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Short Note

Mirror Image Pain: Importance of Recognition in Clinical Practice

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INTRODUCTION

The concept of mirror image pain, also termed mirror pain (MP), is based on an appreciation of a much more complex structure of the nervous system than envisioned by the Cartesian model (named after the French philosopher Rene Descartes) of a hard wired nervous system with fixed connections where the brain receives and processes painful stimuli and elicits an appropriate response. Research has provided information on the role of mechanisms such as glial cell activity, neurotransmitters i.e. glutamate, substance P (SP), and N-methyl-D-aspartate receptors (NMDA) among many others, nerve sprouting, as well development of plasticity and sensitization in the previously "hard wired" nerve connection circuits. Neuroplasticity describes changes in the peripheral and central nervous system (CNS) in response to pain stimulus. With ~~the~~ release of neurotransmitters there is a possibility that neurons in the spinal cord, described below, will be sensitized to further peripheral stimuli. If the neuron does become sensitized, even non-painful stimuli may be perceived as pain (allodynia) and eventually felt in ipsilateral or contra lateral areas apart from the initial point of injury and is referred to as extraterritorial pain [1]. Contra lateral pain is synonymous with MP.

ACUTE PAIN

In general, following peripheral nerve injury, acute pain sensation is transmitted from the site of injury to the central nervous system via thinly myelinated A-δ and un-myelinated Cafferent nerve fibers (first order neurons) the cell bodies of which are located in the dorsal root ganglion (DRG). These nerve axons do not form a synapse in the DRG through which they pass but continue through and synapse with second order neurons in either the spinal cord or medulla. The second order neurons cross over to the opposite side of the spinal cord and ascend to the thalamus by way of the spinal-thalamic tract. In the thalamus they synapse with third order neurons that carry the impulse to the cerebral cortex where it is perceived. At the points of synapse excitatory amino acids i.e. glutamine and asparagine, are released and act on N–methyl-D-aspartic acid (NMDA) receptors causing release of substance P (SP) resulting in a lowered threshold for synaptic excitation in the otherwise normally quiet second-order synapses [2]. In the normal state, the acute pain process is usually self-limiting and pain abates in a relatively short time as healing and recovery take place.

CHRONIC PAIN

Pain is considered chronic usually at 3 months or longer, although the neurophysiologic changes accompanying chronic pain are often well-established within 2 to 4 weeks after the onset of pain [3]. In the chronic pain state, due to neuroplasticity, the sensitized nerve components do not return to their normal state. Consequently, nociceptive input is not necessary to induce pain, allodynia becomes evident, and pain can spread to areas beyond the point of injury [1,4-6]. If chronic pain is related to the development of extraterritorial pain, what mechanisms are involved in the spread of pain to the contra lateral side of the body? Research has focused on the possible links that join the two sides of the body. Koltzenburg [6] published a review of the crossover pain phenomenon (later verified by Dubový [8] et al., and Arguis [9] et al., and considered it to be resulting from either humoral or neuronal mechanisms.

Jančálek presented evidence that contra lateral signaling pathways may be transneuronal but also discussed possibilities for a humoral glial signaling pathway [10-12]. Whereas glial cells were considered to have only a role to support neurons, Garrison linked neuropathic pain and glial activation [13]. Activated glia release amino acids, nitric oxide, prostaglandins, and cytokines (a generic term for a group of soluble proteins and peptides able to facilitate communication among immune system cells and the rest of the body. Cytokine release by microglia increase neural excitability through activation of extracellular signal-regulated kinases (ERK) and cAMP response element binding protein (CREB) [4,10]

Two studies of MP by Cheng et al, using nerve ligation in the rat, found that satellite glia in the contra lateral DRG are activated by tumor necrosis factor alpha (TNF-α) that diffuses from the injured side via cerebrospinal fluid activating the glia to produce extra nerve growth factor (NGF) thereby enhancing nociceptor excitability which induces MP. The second study showed that elevated NGF after peripheral nerve injury induces neurite sprouting and formation of synapse-like structures within the contra lateral DRG also contributing to the development of chronic MP. [14,15]

TRIGEMINAL NERVE

Although the trigeminal nerve is one of the 12 cranial nerves its peripheral and central sensory components bear anatomical similarities to those of the spinal nerve system. Axons within the 3 peripheral sensory branches (first order neurons) with cell bodies in the trigeminal ganglion (Gasserian ganglion) transmit pain impulses from their nerve endings in the face and oral cavity through the ganglion (they do not synapse in the ganglion) then enter the spinal cord and descend through the spinal trigeminal tract and end in the trigeminal nucleus (pars caudalis). Here they synapse with a second order neuron that immediately crosses to the contra lateral side of the spinal cord, enters the ventral trigeminothalamic tract and ascends to the level of the thalamus where it synapses with a third order neuron that carries the impulse to the cerebral cortex.

Similar to the spinal nervous system, chronic pain can cause neuroplastic change and sensitization within the trigeminal nerve resulting in extraterritorial ipsilateral or contra lateral extraterritorial pain. Central sensitization in the trigeminal nerve increases the tonic excitability of wide dynamic range (WDR) neurons and glial cells in the dorsal horn of the nerve's spinal nucleus. The WDR neurons become increasingly permeable to Ca^{2+} ions in response amino acids, especially glutamate from the postsynaptic WDR neurons from the sensitized peripheral nerve. The N-methyl-D-aspartate (NMDA) receptor mediates the glutamate activity. Moreover, ultra structural morphologic changes have been seen in synaptic spine sprouts and receptive plasma membranes. Such regions of plasticity have been associated electro physiologically with spontaneous hyperactivity within the trigeminal central complex [3,16].

IMPLICATIONS FOR CLINICAL PRACTICE

Mechanisms causing human trigeminal MP are not understood. Based on all of the forgoing it would seem reasonable that similar mechanisms of action are probably in place. Regardless of the mechanism involved, MP is a clinical problem that must be considered when examining patients with a history of nerve trauma present complaining of pain on the side contra lateral to the side where injury occurred. Unless there is a clear indication of pathology, invasive procedures such as endodontic treatment or extractions should be avoided. If a procedure was performed and the patient receives no relief, it is not justified to further extirpate another pulp or remove another tooth. Because MP is centrally mediated a nerve block on the MP side will not be effective as a diagnostic tool. A nerve block on the side of the injured nerve may or may not be of a diagnostic benefit.

An injured peripheral nerve can take three months or longer to heal. While this is generally true, if pain is present, corrective action should be taken quickly. Implants found to be encroaching on a nerve and causing pain should be removed immediately. It is also advised that any implant encroaching on a nerve should be removed and not wait for "healing". Patients with lingual and/or inferior alveolar injury following third molar removal can be followed if they continue to show improvement; however, if there is a painful component to the injury treatment should begin immediately. Narcotic analgesics are not particularly effective in treating neuropathic pain. Centrally acting medications such as gabapentin or pregabalin should be prescribed instead of a narcotic. Surgical correction may be required. However, preoperative trigeminal neuropathic pain has been shown to be an accurate predictor of postoperative neuropathic pain following surgical repair and, while surgery is a treatment option, reduction of neuropathic pain intensity is a chance occurrence. Because the understanding of trigeminal neuropathic pain is incomplete, predictive treatment outcomes will improve only after trigeminal nerve pain etiology is better defined [17,18]. Moreover, because chronic neuropathic pain can remain refractory to treatment, acutely painful nerve injuries must be treated effectively to prevent a progression into a chronic pain state with all of its sequelae.

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