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Review

Genes, molecules and patients—Emerging topics to guide clinical pain research

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ABSTRACT

This review selectively explores some areas of pain research that, until recently, have been poorly understood. We have chosen four topics that relate to clinical pain and we discuss the underlying mechanisms and related pathophysiologies contributing to these pain states. A key issue in pain medicine involves crucial events and mediators that contribute to normal and abnormal pain signaling, but remain unseen without genetic, biomarker or imaging analysis. Here we consider how the altered genetic make-up of familial pains reveals the human importance of channels discovered by preclinical research, followed by the contribution of receptors as stimulus transducers in cold sensing and cold pain. Finally we review recent data on the neuro-immune interactions in chronic pain and the potential targets for treatment in cancer-induced bone pain.

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1. Introduction

One of the most important issues in pain research is the translation of basic science findings to the patient, as well as back-translation so that clinical phenomena can be explored and modeled in preclinical studies. Interaction between scientists and clinicians is essential for this process and one obvious shared area of interest is the pharmacological processes that underlie pain conditions. This review selectively explores some areas of pain research that, until recently, have been poorly understood. We have chosen four topics that relate to clinical pain and we discuss the underlying mechanisms and related pathophysiologies contributing to these pain states. A key issue in pain medicine involves crucial events and mediators that contribute to normal and abnormal pain signaling, but remain unseen without genetic, biomarker or imaging analysis. Here we consider how the heritable pain states reveal the importance of channels discovered by preclinical research of pain disorders, followed by the contribution of receptors as stimulus transducers in cold sensing and cold pain. Finally we review recent data on the neuro-immune interactions in chronic pain and the potential targets for treatment in cancer-induced bone pain.

2. Familial pain syndromes

Adequate analgesic treatments for a number of chronic pain conditions remain a challenge, partly due to the robust inter-individual variability in sensitivity to pain and analgesics, as well as the individual susceptibility to developing chronic pain Table 1. There is now increasing evidence that a large component of the pain experience is inherited and that pain phenotypes result as a variation in genetic-environmental interactions, including a role for epigenetic factors.

The increasing sophistication and decreasing cost of high-throughput methodologies for identification of genetic components that contribute to human pain disorders have successfully highlighted numerous channelopathies and mutations that underlie familial pain syndromes. Genome-wide linkage mapping, quantitative trait locus mapping and microarray-based gene expression profiling are all advancing techniques, and here we discuss their revelation of some inherited pain states.

2.1. Sodium channel $Na_v1.7$ mutations

Nine sodium channels have been identified in the nervous system, of which the tetrodotoxin-sensitive $Na_v1.7$ channel is expressed in almost all dorsal root ganglia neurones. $Na_v1.7$ has fast activation and inactivation kinetics, and is also characterised by slow closed-state inactivation, permitting the channel to respond to small slow depolarisations and thereby acting as a threshold channel to amplify generator potentials to sub-threshold stimuli (Dib-Hajj et al., 2007). Recent human studies have directly linked $Na_v1.7$ to four pain disorders: Primary erythromelalgia (PE), paroxysmal extreme pain disorder (PEPD), $Na_v1.7$-associated congenital insensitivity to pain (CIP) and small fibre neuropathy (Dib-Hajj et al., 2007; Faber et al., 2012). A difference in perceived pain intensity among neuropathic pain patients is also linked to an *SCN9A* single nucleotide polymorphism and in normal individuals this has been shown to affect heat pain sensitivity (which is predominately C fibre-mediated) (Reimann et al., 2010). PE was the first human pain disorder mapped to an ion channel mutation, where Yang et al. used linkage analysis to identify two missense mutations in the *SCN9A* gene that encodes $Na_v1.7$ (Yang et al., 2004).

More than ten independent mutations of *SCN9A* are now linked to PE of varying severity, characterised by intense episodic burning pain and redness in the extremities that are triggered by warm stimuli or exercise (Yang et al., 2004). The clinical onset of PE has been reported in early childhood with severity of pain worsening with age. Effective pain relief can be achieved by repeated immersion of hands and feet in ice-cold water, although this can lead to skin lesions (Michiels et al., 2005). The 'gain-of-function' channel mutations underlie hyperexcitability of nociceptors and reduced activation thresholds for action potentials. The redness and swelling of extremities that accompanies PE pain likely involves a dysfunction in sympathetic innervation of the vasculature in affected limbs (Rush et al., 2006).

Another autosomal dominant pain disorder resulting from a different set of 'gain-of-function' $Na_v1.7$ mutations is PEPD, formerly known as familial rectal pain. PEPD patients suffer from excruciating burning pain and flushing in the anorectal region or around the eyes, also from early childhood (Fertleman et al., 2006). Ocular attacks tend to dominate over rectal pain with increasing

Table 1
Inherited pain syndromes and associated channel dysfunctions. PE: Primary erythromelalgia; PEPD: paroxysmal extreme pain disorder; CIP: $Na_v1.7$-associated congenital insensitivity to pain; FHM: familial hemiplegic migraine; HSAN: hereditary sensory and autonomic neuropathy; FEPS: familial episodic pain syndrome.

Inherited disorder	Gene (protein)	Gain (+)/loss (+)	Change in channel function	Pathophysiology
PE	*SCN9A* ($Na_V1.7$)	+	Hypolarized voltage-dependence (reduced activation theshold) and slowed deactivation	Nociceptor hyperexcitability
PEDP	*SCN9A* ($Na_V1.7$)	+	Impaired Inactivation	Nociceptor hyperexcitability; persistent sodium currents/repetitive neuronal firing
CIP	*SCN9A* ($Na_V1.7$)	–	Frameshift splicing alteration and premature mtermination of protein	Impaired nociceptor function
FHM1	*CACNL1A4* ($Ca_v2.1$)	+	Reduced activation threshold and enhanced open channel probability	Enhanced cortical spreading depression
FHM2	*ATP1A2* Na^+/K^+ ATPase	–	Impaired pump action	Increased K^+ in extracellular space
FHM3	*SCN9A* ($Na_V1.1$)	+/–	Loss or gain of function depending on mutation type	Neuronal hyperexcitability
HSAN-V	*NGF* (β-NGF)	–	Impaired β-NGF signaling through $p75^{NTR}$	Reduced nociceptive acitivity
FEPS	*TRPA* (TRPA1)	+	Increased activation current at resting membrance prtential	Excessive neuronal firing