

**The biochemical origin of pain:
The origin of all pain is inflammation and the inflammatory response:
Inflammatory profile of pain syndromes**

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FROM ABSTRACT:

Every pain syndrome has an inflammatory profile consisting of the inflammatory mediators that are present in the pain syndrome. The inflammatory profile may have variations from one person to another and may have variations in the same person at different times.

The key to treatment of Pain Syndromes is an understanding of their inflammatory profile.

The treatment goal should be inhibition or suppression of production of the inflammatory mediators and inhibition, suppression or modulation of neuronal afferent and efferent (motor) transmission. A successful outcome is one that results in less inflammation and thus less pain.

Our unifying theory or law of pain states: the origin of all pain is inflammation and the inflammatory response. The biochemical mediators of inflammation include cytokines, neuropeptides, growth factors and neurotransmitters.

Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and the inflammatory response.

Activation of pain receptors, transmission and modulation of pain signals, neuroplasticity and central sensitization are all one continuum of inflammation and the inflammatory response.

Irrespective of the characteristic of the pain, whether it is sharp, dull, aching, burning, stabbing, numbing or tingling, all pain arises from inflammation and the inflammatory response.

THIS AUTHOR ALSO NOTES:

This article presents a unifying **Law of Pain**.

There is an inflammatory soup of biochemical mediators that are present in all pain syndromes.

Although osteoarthritis has previously been considered a non-inflammatory form of arthritis, "its underlying origin, like all other pain syndromes is inflammation and the inflammatory response."

Inflammation may be absent in the earlier stages of osteoarthritis, but as the disease progresses, synovial inflammation exists and the "synovial membrane becomes thickened."

Osteoarthritic cartilage "stimulates the production of prostaglandin E2."

"Prostaglandin E2 [PGE2] has important pro-inflammatory properties and contributes to vasodilatation and pain in patients with osteoarthritis."

"Back pain is most commonly a result of injury to the muscle, disk, nerve, ligament or facet joints with subsequent inflammation and spasm."

"Herniation of disk tissue (nucleus pulposus) produces a profound inflammatory reaction with release of inflammatory mediators, especially tumor necrosis factor alpha (TNF-alpha)."

TNF-alpha activates enzyme phospholipase A2 which liberates arachidonic acid from cell membranes increasing the production of inflammatory mediators prostaglandins [PGE2] and leukotrienes [LTB4].

Therefore subsequent to the disk release of TNF-alpha, there is an increase in the inflammatory mediators PGE2 and nitric oxide (NO).

TNF-alpha, PGE2, and NO all add to adjacent nerve fiber injury causing neurological dysfunction, excessive muscle tension, spasm, and pain.

"Back or neck pain with or without a herniated disk is due to inflammation and the inflammatory response."

Migraines are caused by the activation of trigeminal sensory fibers and subsequent release of inflammatory mediators from the trigeminal nerve. Blood vessels of the cranial dura mater are the most pain sensitive intracranial structures. These blood vessels are supplied by trigeminal nerve fibers, and they dilate in response to activation of the trigeminal nerve, stimulating the release of inflammatory mediators.

Nociceptive pain is mediated by A-delta and C-nerve fibers located in skin, bone, connective tissue, muscle and viscera.

Somatic nociceptive pain tends to be well-localized constant pain, described as sharp, aching, throbbing, or gnawing.

Visceral nociceptive pain tends to be vague in distribution, spasmodic in nature, and is often described as deep, aching, squeezing, and colicky in nature.

Nociceptive pain is caused by the peripheral tissue release of inflammatory mediators.

Neuropathic pain, in contrast to nociceptive pain, is described as burning, electric, tingling, and shooting in nature.

Neuropathic pain is characterized by:

- 1) Chronic **Allodynia**: pain resulting from a stimulus that ordinarily does not elicit a painful response, like light touch.
- 2) Chronic **Hyperalgesia**: increased sensitivity to normally painful stimuli.

Neuropathic pain is caused by inflammatory mediators released by injury to the nervous system itself (both peripheral or central).

Examples of neuropathic pain include:

Carpel tunnel syndrome
 Trigeminal Neuralgia
 Post Herpetic Neuralgia
 Phantom Limb Pain
 Complex Regional Pain Syndrome
 Various Peripheral Neuropathies

In neuropathic pain, the magnitude of the inflammatory response is not related to the extent of nerve damage. Complete transection of a nerve is a very severe injury but causes a lower production of inflammatory mediators. Therefore, it is common for minor nerve injury to cause greater inflammation and "result in severe pain that is out of proportion to the injury."

Reflex Sympathetic Dystrophy (RSD) is also called Complex Regional Pain Syndrome (CRPS). It is caused by trauma to a nerve, neural plexus or soft tissue. It is characterized by regional pain and changes in skin color, changes in skin temperature, abnormal sweating, and tissue swelling. The affected area gradually enlarges and the syndrome can spread to ipsilateral and/or adjacent extremities.

In RSD/CRPS, the hyperactive sympathetic response is provoked by an exaggerated inflammatory response, as follows:

- 1) Soft tissue injury causes local inflammation and excitation of sensory nerve fibers.
- 2) In the spinal cord, the sensory nerve fibers release inflammatory neuropeptides which increases the rate of firing of the sympathetic nerves to the injured extremity.

- 3) Increased sympathetic firing to the extremity is associated with excessive sweating, temperature instability, and vasoconstriction, which causes additional sensitization of pain receptors, causing allodynia.
- 4) "Prolonged ischemia from the sympathetic vasoconstriction produces more pain, establishing a reflex arc that promotes further sympathetic discharge and vasospasm."

CONCLUSION

"The origin of all pain is inflammation and the inflammatory response."

"Irrespective of the type of pain, whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and the inflammatory response."

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KEY POINTS FROM DAN MURPHY

- 1) The unifying **Law of Pain** indicates that there is an inflammatory soup of biochemical mediators that are present in all pain syndromes.
- 2) Although osteoarthritis has previously been considered a non-inflammatory form of arthritis, "its underlying origin, like all other pain syndromes is inflammation and the inflammatory response."
- 3) Inflammation may be absent in the earlier stages of osteoarthritis, but as the disease progresses, synovial inflammation exists and the "synovial membrane becomes thickened."
- 4) Osteoarthritic cartilage "stimulates the production of prostaglandin E2."
- 5) "Prostaglandin E2 [PGE2] has important pro-inflammatory properties and contributes to vasodilatation and pain in patients with osteoarthritis."
- 6) "Back pain is most commonly a result of injury to the muscle, disk, nerve, ligament or facet joints with subsequent inflammation and spasm."
- 7) "Herniation of disk tissue (nucleus pulposus) produces a profound inflammatory reaction with release of inflammatory mediators, especially tumor necrosis factor alpha [TNF-alpha]."

- 8) TNF-alpha activates enzyme phospholipase A2 which liberates arachidonic acid from cell membranes increasing the production of inflammatory mediators prostaglandins [PGE2] and leukotrienes [LTB4].
- 9) Subsequent to the disk release of TNF-alpha, there is an increase in the inflammatory mediators PGE2 and nitric oxide (NO).
- 10) TNF-alpha, PGE2, and NO all add to adjacent nerve fiber injury causing neurological dysfunction, excessive muscle tension, spasm, and pain.
- 11) "Back or neck pain with or without a herniated disk is due to inflammation and the inflammatory response."
- 12) Migraines are caused by the activation of trigeminal sensory fibers and subsequent release of inflammatory mediators from the trigeminal nerve. Blood vessels of the cranial dura mater are the most pain sensitive intracranial structures. These blood vessels are supplied by trigeminal nerve fibers, and they dilate in response to activation of the trigeminal nerve, stimulating the release of inflammatory mediators.
- 13) **Nociceptive** pain is mediated by A-delta and C-nerve fibers located in skin, bone, connective tissue, muscle and viscera.
- 14) **Somatic nociceptive** pain tends to be well-localized constant pain, described as sharp, aching, throbbing, or gnawing.
- 15) **Visceral nociceptive** pain tends to be vague in distribution, spasmodic in nature, and is often described as deep, aching, squeezing, and colicky in nature.
- 16) **Nociceptive** pain is caused by the peripheral tissue release of inflammatory mediators.
- 17) **Neuropathic** pain, in contrast to nociceptive pain, is described as burning, electric, tingling, and shooting in nature.
- 18) **Neuropathic** pain is characterized by:
 A)) Chronic **Allodynia**: pain resulting from a stimulus that ordinarily does not elicit a painful response, like light touch.
 B)) Chronic **Hyperalgesia**: increased sensitivity to normally painful stimuli.
- 19) **Neuropathic** pain is caused by inflammatory mediators released by injury to the nervous system itself (both peripheral or central).
- 20) Examples of neuropathic pain include: Carpel tunnel syndrome
 Trigeminal Neuralgia Post Herpetic Neuralgia Phantom Limb Pain
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21) In neuropathic pain, the magnitude of the inflammatory response is not related to the extent of nerve damage. Complete transection of a nerve is a very severe injury but causes a lower production of inflammatory mediators. Therefore, it is common for minor nerve injury to cause greater inflammation and "result in severe pain that is out of proportion to the injury."

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D)) "Prolonged ischemia from the sympathetic vasoconstriction produces more pain, establishing a reflex arc that promotes further sympathetic discharge and vasospasm."

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COMMENTS FROM DAN MURPHY:

This article underscores the importance of putting all of our pain patients on an anti-inflammatory dose of omega-3 essential fatty acids. Studies we have reviewed indicate that an anti-inflammatory dose of omega-3 fatty acids is 3000 mg of EPA + DHA per day for at least 3 months, and then maintaining that dose.