What Do We Know About the Pathophysiology of Chronic Pain?

Implications for Treatment Considerations

Gerald M. Aronoff, MD

KEYWORDS

• Nociceptive processes • Neuropathic pain • Cold hyperalgesia
• Peripheral nerve injury • Wind-up pain • Central sensitization • Pain pathophysiology

KEY POINTS

- Treatment of the specific mechanisms responsible for the pain experience should be aimed at preventing and or reducing dysfunction neuro-plasticity resulting from poorly controlled chronic pain.
- Acquiring a greater understanding of specific pain mechanisms will improve the treatment plan for chronic pain patients.
- Further study of such mechanisms is needed to reduce the probability of persistent changes that cause chronic pain.

Chronic pain has been a mystification to mankind for ages. Descartes explored the pathophysiology of chronic pain in his *Treatise of Man*, and in his writings he described the human body as a "machine" with intricate and fine-tuned systems within systems.[1] He also described a hollow pathway controlling sensory and motor perception as well as a pain pathway. The pain pathway or pathophysiology of chronic pain continued to be a perplexing factor in the field of medicine for centuries. In this article, we discuss the complex features of the pathophysiology of chronic pain and the implications for treatment.

In 1994, pain was defined by the International Association for the Study of Pain (IASP) as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[2] When considering the pathophysiology of pain in context with the above-noted definition, it is important to acknowledge that chronic pain need not involve any structural pathology. This is consistent with our recognition that pain is a complex biopsychosocial experience. We now recognize that the traditional biomedical model of an acute injury with associated tissue damage does not explain the persistent pain seen in patients who

Carolina Pain Associates, PA, 1900 Randolph Road, Suite 1016, Charlotte, NC 28207, USA
E-mail address: painexpert@painexpert.com

Med Clin N Am 100 (2016) 31–42
http://dx.doi.org/10.1016/j.mcna.2015.08.004 **medical.theclinics.com**
0025-7125/16/$ – see front matter

develop delayed recovery and chronic pain syndromes that persist long after all structural pathology has healed. It also does not explain the persistent pain of many of the patients who have chronic daily headaches. To explain these, we need to look to central nervous system (CNS), genetic, and psycho-social factors. Chronic pain has become a major public health problem in the United States and many other countries. In fact, market research from 2011 reported 1.5 billion people worldwide as suffering from chronic pain.[3] An estimated 100 million persons of our adult population in the United States suffer from chronic pain,[4] causing an estimated $560 to $635 billion in direct and indirect costs and is a major reason for occupational disability. Therefore, we must attempt to better understand, evaluate, and treat this multifactorial problem.

In 1999, discussing the neurobiology of normal and pathophysiological pain, Devor[5] wrote "*The role of the pain system is to process information on the intensity, location, and dynamics of strong tissue-threatening stimuli. Traditionally it is presented as a serial bottom-up system in which afferent (sensory) impulses generated by noxious stimuli are encoded in the periphery, propagated centrally, processed and perceived. While retaining this basic layout, the new synthesis adds powerful modulatory (gating) influences among the adjacent system modules. Abnormal and chronic pain states are understood in terms of the functioning of these modulatory processes as much as by variations in the primary noxious input.*"

PAIN SIGNAL TRANSMISSIONS

Pathophysiological pain research studies have taught us that the pain signal initiates from the stimulation of peripheral nociceptor nerve terminals from specific receptors/ion channels. Pain circuitry activates nociceptors in response to painful stimuli. Pain is signaled to the brain via a wave of depolarization.

Such depolarization encompasses a discharge of sodium and potassium, via sodium channels. The surge of sodium is transmitted to first-order neurons ending in the brain stem within the trigeminal nucleus or dorsal horn of the spinal cord. Sensory information is then spread via small-diameter C-fibers terminating within individual regions of the dorsal horn of the spinal cord (laminae I-IV), from where the signal is transmitted to the brainstem, thalamus, and higher cortical centers.[6] Within this structure, the electrochemical signal opens voltage-gated calcium channels in the presynaptic terminal for calcium to enter and allow glutamate to release into the synaptic space. Glutamate connects with N-methyl-D-aspartate (NMDA) receptors on the second-order neurons producing depolarization. These neurons cross over the spinal cord and ascend to the thalamus, where they synapse with third-order neurons, after which they connect to the limbic system and cerebral cortex.

INHIBITORY PATHWAYS

Pathways that prevent pain signals from transmitting into the dorsal horn are referred to as inhibitory. Antinociceptive neurons start at the brain stem and stream down the spinal cord synapsing with short interneurons in the dorsal horn by releasing serotonin and norepinephrine. Interneurons modulate the synapse between first-order neuron and second-order neuron by releasing gamma amino butyric acid (GABA) an inhibitory neurotransmitter. Pain cessation is a result of synaptic inhibition between first-order and second-order synapses.

NOCICEPTIVE PAIN

Nociception is the activity in peripheral pain pathways that transmit or process information about noxious events to the brain. The process is usually associated with