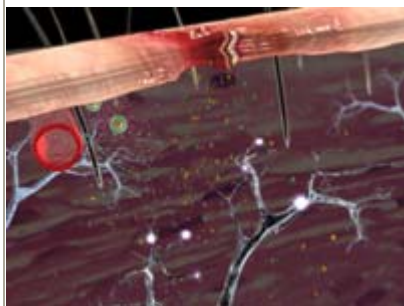


Sequence 1: Tissue injury

Injury

- Tissue injury occurs

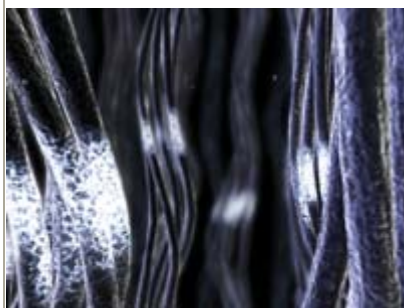


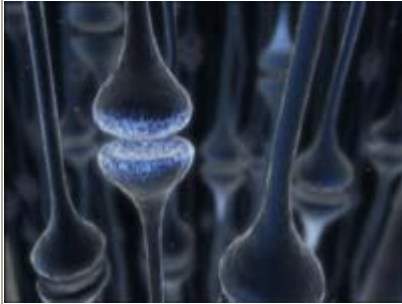
Pain inflammatory mediators

- Tissue injury causes the release of various inflammatory and pain mediators resulting in peripheral sensitization ^{1,2,3}
- Pain response mediators: ATP, acetylcholine and serotonin are released from damaged endothelial cells and platelets; prostaglandin E2 is synthesized by Cyclooxygenase I and II enzymes in damaged cells; bradykinin is released from plasma from damaged vessels ^{1,2}
- Inflammatory response mediators: Histamine is released from mast cells in response to Substance P and calcitonin gene-related peptide (CGRP) released by primary afferent sensory fibers; additional mediators are released from blood cells (cytokines, complement factors C3a and C5a, serotonin, platelet-activating factor, neutrophil chemotactic factor, fibrinopeptides, leukotrienes) ^{1,2}
- Together with bradykinin and prostaglandins, these inflammatory mediators cause peripheral vasodilation, increased vascular permeability, plasma extravasation, migration of leucocytes to the site of injury, and clotting responses ¹

Peripheral sensitization

- Bradykinin stimulates further synthesis/release of prostaglandins, and, together with the prostaglandins, sensitizes the primary afferent sensory fibers in response to stimulation by ATP, acetylcholine, serotonin and mechanical and thermal stimuli ^{1,2,3}
- Substance P and CGRP released by the primary afferent sensory fibers contribute to the pain response by triggering the release of histamine from mast cells which, in turn, excites the peripheral afferent sensory fibers ^{1,2,3}
- " Sensitization of the primary afferent sensory fibers by mediators of the pain response results in greater, more frequent transmission of action potentials to the nociceptive neurons than in 'normal' pain responses ^{1,2,5}





Hyperexcitation

- At the synapse level, sensitized primary afferent sensory fibers decrease the threshold for activation of nociceptor neurons which become hyperexcitable and transmit frequent action potentials 1,2



Central sensitization

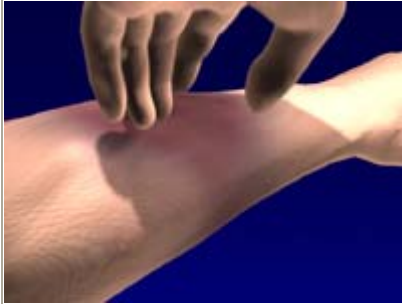
- Central sensitization results and the individual perceives greater and more prolonged pain 1,2,3.

Sequence 2: Nociceptive pain

Allodynia

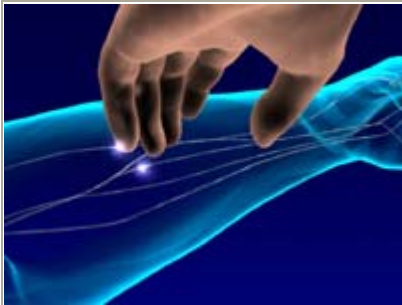


- Tissue injury often results in nociceptive pain, in which persistent pain is felt in response to direct activation of peripheral nerve terminals in the skin by pain response mediators from the damaged tissue 1,2
- Nociceptive pain: Following tissue injury, Substance P, CGRP and glutamate are released by peripheral afferent sensory fibers and act on peptide and glutamate receptors on the post-synaptic membrane to cause greater excitability of nociceptive neurons. Nociceptive neurons become hyperexcitable, resulting in central sensitization and thus greater perception of pain in the higher centers 1,2,3
- Nociceptive pain may involve the abnormal pain states of allodynia or hyperalgesia which result from both peripheral and central hypersensitivity 1,2,3
- Allodynia: Certain types of noxious stimulus (e.g. sunburn, injury, post-surgical wounds) may result in the individual perceiving pain in response to stimuli that are not normally painful, such as a light stroking of the skin 1,2,4



Hyperalgesia

- Hyperalgesia: Certain noxious stimuli (e.g. severe bruising) can result in the individual perceiving abnormally high levels of pain in response to normal noxious stimuli such as a small scratch; in such cases, patients often perceive spontaneous pain 1,2,4



Greater transmission of AP's

- Allodynia and hyperalgesia result in greater and continued transmission of action potentials along the peripheral afferent sensory fibers 1,3



Perception in higher centers

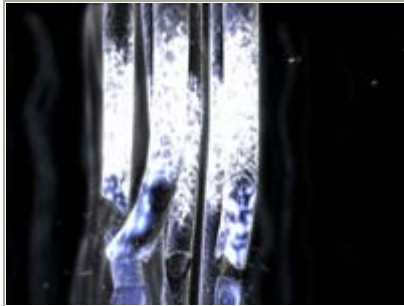
- Allodynia and hyperalgesia result in greater perception of pain in the higher centers 1,3.

Sequence 3: Nueropathic Pain



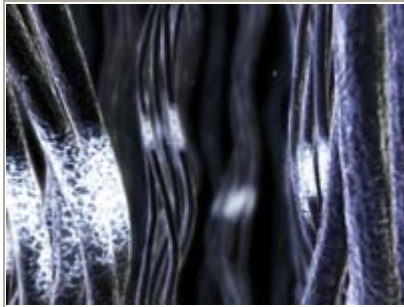
Partial Nerve Severance

- Neuropathic pain occurs following direct injury to the nerves in the peripheral or central nervous systems. Neuropathic pain can result from complete or partial nerve transection, nerve compression, infiltration or infectious/inflammatory/ischemic etiologies 1,2,4
 - Partial severance of peripheral afferent sensory fibers results in neuropathic pain in the form of ectopic activity⁴



Ectopic Activity

- Ectopic activity: Nerve damage results in the accumulation of sodium channels 2,5
- The accumulation of sodium channels generates action potentials in the damaged peripheral afferent sensory fibers proximal to the injury site 2,5



Hyperexcitability

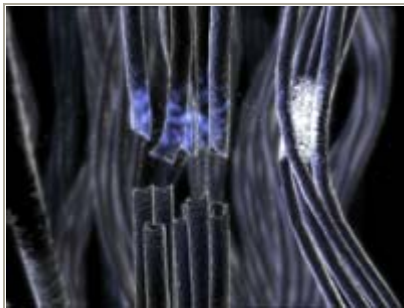
- The focus of excitability in the damaged sensory fibers causes the stimulation of the higher centers to perceive spontaneous pain (e.g. phantom pain, sciatica) 2,4,5.



Sequence 4: Neuropathic pain: Ephaptic

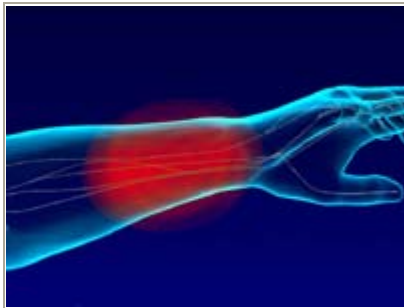
Ephaptic activity

- In addition to ectopic activity, direct nerve injury can cause a different form of neuropathic pain due to ephaptic activity 4



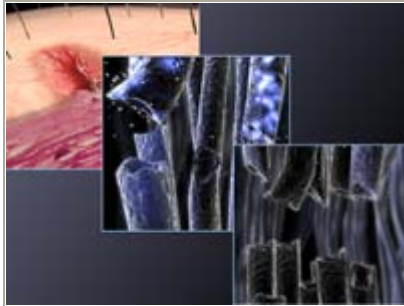
Cross talk

- Ephaptic transmission: Complete severance of peripheral afferent sensory fibers results in hyperexcitability of damaged nerves and transmission of action potentials along adjacent, undamaged unstimulated sensory fibers, or cross talk 4



Receptive field expands

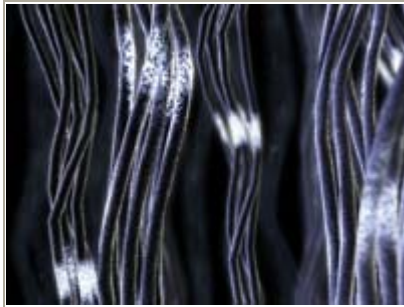
- Cross-talk between damaged, stimulated peripheral afferent sensory fibers and adjacent unstimulated fibers results in an expansion of the area in which pain is perceived in and around the area of the damaged nerve 4.



Section 5: Wind up

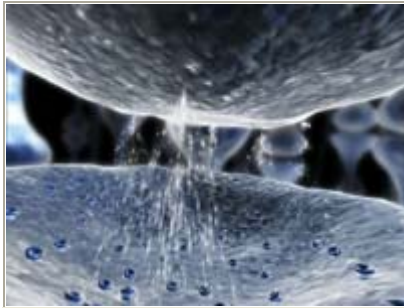
Tissue injury/nerve damage

- Both the tissue injury and nerve damage responsible for severe/persistent nociceptive and neuropathic pain can result in a process termed wind-up^{1,3,4}



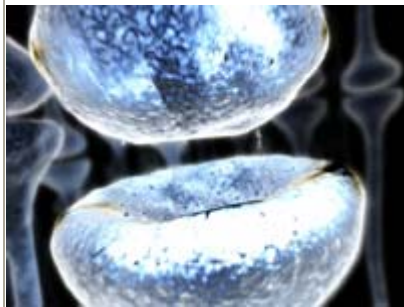
Repeated firing of PAF's

- During wind up, the peripheral afferent sensory fibers fire repeatedly, there is increased transmitter release into the spinal cord, and the response by spinal cord neurons increases progressively^{1,3,4}



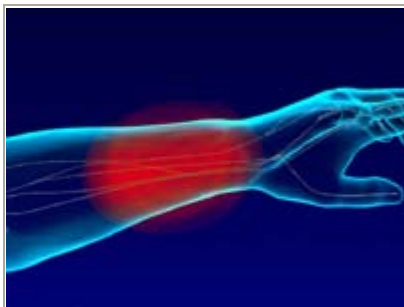
Ion channels

- In the synapse, repeated firing from peripheral afferent sensory fibers and consequent release of glutamate results in the prolonged opening of post-synaptic ion channels gated by N-methyl-D-aspartate (NMDA)-type glutamate receptors^{1,2,3}



Wind up

- Prolonged opening of the ion channels enables greater influx of calcium and sodium across the post-synaptic membrane and greater excitation of nociceptive neurons^{2,3}
- Wind-up causes long-term changes in nociceptive neurons, which become hyperexcitable such that they respond to lower stimuli; central sensitization results. NMDA-type glutamate receptors play an important role in this process^{1,2,3,4}



Receptive field expands

- The hyperexcitability resulting from wind-up causes a higher perception of pain, such that weak stimuli cause pain, spontaneous pain may be perceived, and the receptive field expands^{1,2,4}.

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