The Mechanisms of Neuropathic Pain: an Overview for Psychiatrists

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Abstract

Objective: To present an overview of the mechanisms of neuropathic pain. Method: An extensive review of the scientific literature. Results: Neuroplastic changes are described under the headings of: ectopic discharge, sensitization of sensory terminals, cross-excitation, neurotransmitter change, coupling between the sympathetic and sensory nervous systems, spinal cord reorganization, spinal cord increased excitability, spinal cord decreased inhibition, supraspinal influences. Conclusions: These mechanisms increase our understanding of the patient with neuropathic pain and open the door for therapeutic advances in this field. They also extend our understanding of the nature of the nervous system more generally, and may provide pathophysiologic models of psychiatric disorders (German J Psychiatry 2002: 5:34-39).

Introduction

The mechanisms of neuropathic pain are being elucidated. This new information is important to psychiatrists who deal with chronic pain in the therapeutic or medico-legal arenas. It is also important more generally in psychiatry as it informs regarding the plasticity of the nervous system in response to trauma. The objective of this paper is to present an overview of these mechanisms.

Three types of chronic pain have been recognized: psychogenic, inflammatory, and neuropathic. Neuropathic pain is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (Mersky and Bogduk, 1994). It depends on neuroplasticity, that is, alterations in the function, chemistry and structure of neurons. Accordingly, it depends on alterations in gene expression and phenotype (Hunt and Mantyh, 2001).

The symptoms which suggest neuropathic pain include spontaneous pain, hyperalgesia and allodynia. The spontaneous pain is characteristically burning or shooting in nature. Hyperalgesia is an increased pain response to a suprathreshold noxious stimulus (that is, a painful stimulus hurts more than it should). Allodynia is the sensation of pain elicited by a non-noxious stimulus, such as the gentle touch of clothes or the bending of a cutaneous hair by a puff of wind. Spontaneous pain may be conceptualized as "stimulus independent" and hyperalgesia allodynia as "stimulus dependent" pain.

Focusing on symptoms and etiology has not provided a suitable model for understanding or intervention. However, an extensive range of mechanisms, which operate at the peripheral, spinal cord and supraspinal levels (Taylor, 2001) and underpin symptoms are now being described. No particular injury or disease process is associated with a unique pain mechanism, and many different mechanisms may produce same symptom. In any given patient suffering neuropathic pain, a number of mechanisms are usually

operating at the same time, and they usually change over time.

Even at this early stage, knowledge of the mechanisms is helpful. They give a more complete understanding of the neuropathic pain patient, legitimizing a range of claimed symptoms which have often been doubted by clinicians. They explain how pain can be felt when there is no activity and how activity may make pain worse. They explain how pain can be triggered by the slightest touch, how pain can spread beyond the site of trauma and, with the change of mechanisms over time, how one agent may be useful at one time but become frustratingly useless later on. These mechanisms give a better understanding of the mode of action of some of our rudimentary interventions. For example, in neuropathic pain the tricyclic antidepressants function not only on neurotransmitters but also as sodium channel blockers, thus reducing ectopic discharge.

Support for theoretical issues in psychiatry may also emerge from consideration of these mechanisms. Just as genetic influences have been established in many psychiatric disorders, so recent evidence indicates an inherited predisposition to chronic pain (Mogil et al, 1999). Also, it has been recently found that neuropathic changes may be associated not only with direct trauma to neural tissue, but also with continuous or severe nociceptive (pain) input from inflammatory lesions (Terayama et al, 2000). This may serve as a model for post traumatic stress disorder or other psychiatric disorders.

Method and Results

Electronic literature searches were conducted using the words "pain", "chronic pain" and "neuropathic pain". This generated over three hundred papers. Many described esoteric preclinical studies and others were unavailable in full form to the present authors. Ultimately, fifty papers were studied, providing comprehensive, if not exhaustive, coverage of the field.

A range of mechanisms was described, and a brief account of each is presented under headings.

Ectopic discharge

Spontaneous activity in normal primary sensory neurons is low. After injury, however, spontaneous ectopic discharges are observed in skeletal muscle afferents (Michaelis et al, 2000). These are the result of phenotypic changes in the nature and distribution of sodium and calcium channels, which occur throughout the damaged neuron, including the dorsal root ganglion. These changes may result not only in spontaneous pain, but may also contribute to central sensitization (see below). Interestingly, after insult to a

region, some uninjured neurons may also demonstrate ectopic discharge (Bridges et al, 2001).

Sensitization of sensory terminals

Nociceptor (pain sensitive neuron) peripheral terminals of injured and uninjured neurons are sensitized by substance P, released from the terminals of local damaged neurons. Axons transmit potentials in both directions, and such agents are released by antidromic potentials, which proceed from ectopic discharges (Woolf and Mannion, 1999). This provides a basis for hyperalgesia.

Cross-excitation

Injury may lead to disruption of glial sheaths. Adjacent denuded axons may make electrical or chemical contact, resulting in cross-excitation. Undamaged neurons may also become involved (Amir et al, 2000). When A-beta fibers (touch sensitive neurons) activate C fibers (pain sensitive neurons), non-noxious stimuli may produce pain.

Neurotransmitter change

After injury, phenotypic change may be reflected in the production by peripheral nerves of neurotransmitters which cause pain. A-beta fibers, which normally transmit non-noxious tactile messages, may begin to release pro-nociceptive transmitters, such as substance P, at the spinal cord (Noguchi et al, 1995). Thus, touch may cause pain.

A large number of factors may trigger phenotypic change. The biology of sensory neurons depends on growth factors which proceed from the innervated tissues, along the neuron, to the cell body. Following inflammation or injury, changes in neurotransmitter expression may be secondary to changes in the factors released at the injury site (Hunt and Mantyh, 2001).

Coupling between the sympathetic and sensory nervous systems

In normal physiological conditions, the sympathetic nervous system cannot cause pain. Uninjured primary sensory nerve endings are not sensitive to catecholamines and are functionally distinct from sympathetic nervous system efferents.

After injury, however, there are at least two mechanisms by which coupling of the sympathetic and sensory motor systems may be established, providing potential mechanisms for neuropathic pain. First, both injured and uninjured neurons develop alpha-adrenoreceptors, which makes

them responsive noradrenalin from sympathetic nerve terminals. [Injured neurons are also believed to be responsive to circulating adrenalin and noradrenalin.] Second, sproutings from sympathetic axons into the dorsal root ganglions forms baskets around the cell bodies of sensory neurons and thereby, appear capable of causing depolarization (Woolf and Mannion, 1999).

In spite of these potential mechanisms, the actual proportion of cases of neuropathic pain in which there is significant contribution from sympathetic nervous system is probably small. Treatments of neuropathic pain which are aimed at the sympathetic system have produced equivocal results (Kingery, 1997).

Spinal cord reorganization

The normal arrangement is that primary afferent neurons terminate in particular layers of the dorsal horn of the spinal cord, synapsing with particular, predetermined second order neurons. Lamina II receives nociceptor C-fibers exclusively. After nerve injury, however, there may be substantial degeneration and loss of the central terminals of C fibers in lamina II. Subsequently, the central projections of surviving A-beta fibers in lamina III and IV may sprout into the territory vacated by the C-fiber terminals and make contact with second order pain transmission neurons in lamina II (Woolf et al 1995). Thus, non-noxious information, such as proprioceptive information or touch may be interpreted as being of noxious origin. This is a pathophysiological explanation for pain from movement and allodynia (Kohama et al 2000).

Spinal cord increased excitability

Any prolonged or excessive sensory input from persistent inflammation or nerve injury may result in increased excitability in the spinal cord (Woolf, 1986). This has been called "central sensitization". The physiological changes have not been fully elucidated, however, it is believed that nociceptor input may lead directly to sensitization of secondary dorsal horn neurons (Woolf, 1986). Also, peripheral nerve injury may lead to elevated spinal dynorphin (endogenous opioid) which may sensitize the second order neurons in the cord. Such elevation may be "multisegmental", occurring at levels adjacent the segment of the injured nerve, causing "extraterritorial" neuropathic pain, or pain in a region not supplied by the damaged nerve (Malan et al, 2000).

With healing, central sensitization may subside. However, through ectopic activity in A-beta neurons, it may be sustained indefinitely.

Spinal cord decreased inhibition

Nerve injury may result in death of inhibitory dorsal horn interneurons. This results in loss of inhibition and an increased likelihood of dorsal horn neurons firing spontaneously or in an exaggerated manner (Woolf and Mannion, 1999). Decreased spinal cord gamma amino butyric acid (GABA) concentration and GABA receptor binding sites have been reported (Castro-Lopes et al, 1993). Thus, the "gate" (Melzack and Wall, 1965) can no longer be closed by stimulating intact peripheral A-beta fibers or via descending impulses from higher centers.

Supraspinal influences

The ability of descending fibers to inhibit nociception is well established. More recently, descending fibers with an ability to facilitate nociception have been reported. Evidence indicates that injury and persistent noxious input associated with inflammatory pain causes long-term changes in the activity of brain stem neurons which enhance facilitation and contribute to neuropathic pain (Ossipov et al, 2000). This facilitation appears to be driven by brainstem cholecystokinin (Kovelowski et al, 2000). These findings are from single cell neurophysiology studies of experimental animals. Such techniques are not presently available in clinical practice. Valuable human information, however, can be derived from imaging and related studies.

The thalamus is believed to experience pain related plastic change (Lenz et al, 2000). Quantitative sensory testing, neurophysiological and psychological examination of patients with complex regional pain syndrome suggest thalamic plasticity in chronic pain (Rommel et al, 2001). Regional blood flow changes have been observed in the basal ganglia of patients with chronic pain (Mountz et al 1995). Altered facilitation and inhibition of the motor cortex using transcranial magnetic stimulation in two groups of patients with two painful disorders, fibromyalgia and rheumatoid arthritis, have been demonstrated (Salerno et al 2000). Those authors hypothesized their findings were secondary to pain induced changes in the basal ganglia.

Chronic back pain (Flor et al, 1997) and amputation (Wiech et al, 2000) are associated with spatial reorganization of somatosensory cortical mapping, and the "corticalization" of chronic pain has been proposed (Birbaumer et al, 1995). Such changes have yet to be thoroughly investigated, however, it is probable, that plastic brain changes secondary to pain are important in causing and maintaining neuropathic pain.

Discussion and Conclusion

Psychiatry and neurology were once one. There was a parting of the ways, but with the recent birth of "biological" psychiatry and rebirth of neuropsychiatry, parts of these two bodies of knowledge and skill are reuniting. The mechanisms of neuropathic pain may facilitate this process. Neuropathic pain is characterized by spontaneous pain, hyperalgesia and allodynia. Focusing on these symptoms did not advance the field, however, recent elucidation of the physiological mechanisms underpinning these symptoms has ushered in new understanding and therapeutic promise.

The mechanisms of neuropathic pain are of greatest interest to psychiatrists involved in pain management or compensation issues, but they are also of general interest and offer important insights into the nervous system. They provide pathophysiological explanations for spontaneous pain, hyperalgesia and allodynia. They explain how movement may cause pain, and how pain can be felt in a region adjacent to that of a damaged nerve. The designation of such "expansion" of painful sites as "hysterical" now needs to be applied with caution.

Of interest is the finding that stimulation of peripheral nerves which is strong, but not destructive of the peripheral nerve, may result in prolonged modification to the function of the spinal cord. Electrical stimulation of cutaneous nerve and muscle, and chemical stimulant (mustard oil) applied to skin or injected into muscle, have produced facilitation or flexor withdrawal in the rat, which lasted more than three hours (Woolf and Wall, 1986). These studies may form a pathophysiological model of post traumatic stress disorder, in which stimulation of the sensory system produces long term modification of the CNS.

Strong evidence also indicates that chronic pain in humans causes plastic changes in the basal ganglia (Mountz et al, 1995) and cortex (Salerno et al, 2000). This may be analogous to the emotionally painful loss of a spouse leading in time to brain changes and eventual major depressive episode.

Medicine is waiting for the new understanding of pathophysiologic mechanisms of neuropathic pain to bear fruit. Clinical tests are required to identify which mechanisms are present, and new therapeutic options will be necessary to address each. Research is currently being conducted on many potentially useful pharmacological agents, including revolutionary sodium channel blocker and nerve growth factors. It is reasonable to hope that some of these agents will also find application in certain psychiatric disorders.

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