ANNALS
COMP REVIEW

Signaling mechanisms in mirror image pain pathogenesis

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ABSTRACT

It is now clear that a peripheral nerve lesion affects contralateral non-lesioned structures, and thus such a lesion can result in mirror image pain. The pathogenesis is still not exactly known, but there are some possible signaling pathways in the contralateral reaction of the nerve tissue after unilateral nerve injury. Potential signaling pathways of contralateral changes can be generally divided into humoral and neuronal mechanisms. Damage to peripheral nerves or spinal roots produces a number of breakdown products with development of an aseptic inflammatory reaction. Released immunomodulatory cytokines are believed to be transported via blood or cerebrospinal fluid into the contralateral part of the body affecting spinal roots, dorsal root ganglia or peripheral nerves. Because neurons are elements of a highly organized network, injury to the peripheral neuron results in signals that travel transneuronally into the central nervous system and affects the contralateral homonymous neurons. There is also evidence that spinal glia creates and maintain pathological pain. Additionally, there may be compensatory changes in behavior of animals with an impact on contralateral neurons, such as altered stance and motor performance or autonomic reflex changes. Although the transneuronal signaling pathway appears to be plausible, the humoral signaling pathway or other communication systems cannot be excluded at this time. Knowledge about these processes has clinical implications for the understanding of chronic neuropathic pain states, and, therefore, further studies will be necessary. Understanding signaling mechanisms in mirror image pain pathogenesis may provide novel therapeutic targets for the management of neuropathic pain.

KEYWORDS : nerve injury, contralateral reaction, neurons, cytokines, glia

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doi : 10.5214/ans.0972.7531.11183010

Introduction

Damage to peripheral nerves results in structural changes of nerve tissue as well as functional alterations including neuropathic pain. Although stimuli for chronic neuropathic pain arises from the area innervated by the damaged nerve, there have been reported signs in areas other than those attributed to the injured nerve, i.e., in contralateral regions.

So-called "mirror image pain" is typically characterized by mechanical allodynia and occurs in chronic pain conditions, including reflex sympathetic dystrophy,[1] causalgia,[2] and/or atypical facial pain.[3] Pathogenesis of mirror image pain is still not exactly known, but there are some possible signaling mechanisms in the contralateral reaction of the nerve tissue after unilateral nerve injury.

Many previous studies dealing with the reaction of a peripheral nerve injury use a contralateral non-injured one as a control sample. However, there is increasing evidence that unilateral nerve injury induces contralateral changes. The pioneering review about the effect of a peripheral nerve lesion on contralateral non-lesioned structures was written by Koltzenburg and colleagues in 1999.[4] Studies that are more recent verify the concept of the contralateral reaction.[5,6]

A damage of nervous tissue leads to changes already described by Waller.[7] This reaction is generally an aseptic inflammation with an increase in many immunomodulatory cytokines.[8] Since local injury to an organism causes the widespread reaction of the inflammatory system exceeding the borders of the tissue damage, it is presumed that injury to nervous tissue also induces such a response.

The nervous system is a highly organized structure with many connections. Each neuron, the basic functional units of nervous tissue, is closely connected with many other ones. There is also a complex relationship between neurons and glia. Thus, the contralateral reaction of the nervous system on local injury is not a surprising and unexpected finding. In this review, we discuss a possible pathogenetic background for the contralateral changes of the nervous system.

Signaling pathways of the contralateral reaction

Although neuropathic pain is associated with dysfunction (hyperexcitability) of neurons, it is obvious that "inflammatory changes" have a decisive role in the pathogenesis of neuropathic pain. Therefore, when addressing possible signaling mechanisms of the contralateral reaction after nerve injury, one has to also take into consideration immunocompetent cells (such as macrophages, lymphocytes, Schwann cells, astrocytes, and/or microglia) and secreted immunomodulatory factors.

"Cytokines" is a generic name for a diverse group of soluble proteins and peptides that act as "messenger" molecules and mediate communication among immune system cells and between immune system cells and the rest of the body. Many experimental studies have documented the important role of cytokines and immune cells during different types of neuropathy and their potential to induce or facilitate neuropathic pain.[9,10] Nevertheless, the majority of the studies have been focused on local or homolateral neuroinflammatory reactions to nerve damage. Studies aimed at the contralateral expression of cytokines after unilateral nerve injury are still rare.

Ruohonen and colleagues investigated contralateral changes of different proinflammatory and anti-inflammatory cytokines after transaction of the rat sciatic nerves.[11] They described significantly higher expressions of transforming growth factor beta (TGF-β1), interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and interleukin 10 (IL-10) in the contralateral nerve than in the non-injured control one. Other authors reported alterations in expression of bradykinin receptors and tetrodotoxin resistant Na+ channels in the contralateral dorsal root ganglion (DRG) after damage of the sciatic or saphenous nerve.[12,13]

Koltzenburg has noted that responses to contralateral injuries are usually qualitatively similar but smaller in magnitude

and have a briefer time course compared to ipsilateral changes.[4] Although the contralateral IL-1β, IL-10 and monocyte chemoattractant protein 1 (MCP-1) mRNA expression levels were comparable with the ipsilateral expression profile after chronic constriction injury in Kleinschnitz's study, the contralateral TNF-α level remained unchanged, while at the site of nerve injury, this proinflammatory cytokine was strongly induced.[14] Thus, the contralateral cytokine gene expression is not just an unspecific phenomenon but seems to be differentially regulated.

The recruitment of circulating macrophages into the peripheral nerve is essential for degeneration and subsequently for successful regeneration after nerve injury. Chemokines (cytokines with chemotactic activities) are factors influencing such recruitment. Since an increased expression of chemokines was observed in the non-injured contralateral nerves, one can assume that there are local conditions suitable for macrophage invasion.[15] In line with this assumption, Dubovy and colleagues found a significantly higher number of ED-1+ macrophages in both ipsilateral and contralateral DRG up to 4 weeks after nerve injury.[5] Nonetheless, Taskinen and Roytta came to a different conclusion. They have not found macrophages or other inflammatory cells in the side contralateral to injury.[15] Therefore, the reaction of the contralateral nerves to injury is not uniform but reflects differences in the experimental models used (site and mode of injury, timing of experiment, used processing methods, etc.).

A comparative study revealing differences between crush and chronic constriction injury indicates that the mode of nerve injury determines contralateral effects, both qualitatively and quantitatively, as shown in a study of ipsilateral response.[14,16] Overall, the level of cytokines is higher and more sustained after chronic constriction injury than after peripheral nerve crush. As a possible explanation, chronic constriction injury appears to be a stronger stimulus due to persisting ligatures and long-lasting perineurial inflammation.[17] On the other hand, nerve injury by crush is a monophasic event promptly followed by robust regeneration of nerve fibers.

Although the exact signaling mechanisms that link the two sides of the body and induce the contralateral reaction in cytokines are still unknown, the synthesis of cytokines was proven in endothelial cells, proliferating Schwann cells, affected DRG neurons, and macrophages.[15,18-20] Upregulation of satellite cells and TNF-α in the contralateral DRG after unilateral spinal nerve injury is associated with contralateral mechanical allodynia.[21] Thus, the presence of cytokines may be responsible for development of mirror image neuropathic pain.

Transneuronal signaling pathway

Neurons of the nervous system are not separate from but rather parts of a highly organized neural network. Thus, damage of a peripheral neuron induces reactive changes in related neurons at the different levels of neuronal organization (plasticity of nervous system). Despite some midline structures that appear to have bilateral innervations (e.g., the urinary bladder), great importance is attached to the spinal commissural interneurons that connect the dorsal horns by way of the dorsal commissure and have the capacity to mediate specific contralateral changes unrestricted to the axial body regions. These functional connections in the spinal cord that coordinate the two body halves have already been shown by Sherrington in 1910 and verified by recent report.[22] More recent electrophysiological and morphological studies also strongly support the existence of commissural interneurons connecting both dorsal horns within the spinal cord.[23-25]

Transmedian signaling via interneurons requires that signals cross through separate neurons. Action potential achieves this, but only in one direction. There are numerous precedents for trans synaptic signaling of trophic factors, both anterograde and retrograde. After damage of motor and sensory neurons, molecules including brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT3) can be released from neurons and may therefore be able to affect neurons in the spinal cord.[4] A partial attenuation of a transneuronal signal also explains relative delay and the smaller magnitude of the contralateral effects.

The transneuronal signaling pathway supports findings of retrograde transneuronal degeneration that occurs, for example, after amputation. Subsequently to this, degeneration of the commissural neurons in the intermediate zone may induce degeneration of the neurons on the spared side.[26]

Although the understanding of transneuronal signaling pathways in contralateral reactions is mainly based on peripheral nerve lesion studies, it is now widely accepted that the nervous system also plays an important role in the contralateral spread of primary inflammatory diseases. For example, symmetry of inflammation is a fundamental characteristic of rheumatoid arthritis.[27] Levine and colleagues have proposed that this symmetry may be underpinned by joint innervations, and they have proposed a neurogenic contribution to both existing inflammation and the symmetrical pattern of rheumatoid arthritis.[28,29] Animal models of rheumatoid arthritis also support the neurogenic hypothesis of the contralateral effect.[30,31]

Glial signaling pathway

Conventionally, glia have been considered only as supportive cells for neurons. In the early 1990s, Garrison and colleagues made the first links between neuropathic pain and glial activation after nerve injury.[32] Activated glia release many immunomodulatory products, including excitatory amino acids, nitric oxide, prostaglandins, and cytokines. The proinflammatory cytokines, derived largely from glia, are key mediators modulating neuronal activity and leading to induction and maintenance of neuropathic pain. Proinflammatory cytokines activate neurons as well as glia via binding to specific receptors. Thus, this is a means by which glia can influence neurons as well as other glia.[33]

In a basal state, resting astrocytes are involved in maintaining homeostasis of microenvironments, and resting microglia have no recognized function. Astrocytes and microglia become activated in response to peripheral and/or central nervous system trauma resulting in morphological and functional changes.

Experimental studies demonstrate that microglia and astrocytes are activated following peripheral nerve injury and that increase in immunoreactivity for the specific cell markers (OX42 – microglia, GFAP - astroglia) correlates with the development of allodynic behavior.[34] Activated microglia and astrocytes produce multiple immunomodulatory mediators and neuromodulators, acting on primary afferents or dorsal horn neurons and leading to the enhancement and maintenance of dorsal horn neuron sensitization and subsequent pain sensitization. This neural-glial interaction after peripheral nerve injury is likely to be triggered by signaling molecules released in the spinal cord from central terminals of damaged sensory neurons, stimulating surrounding

glial cells. In addition, there is a microglia-astrocyte interaction; activation of microglia occurs before astrocyte activation and is known to cause astrocyte activation. Glial activation is further enhanced by microglia-microglia interaction and astrocyte-astrocyte interactions. Many signaling molecules (e.g., MAP kinases, ATP receptors, chemokine receptors) are exclusively activated in spinal microglia or astrocytes after nerve injury and an inhibition of these molecules can attenuate neuropathic pain.[35]

Although pain is regarded traditionally as neuronally mediated, recent progress shows an important role for spinal glial cells in persistent pain sensitization. Mounting evidence has implicated spinal microglia in the development of chronic pain (e.g., neuropathic pain after peripheral nerve injury). Less is known about the role of astrocytes in pain regulation. However, astrocytes have very close contact with synapses and maintain homeostasis in the extracellular environment. Thus, glial cell activation has also been proposed to be involved in the phenomenon of the spread of pain sensation ipsilaterally or to the contralateral side.

Reactive changes in blood

Damage to a peripheral nerve produces a number of breakdown products at the site of the lesion and beyond with consequent reactions of immune cells and peripheral glia. These cells release a number of cytokines, which modulate an inflammatory reaction. During these changes, the blood-nerve barrier becomes more permeable to large molecules.[36] Therefore, blood flow may be a nonspecific way for delivery of factors from injured nerve to the contralateral one.

Nevertheless, a sporadic study focused on concentrations of proinflammatory cytokines in serum after nerve compression found normal values of TNF-α, IL-1β, IL-6, and IL-8.[37] The authors concluded that nerve compression does not induce a significant systemic inflammatory reaction. However, cytokines mentioned in the study predominantly participate in the acute stage of the inflammatory reaction; thus, the negative results of the systemic reaction may reflect only a later stage of sciatica because the mean duration of the sciatic pain was 196±233 days.

The majority of the studies dealing with peripheral nerve injury report the contralateral changes at homonymous nerves but there are only sporadic studies aimed at reactions that are more widespread. Kleinschnitz and colleagues conclude that contralateral responses after nerve injury are restricted to the homonymous nerves which argue against an unspecific peripheral mechanism via circulating factors.[16] Since there are not enough data to reject the role of circulation factors definitely, additional research is required.

Spinal root compression and reactive changes in cerebrospinal fluid

Inspite of morphologic differences as well as differences in reaction to injury between peripheral nerves and spinal roots, there are only a few studies dealing with the contralateral reaction after spinal root injury today. Homeostasis of the spinal roots is closely connected to barrier systems that separate nerve tissue from the environment of blood and cerebrospinal fluid (CSF). The injury to spinal roots leads to affection of the barrier systems with increased vascular permeability as well as release of markers of nerve tissue damage into CSF.[38-40]

In 1934, Mixter and Barr reported that prolapsed intervertebral discs cause sciatic pain.[41] They also found an increase in the concentration of total protein in the CSF of patients with lumbar disc herniation. Later, several authors verified that the increased concentrations of total protein in the CSF of patients with lumbar disc herniation are related to nerve root compression and clinical findings indicating radiculopathy.[42-44] Furthermore, TNF, IL-1 and IL-6 released into lumbar cerebrospinal fluid have been observed under conditions of pain facilitation.[45]

The clinical findings are supported by experimental studies. Skouen and colleagues have found a several-fold but transient increase of the total protein concentration in the CSF of pigs with spinal root compression for 1 week as compared with control and sham animals.[39] The authors concluded that the elevated CSF total protein found in the patients with sciatica is due to leaking of plasma proteins primarily from the injured spinal root into the CSF. The proteins were derived from the serum in response to increased endothelial cell permeability of capillaries. This process is suggested to be caused by mechanical compression of the spinal roots and local inflammatory reactions with breakdown of the blood-nerve barrier.[38,44] Another part of proteins in CSF comes from the damaged nerve tissue and can be used as markers of the nerve injury (e.g., neurofilaments, S-100, glial fibrillary acidic protein, and neuron-specific enolase).[40,46]

Because of changes in CSF proteins, they can be used as diagnostic parameters for radiculopathy, especially when surgery is considered or in patients in whom sciatica is unlikely. However, the studies dealing with the content of proinflammatory cytokines after spinal root compression by disc herniation are trying to predict a course of clinical symptomatology giving similar results.

Brisby and colleagues have demonstrated that the concentrations of IL-1β, IL-6, IFN-γ and TNF-α in CSF were normal in patients with sciatic pain and a CT-verified disc herniation at the time of surgery, while IL-8 concentrations in CSF were elevated in approximately one-third of the patients.[37] They also showed that the elevated concentrations of IL-8 correlate with a short duration of sciatic pain and a more pronounced herniation (sequestration or extrusion). Nevertheless, the authors found no relationship between the concentration of IL-8 and pain intensity or neurological findings.

The relationship between the extent of herniation and the IL-8 concentration indicates that mechanical factors may cause the increase in IL-8 within CSF. The result also indicates that there is a biochemical effect induced by the intervertebral disc, since substances from the inner part of the disc (nucleus pulposus) reach the surrounding tissue largely if the extruded nucleus pulposus is not covered with annulus fibrosus and ligament tissue.

On the other hand, Cornefjord and colleagues detected no increase in IL-8 concentration in CSF after slow-onset compression and the application of nucleus pulposus on the spinal root using a pig experimental model.[40] Despite the fact that inflammatory changes have been demonstrated to take place in the nerve root, the authors could not detect any inflammatory response by measuring IL-8 in CSF. It is necessary to note that the study was focused on biomarkers for nerve tissue injury.

More studies are needed in order to substantiate the results of the published studies. It is obvious that the proinflammatory cytokines are involved mainly at the onset of sciatica, and thus it is crucial to plan the timing of experiments properly. The samples that have been collected late demonstrate significant changes in

the level of acute inflammatory cytokines but cannot rule out the possibility of an inflammatory reaction in CSF after the spinal root compression with a subsequent effect on the contralateral spinal roots and DRG. It is important to realize that age and sex affects the inflammatory response as well as the biological instability of cytokines after CSF collection as well as the detection methods used.[47-49]

Conclusions

Many studies describe contralateral changes after unilateral peripheral nerve treatment as incidental and unexpected observations in a control group of the main experiment. Although there are only a few studies designed for research on contralateral changes, it is now clear that peripheral nerve lesions affect the contralateral non-lesioned structures. Potential mechanisms of contralateral change after peripheral nerve lesion can be divided into humoral mechanisms and neuronal mechanisms. Damage to peripheral nerves or spinal roots produces a number of breakdown products at the lesion and beyond with the subsequent reaction of immunocompetent cells. A number of immunomodulatory cytokines are released by this aseptic inflammatory reaction, and they can be transported via blood or CSF into the contralateral part of the body and affect spinal roots or peripheral nerves. An objection to such a mechanism is the different rate and extent of development of contralateral changes after proximal versus distal nerve lesions, as reported in some works.

The local damage to peripheral nerves and spinal roots also leads to reactive changes in affected axons and their perikarya. Cytokines play an important role in this reaction. Whereas the neurons are elements of a highly organized neuronal network, injury of a peripheral neuron results in signals that travel transneuronally into the CNS and then ultimately affect contralateral homonymous neurons. Glial cell activation has also been proposed to be involved in the phenomenon of spread of pain sensation ipsilaterally or to the contralateral side. Neural–glial interactions are bidirectional. On the one hand, glia express different types of neurotransmitter receptors, which enables them to respond to neural signals. On the other hand, glial cells produce numerous mediators (e.g., proinflammatory cytokines and growth factors) that are neuroactive. Additionally, there may be compensatory changes in the behavior of the animals with an impact on contralateral neurons, such as altered stance and motor performance or autonomic reflex changes, after peripheral nerve damage.

Although the transneuronal signaling pathway appears to be plausible, the humoral signal pathway or other communication systems cannot be excluded at the present time. Knowledge about these systems has clinical implications for the understanding of chronic neuropathic pain states, and, therefore, further studies will be necessary. Understanding signaling mechanisms in mirror image pain pathogenesis may provide a novel therapeutic target for the control of neuropathic pain.

The article complies with International Committee of Medical Journal Editor's uniform requirements for the manuscripts.

Competing interests – None, Source of Funding – None

Received Date : 25 March 2011

Revised Date: 11May 2011

Accepted Date : 8 June 2011

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