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REVIEW

OPRM1 A118G Polymorphisms and Its Role in Opioid Addiction: Implication on Severity and Treatment Approaches

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Abstract: The epidemic of opioid addiction is shaping up as the most serious clinical issues of current times. Opioids have the greatest propensity to develop addiction after first exposure. Molecular, genetic variations, epigenetic alterations, and environmental factors are also implicated in the development of opioid addiction. Genetic and epigenetic variations in candidate genes have been identified for their associations with opioid addiction. *OPRM1* nonsynonymous single nucleotide polymorphism rs1799971 (A118G) is the most prominent candidate due to its significant association with onset and treatment of opioid addiction. Marked inter-individual variability in response to available maintenance pharmacotherapies is the common feature observed in individuals with opioid addiction. Several therapies are only effective among subgroups of opioid individuals which indicate that ethnic, environmental factors and genetic polymorphism including rs1799971 may be responsible for the response to treatment. Pharmacogenetics has the potential to enhance our understanding around the underlying genetic, epigenetic and molecular mechanisms responsible for the heterogeneous response of maintenance pharmacotherapies in opioid addiction. A more detailed understanding of molecular, epigenetic and genetic variants especially the implication of *OPRM1* A118G polymorphism in an individual may serve as the way forward to address the opioid epidemic. Personalized medicine, which involves developing targeted pharmacotherapies in accordance with individual genetic and epigenetic makeup, are required to develop safe and effective treatments for opioid addiction.

Keywords: opioid addiction, personalized medicine, pharmacotherapies, epigenetic and genetic variants

Introduction

Exposure to illicit drugs dysregulates brain reward circuits leading to compulsive drug-seeking behaviour. Short term or chronic use of addictive drugs is associated with changes in brain chemistry, particularly in the reward circuits. Chronic misuse of drugs can result in physical dependence where individuals require higher doses of the drug to achieve the same effects. Furthermore chronic use has the potential to cause permanent molecular and structural adaptation in brain circuits resulting in compulsive drug-seeking behaviour; addiction.[1]

Incidence of drug addiction is on the rise globally. It is well recognised that opioids have the highest addiction causing potential after first exposure compared to other substances. Once exposed to opioids, approximately 23% of individuals may go onto develop opioid addiction in their life span. The economic cost of opioid

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addiction on health and social care, crime, deterioration of social and family fabric is remarkably high.[2,3]

Efficacy of pharmacotherapies for opioid addictive disorders is estimated to be between 60–70%. It is widely acknowledged that there is a strong interplay between responsiveness and genetic profile accounting for poor success rates. Responsiveness to treatment is dependent on genes that regulate the synthesis, metabolism, and transport of major neurotransmitters involved in reward behaviours and drug use, therefore, developing a more detailed understanding of alterations in the mechanism of action of pharmacotherapy due to genetic polymorphism is critical.[4]

The opioid response is mediated by G protein-coupled receptors (μ, κ, and δ) in the central nervous system which binds endogenous and exogenous opioids with high affinity. This causes reduced transmission of nerve impulses and inhibits neurotransmitter release.[5] The most widely studied gene for addiction is the gene encoding the mu-opioid receptor (*OPRM1*) to which opioids bind and exert their therapeutic effect. Most pharmacotherapies on the current market such as methadone, buprenorphine, naloxone or naltrexone target this receptor. Other aspects of the opioidergic system such as *OPRK1* and *OPRD1* have been studied in terms of their role in opioid addiction but yielded inconsistent results.[6,7]

Opioids exert their effects through endogenous opioid receptors which are implicated in the regulation of reward, motivation, and addiction-related behaviours. One of the key endogenous opioid receptor (μ opioid receptor 1) is encoded by the *OPRM1* gene which mediates positive reinforcement following its activation and serves as a gateway for the development of addiction. Several studies have shown that single nucleotide polymorphism (SNP) in the *OPRM1* gene is associated with dependence related behavioural changes. The *OPRM1* gene SNP A118G encodes μ opioid receptor's isoform (Asp40 variant) which has a 3 fold higher binding affinity for opioid ligands.[8–10] Altered receptor binding affinity towards opioid ligands may trigger elevated positive reinforcement that may consequently contribute to the susceptibility for developing opioid dependence.[11]

OPRM1 A118G polymorphism also governs the success of maintenance pharmacotherapies such as; methadone, naltrexone, buprenorphine and buprenorphine-naloxone. Methadone is regarded as the primary maintenance therapy to treat opioid addiction. Individuals with *OPRM1* A118G variation demonstrate approximately 2.3 times higher methadone plasma concentration, leading to increased pharmacological effects compared to non-carriers. Animal and *in vitro* studies have shown that *OPRM1* A118G polymorphism regulates buprenorphine efficacy in allele-specific manner.[12] Individuals with *OPRM1* G-allele responded well to naltrexone compared to patients carrying the AA genotype.[13]

Individuals with opioid addiction when treated with maintenance pharmacotherapies have demonstrated heterogeneous responses to treatments.[13–15] Available maintenance pharmacotherapies are only effective in 60–70% of addicts suggesting further research is needed to understand inter-individual variation.

Pharmacogenetics has the potential to reveal the underlying molecular, genetic and epigenetic mechanisms responsible for the heterogeneous response. Detailed understanding of genetic variants especially the implication of *OPRM1* A118G polymorphism in an individual's vulnerability to developing opioid addiction is the key to choose the most appropriate and effective pharmacotherapies to address both opioid addiction. Hence, personalized medicine; therapeutic treatments developed in accordance with individual human genetic patterns are warranted to develop safe and effective treatments for opioid addiction.

Medication Strategies for Opioid Addiction

Pharmacogenetic Approaches

Genetic and epigenetic variations are implicated in complex and heterogeneous therapeutic response to maintenance pharmacotherapies.[15] Pharmacogenetic approaches can assist to determine the implication of genetic polymorphism (in the endogenous opioid system and CYP450 2B6, CYP2D6, CYP1A2 and CYP3A4 encoding genes) on the possible dosage regime and outcome of maintenance pharmacotherapies. Genetic polymorphisms in enzyme (which metabolize maintenance pharmacotherapies) encoding genes may determine individual-specific therapeutic doses[16] while *OPRM1* polymorphisms severe as a predictor for individual response to maintenance pharmacotherapies.[17–19] Understanding of molecular, epigenetic and genetic variants particularly in endogenous opioid encoding genes and metabolizing enzymes especially *OPRM1* A118G polymorphism will assist clinicians to use pharmacogenetic tools to address the opioid epidemic by tailoring the treatment to meet the needs of the individual.

Endogenous Opioid System

The endogenous opioid system consists of Mu (μ), delta (δ) and kappa (κ) receptors, and their endogenous ligands play a key role in the regulation of reward, well-being, motivation, and developing addictive behaviours. The endogenous opioid system particularly μ opioid receptor system serves as a gateway to developing an addiction as repeated and aberrant activation and modifications of μ receptors contribute to drug craving and relapse. Drugs with addictive properties can trigger cellular, molecular, structural and epigenetic adaptation in the endogenous opioid system.[20] This modulation in endogenous opioid system particularly μ opioid system in central reward site alters reinforcing effects of addictive drugs but also dysregulates local release of endogenous opioids which contributes to underlying neuroadaptations responsible for the development drug addiction.[21]

The endogenous opioid receptor system is encoded by *OPRM1, OPRK1, OPRD1*, and *OPRL1* genes. Several studies have shown that genetic variations in opioid system encoding genes are significantly associated with drug addiction.[22–24] In addition to opioid system encoding genes, *GAL*, cytochrome P450, and *ABCB1* and their related molecular pathways are reported for their implication both in the development and treatment of opioid addiction.[25,26]

OPRM1 A118G Polymorphisms

μ opioid receptors in reward sites serve as a gateway for reward, motivation and addiction behaviour triggered by opioids. Variation in responses to opioids can be explained by an individual genetic polymorphism in the *OPRM1* gene. Genetic variations in the *OPRM1* gene are responsible for opioid-mediated clinical presentations but also involved in the risk of developing opioid addiction.[9,11,27,28] The most studied genetic polymorphism isthe *OPRM1* A118G gene which is implicated in opiate-mediated pharmacological, psychological and opioid addiction-related behaviours.[29,30] The polymorphism is located within exon 1 region of the *OPRM1* gene and causes amino acid exchange from asparagines to aspartate at position 40 of the μ opioid receptor. μ opioid receptors carrying aspartate instead of asparagines receptors demonstrate increased sensitivity to opioids which contributes towards the development of opioid addiction.[31–33] Several studies have demonstrated a significant association of *OPRM1* A118G with the vulnerability to develop an opioid addiction, although findings are inconsistent.[10,23,34] *OPRM1* gene polymorphisms including A118G play a critical role in the outcome of maintenance pharmacotherapies particularly methadone.[17] The outcome of maintenance pharmacotherapies can be predicted accurately by focusing on genetic variations in enzymes (related to drug metabolism) encoding genes together with *OPRM1* gene polymorphism.[35]

Genetic Polymorphisms Based Approaches

Majority of individuals develop opioid addiction soon after their first exposure to opioids. The course of developing opioid dependence and addiction is a highly variable individual-specific phenomenon. Some individuals have comparatively higher sensitivity for opioid addiction than others. Individual variability may result from the multifaceted complex interplay among neuro-molecular, genetic, epigenetic and environmental factors.[36,37] A profound understanding of genetic markers implicated in altered individual sensitivity to opioids, underlying adaptations in the neurobiology of reward circuit and differential vulnerability to develop an addiction may reveal novel neuro-molecular targets for the development of optimized personalized therapies.[15]

A118G and Pharmacogenetics of Opioid Addiction

The frequency of the A118G polymorphism is highly variable ranging from 2% in Afro-Americans, 8–30% in Caucasians and 50% in Asian populations (Table). Amino acid substitution by A118G polymorphism in the coding region of *OPRM1* modifies mu opioid receptor structure and function which may alter receptor sensitivity towards opioids.[38] *In virtro, in-silico* and animal studies have shown that G118 carriers have 3 folds higher binding affinity towards endogenous but not exogenous ligands compared to A118 carriers.[11,39,40] Several genetic studies (primarily case-control studies) have been carried to determine the impact A118G variant both on the onset and treatment of opioid and other addictions. Outcomes are highly diverse in which some studies have shown a significant association of A118G with opioid addiction while other studies have failed to obtain such evidence.[41] The probability to develop opioid addiction is less in Hispanic 118G carriers compared to individuals with African-American or Caucasian ethnic backgrounds.[11] Similarly, 118A allele enhances vulnerability to develop opioid addiction in Indian individuals (living in Singapore) but not in other ethnic groups such as Malay and Chinese.[42] A significant association between 118G and

opioid addiction is reported in Han Chinese and Swedish individuals.[29,43] While some studies carried out to evaluate the implication of A118G polymorphism in the development of opioid addiction in German Caucasians, American Caucasians and African-Americans populations have not found any association for 118A/118A versus 118A/118G or 118G/118G genotype frequencies.[18,44]

OPRM1 A118G not alone but together with haplotype SNP rs 3778150 may direct it's association with addiction.[45] A collaborative meta-analysis has shown that *OPRM1* A118G has an allele-specific but modest impact on underlying genetic mechanisms implicated in the vulnerability to develop substance dependence.[46]

Positron emission tomography (PET) studies have investigated the association of A118G polymorphism with mu-opioid receptor's density and binding potential in the brain regions implicated in habit formation and addiction. G118 allele is associated with lower mu-opioid receptor binding potential in nucleus accumbens and amygdala which indicates that A118G is responsible in drug reward and individual's predisposition to addiction by affecting mu-opioid receptors density and binding potential.[47–50] A recent Genome-Wide Association Study (GWAS) successfully reported a significant association with methadone doses required to produce intended pharmacological effects and a genomic locus closet to *OPRM1* gene in African-American but no such signification of the locus was reached in European- American and combined population pool.[51]

Inconsistent outcomes can be explained by taking into account the low sample size, less characterized sample pool, gender and ethnicity. GWAS and genetic studies with higher and well-characterized samples pool are warranted to depict the clear picture. GWAS together with previous studies suggests that *OPRM1* A118G polymorphism may govern the development of opioid addiction in allele and ethnic-specific manner.

Pharmacogenetics of Opioid Addiction Treatment

Efficacy of the given pharmacotherapy is determined by a complex interplay between genetic, epigenetic, molecular variations, comorbid substance abuse, psychiatric disorders and related environmental factors. Studies have established that A118G polymorphism may determine the plasma cortisol response to opioid blockade (naltrexone treatment) at *OPRM1* receptors in allele-specific manners. A118G alleles carriers show higher cortisol sensitivity to naloxone than non-carriers.[52,53] A118G polymorphism governs pharmacogenetic responses in allele specific manner by triggering differential responses to morphine and its active metabolite in individuals carrying A118G allele.[54] A118G heterozygous individual responded well to the opioid antagonist, naltrexone, compared to A118A carriers.[29] Lötsch et al have reported that A118G carriers resulted in decreased potency of methadone.[54] Similarly, another study has registered that homozygous variant (GG) of A118G polymorphism carriers show decreased efficacy to morphine therefore requiring higher opioid doses to produce therapeutic effects.[55]

OPRM1 A118G polymorphism may govern the outcome of maintenance pharmacotherapies; methadone, naltrexone, and buprenorphine (Table 1). Methadone, mu-opioid receptor agonist, is one of the most common treatments prescribed for opioid addiction. Methadone oral formulation contains a racemic mixture of two enantiomeric forms; (R-methadone and (S)-methadone,[56] Individuals with *OPRM1* A118G demonstrate 2.3-times higher methadone plasma concentration compared to non-carriers. *OPRM1* A118G carriers may require comparatively low methadone doses to produce it's desired therapeutic effect. Pharmacogenetic studies have assisted to adjust methadone therapeutic doses to address high dose related toxicity and even death in worst cases.[57,58]

Buprenorphine is a weak mu-opioid agonist and is another commonly used maintenance pharmacotherapy for the treatment of opioid addiction.[59] Depending on the formulation of buprenorphine it can exert its effect over 36 hours for sublingual preparations or up to one month

Table 1 Mechanism of Actions for Available Maintenance Pharmacotherapies for Opioid Addiction

Patients	Treatment	Mechanism of Action	Authors, Year
Opioid addiction	Methadone	μ opioid receptors agonist	Chamorro et al,[13] 2012; Kharasch et al,[16] 2015; Wang et al,[17] 2013
Opioid addiction	Buprenorphine	μ opioid receptors agonist	Berrettini, et al,[15] 2017
Opioid addiction	Naltrexone	μ opioid receptors antagonist	Chamorro et al,[13] 2012; Berrettini, et al,[15] 2017

with the sustained-release preparations and with transdermal patches effects can last for 6 months.[59–61]

Naltrexone, opioid antagonist, with the highest affinity towards μ receptors, represents another important therapeutic agent for maintenance therapy. Naltrexone, both oral and parenteral formulations has least abuse potential and is approved by Food and Drug Administration (FDA) in the USA for the treatment of opioid addiction. Therapeutic effects range from 24–36 hours to one month for oral and parenteral preparations respectively.[62,63] Several studies support the notion that individuals with *OPRM1* A118G polymorphism respond well to naltrexone treatment compared to patients carrying the AA genotype.[13] These studies highlight the importance of *OPRM1* A118G and genetic polymorphism in enzymes encoding genes (which metabolize maintenance pharmacotherapies) to understand the pharmacodynamics and pharmacokinetics of maintenance pharmacotherapies.[64,65]

Cytochrome P450 Polymorphism; Dose Requirements

They are several cytochrome P450 isoenzymes (CYP 2B6, CYP2D6, CYP1A2 and CYP3A4) that are involved in the metabolism of currently available maintenance pharmacotherapies.[66] Metabolizing activity of these isoenzymes is variable and highly individual specific. These functional variations are due to the individual's genetic polymorphism and environmental factors.[66–68] Individuals carrying different sets of genetic polymorphisms (in the genes encoding cytochrome P450 isoenzymes) will metabolize maintenance therapies at different rates depending upon their genetic makeup.[69] These genetic variations have clinical relevance by affecting dose requirement for maintenance therapies.[66]

Alternative Splicing Based Approaches

Alternative splicing is an efficient process that results in multiple subtypes of a wild type protein with differential and diverse functional spectrum. Alternative splicing in μ opioid receptors is responsible for the generation of multiple subtypes of μ opioid receptors with heterogeneous and diverse functions.[70] Studies have shown that subtypes of μ opioid receptors may differ from each other in the term of their amino acid and axons patterns and functional spectrum.[71,72] Animal studies have identified three distinct splice variants of μ opioid receptors.[73] These μ opioid receptor isoforms may selectively trigger different downstream signalling pathways to prompt a diverse spectrum of clinical presentations. Alternatively, spliced C-terminal truncated μ opioid receptor isoforms have shown the same therapeutic effect while reducing tolerance.[71] These findings augment human studies to develop novel μ opioid receptors ligands having therapeutic potential while avoiding tolerance.[74] Multiple receptors subtypes (isoforms) play a critical role in an individual's response to maintenance pharmacotherapies that warrant the need to consider each subtype of μ opioid receptor splice variants while developing novel and effective personalized medications for addiction.[70,75,76]

Epigenetic Based Approaches

Alteration in signalling pathways, genetic variations and environmental factors including epigenetic modifications may play a critical role in the development of opioid addiction and individual-specific response to maintenance pharmacotherapies.[77–79] Chronic exposure to higher doses of opioids is significantly associated with hypermethylation in the promoter region of *OPRM1* gene that may impede gene expression and consequently result in reduced μ opioid expression in human reward regions.[33,78,80] Reduced μ opioid receptor density in human reward regions require higher opioid doses to produce intended effects in opioid misusers.

Several studies have documented significant alteration in the epigenetic landscape (DNA methylation, histone modifications) in opioid addiction-related genes in the human reward system.[81,82] It suggests that epigenetics may play a key role in the onset and treatment of opioids addiction. Comprehensive understanding of epigenetic implication in opioid addiction and its treatment may help to develop targeted personalized therapies.

Personalized Medication Therapy; a Way Forward

We cannot address effectively the current opioid epidemic with available maintenance pharmacotherapies as these are effective only in a subgroup of the population. Partial successes of available maintenance pharmacotherapies suggest that some crucial links are missing to develop safe, effective and optimized therapies against opioid addiction. Approaches should deal with the improvement of current maintenance pharmacotherapies by using latest knowledge acquired by current research that addresses the implication of neuro-molecular, genetic and epigenetic mechanisms in opioid addiction. Novel pharmacotherapies

should specifically restore normal synaptic plasticity in opioid addicts. These strategies may also prevent the transition from dependence to addiction.

The opioid crisis also warrants the need to develop novel personalized pharmacotherapies by integrating patient's clinical phenotypes, individual genetic variation, and epigenetic landscape. Such approaches may provide stronger foundations to develop safe, effective, optimized and targeted personalized pharmacotherapies.

Disclosure

The authors report no conflicts of interest in this work.

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