REVIEW ARTICLE

Pharmacogenomics of neuropathic pain

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Abstract

Variation in pain sensitivity and analgesic drug response is well recognized among individuals. Pharmacogenomics hypothesis dictates that a patient's response to a drug or development of adverse drug effects may depend on variation in genetic profile, in particular, the different alleles for the same gene that an individual carries. A review of the role of genetic variations in determining the receptor sensitivity and modulation of pain, response to analgesics drugs and their interactions are presented in this article. It is already known that genomic variations affect the pharmacokinetic and pharmacodynamic properties of various analgesic drugs. Genes related to the expression of mu-opioid receptor, ATP-binding cassette B1 (ABCB1), catechol-O-Methyl Transferase (COMT), Cytochrome P450 enzymes have been widely studied and show some promise in determining the drug response in individuals. Some recent studies on sodium channel mutations (SCN9A, SCN11A) have been implicated in congenital insensitivity to pain. Voltage gated ion channels such as sodium, calcium and potassium channels are being targeted for development of novel analgesics. Based on the available research, the clinical implementation of pharmacogenomics for personalized pain medicine is still in its infancy, but is promising. These are opening further opportunities for development of newer analgesics targeting pain receptors and ion channels.

Key words: Genetics, neuropathic pain, pharmacogenetics, pharmacogenomics

INTRODUCTION

With the advent of the science of pharmacogenomics, we move closer towards the practice of 'personalised medicine' rather than the classic principle of 'one dose fits all'. The fact that different patients respond variably to the same medication has been observed for ages; however, little was known that the answer to this variable drug effect was related to the differences in their genetic makeup. Each individual has a distinctive genetic blueprint generated from the unique DNA sequence pattern that translates into a variable expression of different proteins. The drug effect variability among the individuals stems from the changes that could be as subtle as a shift of one DNA nucleotide (single nucleotide polymorphisms [SNPs]) or as complex as a complete gene mutation. The implications of this variability in pain medicine can be tremendous, as the corresponding phenotype dictates alterations in pain perception[1] and modulation, analgesic dose requirements and sensitivity,[2,3] drug metabolism as well as drug interactions with other concomitantly administered drugs.

Current literature shows that after a major nerve injury, a small percentage of patients progress to chronic neuropathic pain states. The transition into the chronic pain state is greatly unpredictable, in terms of severity of

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Access this article online	
Quick Response Code:	Website: www.jnaccjournal.org
	DOI: 10.4103/2348-0548.197431

How to cite this article: Sharma V, Munish. Pharmacogenomics of neuropathic pain. J Neuroanaesthesiol Crit Care 2017;4:4-9.

the symptoms, the analgesics response, and the tolerance to neuropathic modulating drugs. It is perceivable that this variability cannot be explained on the basis of genetics alone and other factors such as environment may play a role as well which is beyond the scope of this article.

Several animal and human models have been used to study the pathophysiology and modulation of neuropathic pain and have added immensely to the current concepts of pharmacogenomics of neuropathic pain. An interesting paper by Rode *et al*.[4] showed different pain behaviours and pharmacologic sensitivity in four different rat strains using a spared peripheral nerve injury model. The strains, which had different genetic backgrounds showed a marked dissimilarity in their susceptibility to develop hyperalgesia. They also showed a distinct variation in resolution of post-injury hyperalgesia in response to morphine, gabapentin and gaboxadol. Similarly, in humans, wide inter-variability has been proven with respect to the response to opioids, tricyclic antidepressants and duloxetine, when used for the treatment of pain, particularly neuropathic pain.[3,5-7]

To elucidate the underlying process further in detail, we will first discuss the concept of SNPs. Each SNP (pronounced as 'snip') represents a change in the sequence of DNA building blocks known as nucleotides (A, T, C or G) at a certain position in the genome. For example, in a DNA sequence, nucleotide adenosine (A) may replace cytosine (C) resulting in a different allele of the same gene. Based on the SNP consortium and the analysis of clone overlaps by the international human genome consortium, a map of 1.42 million SNPs distributed throughout the human genome has been described.[8] The map highlights an average density of one SNP every 1.9 kilobases. The frequently of SNPs in the genome may explain the basis of genetic variation among different individuals and also susceptibility to different diseases depending on where they fall in the genomic sequence (coding or non-coding regions). For example, catecholamine O-methyltransferase (COMT) is an enzyme responsible for the metabolism of catecholamines by transferring the methyl group from S-adenosyl methionine to the catecholamine molecule. SNP variations in the COMT gene located in chromosome 22 can result in a dramatic reduction in the enzyme activity in homozygous individuals. This decrease in activity can result in high catecholamine levels manifesting as exaggerated pain perception.[9,10] In other studies, SNP variations in COMT gene have been associated with susceptibility to various pain states such as migraine and fibromyalgia as well as variation in the response to opioids.[9,11,12] Moving on to the example of the most well analysed SNP in the pain pharmacogenomics, opioid receptor mu 1 (OPRM1) at site 118A>G. OPRM1 gene codes for the mu-opioid receptor, which is the main target of both endogenous and exogenous opioids. Polymorphism at 118A>G is associated with modulation of opioid efficacy and the variation seen with opioid effect in different individuals.

The terms 'pharmacogenetics' and 'pharmacogenomics' are often used interchangeably; however, pharmacogenomics is a wider term that encompasses the variability in drug responses based on the whole genome of an individual, whereas pharmacogenetics involves single gene variation and its effects on drug response. Even although the application of pharmacogenomics in pain is still in its infancy, it holds promise for individualised treatment and preventing drug interactions in the future.

In this article, we will discuss the pharmacogenomics of neuropathic pain, which can be divided for the ease of study to gene variations affecting the pain sensitivity and gene variations affecting drug metabolism within the realm of neuropathic pain. A short summary of these effects is presented in Table 1.

GENE VARIATIONS AND PAIN SENSITIVITY

Catecholamine O-methyltransferase and opioid receptor mu 1 polymorphisms

We briefly discussed the polymorphisms in COMT gene and OPRM1 genes in affecting individual pain sensitivity and response to opioids. COMT contains a frequent coding SNP (G1947A) that codes for a Val158Met substitution that results in reduced COMT activity. An important paper by Zubieta *et al*.[13] showed that individuals who are homozygous for the methionine allele showed the most reduced activity of COMT, which correlated with diminished regional mu-opioid system activation to pain stimuli compared with the heterozygotes. Conceivably, these effects were associated with increased pain sensitivity as measured by higher sensory and affective ratings of pain stimuli. Opposite effects were observed in the valine homozygotes group.

As for OPRM, several studies have examined the link between the 118A>G polymorphism and opioid effects as well as dependence; the results were inconclusive yet.[14] A meta-analysis of phenotypes by OPRM1 genotype showed a weak association of increased opioid dosage requirements in homozygous carriers of the G allele.[15] However, the effect of gene variation was not strong clinically, as it is reflected in only a small increase in peri- and post-operative opioid requirements.[16] Hence, this association was considered overstated. Further studies elaborated on the difference in OPRM1 gene expression between different ethnic groups and found

Table 1: Genetic polymorphisms affecting analgesic pharmacology and pain phenotypes

Protein function	Protein/enzyme	Polymorphism	Drugs affected	Effects of polymorphism
Metabolic enzyme: Drug oxidation	CYP2D6		Codeine, tramadol, oxycodone, hydrocodone, tricyclic antidepressants	Over or under-dose of drug depending on phenotype
	CYP2C9		NSAIDs, celecoxib	NSAID toxicity
	CYP3A4		Fentanyl, oxycodone, tramadol, methadone, buprenorphine	Altered drug concentrations in plasma
	CYP2B6		Methadone	
Drug efflux transporter	ABCB1	C3435T	Morphine	Reduced morphine transport from CSF: Respiratory depressant effects of opioids
Metabolic enzyme: Drug glucuronidation	UGT	UGT2B7-840G>A	Morphine	Reduced morphine glucuronidation to M6G, less CNS side effects
Metabolism of catecholamines and modulation of pain	COMT	Val158Met		Altered pain perception
Mu-opioid receptor function	OPRM1	118A>G	Opioids	Altered opioid sensitivity

Adapted from Norbury *et al*.[24] CYP=Cytochrome P, NSAIDs=Non-steroidal anti-inflammatory drugs, CSF=Cerebrospinal fluid, UGT=Uridine 5'-diphospho-glucuronosyl transferase, M6G=Morphine 6-Glucuronide, COMT=Catecholamine O- methyltransferase, OPRM1=Opioid receptor Mu 1, CNS=Central nervous system, ABCB1=ATP binding cassette subfamily B member 1

that OPRM1 polymorphism was indeed associated with higher incidence of opioid and alcohol dependence among Asians.[14]

A118G polymorphism in both heterozygous, as well as homozygous individuals, has been linked to a reduction in potency of morphine-6-glucuronidation[17] or even protection from the toxic effects of morphine-6-glucuronide.

Given the separate effects of both COMT and OPRM1, it would be interesting to see the phenotypic expression of such combined polymorphisms. A prospective observational study by Kolesnikov *et al*. assessed the effects of combined polymorphisms OPRM1 (A118G) and COMT genes in the patients undergoing abdominal surgery.[18] The authors reported that the heterozygous patients with above polymorphisms required significantly less morphine in recovery period immediately as well as 48 h after surgery, less nausea and sedation compared with homozygous alleles. The authors could not identify individuals who were homozygous for both these polymorphisms but raised an important question whether this population would require even lesser doses of morphine than the heterozygous individuals.

With a series of smaller, low power studies and inconclusive findings, it is hard to draw any conclusions on the actual effects of COMT and OPRM gene polymorphisms on clinically significant effects in patients. It worth remembering that in the post-operative period, a multitude of environmental and behavioural factors play a role in determining opioid requirements and toxicity. So far, a clinically meaningful role of genetic factors has not been fully elucidated.

ATP binding cassette subfamily B member 1 polymorphisms

The ATP-binding cassette subfamily B member 1 (ABCB1) gene encodes a major efflux transporter P-glycoprotein. This P-glycoprotein is present in the central nervous system (CNS) and limits the entry of some opiates into the brain by actively pumping a variety of drugs out of the CNS.[19] Thus, it is an important component of the blood-brain barrier. The most commonly studied polymorphism in ABCB1 gene is C3435T. This SNP is associated with reduced expression of P-glycoprotein. As a result, patients with mutant genotype could have a higher concentration of morphine in the cerebrospinal fluid and require smaller doses of morphine for pain control.[20] A recent study tested the association of SNO C3435T in ABCB1 and opioid consumption in the post-operative period in 152 patients after nephrectomy.[21] The authors found that the TT genotype had significantly lower opioid consumption compared with the CC genotype in the first 24 h after surgery.

A more recent study investigated the association of OPRM1, ABCB1 and COMT polymorphisms and the analgesic effects of morphine for post-operative pain in children. The authors found that children with G allele for OPRM1 had higher post-operative pain scores compared with the AA genotypes. They did not find a significant relationship between genotypes and post-operative pain in ABCB1 and COMT polymorphisms.[22]

On similar lines, another study on the association of ABCB1 and OPRM1 gene polymorphisms with morphine pain relief found that in 145 adult patients, pain relief variability was significantly associated with both polymorphisms. In patients with combined homozygous polymorphic alleles of both genes, pain relief was significantly improved with morphine therapy.[23]

Voltage gated sodium channels

Congenital insensitivity to pain (CIP) is another rare genetic disorder in which a number of mutations have been implicated. Pedigree studies on families with this rare condition have been performed. So far gain of function mutations in sodium channels NaV 1.7 (SCN9A) and NaV 1.9 (SCN11A) have been shown to cause some forms of CIP. The same gene SCN9A also exhibits increased sense mutations, which cause the rare opposite phenotype erythromelalgia, including congestion, vasodilation and burning pain in feet and lower extremities.[24] Another pedigree trial by Chen *et al*. recruited subjects with CIP from 11 families throughout the world.[25] They identified ten homozygous mutations in PRDM12 protein, which is a regulator protein class expressed in nociceptors and controls neurogenesis. The phenotype of affected individuals was same across these pedigrees, as they displayed an inability to detect pain or thermal noxious stimuli. Further research into mutations like this could potentially form a platform for discovering novel analgesics that could target pain at a genetic level.

Genetic variation effects on drug metabolism

After oral administration, analgesic drugs are carried from the gastrointestinal mucosa to the liver where the drugs are metabolised by the first pass metabolism before entering the systemic circulation. The enzymes responsible for the first pass metabolism are classified as Phase 1 and Phase 2 enzymes. The broad category of Phase 1 enzymes includes the cytochrome P450 (CYP 450) family, whereas the Phase 2 enzymes include the uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes. The apparent potency of analgesic drugs is, therefore, potentially affected by SNPs in genes encoding these enzymes.

Cytochrome P polymorphisms could result in four phenotypes

Poor metabolisers, intermediate metabolisers, extensive metabolisers and ultrarapid metabolisers based on the presence of one or more non-functional variant alleles.[26] The incidence of different phenotypes varies in different ethnic groups [Table 2].[27]

CYP2D6 enzyme is involved in metabolism of multiple drugs used in the management of neuropathic pain such as opioids, tramadol and antidepressants (tricyclic antidepressants, duloxetine). Poor metabolisers are homozygous for non-functional variants and therefore have a high risk for drug overdose or no drug efficacy due to poor transformation of prodrug to active drug metabolites (e.g., codeine to morphine). Similarly, ultrarapid metaboliser phenotype may suffer from morphine toxicity resulting from the excessive metabolism of pro-drug codeine to its

Table 2: Incidence of cytochrome P450, cytochrome P2D6 enzyme phenotypes among different ethnic groups

Population	Poor metabolizer phenotype (%)	Ultra-rapid metabolizer phenotype (%)
Caucasian		
American	7.7	4.3
British	8.9	
African		
African-American	1.9–7.3	4.9
South African	19	
Asian		
Indian	1.8–4.8	0.9
Chinese	<1.0	
Japanese	0	
Hispanic		
Mexican	3.2	

Adapted from Lee *et al*.[22]

metabolite morphine. Therefore, codeine should not be administered to paediatric population or to breastfeeding mothers. Tricyclic antidepressants are widely used as first and second line agents for various neuropathic pain states. They are metabolised by CYP2D6 and CYP 2C19, which are both expressed by highly polymorphic genes. Patients may be predisposed to treatment failure or adverse effects due to polymorphism in these enzyme genes.[6,28] Adverse effects from tricyclic overdose may be life-threatening and include anticholinergic, CNS and cardiac effects. They should be started at lower doses and then titrated higher based on the clinical response. Clinical pharmacogenetics implementation consortium guidelines recommend avoiding TCAs in CYP2D6 ultrarapid or poor metabolisers, and 25% dose reduction is recommended for CYP2D6 intermediate metabolisers.[28]

CYP3A4 enzyme is involved in the metabolism of several opioids such as fentanyl, tramadol, methadone, oxycodone, codeine and buprenorphine. Marked differences in the sensitivity of intravenously administered Fentanyl can be seen in the immediate post-operative period, which may be explained by its metabolic enzyme polymorphisms. Methadone is a long-acting opioid used in the management of both somatic as well as neuropathic pain due to its N-methyl-D-aspartate receptor activity. This drug is metabolized by CYP3A4 to a major extent and CYP2D6 to a minor extent.

The principle of careful titration to effect should be used when administering opioids for pain relief to minimise the life-threatening side effects, as it is impossible to tell clinically which patients would require higher or lower doses.[29] Thus a personalised approach utilising pharmacogenomics may help predict the poor metabolisers versus ultrarapid metabolisers and the associated drug effects. The use of pharmacogenomics testing is still not prevalent in the United States at a larger level.

Uridine 5'-diphospho-glucuronosyltransferase enzyme pathways

Several polymorphisms of UGT enzymes have been described. Enzyme UGT1A1 catalyses the glucuronidation of opioids such as morphine, buprenorphine and norbuprenorphine.[30] The effect of UGT1A1 polymorphism has been investigated in cancer patients, but no association has been demonstrated.[31] Another enzyme involved in morphine metabolism is UGT2B7. It has been shown that UGT2B7 promoter variant-840G>A is associated with reduced glucuronidation of morphine contributing to its variable hepatic clearance in sickle cell patients.[32]

One study looked at genetic polymorphisms in UDT1A1 and its association with inter-individual variability in acetaminophen glucuronidation in liver. They found that polymorphism in UGT1A1 (rs8330) is associated with increased acetaminophen glucuronidation and therefore decreased risk of unintentional acetaminophen-induced acute liver failure.[33]

CONCLUSIONS

Despite several advances in the field of pharmacogenomics and its application in the treatment of neuropathic pain, there are very few clinically significant markers that are practical as well as cost-effective in determining pain sensitivity and individual response to pain medications. More robust studies are needed in this field. At the same time, it is important to realise that it is the complex interplay between both the genetic and environmental factors that determines the drug response. We are still awaiting the maturation of meaningful genetic testing on a more conventional basis that could predict the drug dose adjustment to avoid drug toxicity.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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