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Topical review

Idiopathic pain disorders – Pathways of vulnerability

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1. Introduction

Idiopathic pain disorders[1] (IPDs) consist of such conditions as temporomandibular joint disorders (TMJD), fibromyalgia syndrome (FMS), irritable bowel syndrome (IBS), chronic headaches, interstitial cystitis, chronic pelvic pain, chronic tinnitus, whiplash-associated disorders, and vulvar vestibulitis (VVS). IPDs commonly aggregate as "comorbid" conditions that are characterized by a complaint of pain as well as a mosaic of abnormalities in motor function, autonomic balance, neuroendocrine function, and sleep. Although the mechanisms that underlie the majority of these conditions are poorly understood, IPDs have been associated with a state of pain amplification and psychological distress (McBeth et al., 2001; Bradley and McKendree-Smith, 2002; Verne and Price, 2002; Gracely et al., 2004).

Importantly, there is substantial individual variability in the relative contribution of pain amplification and psychological phenotypes to IPDs. In this brief review, we suggest that pain amplification and psychological distress, which are mediated by an individual's genetic variability and exposure to environmental events, represent two primary pathways of vulnerability that underlie the development of highly prevalent IPDs (Fig. 1; Maixner et al., 1995; Maixner, 2004; Diatchenko et al., 2005). We highlight findings associated with TMJD, which represents a "prototypic" IPD.

2. Pain amplification: A determinant of onset and persistence of TMJD and related IPDs

A handful of studies have sought to prospectively identify risk factors or risk determinants that are associated with or mediate the onset and maintenance of IPDs. A well-established predictor of onset is the presence of another chronic pain condition, characterized by a state of pain amplification (Von Korff et al., 1988). Additionally, widespread pain is a risk indicator for dysfunction associated with painful TMJD and for lack of response to treatment (Raphael and Marbach, 2001). Recently, we demonstrated that individuals who are more sensitive to noxious stimuli are significantly more likely to develop painful TMJD than those who are less sensitive (risk ratio = 2.7; Slade et al., 2005).

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[1] For the purpose of this review, idiopathic pain disorders refer to a set of complex medical conditions where the report of clinical pain is a primary complaint that appears to be disproportional to that expected by physical (Axis I) findings. These conditions are also frequently associated with a mosaic of motor, autonomic, neuroendocrine, and sleep abnormalities.

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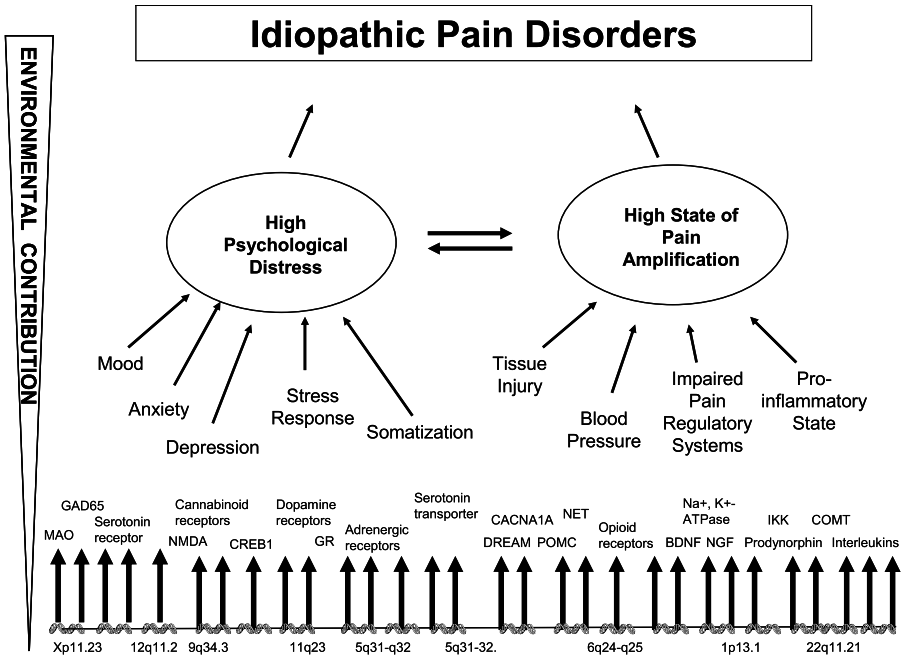

Fig. 1. This model depicts likely determinants that contribute to the risk of onset and maintenance of common IPDs. These factors are determined by both genetic variability and environmental events that determine an individual's psychological profile and pain amplification status. These two primary domains are interactive and influence the risk of pain onset and persistence. Likely modifiers of the interaction between genetic and environmental factors include sex and ethnicity.

The outcomes of several cross-sectional studies also suggest that IPDs, including TMJD, are influenced by a state of pain amplification (Sarlani and Greenspan, 2003; Maixner, 2004). In general, a relatively high percentage of patients with IPDs show enhanced responses to noxious stimulation compared to controls (McBeth et al., 2001; Bradley and McKendree-Smith, 2002; Verne and Price, 2002; Gracely et al., 2004). Enhanced pain perception experienced by patients with IPDs may result from a dysregulation in peripheral afferent and central nervous system pathways that produces dynamic, time-dependent changes in the excitability and response characteristics of neuronal and glial cells. This dysregulation likely contributes to altered mood, motor, autonomic, and neuroendocrine responses as well as pain perception (Fig. 1; Maixner et al., 1995; Watkins et al., 2003; Maixner, 2004). Much more work is necessary to identify the specific underlying mechanisms that contribute to pain amplification in patients with IPDs.

3. Psychological distress: A determinant of onset and persistence of TMJD and related IPDs

Heightened psychological distress is another domain or pathway of vulnerability that can lead to IPDs (Fig. 1). Patients with TMJD, and other IPDs, display a complex mosaic of depression, anxiety (Vassend et al., 1995), and perceived stress relative to pain-free controls (Beaton et al., 1991). Somatization, which is the tendency to report numerous physical symptoms in excess to that expected from physical exam (Escobar et al., 1987), is associated with more than a twofold increase in TMJD incidence, decreased improvement in TMJD facial pain after 5 years (Ohrbach and Dworkin, 1998), and increased pain following treatment (McCreary et al., 1992). Somatization is also highly associated with widespread pain, the number of muscle sites painful to palpation (Wilson et al., 1994), and the progression from acute to chronic TMJD (Garofalo et al., 1998). In our pilot prospective study on 244 initially TMJD-free females, we found that somatization, anxiety, depression and perceived stress represent significant risk factors for TMJD onset (Significant Risk Ratios ranging from 2.1 to 6.0; Slade et al., 2005). These results suggest that somatization, negative affect/mood, and environmental stress independently or jointly contribute to the risk of onset and maintenance of IPDs.

4. Genetic variations influencing pain amplification and psychological distress

Given the above discussion, we suggest that there are two major domains that contribute to the vulnerability of developing common IPDs: enhanced pain sensitivity and psychological distress (Fig. 1). Both of these domains are influenced by specific genetic variants mediating the activity of physiological pathways that underlie pain amplification and psychological distress. Thus, individual polymorphic variations in genes coding for key regulators of these pathways, when coupled with

environmental factors such as physical or emotional stress, interact with each other to produce a phenotype that is vulnerable to IPDs.

Both clinical and experimental pain perception are influenced by genetic variants (Mogil, 1999; Zubieta et al., 2003; Diatchenko et al., 2005). Although the relative importance of genetic versus environmental factors in human pain perception remains unclear, reported heritability for nociceptive and analgesic sensitivity in mice is estimated to range from 28% to 76% (Mogil, 1999). Several recent studies have also established a genetic association with a variety of psychological traits and disorders, that influence risk of developing IPDs. Twin studies show that 30–50% of individual variability in the risk to develop an anxiety disorder is due to genetic factors (Gordon and Hen, 2004). The heritability of unipolar depression is also remarkable, with estimates ranging from 40% to 70% (Lesich, 2004). Moreover, normal variations in these psychological traits show substantial heritability (Bouchard and McGue, 2003; Eid et al., 2003; Exton et al., 2003).

With advances in high throughput genotyping methods, the number of genes associated with pain sensitivity and complex psychological disorders such as depression, anxiety, stress response and somatization has increased exponentially. A few examples of the genes associated with these traits include catechol-*O*-methyltransferase (*COMT*; Wiesenfeld-Hallin and Duranti, 1987; Gursoy et al., 2003; Diatchenko et al., 2005), adrenergic receptor β_2 (*ADRB2*; Diatchenko et al., 2006), serotonin transporter (*5-HTT*; Herken et al., 2001; Caspi et al., 2003; Gordon and Hen, 2004), cyclic AMP-response element binding protein 1 (Zubenko et al., 2003), monoamine oxidase A (Deckert et al., 1999), GABA-synthetic enzyme (Smoller et al., 2001), D2 dopamine receptor (Lawford et al., 2003), glucocorticoid receptor (Wust et al., 2004), interleukins 1 β and α (Yu et al., 2003), Na+, K+-ATPase and voltage gated calcium channel gene (Estevez and Gardner, 2004).

We have reported that the gene encoding COMT, an enzyme involved in catechol and estrogen metabolism, has been implicated in the onset of TMJD (Diatchenko et al., 2005). We showed that three common haplotypes of the human *COMT* gene are associated with pain sensitivity and the likelihood of developing TMJD. Haplotypes associated with heightened pain sensitivity produce lower COMT activity. Furthermore, inhibition of COMT activity results in heightened pain sensitivity and proinflammatory cytokine release in animal models via activation of $\beta_{2/3}$-adrenergic receptors (Nackley et al., 2006). Consistent with these observations, our group has also reported that three major haplotypes of the human *ADRB2* are strongly associated with the risk of developing a TMJD (Diatchenko et al., 2006).

Because it is highly likely that IPDs share common underlying pathophysiological mechanisms, it is expected that the same functional genetic variants will often be associated with comorbid IPDs and related signs and symptoms. For example, a common SNP in codon 158 ($val^{158}met$) of *COMT* gene is associated with pain ratings, μ-opioid system responses (Rakvag et al., 2005), TMJD risk (Diatchenko et al., 2005), and FMS development (Gursoy et al., 2003) as well as addiction, cognitive functions, and common affective disorders (Oroszi and Goldman, 2004). Common polymorphisms in the promoter of the *5-HTT* gene are associated with depression, stress-related suicidality (Caspi et al., 2003), anxiety (Gordon and Hen, 2004), somatization, and TMJD risk (Herken et al., 2001).

On the other hand, a defining feature of complex common phenotypes is that no single genetic locus contains alleles that are necessary or sufficient to produce a complex disease or disorder. A substantial percentage of the variability observed with complex clinical phenotypes can be explained by genetic polymorphisms that are relatively common (i.e., greater than 10%) in the population, although the phenotypic penetrance of these common variants is frequently not very high (Risch, 2000). Thus, the varied clinical phenotypes associated with IPDs are likely the result of interactions between many genetic variants of multiple genes. As a result, interactions among these distinct variants produce a wide range of clinical signs and symptoms so that not all patients show the same spectrum of abnormalities in pain amplification and psychological distress. Furthermore, environmental factors also play a crucial role in gene penetrance in multifactorial complex diseases. For example, functional polymorphism in the promoter region of the *5-HTT* gene is associated with the influence of stressful life events on depression, providing the first evidence of a gene-by-environment interaction, in which an individual's response to environmental insult is moderated by his or her genetic makeup (Caspi et al., 2003).

Since each individual patient will experience unique environmental exposures and possesses unique genetic antecedents to ISD vulnerability, the most efficient approach to identify genetic markers for IPDs and to identify therapeutic targets is to analyze the interactive effects of polymorphic variants of multiple functionally related candidate genes. The complex interaction between these polymorphic variants will yield several unique subtypes of patients who are susceptible to a variety of IPDs. Recognition of the fact that multiple genetic pathways and environmental factors interact to produce a diverse set of IPDs, with persistent pain as a primary symptom, requires a new paradigm to diagnose, classify, and treat IPDs patients.

5. Current and future directions

To address this need, a group of internationally recognized epidemiologists, pain researchers, geneticists,

and biostatisticians have begun a 7-year prospective cohort study on 3200 initially TMJD-free females (see OPPERA.org). This study seeks to identify the psychological and physiological risk factors, and associated genetic polymorphisms, that influence pain amplification and psychological profiles in enrollees who develop TMJD. Additionally, this study will seek to characterize the biological pathways through which these genetic variations causally influence TMJD risk. Based on our preliminary results and published genetic, biochemical, physiological, and pharmacological studies, which link specific genes or their proteins to pain sensitivity and/or associated psychological functions, we have selected a number of candidate genes for this association study. We have classified these identified genes into four major clusters: genes that are able to influence (1) the activity of peripheral afferent pain fibers, (2) central nervous system pain processing systems, (3) the activity of peripheral cells (e.g., monocytes) that release proinflammatory mediators, and (4) the production of proinflammatory mediators from cells within the central nervous system (e.g., microglia and astrocytes). We predict that common functional polymorphisms in these genes will represent areas of genetic vulnerability that when coupled to environmental triggers will contribute to enhanced pain perception, psychological dysfunction, and risk of onset and persistence of TMJD and related IPDs. Because environmental factors strongly influence pain and psychological profiles, assessments of individuals' pain sensitivity, autonomic function, and psychological distress are required to delineate the degree to which specific genetic polymorphisms and environmental exposures interacted to produce the observed clinical signs and symptoms.

6. Conclusions

There is growing evidence that the onset of IPDs is associated with both physical (e.g., joint trauma or muscle trauma) and psychological (e.g., psychological or emotional stress) triggers that initiate pain amplification and psychological distress. However, each individual will develop these conditions with different probability. This probability is defined by a complex interaction between the individual's genetic background and the extent of exposure to specific environmental events. Elucidation of the physiological and psychological factors that contribute to pain amplification and psychological distress, as well as the underlying genetics, will substantially contribute to our understanding of the mechanisms that evoke painful sensations in patients with a variety of IPDs. Moreover, there is a considerable need to develop methodologies that permit the subclassification of IPDs based on the specific network of genetic variations in each individual, which will allow better and more informed individually based treatments.

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