., 2009). The initial receptor subtype, MOPR-1, spanning approximately 80kb and containing 4 exons (http://genome.ucsc.edu), is abundantly expressed and has been most intensely studied. Its haplotype structure includes three large blocks with >100 polymorphisms reported (http://www.hapmap.org). In addition to the exon 1 A118G, there is *in vitro* functional evidence for only a few of these other polymorphisms. Two promoter polymorphisms, G–554A and A–1320G have been shown to affect transcription: G–554A decreases MOPR transcription but is extremely rare (MAF<0.001) and the A–1320G variant increases transcription, although the exact transcription factor binding to the site is unknown (MAF= 0.21) (Bayerer et al., 2007). In exon 3, G779A (R260H), G794A (R265H), and T802C (S268P) have been shown to decrease receptor coupling and signaling (Befort et al., 2001; Koch et al., 2000; Wang et al., 2001). Other *OPRM1* polymorphisms that have been identified and associated with pain or opioid dependence including a short tandem $(CA)_n$ repeat (Kranzler et al., 1998), C17T (A6V), which is found primarily in African Americans (Berrettini et al., 1997), and C440G (S147C), which is extremely rare in the general population (MAF< 0.006) (Glatt et al., 2007). To date, none of these polymorphisms have *in vitro* evidence supporting a functional consequence.

3. A118G and drug dependence

Mesolimbic dopamine (DA) neurons in the ventral tegmental area (VTA) that project to the nucleus accumbens (NAc) are part of a well-defined pathway involved in reward processing (Nestler, 2005). GABAergic interneurons in the VTA maintain a tonic inhibition over dopaminergic neurons. Binding of β-endorphin or morphine to MOPRs on these interneurons will decrease their activity, resulting in disinhibition of the DA neurons and elevations of DA in the NAc (Johnson and North, 1992). This dopamine influx has been associated with reward and reinforcement and is believed to contribute to the development of drug dependence (Di Chiara and Imperato, 1988; Wise and Bozarth, 1985).

A number of studies have examined *OPRM1* as a candidate for genetic contribution to the risk for substance dependence. The minor G118 allele has been associated with an altered susceptibility for developing drug dependence, with some studies suggesting that the SNP is a risk factor and others finding it to be protective, in addition to several studies that did not report any significant contribution of the G118 allele (Table 1). For instance, in a sample of 476 Caucasians grouped according to drug history – alcohol alone, alcohol and nicotine, or alcohol, nicotine, and illicit drug use and compared to two control groups – it was found that individuals homozygous for the A118 allele were present in greater frequency in the drug groups compared to controls. The absence of the G118 allele in the drug groups suggested it was protective against developing drug dependence (Schinka et al., 2002). Alternatively, in drug-dependent individuals in Eastern European and Russian populations, the G118 allele occurred more frequently (Zhang et al., 2006a). In addition, several studies using linkage disequilibrium or haplotype analysis (Crowley et al., 2003;Luo et al., 2003), case- or family-controlled studies (Franke et al., 2001;Gelernter et al., 1999;Xuei et al., 2007), or meta-analyses

of past studies (Arias et al., 2006) failed to detect a significant involvement of A118G in drug dependence.

3.1. Alcohol

Alcohol has been shown to affect a wide variety of transmitter systems; however, the rewarding and reinforcing aspects of alcohol intake seem to be mediated by the opioid system (Gianoulakis, 2004; Oswald and Wand, 2004). Indeed, acute alcohol administration has been shown to cause β-endorphin release measured in the plasma (Gianoulakis and Barcomb, 1987) or in reward-related brain regions (Rasmussen et al., 1998). MOPRs appear critical for mediating alcohol effects as MOPR knock-out mice show reduced ethanol intake and reward (Hall et al., 2001; Roberts et al., 2000). Likewise, antagonism of the receptor by naloxone in rats (Reid et al., 1986) and naltrexone in humans (O'Malley et al., 1992; Volpicelli et al., 1992) has been shown to reduce alcohol intake.

Studies investigating alcohol-dependence specifically have reported positive associations with the A118G SNP (Bart et al., 2005; Kim et al., 2004b; Miranda et al., 2009; Nishizawa et al., 2006; Rommelspacher et al., 2001), no association (Bergen et al., 1997; Gscheidel et al., 2000; Kim et al., 2004a; Loh el et al., 2004; Sander et al., 1998), or a protective effect (Du and Wan, 2009; Town et al., 1999) in individuals possessing the G118 allele (Table 1). [For a detailed review of 12 of these clinical association studies, see (van der Zwaluw et al., 2007).].

A number of clinical studies have investigated altered effects of alcohol in individuals with the G118 allele. For instance, in a sample of 38 moderate and heavy drinkers without a history of alcohol problems or quit attempts, it was shown that G118 allele-carriers reported higher feelings of intoxication, stimulation, sedation, and happiness compared to A118 allele-carriers. Subjects carrying the G118 allele were also three times more likely to report a family history of alcohol use (Ray and Hutchison, 2004). In male heavy drinkers, G118 allele-carriers showed automatic approach tendencies for alcohol and other appetitive stimuli, but not for generally positive or negative stimuli (Wiers et al., 2009) and reported greater alcohol craving in a cue-reactivity task (van den Wildenberg et al., 2007). A recent study investigating the involvement of A118G in adolescent alcohol misuse found that a higher percentage of G118 allele-carriers tested positive for an alcohol use disorder, and that the G118 allele was associated with increased self-reports of drinking in order to enhance positive affect (Miranda et al., 2009). Functionally, G118 allele-carriers have demonstrated an increased BOLD response in fMRI in the orbitofrontal cortex, ventromedial prefrontal cortex, and striatum in response to alcohol and alcohol-related cues (Filbey et al., 2008). Additionally, a significant increase in dopamine receptor sensitivity, as measured by increases in apomorphine-induced growth hormone secretion, was found in G118 allele-carrying alcoholics following one week of alcohol abstinence (Smolka et al., 1999).

One of the more therapeutically relevant findings regarding the A118G SNP is in the treatment of alcoholism. It was discovered that individuals carrying the G118 allele were more likely to respond positively to naltrexone treatment (Oslin et al., 2003). In this study, there were 3.5 times more naltrexone-treated G118 allele-carriers, compared with A118 allele-carriers, who did not relapse to heavy drinking. There were no differences in rates of abstinence, suggesting that individuals with the G118 allele may better handle alcohol exposure without fully relapsing to heavy drinking. There were no differences between genotypes for those receiving placebo treatments, demonstrating that the benefit of the G118 allele is specific for naltrexone treatment and does not confer an enhanced ability for the individual to refrain from relapse. Subsequent studies investigating the involvement of this SNP in naltrexone response have replicated these initial findings (Anton et al., 2008; Kim et al., 2009; Oroszi et al., 2009; Oslin et al., 2003). For instance, using a haplotype-based approach, the A118G locus, and not SNPs found in the same haplotype block, contributed to the improved response to naltrexone treatment in alcohol-

dependent subjects with the G118 allele (Oroszi et al., 2009). However, other studies failed to find an association between the G118 allele and an improved response to naltrexone (Arias et al., 2008; Gelernter et al., 2007; Tidey et al., 2008) or nalmefene treatment (Arias et al., 2008).

The mechanisms underlying the interaction of the A118G SNP and the potential benefits of naltrexone in alcohol dependence are unknown. It is thought that the effect of naltrexone is mediated by its ability to block the elevations in β-endorphin induced by alcohol administration, which are thought to contribute to the subsequent euphoria. Indeed, it has been shown that naltrexone has a greater propensity to block alcohol-induced highs in individuals with the G118 allele (Ray and Hutchison, 2007), which may, in part, explain the reduction in rates of relapse. In contrast, it was shown that the urge to drink following naltrexone treatment was greater in G118 allele-carriers (McGeary et al., 2006). However, it should be noted that in this study, conducted in non-treatment seekers, the urge to drink was evaluated following exposure to alcohol cues rather than alcohol administration.

Cortisol responses have also been implicated in drinking behavior. A study in non-treatment-seeking alcohol-dependent subjects found that G118 allele-carriers showed a trend towards decreased cortisol responses to stress, but elevated alcohol craving and intake following the stress (Pratt and Davidson, 2009). In animal models of addiction, discrete brain substrates have been identified for drug-, cue-, and stress-mediated reinstatement to drug-seeking behavior (Kalivas and McFarland, 2003). As such, it is possible that this SNP may confer benefits in certain situations, but could serve as a detriment (or not play a role) in others. [For additional information on alteration in stress-related responses, see section 4.2 “OPRM1 A118G and physiological response: Stress”.]

3.2. Heroin

Heroin directly stimulates MOPRs when converted to morphine in the brain and periphery. Similarly to alcohol, this results in activation of reward-related pathways, initially resulting in euphoria, but eventually leading to abuse and dependence. Studies evaluating the role of G118 allele in heroin dependence have reported positive associations (Bart et al., 2004; Drakenberg et al., 2006; Kapur et al., 2007; Szeto et al., 2001), negative associations (Bond et al., 1998; Tan et al., 2003), or no association (Glatt et al., 2007; Shi et al., 2002) (Table 1). For instance, one study found that approximately 90% of G118 allele-carriers were heroin users. Additionally, they found that preproenkephalin and preprodynorphin levels, which were reduced in heroin-dependent subjects, were even lower in G118 allele-carriers compared with A118 allele-carriers (Drakenberg et al., 2006). Shi and colleagues found that the G118 allele was associated with elevated daily intake of heroin in dependent subjects, though they did not find a significant effect of genotype and heroin dependence (Shi et al., 2002). A positive response to initial drug exposure is typically associated with continued use and abuse. In a study investigating the relationship between initial drug response and *OPRM1* SNPs, the G118 allele was not associated with positive or negative subjective responses to first-time heroin use (Zhang et al., 2007), suggesting that differences in rates of dependence may not be explained by differences in initial euphoric experience.

3.3. Nicotine

The rewarding properties of nicotine are, in part, mediated by opioid transmission. For instance, it has been shown that nicotine stimulates the release of endogenous opioids in reward-related brain regions (Davenport et al., 1990; Pomerleau, 1998), blockade of MOPRs with systemic injections of naloxone blocks acute nicotine reward (Walters et al., 2005), MOPR null mutant mice do not show nicotine reward (Berrendero et al., 2002), and repeated treatment with nicotine elevates MOPR mRNA in the VTA (Walters et al., 2005). Human studies have

reported an association of chromosome 6, which contains *OPRM1*, with nicotine dependence (Sullivan et al., 2004; Vink et al., 2004) (Table 1). Another study, however, found that the A118G SNP was not significantly associated with nicotine dependence, though it was in high linkage disequilibrium with haplotypes that did reach significance, suggesting there may be other SNPs nearby that confer an increased susceptibility for developing nicotine dependence (Zhang et al., 2006b). As in the case with alcohol, studies examining differences in response to nicotine administration have revealed some interesting associations. For instance, female G118 allele-carriers report attenuated rewarding effects of nicotine (Ray et al., 2006). In a separate study, nicotine was administered following the induction of a positive or negative mood via pictures and music. Smoking was reported as more rewarding to A118 allele-carriers when in a negative mood than it was for those with the G118 allele, suggesting that the A118 allele-carriers may respond more to the mood-enhancing properties of nicotine (Perkins et al., 2008). Accordingly, increases in cerebral blood flow to brain regions associated with cigarette craving were detected in smokers with the A118 allele compared to the G118 allele (Wang et al., 2008).

Consistent with alcohol studies, the A118G SNP may better predict treatment outcomes and relapse rates for those attempting to quit smoking rather than predict the susceptibility for developing nicotine dependence. Lerman and colleagues have shown that smokers with the G118 allele are significantly less likely to relapse and report fewer abstinence symptoms than smokers homozygous for the A118 allele (Lerman et al., 2004). A group in the UK reported that female G118 allele-carriers had significantly higher quit rates than female A118 allele-carriers; while the reverse was true for males (Munafo et al., 2007). It should be noted, however, that this study obtained DNA from only 50% of subjects, raising the possibility of ascertainment bias. This evidence supporting the role of the G118 allele in dependence phenotypes, such as liking and craving in chronic smokers, is more robust than evidence for association with the development of nicotine dependence.

3.4. Methamphetamine

The effects of methamphetamine (MA), which are predominantly mediated by dopaminergic and serotonergic systems, may also involve the endogenous opioid systems. Indeed, work in animals has shown that naloxone administration can block behavioral sensitization to repeated MA exposure (Chiu et al., 2005). However, the few studies investigating the effect of the A118G SNP in MA dependence failed to find an association (Ide et al., 2004; Ide et al., 2006) (Table 1).

4. A118G and physiological response

4.1. Pain and analgesia

The relationship between altered pain thresholds and analgesic responses to opioid administration for the A118G SNP has been well characterized. In a variety of populations, the G118 allele has been associated with elevated pain responses and decreased pain thresholds (Sia et al., 2008; Tan et al., 2009) and a reduced response to morphine or other opioids for patients receiving treatment for post-operative or chronic pain (Campa et al., 2008; Chou et al., 2006a; Chou et al., 2006b; Coulbault et al., 2006; Fillingim et al., 2005; Hayashida et al., 2008; Janicki et al., 2006; Klepstad et al., 2004; Landau et al., 2008; Oertel et al., 2006; Reyes-Gibby et al., 2007; Sia et al., 2008; Tan et al., 2009) (Table 2). Additionally, in healthy volunteers carrying the G118 allele, higher concentrations of alfentanil, an opioid analgesic, were required for pain relief following electrical pain stimulation (Oertel et al., 2006); of interest, this dose did not increase respiratory depression, suggesting it may be safe to give a higher dose of opioid analgesics to patients that carry the G118 allele. Other studies, however, have reported divergent results, showing that G118 was associated with reduced pain

responses. For instance, in healthy volunteers receiving different experimental pain procedures, the G118 allele was associated with reduced pain responses to pressure (Fillingim et al., 2005). Additionally, males carrying the G118 allele rated thermal pain lower than those carrying the A118 allele. However, the G118 allele-carrying females reported higher pain scores following this thermal pain administration, consistent with previous literature demonstrating elevated pain responses (Fillingim et al., 2005).

Morphine-6β-glucuronide (M6G) is an active metabolite of morphine that has a greater analgesic potency but a reduced potency in affecting respiratory depression (Mantione et al., 2005). In G118 allele-carrying subjects, there was a reduced potency of M6G in eliciting an analgesic response, though there was no difference in M6G-induced respiratory depression (Romberg et al., 2005). A reduction in M6G-induced miosis was also found in G118 allele-carriers (Lotsch et al., 2002).

MOPRs also play a role in social pain, described as the feelings that result from social rejection, separation, or loss. Accordingly, the G118 allele was associated with increased self-reported sensitivity to rejection (Way et al., 2009). Subsequent fMRI measurement of neural responses in these individuals found greater activation in the dorsal anterior cingulate cortex and anterior insula while experiencing social rejection, suggesting a decrease in MOPR inhibitory modulation in G118 allele-carriers. These brain regions are associated with both physical and social pain (Eisenberger and Lieberman, 2004). Together, these data support a loss of function of the MOPR in individuals harboring the G118 allele in some, but not all, responses mediated by the same compounds.

4.2. Stress response

Activation of the hypothalamic-pituitary-adrenal (HPA) axis plays an integral role in responses to stress. Following a stressor, corticotropin-releasing factor (CRF) is released from the paraventricular nucleus (PVN) of the hypothalamus, stimulating POMC synthesis in the pituitary and the release of two POMC metabolites: adrenocorticotropic hormone (ACTH) and β-endorphin. Acting on the adrenal glands, ACTH stimulates the release of glucocorticoids (cortisol in primates and corticosterone in rodents; CORT), which can then have many central and peripheral effects. MOPRs located on CRF neurons in the PVN serve to tonically inhibit HPA axis stimulation; thus, differences in endogenous opioid transmission or receptor activity can alter basal CORT levels or stress-mediated CORT responses. Just as genetic differences can affect response to drugs (pharmacogenetics), alterations in responses to an individual's own biologically active compounds (physiogenetics) are influenced by genetic differences (Kreek and LaForge, 2007). Indeed, individuals with the G118 allele have baseline elevations in CORT levels (Bart et al., 2006; Hernandez-Avila et al., 2003). Several studies have shown that the CORT-response to a behavioral stressor is lower in G118 allele-carriers (Chong et al., 2006; Pratt and Davidson, 2009).

In contrast, a greater CORT response has been observed in G118 allele-carriers following a naloxone challenge, which may suggest an elevated tonic inhibition of CRF by β-endorphin (Chong et al., 2006; Hernandez-Avila et al., 2007; Hernandez-Avila et al., 2003). Interestingly, one of these studies found population-specific effects in which G118 allele-carriers of European descent displayed elevations in CORT responses to naloxone, while G118 allele-carriers of East Asian descent did not (Hernandez-Avila et al., 2007). These population-specific differences could suggest that the A118G SNP is in high linkage disequilibrium (LD) with other SNPs that may mediate the observed alterations.

5. Functional relevance of A118G

Most studies to date have examined the functional consequences of this SNP *in vitro* using various cell culture systems. Initial studies identified an elevated binding affinity of β-endorphin, but not exogenous ligands, in the G118 variant to 3-fold higher than that of the A118 in AV-12 cells stably expressing the human MOPR (hMOPR) variants (Bond et al., 1998). Additionally, β-endorphin was found to be three times more potent in activating GIRK channels in *Xenopus* oocytes injected with *in vitro* transcribed mRNAs for the A118 or G118 variants (Bond et al., 1998). Together, these data suggested a gain-of-function of the MOPR as a consequence of the A118G point mutation. However, subsequent studies using other cell culture systems – COS cells (Simian fibroblasts) (Befort et al., 2001) or HEK 293 cells (Human embryonic kidney) (Beyer et al., 2004) – were less conclusive with regard to this altered function of the G118 allele. Another consequence of MOPR activation, Ca^{2+} inhibition, was investigated using rat sympathetic superior ganglion (SCG) neurons expressing either the A118 or G118 variant of the hMOPR. In these studies, the potencies of both DAMGO- and morphine-mediated Ca^{2+} current inhibition (but not morphine-6-glucuronide or endomorphin I) were increased in SCG neurons expressing the G118 variant (Margas et al., 2007), again suggesting enhanced response for some but not all opioid compounds.

A human post-mortem study examined allele-specific mRNA expression from heterozygous individuals with the A118G polymorphism and found significant reductions in mRNA transcribed from the G118 allele. Additionally, the authors transiently expressed both variants of the MOPR in CHO cells and showed a reduction in mRNA and protein expression with the G118 allele (Zhang et al., 2005). The mechanisms underlying the decrease in expression is unclear. As the mutation occurs in a coding region, rather than a promotor, it might seem unlikely that transcription would be affected. However, using *in silico* tools (bioinformatics), it has been proposed that the A118G SNP may inactivate three transcription factor binding sites while creating two new ones, including a p53 site (Pang et al., 2009), suggesting that cis-acting factors could explain the alterations in expression. While transcriptional regulation using exonic sequence is rare, some examples do exist. Using Mfold technology, in which theoretical mRNA folding can be evaluated for different sequences, it was shown that the G118 variant demonstrated altered folding compared to other permutations which could affect mRNA stability (Johnson et al., 2008; Zhang et al., 2005).

Further evidence for a decrease in MOPR expression was demonstrated by studies showing a reduction in B_{max}, indicative of a lower receptor number, following [^{3}H]-DAMGO binding using both transient and stable expression of MOPR in AV-12 and HEK293 cells (Kroslak et al., 2007). Additionally, there was a decrease in agonist-mediated cAMP signaling for morphine, methadone, and DAMGO, but not β-endorphin, using stable expression in the two lines; this alteration in cAMP signaling was not seen in cell lines transiently expressing the receptor (Kroslak et al., 2007). Another study using HEK293 cells stably expressing the hMOPR also found a decrease in B_{max} using DAMGO binding in the G118 variant, though they did not find alterations in binding affinity or signal transduction (Beyer et al., 2004). Conversely, a recent study investigating MOPR expression, binding, and signaling in post mortem human tissue from G118 allele-carriers found decreased agonist-induced receptor signaling efficacy in tissue from secondary somatosensory cortex, but not thalamus. However, there were no alterations in receptor expression or binding affinity (Oertel et al., 2009). Together, studies demonstrating that the G118 variant results in significantly reduced levels of MOPR expression and/or signaling suggest a loss-of-function of the mutation, while others reporting an increase in affinity and signaling suggest a gain-of-function.

6. Species-specific SNPs in *OPRM1*: Spontaneous and generated

6.1. Monkey orthologue (C77G)

Non-human primate research has been invaluable in the study of human disease and behavior. A conserved SNP, in which a cystine is replaced by a guanine at position 77 (C77G) resulting in a substitution of arginine with proline (R26P), occurs in the N-terminal arm of the monkey orthologue *OPRM1* and has been suggested to be comparable to the A118G SNP (Miller et al., 2004). In this initial characterization of 32 male and female macaques, 44% were homozygous for the C77-allele, 50% heterozygous, and 6% homozygous for the G77 allele. It was demonstrated that monkeys possessing the minor allele (G77), had lower CORT levels both at baseline and following dexamethasone suppression and subsequent ACTH challenge. In addition to lower CORT levels, the G77 allele was associated with an increase in aggression threat, which is the early communicative aspect of aggression occurring prior to actual physical actions. By expressing these receptor-coding regions in HEK-293, the authors were able to identify an elevated affinity of the G77 allele for β-endorphin (~3.5 fold), but not exogenous ligands, similarly to original *in vitro* work in the A118G SNP (Bond et al., 1998). Subsequent studies have shown an increase in attachment behavior in G77 allele-carrying infants, who displayed increased distress vocalization during protracted periods of mother-infant separation and increased maternal contact during mother-infant reunion (Barr et al., 2008), possibly reflecting increased attachment reward through enhanced β-endorphin function. However, in light of the recent reports of increased social pain associated with the G118 allele (Way et al., 2009), an alternate explanation could be that the infants carrying the G118 allele had a greater sensitivity to maternal rejection, possibly through reduced MOPR function in the neocortex.

A haplotype containing the C77G SNP was shown to result in an increase in MOPR mRNA expression (Vallender et al., 2008). Though the human A118G SNP has been shown to reduce mRNA expression rather than increase it, this serves as further evidence that coding region SNPs may alter mRNA production, folding, or stability. Interestingly, in studying alcohol consumption in these macaques, a sex × genotype interaction was found, in which male carriers of the G77 allele showed elevated ethanol preference and consumption (Barr et al., 2007). In a subsequent study, macaques carrying the G77 allele showed both enhanced alcohol preferences following vehicle administration and greater reductions of alcohol preference following naltrexone administration (Barr et al., 2010).

6.2. Knock-in mouse model (A112G)

Despite information gained from human post mortem tissues, a full understanding of the *OPRM1* A118G polymorphism requires extensive biochemical characterization aligned with behavioral analysis, which is not feasible in human subjects. The mouse is a tractable model system to study behavioral effects of this SNP while at the same time allowing for detailed molecular and biochemical analysis in vivo. Homologous recombination technology can now be used to generate point mutations in mice for those genes in which human SNPs have been identified. This approach, however, has not been fully utilized due in part to the labor-intensive procedures involved in building the complex targeting vectors required. Recent advances and the availability of bacterial artificial chromosome (BAC) vectors have streamlined this process, making the use of knock-in mice a natural progression to investigate human disease. To gain insight into the role of the A118G variant in humans, we have generated the equivalent point mutation in mice, A112G, which alters the same amino acid coding from an asparagine to aspartic acid at position 38 (Asn38Asp; N38D), eliminating an N-linked glycosylation site.

A number of molecular, biochemical, and behavioral alterations that resemble those previously identified in human and *in vitro* studies have been identified in G112 mice (Mague et al., 2009). For instance, the presence of the G112 allele results in decreased MOPR mRNA and

protein expression. This decrease in receptor expression was also seen using [^{3}H]-DAMGO binding, though there were no alterations in affinity for β-endorphin or exogenous ligands (morphine, DAMGO, or naloxone). Mice with the G112 allele showed only a modest elevation in locomotor activity following acute morphine administration and failed to develop sensitization to repeated, intermittent injections. Similarly, G112 mice had reduced morphine-induced antinociceptive responses, though they showed similar signs of tolerance following repeated treatments. A sex × genotype interaction was found in measures of hedonia: female G112-carriers did not display a preference for morphine-associated environments nor did they demonstrate an aversion to environments associated with naloxone-precipitated withdrawal.

Since the A112G SNP alters MOPR expression, some of the behavioral outcomes could be explained by the reduction in protein levels. Indeed, studies investigating opioid responses in MOPR knockout heterozygous mice have found similar reductions in morphine-mediated antinociception using tail flick and hot plate tests (Sora et al., 1997) and sex-specific decreases in alcohol reward using voluntary ethanol consumption and place-conditioning paradigms (Hall et al., 2001). However, these sex-specific differences in ethanol reward were due in large part to elevated responses in wild type female mice compared to wild type male mice, with little differences reported between male and female heterozygous mice. Indeed in wild type male mice, no ethanol preference was observed; therefore, it is difficult to assess whether or not heterozygous MOPR knockout males displayed ethanol reward deficits. In addition to reducing expression levels, it should be emphasized that one consequence of the A112G knockin mouse (and the A118G SNP) is the deletion of an N-linked glycosylation site. Glycosylation plays a role in receptor sorting, expression, trafficking, ligand binding, and signal transduction (Fan et al., 1997; Rathz et al., 2002; Zhang et al., 2001); alterations in these processes could affect MOPR function in ways distinct from protein level changes.

The A112G mouse model, similarly to the C77G non-human primate model, possesses analogous phenotypes as those reported in human studies and identifies new behaviors that have not been investigated. The A112G mouse model seems to replicate the loss-of-function phenotypes (e.g., decreased expression, reduced morphine-mediated antinociception, decreased hedonic reward), though it should be noted that decreases are not present in all morphine-mediated behaviors, suggesting that the alterations are dependent on other factors, including brain region, other neurotransmitter systems, and sex. Future work will investigate the effects of the A112G SNP on alcohol consumption and stress responsivity to evaluate whether or not these animals display any gain-of-function phenotypes as suggested by human studies.

7. Conclusion

The A118G SNP in the human *OPRM1* gene has been studied intensely and implicated in a variety of disease states and treatment responses. In particular, alterations in receptor function resulting from this SNP are believed to contribute to the susceptibility for developing drug dependence. The strongest evidence for a beneficial effect of the A118G polymorphism stems from studies evaluating the response to naltrexone for alcohol and nicotine consumption, highlighting the importance of pharmacogenetics when devising treatment options to determine who may be more likely to benefit from a given therapy. In addition to choosing treatment options, understanding the mechanisms underlying these beneficial effects may allow us to develop therapies for individuals with the common A118 allele.

As acute overdose and long-term dependence are concerns when treating acute and chronic pain with opiates, it is important to minimize the dose prescribed in order to reduce the amount of drug the patient receives. The evidence showing a diminished response to opioid-mediated analgesia in G118 subjects illustrates the need for utilizing pharmacogenetics when developing

treatment options. For instance, though G118 patients require higher doses of opioids for pain management, it has also been shown that they may be more resistant to the respiratory depressive effects of alfentanil than A118 allele-carrying individuals, suggesting that there may be less risk in providing these higher doses (Oertel et al., 2006).

Cross-species experiments allow investigators to validate both pharmacogenetic and physiogenetic phenotypes. Despite the potential of this approach to yield valuable information for treatment development, few mouse/human comparisons of SNPs have been reported. The derivation of the *Oprm1* A112G mouse will allow for such studies to investigate aspects of this SNP that have yet to be delineated in human populations. We know from human studies that the *OPRM1* A118G SNP can impact the response to treatment; however, we have learned from studies in mice that this SNP also influences sex-specific drug behaviors, differences that have been largely ignored in human association studies. Moreover, we anticipate that this mouse model may assist in drug design to generate effective analgesics and other opioid therapies without the risk of abuse liability.

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Table 1

Association studies investigating OPRM1 A118G involvement in drug dependence in humans

Direction of effect	Drug	Method	Finding	Population (number of subjects)	Reference
Protective	Substance dependence	Association	Greater frequency of A118 in drug groups	European American (476)	(Schinka et al., 2002)
Risk	Substance dependence	Haplotype analysis	Greater frequency of haplotype containing G118 in drug-dependent individuals	Eastern European and Russian (720)	(Zhang et al., 2006a)
No association	Substance dependence	Case-controlled association		European American (891)	(Gelernter et al., 1999)
No association	Substance dependence	Case- and family-controlled association		German Caucasian	(Franke et al., 2001)
No association	Substance dependence	Family-based association		European American (1923, from 219 multiplex alcohol dependent families)	(Xuei et al., 2007)
No association	Substance dependence	Haplotype analysis		European American and African American (213 opioid dependence and 196 “supercontrols”)	(Crowley et al., 2003)
No association	Substance dependence	Linkage disequilibrium		European-American and African American (442 substance dependence and 234 control)	(Luo et al., 2003)
No association	Substance dependence	Meta-analysis		Caucasian (German, Finnish, Swedish, EA), African-American, Asian, Hispanic, Native-American (8000)	(Arias et al., 2006)
Risk	Alcohol	Case-controlled association	G118 associated with alcohol dependence	Swedish (467 alcohol-dependent and 170 healthy volunteers)	(Bart et al., 2005)
Risk	Alcohol	Case-controlled association	G118 associated with alcohol dependence	Japanese (64 alcohol dependent and 74 control)	(Nishizawa et al., 2006)
Risk	Alcohol	Association	G118 associated with more days drinking per month, but no significant increase in alcohol-dependence	Korean (112 alcohol dependent and 140 control)	(Kim et al., 2004)
Risk	Alcohol	Association	Trend towards increase of G118 in alcohol-dependent subjects	German (327 alcohol-dependent, 340 control)	(Rommelspacher et al., 2001)
Risk	Alcohol	Association	G118 associated with increased alcohol use disorder (AUD) diagnoses in adolescents	Mostly Caucasian (27 AUD and 160 control)	(Miranda et al., 2010)
Protective	Alcohol	Association	A118 associated with risk for alcoholism	Mexican Americans (365 alcohol-dependent and 338 control)	(Du and Wan et al., 2009)
Protective	Alcohol	Association	A118 had two-fold greater risk for alcohol dependence	Caucasian (105 alcohol-dependent and 122 control)	(Town et al., 1999)

Direction of effect	Drug	Method	Finding	Population (number of subjects)	Reference
No association	Alcohol	Case-controlled association		German (327 alcohol dependent; and 340 control)	(Sander et al., 1998)
No association	Alcohol	Association		US-Caucasian, Finnish-Caucasian, Souithwestern American-Indian (791)	(Bergen et al., 1997)
No association	Alcohol	Association		German (327 alcohol-dependent and 340 control)	(Gscheidel et al., 2000)
No association	Alcohol	Association		Tawainese (158 alcohol-dependent, 149 control)	(Loh et al., 2004)
Risk	Heroin	Association	G118 associated with heroin dependence	Swedish (139 heroin-dependent and 170 control)	(Bart et al., 2004)
Risk	Heroin	Association	90% of G118 were heroin users	European Caucasian (118)	(Drakenberg et al., 2006)
Risk	Heroin	Association	2.5-fold higher frequency of G118 in opioid dependent subjects	Indian (126 opioid dependent and 156 control)	(Kapur et al., 2007)
Risk	Heroin	Association	G118 associated with heroin dependence	Chinese men (200 heroin dependent and 97 control)	(Szeto et al., 2001)
Protective	Heroin	Association	A118 associated with heroin in Indian, but not East Asian populations	Indian (20 dependent, 117 control) Malaysian (25 dependent, 131 control) Chinese (52 dependent, 156 control)	(Tan et al., 2003)
Protective	Heroin	Association	A118 associated with heroin dependence in Hispanic subjects	African-American (46 dependent, 16 controls) Caucasian (60 dependent, 44 control) Hispanic (116 dependent, 78 control)	(Bond et al., 1998)
No association	Heroin	Association		Chinese (48 heroin-dependent, 48 control)	(Shi et al., 2002)
No association	Heroin	Family-based association		Chinese (1208 from 473 families with at least two siblings with opioid dependence)	(Glatt et al., 2007)
Risk	Nicotine	Linkage disequilibrium	QTLs on chromosome 6 associated with nicotine dependence	Dutch twins (536 DZ from 192 families)	(Vink et al., 2004)
Risk	Nicotine	Linkage analysis	Chromosome 6 associated with nicotine dependence	Caucasians from New Zealand (sibling pairs from 129 families with nicotine dependence)	(Sullivan et al., 2004)
No association	Nicotine	Haplotype analysis		Caucasians twins of European ancenstry (688)	(Zhang et al., 2006)

Table 2

Association studies investigating OPRM1 A118G in pain experience and opioid-mediated analgesia

Drug	Method	Finding	Population (number of subjects)	Reference
Morphine	Pain Score and morphine consumption	Reported pain and morphine consumption lowest in AA and highest in GG	Singapore and Han Chinese women receiving morphine for post-cesarean pain (588)	(Sia et al., 2008)
Chronic morphine	Pain Score and morphine consumption	GG required more morphine; no difference in reported pain	Norwegian Caucasians receiving morphine for cancer pain treatment (207)	(Reyes-Gibby et al., 2007)
Chronic morphine	Morphine consumption	GG required more morphine to control pain	Norwegian Caucasians receiving morphine treatment for cancer pain (99)	(Klepstad et al., 2004)
Morphine	Morphine consumption	GG consumed more morphine that AA and AG; no difference in reported pain	Taiwanese patients receiving morphine following arthroplastic knee surgery (147)	(Chou et al,, 2006b)
Morphine	Morphine consumption	G118 required more morphine 24 hours following surgery, but not at 48; no differences in reported pain	Taiwanese female patients receiving morphine following total abdominal hysterectomy (80)	(Chou et al., 2006a)
Morphine	NRS and PPI	G118 were poor responders to morphine treatment	Italian Caucasian patients receiving morphine treatment for cancer pain (145)	(Campa et al., 2008)
Morphine	Morphine consumption	Trend towards an increase in morphine consumption in G118	Mostly Caucasian colorectal surgical patients (74)	(Coulbault et al., 2006)
Morphine or fentanyl	Opioid consumption	GG required more opioid at 24-hr post operation compared to AA and AG	Japanese patients receiving opioid treatment for open abdominal surgery pain (138)	(Hayashida et al., 2008)
Alfentanil	Electrical pain stimulation	GG required higher opioid concentration for pain relief; respiratory depression was not increased with the elevated dose	Healthy German volunteers (20)	(Oertel et al., 2006)
Opioid (Oxycodone, morphine, methadone, fentanyl patch, intrathecal pump)	Pain score (NRS) and evaluation of chronic pain presence x genotype interaction	G118 was less common in members of the chronic pain group; more A118 members were resistant to high-dose opioids.	Mostly Caucasian patients receiving opioid treatment for elecetive laproscopic abdominal surgery (101)	(Janicki et al., 2006)
No drug	Three experimental pain procedures: pressure, thermal, and ischemic	G118 had higher pressure-pain thresholds. Lower thermal pain in G118- allele men, higher in G118-allele women.	Healthy volunteers (mostly Caucasian) (167)	(Fillingim et al., 2005)
Morphine	Pain score and morphine consumption	G118 allele associated with increased pain, increased morphine consumption, but reduced nausea	Women of varying Asian ethnicities receiving voluntary cesarian section (994)	(Tan et al., 2009)