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Genetics of pain, opioids, and opioid responsiveness

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Abstract

Pain is an integral part of the defense mechanisms required for survival. Several hereditary syndromes of complete or almost complete insensitivity to pain have been identified and include channelopathy-associated pain insensitivity, of which the most likely candidate gene is the α-subunit of the voltage-gated sodium channel known as *Na(v)1.7*. Five hereditary sensory and autonomic neuropathy syndromes have been described. Variable pain sensitivity in the general population has been linked to common variants of the μ-opioid receptor and of the catecholamine-*O*-methyltransferase genes potentially leading to increased opioid tonus. Variants of the guanosine triphosphate cyclohydrolase 1/dopa-responsive dystonia gene appear to regulate nociception. Other candidate genes are the transient receptor potential cation channel, subfamily 5 member 1, gene and the melanocortin-1 receptor gene. Candidate genes for predicting opioid efficacy are drug-metabolizing enzymes and transporters—including cytochrome P450, uridine 5′-diphosphate-glucuronosyltransferases, and adenosine triphosphate–binding cassette transporters—that are involved in opioid metabolism. Most current knowledge on the genetic regulation of pain has been derived from animal models developed mainly in mice. Genomics has the potential to contribute to therapeutic advances with the promising approach of using small interfering RNA in the control of neuropathic pain. Knowledge of the genetic factors that affect opioid efficacy, metabolism, and adverse effects has the potential for personalizing both acute and chronic pain management, and for designing more useful opiate pain medications with lower adverse event profiles.

1. Introduction

The ability to sense pain (nociception) is variable in human populations as well as in animals; its heritability, genetic correlations, and linkage point to the importance of its genetic determinants [1]. Pain perception is a defense mechanism that alerts us to injury-producing events. The severity of pain is controlled by several genetic variants affecting the expression or function of nociceptive sensory system components. Migraine is among the first of painful diseases to be associated with a genetic component, and several of its variants have been identified [2,3]. Pain is a common symptom of cancer and its treatment, and several genetic polymorphisms have been discovered to be associated with both cancer risk and cancer-induced pain [4]. Other pain syndromes are also under genetic control. Our understanding of the neurobiology of pain pathways has grown in the last decade, and several membrane receptors and channels that respond to pain-provoking stimuli have been found and characterized. This review will focus on the genetics of sensitivity to pain and opioid responses as well as its importance in the development of better pain therapies.

2. Rare hereditary syndromes of complete insensitivity to pain

The complete inability to sense pain is a very rare phenotype. Several hereditary syndromes that involve complete or almost complete insensitivity to pain have been discovered and are listed in the Online Mendelian Inheritance in Man database. They include channelopathy-associated insensitivity to pain syndrome, of which the most likely candidate gene is the α-subunit of the voltage-gated sodium channel Na(v)1.7, encoded by the gene *SCN9A* at locus 2q24.3. The gene is preferentially expressed in nociceptive primary sensory neurons, where it amplifies small depolarizations. It is responsible for 3 human pain disorders: (1) Non-sense mutations in Nav1.7 cause

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complete insensitivity to pain, whereas (2) activating mutations elicit severe paroxysmal extreme pain disorder and (3) primary erythromelalgia (also called *erythermalgia*) [5]. There are 5 hereditary sensory and autonomic neuropathy known as HSAN-I to -V (for more details, see Oertel et al [6]). Briefly, HSAN-I is a dominant sensorimotor axonal neuropathy accompanied by painless injuries, chronic skin ulcers, and distal amputations. The disease maps to chromosome 9p22.1-22.3 where the gene coding for the long-chain base subunit 1 of serine palmitoyl transferase, a key enzyme in sphingolipid biosynthesis, is located. The gene coding for HSAN-II is located on chromosome 12p13.33. Patients suffering from HSAN-II exhibit loss of sensitivity to touch, pain, and temperature. Variants in the *HSN2* gene cause premature truncation of the protein HSN2, implicated in the development and/or maintenance of peripheral sensory neurons or their supporting Schwann cells. Familial dysautonomia (HSAN-III) is a congenital sensory neuropathy characterized by widespread sensory and variable autonomic dysfunctions limited almost exclusively to the Ashkenazi Jewish community. The familial dysautonomia gene locus has been mapped to 9p31, site of the gene of the inhibitor of κ light polypeptide enhancer in B-cells, kinase complex-associated protein, a transcription elongation factor affecting the expression of genes involved in cell motility. HSAN-IV involves the neurotrophic tyrosine kinase receptor gene on chromosome 1q23-q22, and HSAN-V syndrome is caused by single nucleotide polymorphism (SNP) variants in the nerve growth factor gene, evoking severe unmyelinated nerve fiber reduction and moderate loss of thin myelinated nerve fibers.

3. The genetics of variable pain sensitivity in the general population

Abnormal responses to tissue injury are common in 1 of 6 adults suffering from a chronic pain condition [7]. Several genetic variants have been shown to modulate the generation, transmission, and processing of nociceptive information or the local availability of active analgesics and their pharmacodynamic effects. Each of them, however, has only a modest impact on the pain phenotype. Variable pain sensitivity in the general population has been associated with common variants of the μ-opioid (MOP) receptor gene (*OPRM1*) and the catecholamine-*O*-methyltransferase gene (*COMT*), potentially leading to increased opioid tonus. For instance, the *COMT* V158M variant has been linked with decreased morphine requirements for analgesia. Variants of the guanosine triphosphate cyclohydrolase 1/dopa-responsive dystonia gene (*GCH1*) have been found to regulate nociception. *GCH1* is the rate-limiting enzyme catalyzing the production of tetrahydrobiopterin (BH4), an essential cofactor of nitric oxide synthase. Excessive BH4 in peripheral sensory neurons after axonal injury contributes to neuropathic pain, and a decrease in pain has been coupled with reduced *GCH1* function [8]. Other candidate genes are the transient receptor potential cation channel, subfamily 5 member 1, gene and the melanocortin-1 receptor gene. A recent study investigated whether SNPs in *SCN9A*, the gene encoding the voltage-gated sodium channel Na(v)1.7 responsible for the rare channelopathy syndrome, could be associated to differing pain perception in the general population. There are multiple SNPs in the *SCN9A* gene, and the association between some of them and pain perception has been explored in 5 cohorts of subjects with a range of pathologic conditions and having individual measures of reported pain. Significant association was observed between pain score and one of the SNPs present in the *SCN9A* gene, for which the minor allele was equated with increased pain. Two alleles of the SNP altered the coding sequence of Na(v)1.7; and when transfected into HEK293 cells, the gene carrying the rare allele had higher Na(v)1.7 activity [9]. There are well-documented sex differences in the prevalence of various pain disorders that appear to be caused by some polymorphisms but most probably mainly by epigenetic modulation and past experience.

4. Pharmacogenomics of pain therapy

Genetic polymorphisms have been shown to contribute in part to interindividual variability in pain therapy. Opioids and other analgesic drugs are widely used to control moderate to severe pain. However, interindividual sensitivity and their severe adverse effects, such as dependence, tolerance, and respiratory depression, often hamper effective pain management. The MOP receptor is a preferred target of morphine, playing a crucial role in mediating the major clinical outcomes of morphine, including analgesia, but also tolerance and dependence. Gene dosage of MOP receptor appears to influence opioid efficacy in mice. In humans, genetic variants of *OPRM1* gene altering MOP receptor expression (SNPs in the promoter) have been associated with opioid effectiveness. More than 100 genetic polymorphisms have been identified in *OPRM1* gene that could explain the clinical variability in morphine responsiveness [10]. Carriers of the MOP receptor variant *N40D* were shown to exhibit a diminished receptor signaling efficacy in brain regions processing sensory pain information [11]. Candidate genes for predicting opioid efficacy are drug-metabolizing enzymes and transporters—including cytochrome P450, uridine 5′-diphosphate-glucuronosyltransferases, and adenosine triphosphate–binding cassette transporters—that are involved in opioid metabolism. Copy number variants in the *CYP4502D6* gene have been associated with variability in drug responses, metabolism, and transport as well as interindividual differences in opioid concentrations [11]. A mutant mouse model with brain neuron-specific reductions of *CYP450* activity showed highly attenuated morphine antinociception compared with its controls. Pharmacologic inhibition of brain P450 arachidonate epoxygenases also

blocked morphine antinociception in mice in this model, indicating that neuronal P450 epoxygenases mediate the pain-relieving properties of morphine [12]. This P450 arachidonate epoxygenase pathway will become the subject of more intensive exploration in the future because novel data support the notion that neuronal P450 epoxygenases are actually part of the MOP transduction mechanism, as illustrated in Fig. 1 [12], showing that opioids activate brain analgesic circuits through P450 epoxygenase signaling. Thus, polymorphisms in any of the enzymes implicated in this novel transduction pathway become interesting candidates, capable of explaining the variance in morphine responses as well as potential therapeutic targets.

5. Studies in animal models

Most current knowledge on the genetic regulation of pain has been derived from monogenetic addition and subtraction models developed mainly in mice. The genetic control of pain has also been demonstrated in polygenic mouse models by quantitative sensory trait approaches [13]; and it has been noted that nociceptive responses behave as a continuous trait

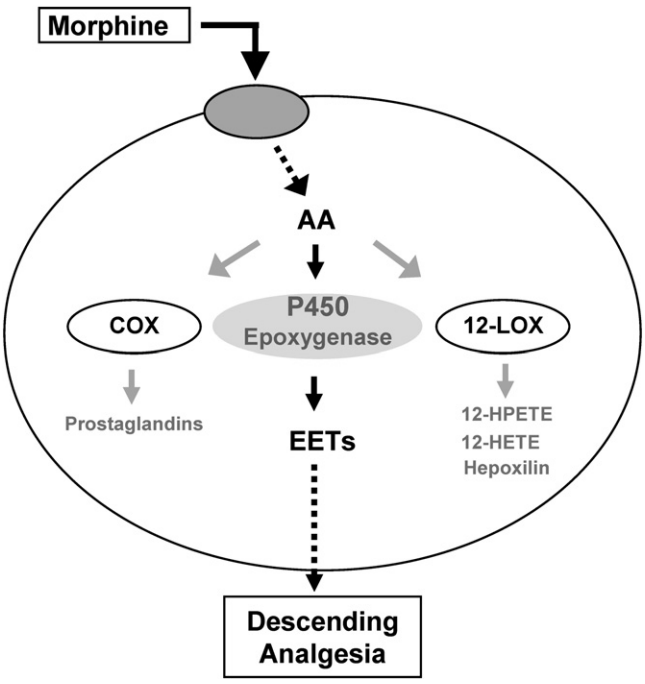

Fig. 1. Epoxygenase signaling pathway for the activation of pain-relieving circuits in the brain stem by morphine. Stimulation of μ-opioid receptors increases the synthesis of arachidonic acid (AA) by steps that could include phospholipase activation Cγ, diacylglycerol synthesis, inositol trisphosphate receptor (IP[3]R) stimulation, and PLA_2 activation. The AA metabolic pathways (cyclooxygenase [COX], P450 epoxygenase, and 12-lipoxygenase [12-LOX]) are shown. The epoxygenase pathway requires P450 activity and produces epoxyeicosatrienoic acids (EETs). Morphine antinociception is attenuated in null mice, which lack P450 activity in selected central nervous system neurons. This effect of morphine is also blocked in control mice and rats by P450 (Supplementary Figure 1 from Conroy et al [12], with permission).

in 11 different inbred mouse strains, underlying its polygenic character. A behavioral quantitative trait locus-mapping strategy has recently been combined with large-scale gene expression profiling studies to identify candidate genes and gene networks specifically associated with analgesic tolerance to morphine [14]. The *Mop2* locus on the proximal region of mouse chromosome 10 has been determined to have a strong influence on the development of tolerance, and genes modified by morphine administration showed their strong presence in neuroadaptation pathways. These mouse models serve as a source of candidates for studies in humans and contribute to our understanding of the sexual dimorphism of pain determinants and perception. A public database of pain genes is available at http://www.jbldesign.com/jmogil/enter.html [15].

Genomics has the potential to contribute to therapeutic development with the promising approach of using small interfering RNA in the control of neuropathic pain, as already suggested for Kir4.1 receptors in glial cells [16] and NMDA receptor subunits in peripheral nerves [17]. Growing evidence suggests that changes in the ion-buffering capacity of glial cells can give rise to neuropathic pain. In the central nervous system, potassium ion (K^+) buffering is dependent on the glia-specific, inward-rectifying K^+ channel Kir4.1. Vit et al [16] established that the satellite glial cells, which surround primary sensory neurons in sensory ganglia of the peripheral nervous system, also express Kir4.1, whereas the neurons themselves do not. They reported that, in rat trigeminal ganglia, the location of primary sensory neurons for face sensation, specific silencing of Kir4.1 by RNA interference induces spontaneous and evokes facial pain-like behavior in freely moving rats. They also noted that Kir4.1 in trigeminal ganglia is reduced after chronic constriction injury of the infraorbital nerve. These findings indicate that neuropathic pain can result from changes in the expression of a single K^+ channel in peripheral glial cells, raising the possibility of targeting Kir4.1 to treat pain in general in a wide variety of neurologic conditions [18].

6. Personalized medicine in pain management

Knowledge of the genetic factors that affect opioid efficacy, metabolism, and adverse effects has the potential for personalizing both acute and chronic pain management, and for designing more useful opiate pain medications with lower adverse event profiles. For instance, it has long been recognized that genetic factors (specifically *CYP2D6* whose absence makes codeine almost completely inefficient) predict individual responses to codeine administration [19,20] or postoperative morphine treatment (*OPRM1* variants) [21]. However, lack of reproducibility of functional genetic association has recently set back the promise of genetics-based personalized approaches. Nonreproducibility of the pain-modulatory effect of *COMT* gene 472G>A SNP is an example. It could be explained by the fact that many of

the pain-relevant variants studied up to now are common, with allelic frequencies of 10% to 50%; and the concomitant presence, in the same individual, of more than one functional polymorphism may result in some being canceled out by others, adding to the complexity of analysis [22]. Furthermore, gene association investigations should ideally be conducted in highly phenotyped populations of homogenous ethnic admixture with identified associations adjusted for patient demographics, risk factors, and medications [3]. The phenotypic responses of patients to opiates are the result of a complex interplay between genetic and environmental variables, and the potential influence of gene-gene interactions should be assessed more thoroughly [23].

In conclusion, phenotypic variances in pain perception [24] and its modulation are significantly dependent on their genomic determinants. Although we are still awaiting the first genomewide association study dissecting pain components, several genes are now recognized for their role in various pain-controlling pathways. The clinical significance of genomic control in the metabolism of pain relievers, via metabolizing enzymes, including the P450 family, has been known for a long time; and new understanding of P450 involvement in MOP receptor pathway signal transduction is pointing to novel targets for further exploration of genomic-driven variance with the potential for new pain relief strategies.

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