Chapter 6
Personalized Medicine in Pain Management

Stephen Campbell and Daniel Pak

Introduction

Before we can understand the treatment of chronic pain and the role for personalized medicine, we have to define the key mechanisms underpinning pain perception. The body perceives and classifies noxious stimuli through nociception, whereby receptors in the periphery relay information along afferent nociceptive neurons to the spinal cord. Ascending pathways carry this information from the spinal cord to the brain, where cortical pathways provide a mechanism for emotion and cognition to play a role in further processing the painful stimulus. Furthermore, endogenous analgesics may be released as part of descending inhibitory mechanisms, thus allowing the brain to modulate nociceptive transmission.

The perception of pain is a critical function of the body's nervous system. Information about the location, intensity, and quality of a noxious stimulus may warn the body of active or imminent tissue damage. Occasionally, the nervous system may adapt after a prior painful experience in anticipation of future painful experiences. This is accomplished by structural, functional, and chemical changes within the peripheral and central nervous systems. Although these neuroplastic changes may allow for easier detection of noxious stimuli and more efficient transduction of nociceptive signals, they are oftentimes maladaptive and may lead to neuropathic pain syndromes (Campbell and Meyer 2006; Siddall 2013; Talebi and Dabbagh 2017).

Chronic neuropathic pain is a frequent source of chronic pain and reflects both peripheral and central sensitization mechanisms. Peripheral sensitization is a term that describes the abnormal neuroplasticity that occurs in the peripheral nervous

S. Campbell
Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA
e-mail: SCAMPBELL@mgh.harvard.edu

D. Pak (✉)
Weill Cornell Medicine, NewYork-Presbyterian Hospital, New York, NY, USA
e-mail: dpak320@gmail.com

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system, while central sensitization describes that which occurs in the central nervous system. By definition, neuropathic pain is characterized by damage to neural tissue, whereas nociceptive pain involves nonneural tissue (e.g., inflammatory pain from osteoarthritis). As a consequence of the neuroplastic changes seen in neuropathic pain, the perception of pain, in terms of magnitude, location, and quality may become altered. In other words, the experience of pain can be decoupled from the stimulus in the periphery. Pain may be evoked from stimuli that should not reach the nociceptor threshold magnitude, or pain may be elicited in the complete absence of a stimulus. These phenomena are classically seen in patients who experience phantom limb pain after an amputation (Subedi and Grossberg 2011). Because the pain is perceived outside the context of obvious nociceptive input, effective treatment remains a challenge.

The complex neural relay of action potentials from peripheral receptors to the dorsal root ganglion to the central nervous system involves many neurotransmitter and protein targets for pharmacologic therapy. However, pharmacologic treatment options lack anatomic specificity. Moreover, surgical techniques are often limited in that they cannot address pain in patients who lack sensory discrimination, pain localization, and other symptoms related to pathological changes in the nervous system. For this reason, there is a need for treatments with anatomical and pharmacological specificity that are tailored to the individual patient. Namely, personalized medicine, in the context of treating chronic pain, accomplishes this goal via cell-based and gene-based therapies. The goal of this chapter is to explore these novel therapies while also reviewing the pathogenesis of chronic pain.

Peripheral Sensitivity

Pain signal transmission begins with noxious stimuli, which causes the release of inflammatory markers that then act on peripheral nociceptors. Action potentials are carried along high threshold primary afferent neurons, such as Aδ or C fibers, before reaching the spinal cord. Peripheral sensitivity occurs when the threshold for neuronal excitation is lowered, thus permitting minor stimulation to incite pain. After a noxious insult and resulting cell death, hydrogen ions and inflammatory cytokines such as prostaglandin E2, TNF alpha, and interleukin 1 beta are directly released into the extracellular environment. With strong nociceptive input, neuropeptide substance P is released and further modulates pain signaling. Specifically, substance P promotes bradykinin release and facilitates histamine release by causing mast cell accumulation and degranulation. This results in increased vascular permeability and spread of inflammatory mediators to nearby peripheral neurons. It is believed that increased inflammatory molecules in the surrounding milieu alters threshold voltages for membrane channels, in addition to affecting intracellular signaling pathways. In the current theory of peripheral sensitization, this mechanism accounts for the hyperexcitability in peripheral nerves that can occur after tissue damage (Riley and Boulis 2006; Sahbaie et al. 2009; Li et al. 2012; Taghizadeh et al. 2019).

Central Sensitization

Central sensitization is conceptually similar to peripheral sensitization in that the transduction threshold of neurons is lowered, however there are a few key differences. Pain signal transmission in the central nervous system begins with activation of central nociceptors (e.g. AMPA, kainate, metabotropic glutamate receptors, and N-methyl-D-aspartate receptors) in the dorsal horn of the spinal cord in response to glutamate released by peripheral afferents—NMDA receptors are typically inactive during normal ascending pain transmission (Riley and Boulis 2006). However, with prolonged or high-frequency stimulation of these central nociceptors, rostral transmission may continue long after the inciting stimulus is removed. This is thought to occur because of NMDA receptor activation, which is enhanced in the presence of inflammatory mediators. Furthermore, second order neurons in the dorsal horn may become activated by non-stimulated sensory fibers in the periphery. This is termed heterosynaptic potentiation (Woolf 2011). Heterosynaptic potentiation explains why an individual may start to experience pain in an uninjured part of the body (secondary hyperalgesia). Patients may also experience increased pain sensitivity (allodynia) as a result of lower activation thresholds in afferent nociceptive fibers. Allodynia and secondary hyperalgesia are the sensory manifestations of central sensitization and synaptic plasticity (Siddall 2013).

Another important feature of central sensitization is that it impairs descending pain modulation, and this impairment can lead to amplification of the pain experience (Meeus and Nijs 2007). Descending pain modulation refers to the release of endogenous opioids and other neurotransmitters from brain stem structures (i.e., periaqueductal gray matter and the rostral ventral medulla) such as norepinephrine and serotonin. Increasing evidence reinforces that the putative mechanisms of central sensitization and its effect on the disruption of top-down modulation provide a neurobiological basis for the development of chronic pain (Campbell and Meyer 2006; Riley and Boulis 2006; Gangadharan and Kuner 2013).

Endogenous Analgesia

To better understand the new strategies of treating chronic pain that will be presented later in the chapter, it is useful to review how the body promotes endogenous analgesia and antinociceptive effects. Endogenous opioids such as endorphins, dynorphins, and enkephalins act on mu, kappa, and delta receptors, respectively. These receptors are located in both the peripheral and central nervous systems, and they function to inhibit ascending spinal transmission from noxious stimulation of sensory afferents. Soon after, acute tissue damage and transmission of pain signals to the brain, antinociceptive mechanisms are activated. Specifically, the dorsal horns receive noradrenergic and serotonergic input via descending pathways, while also

receiving projections from non-nociceptive afferents and inhibitory interneurons, which use GABAergic and glycinergic signaling. Study of the body's sites and mechanisms of intrinsic pain attenuation has led to conceptual models for chronic pain treatment and a therapeutic basis for exogenous treatment modalities (Riley and Boulis 2006; Gangadharan and Kuner 2013).

Personalized Medicine

Despite the tremendous progress made in pain research in recent decades, current drug therapies for treating chronic pain have very limited efficacy. As a consequence of peripheral and central sensitization and the resulting aberrance in pain circuitry, there is a spatial and temporal abstraction of pain that occurs independent of true tissue injury (Riley and Boulis 2006; Basbaum et al. 2009; Nasseri et al. 2016; Taghizadeh et al. 2019). Pain that is not linked to any obvious active insult on the body is only one of the barriers to effective treatment. Common drug classes for treating nociceptive pain include opioids, non-steroidal inflammatory drugs (NSAIDs), and paracetamol. NSAIDs and paracetamol are thought to treat pain by inhibiting cyclooxygenase and thus inhibit production of prostaglandin, an important molecule in the pathogenesis of peripheral sensitization. Opioids exert a central effect by acting on mu opioid receptors in the dorsal horn of the spinal cord. Options for treating neuropathic pain include anticonvulsants, such as gabapentinoids, and tricyclic antidepressants, which increase the norepinephrine and serotonin available for enhancing descending modulation. Antagonists at the NMDA receptor, such as ketamine and magnesium, block rostral signaling pathways that become activated during the central sensitization process. All of the aforementioned exogenous treatments have been in use for many years, and some of them show modest efficacy in treating certain types of pain (Portenoy 2000; Furlan et al. 2006; Noble et al. 2010; Toblin et al. 2011; Dabbagh and Rajaei 2016). However, there are several difficulties associated with generic use of these treatment modalities. Firstly, many of these drugs have major untoward effects, owing to their lack of anatomical specificity and off-target effects. For example, many NSAID users suffer from gastrointestinal injury and cardiovascular effects, while opioid users are at increased risk of addiction, respiratory depression, paradoxical hyperalgesia, and cognitive effects (Portenoy 2000; Noble et al. 2010). Also, given the multitude of chemicals released during pain transmission and the various receptors involved, it is nearly impossible to achieve pharmacological specificity with conventional treatments. These drawbacks are providing the continuous impetus for research on novel therapeutic approaches for the treatment of chronic pain. Personalized medicine, in the context of chronic pain, refers to treatment that is tailored on the molecular and genetic levels for individual patients. A discussion on cell- and gene-based therapies will follow.

Cell- and Gene-Based Therapies

The chief advantage of personalized medicine in the form of cell- and gene-based therapies is that it allows clinicians to achieve anatomic and pharmacological specificity. Consider that a target organ might have multiple tissue types, each having various types of cells, which each expressing different receptors. One might consider ablative surgery as a feasible option; however, all tissue types in the vicinity of the surgical instrument would be destroyed, with no regard for cell type. Alternatively, a pharmacological therapy might be advantageous because a specific receptor type could be targeted. Yet, these receptors may be expressed on other cells far from the target site and have global functions in normal physiology. Stereotactic cell transplantation is a viable solution to this problem, as it offers anatomic and pharmacologic specificity.

The rationale for the use of cell therapy for the treatment of chronic pain stems from the observation that implantation of adrenal chromaffin medullary cells in the spinal arachnoid space of rats decreased the production of markers implicated in central sensitization and reduced chronic pain behaviors (Eaton 2004; Riley and Boulis 2006; Goins et al. 2012). Adrenal chromaffin medullary cells are ideal because of their intrinsic ability to secrete antinociceptive agents and other important neurotransmitters, such as those discussed under section "Endogenous Analgesia." These cell grafts may be taken from a cadaver or directly from the patient, however incomplete homogeneity of the graft tissue was a limitation in early studies (Eaton 2004). "Purification" of the graft may be accomplished by genetically modifying it after the harvest but before transplanting it to the patient. This process is called *ex vivo gene transfer*. For example, a group of cells would be harvested and then immortalized, a process which describes the induction of a mutation that allows the cell line to have an indefinite replicative capacity—immortalized cell lines are different from stem cells which have a natural ability to divide indefinitely before giving rise to specialized cell types (i.e., without requiring a mutation). Nonetheless, genes that code for production of antinociceptive peptides could then be transferred to these bioengineered cell lines, which are then implanted to the patient's central nervous system by intrathecal injection. Alternatively, genes can be directly inserted into the cells of the patient's parenchymal tissue in a process called *in vivo gene transfer*. A common method for delivering genes involves a viral vector, making use of a virus's natural ability to invade cells and transport genomes. For example, synthetic genes that code for opioid peptides have been placed in Herpes simplex virus (HSV) vectors and injected into the subcutaneous tissue of rodents (Goins et al. 2012). These vectors are taken up by peripheral sensory neurons and travel by retrograde axonal transport to the dorsal root ganglion, where these opioid peptides have been shown to provide an analgesic effect in neuropathic pain models (Wolfe et al. 2007). Similar studies have been carried out with adenovirus and retrovirus vectors (Goins et al. 2012).

Analogous to an intrathecal pump, which is a device surgically placed in a patient's subcutaneous tissue and delivers medication into the cerebrospinal fluid through a catheter positioned around the spinal cord, "cellular minipumps" for

specific analgesics allow for secretion of endogenous opioids and other neurotransmitters that serve to modulate pain transmission (Hino et al. 2009; Chattopadhyay et al. 2011). Compared to implantable prosthetics, these microscopic pumps obviate the need for pump maintenance (e.g. refilling and battery changes) and carry little risk for catheter-related infections.

Summary and Future Directions

Evidence for the role of cell-based therapies involving ex-vivo and in-vivo gene transfer looks promising in animal models, although it remains unclear in small experimental studies involving humans. Recent studies, however, have demonstrated clinical translation of stem cell gene therapy for patients with chronic pain. In particular, bone marrow stem cells (BMSCs) have been shown to have immunoregulatory properties and promote strong analgesic effects when injected intrathecally (Huh et al. 2017). This role for BMSCs is borne of the recognition that proinflammatory molecules activate intracellular cascades involved in central sensitization and the transition from acute pain to chronic pain. In a pilot study looking at ten patients with chronic back pain and radiographic evidence of lumbar disc degeneration, injection of autologous stem cells, harvested from the patient's iliac crest, into the nucleus pulposus area resulted in a statistically significant reduction in pain scores up to 12 months post injection (Orozco et al. 2011). These were all patients who did not respond to conservative treatment. In another study, a phase II clinical trial, 11 patients with spinal cord injuries and documented neuropathic pain received three separate administrations of autologous BMSCs in the subarachnoid space via lumbar puncture. All patients experienced a decrease or a complete resolution of neuropathic pain symptoms at the latest follow up interval at 10 months (Vaquero et al. 2018). Although these are small studies, both demonstrated that BMSCs may be efficacious in treating chronic pain. Given the paucity of human trials looking at cell-based therapies in this context, these exciting early clinical results give us a lens for the future direction of the clinical management of chronic pain.

References

Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell. 2009;139:267–84.

Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron. 2006;52:77–92.

Chattopadhyay M, Mata M, Fink DJ. Vector-mediated release of GABA attenuates pain-related behaviors and reduces Na(V)1.7 in DRG neurons. Eur J Pain (London, England). 2011;15:913–20.

Dabbagh A, Rajaei S. Opium abuse and its problems in anesthesia practice: a review from bench to bedside. J Cell Mol Anesth. 2016;1:78–86.

Eaton M. Cell therapy for neuropathic pain in spinal cord injuries. Expert Opin Biol Ther. 2004;4:1861–9.
Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ. 2006;174:1589–94.
Gangadharan V, Kuner R. Pain hypersensitivity mechanisms at a glance. Dis Model Mech. 2013;6:889–95.
Goins WF, Cohen JB, Glorioso JC. Gene therapy for the treatment of chronic peripheral nervous system pain. Neurobiol Dis. 2012;48:255–70.
Hino M, Ogata T, Morino T, Horiuchi H, Yamamoto H. Intrathecal transplantation of autologous macrophages genetically modified to secrete proenkephalin ameliorated hyperalgesia and allodynia following peripheral nerve injury in rats. Neurosci Res. 2009;64:56–62.
Huh Y, Ji RR, Chen G. Neuroinflammation, bone marrow stem cells, and chronic pain. Front Immunol. 2017;8:1014.
Li WW, Guo TZ, Liang DY, Sun Y, Kingery WS, Clark JD. Substance P signaling controls mast cell activation, degranulation, and nociceptive sensitization in a rat fracture model of complex regional pain syndrome. Anesthesiology. 2012;116:882–95.
Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. Clin Rheumatol. 2007;26:465–73.
Nasseri BNV, Manaheji H, Mousavi Z, Zaringhalam. Microglia are involved in pain related behaviors during the acute and chronic phases of arthritis inflammation. J Cell Mol Anesth. 2016;1:137–45.
Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, Schoelles KM. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010;2010:Cd006605.
Orozco L, Soler R, Morera C, Alberca M, Sanchez A, Garcia-Sancho J. Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study. Transplantation. 2011;92:822–8.
Portenoy RK. Current pharmacotherapy of chronic pain. J Pain Symptom Manag. 2000;19:S16–20.
Riley J, Boulis NM. Molecular mechanisms of pain: a basis for chronic pain and therapeutic approaches based on the cell and the gene. Clin Neurosurg. 2006;53:77–97.
Sahbaie P, Shi X, Guo TZ, Qiao Y, Yeomans DC, Kingery WS, Clark JD. Role of substance P signaling in enhanced nociceptive sensitization and local cytokine production after incision. Pain. 2009;145:341–9.
Siddall PJ. Neuroplasticity and pain: what does it all mean? Med J Aust. 2013;198:177–8.
Subedi B, Grossberg GT. Phantom limb pain: mechanisms and treatment approaches. Pain Res Treat. 2011;2011:864605.
Taghizadeh M, Manaheji H, Baniasadi M, Mohammadi M, Zaringhalam J. Immune and opioid system interaction in pain modulation. J Cell Mol Anesth. 2019;4:24–30.
Talebi Z, Dabbagh A. Perioperative pain: molecular mechanisms and future perspectives. J Cell Mol Anesth. 2017;2:134–41.
Toblin RL, Mack KA, Perveen G, Paulozzi LJ. A population-based survey of chronic pain and its treatment with prescription drugs. Pain. 2011;152:1249–55.
Vaquero J, Zurita M, Rico MA, Aguayo C, Bonilla C, Marin E, Tapiador N, Sevilla M, Vazquez D, Carballido J, Fernandez C, Rodriguez-Boto G, Ovejero M. Intrathecal administration of autologous mesenchymal stromal cells for spinal cord injury: safety and efficacy of the 100/3 guideline. Cytotherapy. 2018;20:806–19.
Wolfe D, Hao S, Hu J, Srinivasan R, Goss J, Mata M, Fink DJ, Glorioso JC. Engineering an endomorphin-2 gene for use in neuropathic pain therapy. Pain. 2007;133:29–38.
Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152:S2–15.