Pathophysiology of Chronic Pain

James L. Henry, Ph.D.

Scientific Director

Michael G. DeGroote Institute for Pain Research and Care

McMaster University

1200 Main St. West, HSC 1J11

Hamilton ON

L8N 3Z5

jhenry@mcmaster.ca

In: Chronic Pain: a Health Policy Perspective

Eds. S. Rashiq, D. Schlopflocher, P Taenzer, E. Jonsson

Wiley-Blackwell, Weinheim, Germany

pp. 59-66, 2008

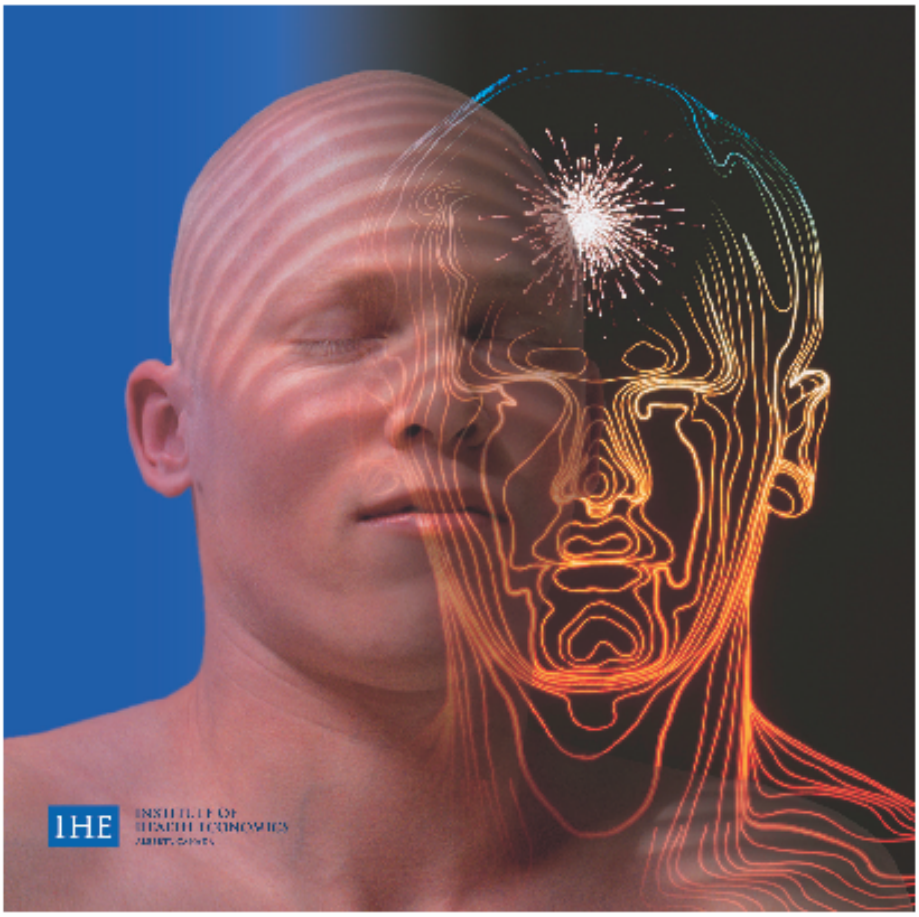
Health Care and Disease Management

Edited by S. Rashiq, D. Schopflocher, P. Taenzer and E. Jonsson

WILEY-BLACKWELL

Chronic Pain

A Health Policy Perspective



- Pain is a complex phenomenon that combines information from the nervous system with thoughts, emotions and social context
- Laboratory research has taught us a great deal about the way in which the nervous system creates and processes the necessary signals for pain , but each discovery raises a whole host of further questions
- Better funding for such research would accelerate the development of further rational, evidence-based treatments for pain, but it is not possible to predict how long this might take

To the person in pain, its existence is self evident and utterly convincing. However, the scientist who tries to demonstrate how the pain comes about knows that he or she is taking on a far more complex challenge than the study of other biological phenomena. What then, can science tell us about what is happening in the cells and tissues of the body during this uniquely human experience?

Scientists study pain at several levels of the nervous system. At the site of injury special nerve cell endings called nociceptors, which have been waiting for exactly this moment, respond to one of a myriad of unpleasant stimuli such as heat, pressure and inflammation, by sending a rapid and urgent signal that something is wrong. Shortly afterwards potent chemicals are released by crushed and broken cells which are detected by other nerves and amplify the pain signal. This whole process is called nociception, the change in the senses induced by a noxious stimulus. Activation of nociceptors can often lead to pain, but this is not always the case. A person may perceive a given event as merely annoying, mildly painful, or excruciating, based not only on the size of the trauma, but also on their thoughts, attitudes and context. An elite athlete or soldier in battle, for example, may be so focussed on the task at hand that he or she does not even notice his broken finger until the moment has long passed. Pain is thus the result of integrated neural input. It is highly individual and subjective in nature, often making pain difficult to define scientifically.

From an experimental perspective, pain can be broken down into three types, each mediated by different mechanisms. Nociceptive pain results from activation of nociceptors in peripheral tissues. Neuropathic pain results from injury or irritation to the nerves themselves such as in shingles or diabetic neuropathy. Inflammatory pain arises from inflamed joints or other tissues.

On a day-to-day basis pain subsides after the recovery from tissue injury, such as a burn, a cut

or even a broken bone. However, in some cases pain does not subside even despite healing of the injury. This is the pathologic condition known as chronic or persistent pain. In this case the individual may experience one or more of the following: spontaneous pain (pain for no apparent reason), hyperpathia (more pain than would be expected after a painful event)), hyperalgesia (increased intensity of pain to a further noxious stimulus), secondary hyperalgesia (spreading of sensitivity or pain to nearby, uninjured tissue) and allodynia (sensation of pain from a normally innocuous stimulus).

Nociception: how it works

Almost all parts of the body are covered with nerve endings that are each programmed to respond to a specific kind of unpleasant sensation. They require a certain intensity of stimulation before they react and will lie silent until this level is reached. When stimulated they create an electrical pulse known as an action potential, which is transmitted along the attached nerve on the first stage of a long but very rapid journey to the spinal cord and then to brain. The nerves are composed of thousands of tiny filaments called axons, lying alongside each other like strands of copper wire in a domestic electrical cable. Axons are classified according to the type of receptor they connect to and their diameter. Some are 'myelinated', i.e. covered with an insulating sheath made from a fatty material called myelin. This protects and nourishes the axon and keeps the electrical pulse within it, resulting in faster transmission of the signal. Large diameter axons are heavily myelinated and these are associated mainly with receptors to movement. There is then a range of axons of diminishing diameter and myelination, dedicated to serving a range of sensory impressions including hair movement, pressure, touch, temperature and nociception.

Subgroups of nerve endings each specialize in distinct sensory modalities such as nociception, or the ability to detect heat, cold or light touch. They differ in size, their destinations in the brain and spinal cord, their degree of myelination and the type of neurotransmitters (chemicals that cause a nerve cell to act in a certain way) that they respond to and secrete. Pain receptors on the skin have been studied more intensely than deeper receptors and are remarkably diverse: we can distinguish more than 20 different types of stimulus for which there is a specific nerve ending programmed and ready to respond to it and each has its own specific trigger. Researchers use specific compounds such as capsaicin (the substance that makes chilli peppers spicy), menthol, camphor, and wasabi to stimulate specific types of these receptors in experimental settings. The conditions required for a given receptor to fire may be highly specific. Thermal nociceptors, for instance, are only activated by temperatures above 45°C or below 5-10°C, especially when applied to the skin for durations of greater than one

minute. Mechanical nociceptors are only activated by strong physical stimuli, especially when applied over a small surface area. On the other hand, some peripheral receptors may respond to several different types of stimulus, including strong mechanical and thermal stimuli, and are often sensitized in time by repeated application of stimuli. These so-called polymodal nociceptors may also be sensitive to chemical stimuli, such as low pH. It is believed that some of these types of receptor are also located in deeper tissues. Since we know that some receptors can be made more likely to be activated by a number of mechanisms including the chemical environment it is theorized that some types of chronic pain may arise from this so called peripheral sensitization.

As indicated above, information is transmitted from the periphery to the spinal cord and brain by a variety of axon types with myelin sheaths of varying degrees of thickness. The more myelinated axons are thought likely to be the most sensitive to changes in myelination resulting from disease processes or injury. In such cases, when myelination is compromised there is thought to be a dysfunction of the mechanisms that transmit action potentials along axons due to the protective and nourishing function of the myelination. This dysfunction can result in extra, unnecessary electrical activity arising from within the nerve itself (ectopic discharge) and amplification of the nociceptive signal. Such mechanisms are thought to be the basis of some types of neuropathic pain.

The bodies of the nerve cells that transmit pain are located in the dorsal root ganglia, small specialized clumps of nerve tissue that run along the length of the spine, very close to the spinal cord. This is where the vastly complex genetic infrastructure and metabolic machinery of each of these nerve cells reside. The genetic component may be of crucial importance in the understanding of pain states. For example, if a normally non-pain transmitting neurone begins to make a chemical known as a substance P, activity in this type of neurone may lead to the perception of pain, even in the absence of a noxious stimulus. Another way in which gene activity might affect pain is in the expression or distribution of sodium channels. These are portals in the wall of the nerve cell through which sodium ions pass in order to generate the action potential. It has recently been reported that a rare inherited disorder in which the person is simply unable to feel pain is associated with a mutation that causes inactivation of a certain specific sodium channel [1]. Interestingly, other mutations that modify the kinetics of this channel but do not render it inoperable, are associated with the presence of an inherited form of a rare painful disease called erythromelalgia [2,3] and with other painful illnesses [4]. Thus, a change in the way genes direct the cell to produce and control sodium channels may lead to the perception of persistent pain, again even in the absence of a noxious stimulus. This is a potentially revolutionary area for scientific research.

The axons carrying the nociceptive signal continue on into the spinal cord and relay onto neurones

projecting to brain. They arrive and are distributed in highly organized ways to specific areas of each. The spinal cord is not, as was once thought, merely a passive relay station for sensory information on its way to the brain, but is the site of a great deal of processing of the nociceptive signal. The dorsal horn is the area of the spinal cord where this takes place.

Nociception, the transmission of a signal to the central nervous system in response to tissue damage, is broadly the same in all creatures and is therefore amenable to study in the laboratory. Pain, however, is a uniquely human experience, the result of not only the neurophysiological process but also of many additional factors that generally lie beyond inspection from a neurophysiological point of view, such as personality, circumstance and emotional state. We are beginning to understand how these domains might interact. For example, there are various changes in the spinal cord that have been suggested as leading to chronic pain, known as central sensitization, wind-up, and microglial activation. Central sensitization results from low frequency and high frequency nociceptive stimulation, and can lead to increased excitability of dorsal horn neurones, manifested as increased spontaneous discharge, increased receptive field size (possibly a cellular basis of secondary hyperalgesia) and increased responsiveness to innocuous stimulation of the peripheral receptive field (possibly a cellular basis of allodynia). Wind-up is initiated by high threshold, C-fibre strength, stimuli delivered at 3 Hz or more to induce cumulative depolarization. Windup does not persist following the conditioning stimulus.

The target areas for pain neurones as they arrive in the spinal cord are highly specific. Their organization is thought to serve both the very site specific sensations associated with some painful stimuli (for example, a pinprick in the finger can be located precisely by the sufferer, even without looking), yet a dull poorly-localized sensation associated with other stimuli (e.g. the widespread, dull pain that heralds the onset of appendicitis). This organization may also account for referred pain, the perception of pain in an area other than that where the injury occurs, such as the shoulder-tip pain that is commonly seen when the diaphragm is irritated and which is a a common complaint of patients with degenerative joint disease.

Chemical mediators of pain

The nervous system is rich in potent chemical substances that are released, detected and broken down in an ornate sequence that scientists are only beginning to understand. The excitement for researchers in this area is that thorough understanding which compounds are in action in a pain state raises the possibility of delivering drugs that affect their action and result in pain relief. An example of this is the amino acid glutamate, which is thought to be part of the sequence of events that results in

neuropathic pain. The discovery by laboratory scientists that the action of glutamate can be blocked at a receptor known as NMDA by existing medications resulted in their more widespread use in the treatment of this debilitating condition and has set in motion efforts to develop new drugs that might do so more effectively. Nociceptors also release other types of compounds that act as transmitters or as modulators of nerve excitability. Perhaps the best documented and understood is substance P, an 11 amino acid peptide identified first by Gaddum and von Euler as an extract in 1932, and termed substanz P, for powder. Substance P is released from one type of pain transmitting nerve fibre in response to intense peripheral stimulation and leads to selective amplification of pain pathways in the spinal cord. Other compounds including amino acids such as GABA and glycine, peptides such as enkephalin and dynorphin, and the nucleoside adenosine act to turn down the nociceptive signal.

These are but examples of what is a chemical correlate to the intricate anatomical and morphological complexities that contribute to nociception. Slight disturbances or prolonged synaptic input can generate long-term or even permanent plastic changes in these neurones and these changes may account for some types of chronic pain.

What have been described thus far are events that take place in nerve tissues, but important scientific discoveries about pain transmission have been made by focussing down further, to events taking place within and around individual nerve cells. Calcium plays a major role in short-term and long-term events triggered by synaptic activation. It regulates the amount of other neurotransmitters sent from one pain nerve to the next in sequence in the dorsal horn of the spinal cord. Intracellular calcium participates in activation of and in regulation of gene expression.

Contribution of non-neuronal cells to nociception

Recently, we have become aware that direct neuronal signalling to other neurones is not the only process that leads to long-term changes. Immune cells within the spinal cord, which were long thought to only have a protective and nutritive role, have also recently been found to contribute to alterations in neuronal hyperexcitability [5-6]. These immune cells, mainly microglia and astrocytes, are activated from their normal quiescent state by injury to peripheral nerves and also by inflammation or injury within the spinal cord or brain. In fact, rather than increasing excitability of spinal nociceptive neurones the processes thought to occur are through removal of an inhibitory influence, or disinhibition [7].

Basic science contributions to pain management

The data that emerge from basic science research on pain mechanisms is yielding ever clearer and

simplified explanations for what we see in humans and animal models. The landmark Gate Control Theory of Ronald Melzack (Canada's pre-eminent scientific pain researcher) and Patrick Wall in 1965 [8] set the stage for theories of pain transmission, and this spurred much research into understanding the nature of pain. Yet, these hypotheses oversimplify the complex mechanisms involved and overlook important facts. For example, we now know that most spinal dorsal horn neurones can be excitatory or inhibitory and receive inputs from higher brain centres and other local interneurones in addition to inputs from the periphery. The precise roles of these interneurones in information processing, particularly processing of nociceptive information, are far from being understood. Several different classifications of dorsal horn neurones have been published along morphological, chemical and electrophysiological lines. Yet no such classification scheme has been able to claim clearly established links to clinical conditions. Due to their very small size, these neurones are difficult to record from electrophysiologically and thus have not been characterized as clearly. Efforts to synthesize what we know from the morphological, electrophysiological and neurochemical points of view about dorsal horn neurones are ongoing, but slow to yield convincing results. For example, neurones in one part of the dorsal horn (Lamina I) are so few, numbering only in the hundreds rather in the tens of thousands in the dorsal horn, that it is hard to accept that the full range of perceptions of pain, including allodynia and hyperalgesia, can be served by so few neurones. Clearly, much further research is necessary if we are to gain the depth of understanding needed.

Establishing a functional role for any of these classifications has not been achieved. We have drawn only tenuous conclusions about the possible roles of the different morphological cell types, the various discharge characteristics or the different chemical mediators of synaptic transmission and intracellular signal transduction. Nevertheless, there is considerable hope that this knowledge will yield novel therapeutic approaches. The GluR-A glutamate receptor, a novel form of the glycine receptor containing $\alpha 3$, the prostaglandin E_2 pathway and the K*v4.2*-type potassium channel are just some of the parts of the complex processes within the nervous system that are under intense scientific scrutiny for answers to the pain mystery.

Thus, while we know much and there are emerging leads that may be useful in developing novel approaches to management of chronic pain, there remains much to learn. Oversimplified theories of sensory processing mechanisms impede our ability to understand fully these mechanisms. We see the pain system now as multiple pathways, with multiple synaptic junctions and an elaborate network of local and remote control systems acting at each junction, and a fathomless capacity for neuroplastic change [9]. If we are to begin to match mechanisms with clinical conditions and to exploit knowledge of mechanisms to develop novel approaches to pain management, we must commit ourselves to the

long and difficult task of accumulating a vast amount of scientific knowledge.

Impact of policy on knowledge generation

Laboratory research has yielded important information about the many aspects of the mechanisms of pain generation. Examples of note include understanding of transduction mechanisms in peripheral sensory nerve terminals and the complexity of mechanisms controlling peripheral sensitivity, the varied nature of the ion channels mediating conduction of action potentials to the central nervous system, the chemical basis of synaptic transmission at the first sensory synapse, recruitment of non-neural cells into pain pathways, the plethora of intracellular signal transduction mechanisms and the resultant forms of altered excitability and finally, the identification, cloning and regulation of expression of critical proteins, whether receptors, ion channels, transporters or synthesizing enzymes.

These innovations have helped some patients but have not addressed the needs of many others who may be suffering a different type of pain. Innovation can be accelerated, but this would require a different approach than what we have had in the past, and this is governed by policy. Innovation comes most rapidly from the best-funded research efforts attracting the most innovative minds. Therefore, we need to accept that if we intend to ramp up innovation we need to increase its funding. There is ample reason to be optimistic that these developments and others will eventually lead to new types of treatment for pain, given adequate support and time. In this context, it is sad to note that the Canadian Institutes of Health Research does not have a review process that specifically addresses pain, either for the basic or for the clinical sciences, and that that funding for knowledge generation in pain is not commensurate with its impact on the individual and society. The European parliament has declared chronic pain to be a disease in and of itself. This highlights the need for increased knowledge generation. The US House of Representatives has declared this to be the Decade of Pain Care and Research. This was backed up by a 10-step approach and by a major influx of funding for pain care and research. Benefits of this policy change will not be seen immediately, yet in the long run Americans will benefit from this influx of funding.

As Canadians, we justifiably pride ourselves on our health care services. However, those people who suffer chronic pain and those others who are engaged in its treatment and research currently see less to be proud of. Bringing research funding up to a level meeting the medical needs imposed by chronic pain would be a valuable first step in addressing the current imbalance.

References:

1. Fertleman, C. R., Baker, M. D., Parker, K. A., et al. (2006) SNC9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. *Neuron 52*, 767-774.

2. Drenth, J. P. H., te Morsche, R. H. M., Guillet, G., Taiev, A., Kirby, R. L., Jansen, J. B. M. J. (2005) SCN9S mutations define primary erythermalgia as a neuropathic disorder of voltage gated sodium channels. *J. Invest. Dermatol. 124*, 1333-1338.

3. Yang, Y., Wang, Y., Li, S., et al. (2004) Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. *J. Med. Gene.t 41*, 171-174.

4. Hayden, R., Grossman, M.. (1959) Rectal, ocular and submaxillary pain. *Am. J. Di.s Child 97*: 479-482.

5. Marchand, F., Perretti, M., McMahon, S. B. (2005) Role of the immune system in chronic pain. *Nat. Rev. Neurosci*. 6, 521-532.

6. Tsuda, M., Inoue, K., Salter, M. W. (2005) Neuropathic pain and spinal microglia: a big problem from molecules in "small" glia. *Trends Neurosci. 28*, 101-107.

7. Sherman, S. E., Loomis, C. W. (1994) Morphine insensitive allodynia is produced by intrathecal strychnine in the lightly anesthetized rat. *Pain 56*, 17-29.

8. Melzack, R., Wall, P. D. (1965) Pain mechanisms: a new theory. *Science 150*, 971-979.

9. Craig, A. D. (2003) Pain mechanisms: labelled lines versus convergence in central processing. *Ann. Rev. Neurosci. 26*, 1-30.