C.M. Egger, DVM, MVSc, Diplomate ACVA, University of Tennessee

Handling Pathologic Pain

Illustration by Bill Celander

You have asked…

>What is the best strategy for addressing abnormal pain in my patients?

The expert says…

The physiologic processes underlying the experience of pain are complex, and nociceptive input is extensively modulated before the final conscious experience of pain. Acute pain is usually brief, resolving, if adequate analgesia is provided, as tissue heals. The goal of any analgesic protocol should be to avoid development of chronic pain states, including peripheral and central sensitization.

Abnormal Pain

Abnormal pain states can result from peripheral sensitization, central sensitization, or neuropathic pain. They frequently include symptoms of hyperalgesia and allodynia.[1] Abnormal pain states are challenging to treat because they develop through a variety of complex mechanisms.[2-5]

Neuropathic Pain

Neuropathic pain occurs when a lesion or disease affects the central or peripheral nervous system; it can manifest as numbness, spontaneous burning, or lacinating pain. Examples of neuropathic pain include diabetic or postherpetic neuropathy and multiple sclerosis in humans, interstitial cystitis in cats and humans, and pain that develops subsequent to nerve trauma, such as a crushing injury or limb amputation.[1-3]

NMDA = N-methyl-d-aspartic acid

With neuropathic pain, nerve injury causes activated glial cells and astrocytes to release cytokines, prostaglandins, and glutamate that activate NMDA receptors and cause sprouting of the central and peripheral ends of damaged fibers. Nerve injury also leads to an increase in the number of spontaneously active Na+ channels in the periphery, dorsal root ganglion, and dorsal horn. The result is an increase in spontaneous generation of action potentials and cross-excitement of inactive neurons. In addition, low-threshold A beta (tactile), motor, and sympathetic neurons may activate sensory afferents, resulting in allodynia.[2-8]

Peripheral Hypersensitivity

With tissue trauma and inflammation, nociceptors on peripheral terminals of C-fiber neurons become sensitized or directly stimulated by many inflammatory mediators, including prostaglandins and leukotrienes. This stimulation leads to further excitation of nerve fibers and activation of normally silent nociceptors. The result is a decrease in the threshold for activation of nociceptors and an increased magnitude and duration of response to a nociceptive stimulus at the site of injury (primary hyperalgesia). Another result is the perception of low-intensity, subthreshold mechanical stimuli as painful (allodynia).

Peripheral sensitization frequently leads to central sensitization and hyperalgesia in the surrounding uninjured tissue (secondary hyperalgesia) because it causes sustained nociceptive input into the dorsal horn. Prevention of inflammation-induced peripheral hypersensitivity and subsequent central hypersensitivity is the rationale for use of corticosteroids and nonsteroidal antiinflammatory drugs.[2-4,6,7]

Central Sensitization

When glutamate is released from primary afferent neurons in the dorsal horn in response to an acute noxious stimulus, it briefly activates AMPA and kainate receptors on second order neurons, resulting in brief activation of central nociceptive pathways. Glutamate also binds to NMDA receptors on second-order neurons, but sustained depolarization of the neuronal membrane is required to remove the Mg^{2+} block of the ion channel of the NMDA receptor, allowing its activation.

If repetitive and high-frequency stimulation of C fibers occurs, as from inflammation, neuropathic pain, osteoarthritis, or other sources of sustained nociceptive input, release of glutamate and concurrent release of substance P and other excitatory neurotransmitters is prolonged. This release causes sustained activation of AMPA receptors; prolonged, slow membrane depolarization; removal of the Mg^{2+}block; and activation of NMDA receptors.[2-5]

Other factors probably involved in the development of central sensitization include loss of tonic inhibition from neurotransmitters such as GABA and glycine and loss of descending inhibition.

Wind-Up Pain

NMDA receptor activation results in a large influx of Ca^{2+} ions into the second-order neuron that activates cellular second messengers (eg, protein kinases), causing early gene induction, altered protein synthesis, changes in neurotransmitter receptor density, and enhanced glutamate release from primary afferent neurons. Na^{+} and Ca^{2+} channels and NMDA and AMPA receptors on second-order neurons are activated, and the resulting increased frequency of firing and increased magnitude and duration of response to subsequent afferent input is termed *wind-up*.

Wind-up is a form of neuroplasticity that lasts for minutes; however, ongoing noxious afferent input for hours or days leads to sustained changes in the spinal cord (ie, central sensitization) that result in expansion of receptor field size, an increase in the magnitude and duration of response to a threshold stimulus, and an overall reduction in threshold. As a result, non-noxious stimuli now activate neurons that transmit nociceptive information.[2-5]

Treatment & Prevention

NMDA Receptor Antagonists

The importance of NMDA receptors in wind-up, central sensitization, and neuropathic pain has led to the use of NMDA receptor antagonists to prevent and treat these conditions. Ketamine, memantine, amantidine, methadone, and dextromethorphan show promise for reducing these conditions in humans, although adequate dosing is often prevented by unpleasant side effects, including sedation and ataxia.[6,8] Although some studies demonstrate clinical efficacy of ketamine, amantidine, and methadone in animals, most treatment recommendations are based on extrapolation from human medicine or anecdotal reports in a few veterinary patients.[5,9]

Antiepileptic Drugs

Both Na^{+} and Ca^{2+} channels have also been targeted. The antiepileptic drugs gabapentin and pregabalin act at the alpha-2-delta subunit of voltage-gated calcium channels to reduce glutamate release and inhibit hyperalgesia and allodynia. Antiepileptic drugs that block Na^{+} channels, such as phenytoin, carbamazepine, and lamotrigine, also inhibit glutamate release and have been effective in treating neuropathic pain in people. Topiramate blocks Na^{+} channels but also potentiates the inhibitory action of GABA and may block glutamate release.[6-8] Clinical efficacy studies in animals are lacking.[9]

Other Medications

Agents that block the reuptake of norepinephrine or serotonin, such as tramadol, tricyclic antidepressants, selective serotonin reuptake inhibitors, or serotonin-norepinephrine reuptake inhibitors, can be beneficial by facilitating descending inhibition. Tricyclic antidepressants also block Na^{+} channels and NMDA receptors. Baclofen, often used as a muscle relaxant,

AMPA = alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; GABA = gamma-aminobutyric acid; MAC = minimum alveolar concentration; NMDA = N-methyl-d-aspartic acid

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provides analgesia in people by activating inhibitory $GABA_B$ receptors.[6-8] Tramadol has shown efficacy in clinical studies in veterinary patients, but similar studies in regard to antidepressants are lacking.[9]

Mexiletine, an oral Na^+ channel blocker used to treat cardiac arrhythmias, has shown some efficacy in treating diabetic neuropathy. However, this agent has a narrow therapeutic window and causes unacceptable adverse affects at plasma levels that result in analgesia.[8]

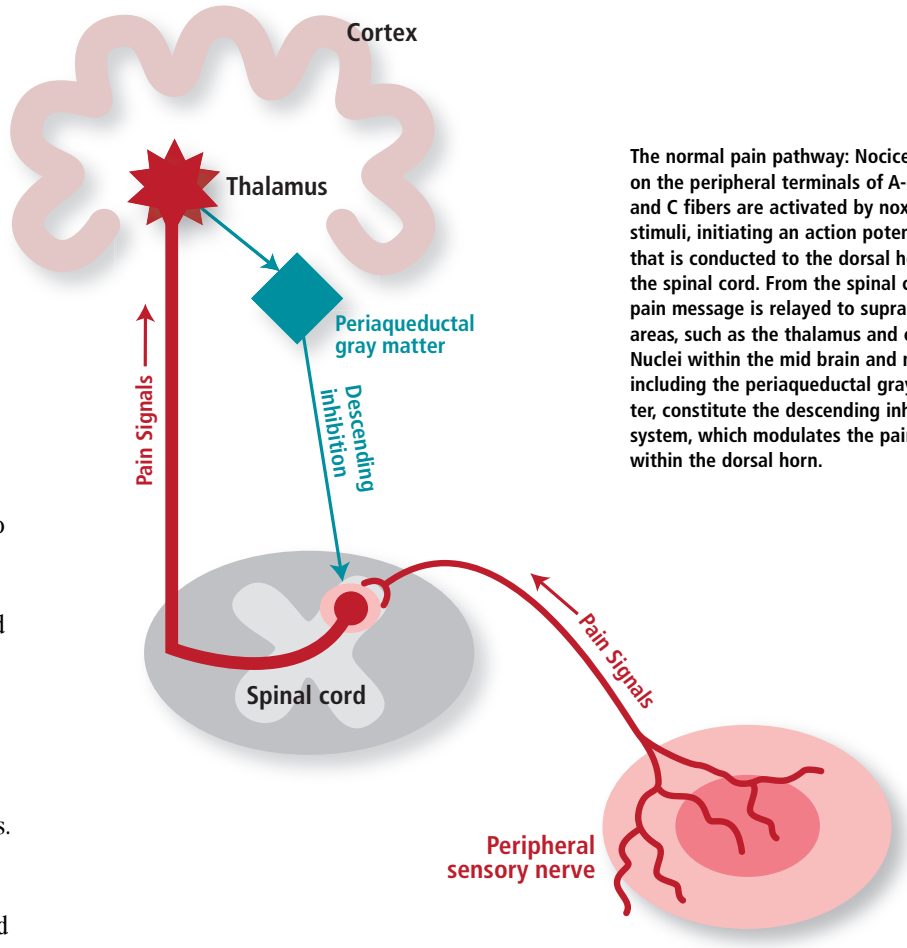
Local Anesthetics

Local anesthetics block Na^+ channels and are frequently used in regional analgesia techniques. Local anesthetics reduce intraoperative anesthetic requirements, postoperative opioid requirements, and the development of sensitized pain states.[7-9]

Intravenous lidocaine has shown benefit in the treatment of diabetic and postherpetic neuropathy, central pain, and sciatic pain; 5% lidocaine patches have successfully relieved pain in postherpetic neuropathy in humans.[6-8] In addition, intravenous lidocaine has provided intraoperative MAC reduction and postoperative analgesia in dogs.[9]

A Multimodal Approach

Abnormal pain states result from complex anatomic and physiologic changes occurring in the peripheral and central nervous systems. Drugs that inhibit NMDA receptor activation, decrease glutamate release, increase GABA release, or facilitate descending inhibition, have shown promise as adjuncts in the treatment of abnormal pain.[2-9]



The normal pain pathway: Nociceptors on the peripheral terminals of A-delta and C fibers are activated by noxious stimuli, initiating an action potential that is conducted to the dorsal horn of the spinal cord. From the spinal cord, the pain message is relayed to supraspinal areas, such as the thalamus and cortex. Nuclei within the mid brain and medulla, including the periaqueductal gray matter, constitute the descending inhibitory system, which modulates the pain signal within the dorsal horn.

Glossary of Terms

Allodynia: Perception of pain in response to a stimulus that is not normally painful

Central sensitization: An increase in excitability of neurons within the central nervous system as a result of sustained noxious input to the spinal cord, which initiates changes in gene expression and transmitter receptor density

Hyperalgesia: Increased responsiveness of nociceptive neurons to their normal or subthreshold afferent input

Neuropathic pain: Pain arising as a direct consequence of a lesion or disease affecting the central or peripheral nervous systems

Nociceptive input: A noxious stimulus capable of activating peripheral nociceptors

Peripheral sensitization: A reduction in threshold and increase in responsiveness of peripheral ends of nociceptors due to action of inflammatory chemicals or mediators released around the site of tissue damage/inflammation

Wind-up pain: A form of short-term spinal neuroplasticity occurring with NMDA receptor activation and leading to increased frequency of firing and increased magnitude and duration of response to subsequent stimuli

See Aids & Resources, back page, for references, contacts, and appendices.
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