Pain Conundrums: Which Hypothesis?

Central Nervous System Sensitization versus Peripheral Nervous System Autonomy

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The two hypotheses, central nervous system (CNS) sensitization and peripheral nervous system (PNS) autonomy are at first glance irreconcilable. CNS sensitization is the reigning paradigm in mainstream pain medicine. It is shared by most members of the medical scientific community.

PNS autonomy is not recognized despite convincing scientific and clinical evidence. It has yet to establish a paradigm status and would require a scientific revolution or paradigm shift for it to gain acceptance, as predicted by Thomas Kuhn.[1]

However, a growing body of scientific evidence, old and new, is addressing anomalies in the CNS sensitization concepts that have been ignored or dismissed.

Historically, ideas culminating in the CNS sensitization theory started with the Melzack-Wall article in 1965[2] on the Gate Control Theory, which "emphasized the mechanisms of the CNS controlling the perception of a noxious stimulus and thus integrated afferent, upstream processes with downstream modulation from the brain".[3] The current definition of pain endorsed by the International Association for the Study of Pain (IASP) is a logical outcome of this theory: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[4]

According to Howard L Fields,[5] "The pain pathway we are all familiar with normally begins with tissue damage, inflammation, and traumatic injury. It starts with impulses out in the periphery. These are propagated to the spinal cord, cross in the contralateral spinothalamic tract, delivered to the thalamus and then widely distributed to the cortex. Injury to a peripheral nerve somehow causes an increase of activity in this pathway somewhere along this pathway." He goes on to say that this increase of activity could come from either greater activity in the nociceptors in the periphery or by removal of some sort of inhibition in the CNS releasing the transmission neurons from inhibition. Further, he argues that these neurons are now spontaneously active and produce a pain signal. Animal studies have shown that these nerves themselves become pain generators. It is also known that damage to selectively large myelinated fibers will cause central fibers to fire more to any peripheral stimulus. There is also evidence that damage to peripheral nerves results in spontaneous activity in second-order neurons. Injury to peripheral nerves can also possibly cause "rewiring" in the spinal cord where fibers from the periphery normally responding to light touch producing the sensation of vibration or tickle now connect to a different second-order cell in the spinal cord. Their activity now may produce a burning pain instead of a tickle. In an article in the *Lancet*, Loeser and Melzack[3] conclude that "The brain contains widely distributed neural networks that create an image of self through genetic programmes and memories of past experience. Afferent inputs act on this neuromatrix and produce output patterns that lead to the report of pain. Stress can change the interactions between the neuromatrix and peripheral stimuli, as can learned experiences and expectation."

As a consequence of the above concepts, the memory of the injury leading to chronic pain and CNS sensitization are now generally considered useful in the "management" of chronic pain by increasingly complex multidisciplinary teams.

One anomaly in the CNS sensitization theory is its impotence in curing chronic pain, despite more than 40 years of millions of dollars of research unraveling the mysteries of the CNS. Loeser and Melzack[3] admit to this when they conclude their article in 1999 by saying, "In both clinical and basic research, we are rapidly gaining useful information that will lead to more effective care for those who suffer pain". In the introduction to the third edition of *The Textbook of Pain*, Wall and Melzack[6] express the hope that in their next edition they will be able to announce to the world a cure for chronic pain. This inability to cure chronic pain has led mainstream medicine to build up an immutable conviction that any health professional claiming the opposite is deluding himself or herself and his or her patients. Popularized books on the management of chronic pain by reputable and leading specialists thus warn patients seeking a cure for their chronic pain to be wary because offering a cure is akin to deception.[7] A further anomaly is the belief there is no demonstrated pathology in the PNS satisfactorily explaining chronic pain. This view is detailed in the introduction to Wall and Melzack's *Textbook of Pain*[6] in 1997.

The last 40 years of basic research into the PNS has shown the opposite. Since Jancso et al. published their *Direct Evidence for Neurogenic Inflammation and its Prevention by Denervation and by Pretreatment with Capsaicin* in 1967[8] a growing number of scientists have systematically unraveled the PNS response to injury. Bennett in 1999[9] summarized this: "Painful peripheral neuropathies begin with nerve injury caused by disease or trauma. This injury will result in an inflammatory reaction, a neuritis that will mobilize the immune system." Subsequent changes may result in more slowly developing mechanisms of

abnormal pain that underlie the chronic phase of painful neuropathy.

Douglas Zochodne from the Neuroscience Research Group in Calgary[10] examined the role of the microenvironment and microcirculation of the injured and regenerating peripheral nerve trunk and concluded in his seminal paper on peripheral nerve response to injury: "Better understanding of these and other events in injured nerve trunks is needed to help solve the two cardinal problems of peripheral nerve injuries:

1) functional disability from impaired regeneration, and
2) the development of disabling neuropathic pain."

Peripheral nerves respond to injury in a unique way. Instead of ischemia, peripheral nerves develop increased endoneurial blood flow. Trauma-induced ischemia in all other tissues may lead to cell death and release of arachidonic acid, stimulating COX I, COX II, and 5-LOX pathways upregulating prostaglandin production and tissue inflammation. Peripheral nerve injury leads to "dumping" of calcitonin gene related peptide (CGRP), substance P (SP) and nitric oxide (NO) from nervi nervorum, the extensive innervations of the connective tissue of peripheral nerve trunks, the epi-perineurium. CGRP, SP, and NO are vasodilators with CGRP and SP also potent upregulators of vascular permeability of the vasa nervorum and neighboring blood vessels. The result is a rapid increase in the endoneurial blood flow and neurogenic inflammation of the nerve trunk itself and the surrounding tissues. This forms the basis of the Triple Response described by Lewis in 1927[11] with the well-known "line, wheal and flare". Lewis also identified the Axon Reflex, showing axonal impulses travelling in an orthodromic (to CNS) and antidromic direction. In 1901 Bayliss[12] found that stimulation of the dorsal root ganglion (DRG) resulted in peripheral vasodilatation. He postulated afferent and efferent conduction. Some 20 neuropeptides and neurotransmitters are known to be involved in neurogenic inflammation.[13] Most of these have been cloned, including their antagonists, their receptors, and receptor antagonists. Evidence of pivotal roles for specific neuropeptides is lacking, hence no drug treatment has yet been developed against neurogenic inflammation and the concept of neuromodulation is rationalizing the impasse. It has also been found that some neuropeptides (CGRP, peptide YY - PYY - and neuropeptide Y - NPY) can be released from non-neuronal cells and also in a paracrine fashion from neurons. Some anti-inflammatory neuropeptides such as melanocyte-stimulating hormone (MSH), vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) may be released to terminate inflammation under physiological conditions. Thus neuromediators are not all pro-inflammatory but regulate all phases of the inflammatory response.

The complexity of responses of the peripheral nervous system was also highlighted by Burnstock in 1976.[14] He introduced the concept of co-transmission in the autonomic nervous system with neuropeptides also contained in cholinergic and adrenergic nerves. The intimate connection between sensory and autonomic nerves is particularly poignant in children born with congenital insensitivity to pain in hereditary sensory and autonomic neuropathy (HSAN type I-IV). The absent or abnormal peripheral nerves are the reason for severe disfiguring sequelae of trauma, inability to repair tissue or adequately mobilize the immune system, often leading to death from infection during childhood. The recent finding of opioid receptors on peripheral sensory axons[15] led to some speculation that these μ opioid receptors (MORs) may have an antinociceptive action. This motivated Zochodne et al,[16] to examine the function and expression of local MORs associated with the chronic constriction injury (CCI)[17] model of sciatic neuropathic pain in rats. Low dose morphine was injected percutaneously near the nerve. They concluded that their positive findings "may provide a therapeutic direction for the treatment of certain focal neuropathic lesions in humans".

Successful treatments of painful peripheral neuropathies or chronic recalcitrant pain have been described in the literature. Whether one goes along with the rationale for these treatments is less relevant. After all, clinicians would consider it unethical to cease treatment with lithium carbonate or chlorpromazine simply because the mode of action is unknown. By 1965 George Hackett[18] had published the results of prolotherapy treatment of 1800 cases of chronic low back pain, with an 82% success rate and a 12-year follow up. He published 16 articles and one book on his treatment. Also in 1965 Melzack and Wall published their Gate Control Theory of Pain. Their *Textbook of Pain,* published in 1997, does not reference prolotherapy. Neither does it reference neural therapy. This treatment was developed in Germany in the 1940s by Drs Ferdinand and Walter Huneke. Lidocaine is used to treat chronic pain by targeting postulated "interference fields" that cause "blocks" in the autonomic nervous system leading to chronic pain. This treatment is highly successful and practised widely in Germany and Spain by more than 5000 medical practitioners. Most of the literature is in German and this may be the reason there is little knowledge of this treatment in the English-speaking world.

The growing scientific evidence supporting the view that neuropathic pain syndromes are caused by unremitting peripheral neurogenic inflammation involving the autonomic and sensory nerves may lead to renewed interest in prolotherapy and neural therapy as these treatments are effective and seem to target the PNS. The author has now treated more than a 1000 patients with subcutaneous prolotherapy targeting neurogenic inflammation of peripheral nerve trunks in much the same way as Zochodne's percutaneous near nerve injections with low-dose opioids. Published results[19-21] are promising for recalcitrant lumbago, shoulder, knee, elbow pain, and achillodynia. Patients with chronic neuropathic pain will continue to suffer needlessly if physicians remain fixed on the reigning paradigm that can suggest only "pain management" when

there are well-documented alternatives available that may offer a cure.

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