Multimodal Pain Management in Veterinary Medicine: The Physiologic Basis of Pharmacologic Therapies

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Multimodal analgesia refers to the practice of combining multiple analgesic drug classes or techniques to target different points along the pain pathway. This approach has become widely accepted in veterinary medicine for two reasons. First, it takes advantage of additive or synergistic analgesic effects that optimize analgesia and improve patient comfort. Second, lower doses of individual analgesic agents are typically required, which reduces the potential for development of undesirable side effects associated with treatment.

Although this strategy seems simple on the surface, effective multimodal pain management plans go beyond the philosophy that more drugs equal better analgesia. A rational multimodal approach to treating pain must be based on an understanding of physiology and pathophysiology. With this foundation, pharmacologic interventions can be tailored to meet the needs of the patient. This article reviews the physiologic basis of pain as it relates to analgesic treatments (Box 1) and also introduces new developments in molecular biology that may guide analgesic drug development in the future (Box 2).

DEFINITIONS

Pain: a sensory event involving the peripheral and central nervous systems in addition to an unpleasant experience arising from, and reciprocally affecting, processes of higher consciousness.
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Analgesia: the absence of pain sensation
Nociception: the physiologic component of pain processing involving the transduction, transmission, and modulation of signals generated by stimulation of peripheral nociceptors
Noxious: a stimulus that damages or threatens to damage tissue; it may be mechanical, chemical, or thermal
Allodynia: pain that is produced by a stimulus that does not normally provoke pain (i.e., by a nonnoxious stimulus)
Hyperalgesia: increased pain response to a noxious stimulus at the site of injury (primary) or in surrounding undamaged tissue (secondary)
There is a tendency when discussing the physiology of pain to paint a simple stimulus-response picture similar to that of the other somatosensations, such as touch or pressure. Although there are certainly fundamental similarities between the pathways that produce pain and those that lead to other types of sensations, the perception of pain in human beings or domestic animals is much more complex than the sum of these nociceptive processes alone. This complexity is exemplified in the chronic and neuropathic pain syndromes that continue to challenge our current understanding of pain, requiring new theories to explain these phenomena better. One such theory, proposed by Melzack,\(^1\),\(^2\) states that the multidimensional experience we call pain is produced by characteristic neurosignature patterns of nerve impulses generated by a widely distributed neural network in the brain that he calls the “body-self neuromatrix.” These neurosignature patterns may be triggered by sensory inputs but, notably, may also be generated independently of them. By recognizing that injury and pain may not always have a simple one-to-one relation, this theory provides a template to explore factors that determine or modulate the body-self neuromatrix, including genetic influences, the stress system, and cognitive brain functions, in addition to traditional sensory inputs.

Thus, although it is understood that a discussion of nociceptive pathways and acute pain is inherently limited in its ability to explain the complexities of the pain experience, a basic understanding of these pathways remains a prerequisite for designing effective clinical pain management strategies. With this in mind, the following sections outline these pathways, beginning in the periphery.

### Peripheral Nociceptors

In cutaneous tissues, muscle, and visceral tissues, transduction of high-threshold (ie, noxious) stimuli into electrical impulses occurs at specialized free nerve endings

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of certain primary afferent fibers known as nociceptors.\textsuperscript{3,4} Most nociceptors are non-selective ion channels that are gated not by voltage but by temperature, chemical ligands, or mechanical shearing forces.\textsuperscript{5} Once they are activated, the channels open and Na\textsuperscript{+} and Ca\textsuperscript{2+} ions flow into the nociceptor peripheral terminal, producing an inward current that depolarizes the membrane.\textsuperscript{6} The presence, specificity, and threshold of these nociceptor transducers constitute the first and most important filter in nociceptive processing and define the different classes of primary afferent fibers.\textsuperscript{4} Most fibers are considered polymodal, responding to multiple types of noxious stimuli, whereas some are unimodal and respond to only one form of stimulus. There has been considerable progress in the past decade in identifying the molecular structure and function of various nociceptor ion channels.

Of all of these “transducers,” the TRP ion channels have emerged as the major family involved in generating thermally and chemically evoked pain.\textsuperscript{7–9} All TRP receptors are considered to be primarily thermoreceptors, but they may also respond to mechanical and chemical activators. Within the TRP family are several subfamilies, including TRPV, TRPM, and TRPA. In the TRPV subfamily, the most important member is TRPV1 (also known as the vanilloid receptor-1).\textsuperscript{10} It is located on C and A\textsubscript{δ} fibers, responds to noxious heat (>42\degree C), and is also capsaicin-sensitive.\textsuperscript{3,6,7} Another type, TRPV2, is capsaicin-insensitive and has a higher thermal threshold (approximately 52\degree C). Two additional TRPV members, TRPV3 and TRPV4, respond to lower thermal ranges and other chemical mediators.\textsuperscript{7} The TRPM and TRPA subfamilies have receptors that respond to cold, with TRPM8 responding at <28\degree C and TRPA1 responding at <18\degree C.\textsuperscript{11,12}

Another potentially important transducer is TREK-1, a member of the 2P-domain K\textsuperscript{+} channel family.\textsuperscript{4,9} The TREK-1 receptor is located on C and A\textsubscript{δ} fibers and responds to mechanical and thermal stimuli. Interestingly, TREK-1 receptors seem to be extensively colocalized with TRPV1 receptors in dorsal root ganglia neurons.\textsuperscript{13} In addition, other transducer channels, such as the acid-sensing ion channels (ASICs), have been identified on nociceptive (A\textsubscript{δ}) and nonnociceptive (A\textsubscript{β} fibers) and are involved in transducing mechanical and chemical stimuli.\textsuperscript{9}

**Analgesic Drugs Acting at Nociceptors**

At present, there are few pharmacologic interventions that specifically target the process of transduction in the nonsensitized nociceptor. One exception is capsaicin, an algogenic substance found in hot peppers. As mentioned previously, capsaicin binds to TRPV1 receptors and activates them, which initiates a pain response. Prolonged application of a topical preparation of capsaicin, however, has been shown to desensitize TRPV1 and, ultimately, to produce analgesia. TRPV1 desensitization seems to depend on calcium and may be mediated by calmodulin.\textsuperscript{14} There are commercial preparations of topical capsaicin available that have been used to treat human patients who have postherpetic neuralgia and other types of neuropathic pain. Resiniferatoxin is a capsaicin analogue, and one recent veterinary study has demonstrated that intrathecal administration of resiniferatoxin produced clinically significant analgesic effects in dogs with spontaneously occurring bone cancer.\textsuperscript{15}

On the horizon for the future, the pharmaceutical industry is currently pursuing development of specific TRPV1 antagonists for potential use as clinical analgesics. Other groups are looking at development of new synthetic capsaicin-like drugs to induce TRPV1 desensitization and produce analgesia.

**Primary Afferent Fibers**

As discussed previously, the transduction of noxious stimuli is manifested by influx of Na\textsuperscript{+} and K\textsuperscript{+} ions into the peripheral terminal of the nociceptor, which initiates
depolarization. If the depolarizing current is of sufficient magnitude, voltage-gated Na\(^+\) channels are activated, further depolarizing the membrane and causing a burst of action potentials.\(^5\) These action potentials are conducted from the periphery to the central nervous system along the axons of primary afferent nociceptive fibers. There are several isoforms of Na\(^+\) channels that have been recognized for their specific role in nociception, including the nociceptor-specific Na\(_v\)1.7, Na\(_v\)1.8, and Na\(_v\)1.9 channels.\(^3\)\(^,\)\(^16\) Under normal conditions, most of these channels are of the tetrodotoxin (TTX)-sensitive type; however, neural insult, inflammation, and exposure to algogenic substances cause increased expression of a TTX-resistant (TTX-R) isoform, which may subserve lowered threshold Na\(^+\) conductance.\(^17\)

It is now well recognized that multiple small-fiber afferents can transmit nociceptive impulses, based on their expression of transductive receptors and TTX-R type Na\(^+\) channels. Aδ and C fibers are still regarded as the principal nociceptive primary afferents, however, and their differential activity is responsible for the unique sensory qualities of fast and slow pain.

Type I and type II Aδ fibers range in size from 1 to 5 \(\mu\)m in diameter, are myelinated, and conduct impulses rapidly at a rate of 5 to 30 m/sec. The conduction rate is correlated to the initial sensation of pain, often referred to as “first pain,” which is sharp, localized, and transient. These afferents have small receptive fields and specific high-threshold ion channels that are activated by noxious thermal or mechanical input.\(^3\)

C-fibers constitute most cutaneous nociceptive innervation. They are small, ranging in size from 0.25 to 1.5 \(\mu\)m in diameter, are unmyelinated with conduction velocities of only 0.5 to 2 m/sec, and have larger receptive fields compared with Aδ fibers.\(^3\) These characteristics contribute to “second pain,” which is the poorly localized, burning, gnawing sensation that persists after termination of the noxious stimulus. C fibers are polymodal and may be activated by thermal, mechanical, or chemical stimuli. In addition to their cutaneous locations, C fibers are also found extensively throughout muscle and viscera.

**Analgesic Drugs Acting at Primary Afferent Fibers**

The local anesthetics, such as lidocaine and bupivacaine, are classic Na\(^+\) channel blockers and are considered to be primary analgesic agents. Their principal effect in the nociceptive pathway is to inhibit nerve impulse conduction along Aδ and C fibers, thereby blocking the transmission of nociceptive signals to the central nervous system. Physicians and veterinarians exploit this class of drugs extensively by using them in local and regional nerve block techniques to prevent and actively manage pain. Techniques like peripheral nerve blocks and epidural anesthesia are extremely effective components of a multimodal pain management plan, and the reader is referred elsewhere in this issue for a detailed discussion of their use.

Another class of drugs, the \(\alpha_2\)-agonists, may also possess some ability to inhibit nerve impulse conduction when applied perineurally and may potentiate the intensity and duration of blockade when coadministered with a local anesthetic.\(^18\)

Despite the clinical utility of the currently available Na\(^+\) channel blockers, such as lidocaine, to inhibit nociceptive transmission, these drugs are all nonselective, and thus have relatively narrow therapeutic indices. Because of the restricted expression patterns of voltage-gated Na\(^+\) channels associated with nociceptive primary afferents, notably Na\(_v\)1.8, this channel has become a target for future drug development.\(^5\)\(^,\)\(^16\) Isoform-specific channel antagonists or gene therapy approaches targeted at downregulating these specific isoforms could, in theory, block only fibers...
transmitting pain input while leaving those transmitting innocuous sensations and motor and autonomic outputs intact.

**Dorsal Horn Neurons and Ascending Spinal Tracts**

The dorsal horn represents the first relay point for somatic sensory information, including nociceptive input, en route to the brain. Aδ and C fibers enter the spinal cord by way of the dorsal roots of spinal nerves and synapse in specific laminae (layers) of the dorsal horn. Aδ fibers terminate in laminae I, II, and IIa, whereas C fibers terminate in laminae II, IIa, and V. Primary afferents may synapse with local interneurons (which may be excitatory or inhibitory), with propriospinal neurons, or with projection neurons that extend beyond the spinal cord to transmit nociceptive input to supraspinal structures. The primary synaptic transmitter present in all types of primary afferents is glutamate. Most transmission between primary afferents and dorsal horn neurons occurs through postsynaptically located ionotropic \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors with a small NMDA component. In addition to neurotransmitters, there is a long and growing list of other substances that can also modulate synaptic transmission in the dorsal horn.

There are two major types of nociceptive projection neurons located in the dorsal horn, wide dynamic range (WDR) and nociceptive-specific (NS) neurons. Most of these neurons extend axons contralaterally to form the spinothalamic tract (STT). WDR neurons predominate in lamina V and receive innocuous input from low-threshold \(\alpha\) and \(\beta\) fibers in addition to nociceptive input from Aδ and C fibers. WDR neurons respond in a graded manner over large receptive fields and often receive convergent deep and visceral input. NS neurons are concentrated in lamina I and respond to input from Aδ and C fibers only. They have smaller receptive fields compared with WDR neurons and function in stimulus localization and discrimination.

WDR and NS neurons project to the reticular formation and thalamus of the brain stem by way of multiple parallel pathways called tracts, including the STT, the spinocervicothalamic tract (SCT), the spinoreticular tract (SRT), the spinomesencephalic tract (SMT), and the postsynaptic dorsal column pathway. Although there is considerable species variation in the relative importance of these tracts with regard to nociception, the STT and SCT seem to be most important in domestic species, with the SCT being of particular note in carnivores. In human beings, the sensory discriminative aspects of pain seem to be mediated by projections to the lateral thalamocortical system, whereas the motivational and affective aspects seem to be mediated by projections to the medial thalamocortical system.

**Analgesic Drugs Acting at the Dorsal Horn**

In the nonsensitized nervous system, the principal analgesic drugs that act in the dorsal horn are the opioids, the \(\alpha_2\)-agonists, and the NSAIDs. The opioids and the \(\alpha_2\)-agonists are used extensively in veterinary medicine to manage pain, and opioids, in particular, remain among the most effective analgesics currently available. Dense populations of opioid receptors exist in the dorsal horn, and activation of these receptors may have pre- and postsynaptic effects. At the presynaptic level, decreased Ca\(^{2+}\) influx reduces the release of excitatory transmitter substances, such as substance P, from primary afferents, which inhibits nociceptive transmission. Postsynaptically, enhanced K\(^+\) efflux causes hyperpolarization of projection neurons, which also inhibits ascending nociceptive pathways. Because \(\alpha_2\)-adrenoceptors belong to the same superfamily as do opioid receptors, the \(\alpha_2\)-agonists have a similar mechanism of analgesic action within the dorsal horn.
The NSAIDs are also widely used in veterinary medicine to manage various types of pain. Although their peripheral antiprostaglandin effects make them obvious choices for minimizing development of peripheral sensitization of nociceptors, they also inhibit cyclooxygenase (COX) within the spinal cord dorsal horn, and thus are also considered to have central-acting analgesic effects.

Although there are numerous other drugs that may have an impact on dorsal horn modulation of nociceptive input, the role of most of these agents is to suppress or inhibit the development of central sensitization rather than to induce analgesia in the nonsensitized state. As such, these agents are discussed in a later section.

**Thalamocortical System**

As mentioned previously, the sensory discriminative aspects of pain are produced in the lateral thalamocortical system, which consists of relay nuclei in the lateral thalamus and the primary and secondary somatosensory cortices. The motivational and affective aspects of the pain experience arise in the medial thalamocortical system, which includes relay nuclei in the medial thalamus that send projections to limbic structures, such as the anterior cingulate gyrus and prefrontal cortex, but that also includes spinal projections to the hypothalamus and amygdala.

**Analgesic Drugs Acting at Thalamocortical Structures**

Drugs like opioids and $\alpha_2$-agonists also have analgesic effects that are mediated at the supraspinal level through their effects on descending inhibitory nociceptive pathways. In addition, the sedative effects induced by these drugs, although not producing analgesia, may act to modify certain aspects of pain perception.

Other drug classes, such as benzodiazepines, phenothiazines, and general anesthetics, have no primary analgesic activity. They are able to decrease or, in the case of general anesthetics, completely obliterate the perception of pain, however, by altering the state of consciousness. Despite the fact that an individual may be totally unaware of pain while under the influence of such drugs, nociceptive processing continues virtually unabated during this time. Consequently, it is universally recognized that patients undergoing painful procedures while under general anesthesia require a multimodal approach to pain management involving analgesic therapy before, during, and after the procedure is completed.

**Descending Antinociceptive Pathways**

In addition to the ascending nociceptive pathways outlined previously, it is equally important to recognize that there are powerful descending pathways that are able to modulate the pain response, upregulating it or downregulating it. This system has four different tiers: (1) the dorsal horn, (2) the periaqueductal gray matter (PAG) of the midbrain, (3) the rostroventral medulla (RVM) and pons of the brain stem, and (4) thalamocortical structures. Of these, the PAG and the RVM are generally viewed as the core of this important system.

Within the RVM, there are unique populations of cells referred to as “on” and “off” cells. Predictably, off cells hyperpolarize in response to STT activation and reduce the transmission of nociceptive volleys in the brain stem. Conversely, on cells are excited by nociceptive input from the STT and engage parabrachial, hypothalamic, cingulate, insular, and septohippocampal pathways subserving arousal and aversive reactions to pain. These cells, it now seems, are critical in producing hyperalgesia after peripheral tissue injury by maintaining central sensitization.

At the level of the midbrain, the PAG has long been recognized as a key structure in the endogenous analgesia system. Afferent input from the STT, efferent projections
from the cingulate gyrus, and nuclei of the limbic forebrain and hypothalamus all activate endorphin-, enkephalin- and nociception-containing neurons of the PAG. Projections extending from the PAG to the brain stem are inhibitory and excitatory. Opioids from the PAG act postsynaptically to suppress GABAergic interneurons in the brain stem, thereby disinhibiting tonic and burst activity of descending serotonergic and adrenergic bulbospinal pathways.

**Analgesic Drugs Acting at Descending Antinociceptive Pathways**

Obviously, the opioids are the class of drugs that play the most significant and best known role in descending nociceptive modulatory pathways through their actions at multiple levels, including the PAG and the dorsal horn. Despite the potential for adverse side effects associated with their administration, physicians and veterinarians continue to use exogenous opioids extensively because they remain among the most powerful and efficacious analgesics available.

Although the analgesic effects of the \( \alpha_2 \)-agonists have traditionally been attributed to their effects at the level of the spinal cord, analgesia may also be mediated at the supraspinal level through descending antinociceptive pathways. The \( \alpha_2 \)-agonists bind receptors in a group of catecholaminergic nuclei in the pons known as the locus ceruleus (LC), which receives noradrenergic efferents from the PAG and also extends noradrenergic axons to the spinal cord. Activation in the LC seems to contribute indirectly to analgesia at the level of the dorsal horn through these descending projections.

**NERVOUS SYSTEM SENSITIZATION**

In the clinical setting, physicians and veterinarians are often called on to manage pain associated with substantial tissue injury. If a noxious stimulus is sufficiently intense to produce such injury, prolonged poststimulus sensory disturbances may be observed, including continued pain, increased sensitivity to noxious stimuli (hyperalgesia), and pain after innocuous stimuli (allodynia). These clinical findings are a result of changes in nervous system processing occurring peripherally and centrally.

**Peripheral Sensitization**

Injury to tissues causes inflammation that results in profound changes to the chemical environment of nociceptor peripheral terminals. Damaged cells release their intracellular contents, such as ATP and \( K^+ \) ions; local pH decreases; and cytokines, chemokines, and growth factors are produced by inflammatory cells that are recruited to the site of damage. Many of these chemicals act on G-protein–coupled receptors or tyrosine kinase (TrK) receptors expressed on nociceptor terminals. Intracellular signaling pathways are then activated, which, by means of phosphorylating receptors and ion channels within the terminal, actually modify nociceptor threshold and kinetics.

Inflammatory mediators may be broadly classified into two categories: direct or indirect acting. Of the direct-acting mediators, some are considered nociceptor activators because they directly stimulate the nociceptor, whereas others are nociceptor sensitizers because they sensitize the terminal, making it hyperresponsive to subsequent inputs. A discussion of all the relevant inflammatory mediators that play a part in peripheral sensitization is beyond the scope of this article; thus, instead, a few selected mediators are presented.

Prostaglandins are considered the prototypic nociceptor sensitizers. Prostaglandin E\(_2\) (PGE\(_2\)), for example, can cause changes in TRPV1 by means of activation of cyclic adenosine monophosphate (cAMP)–dependent protein kinase A (PKA).
and Ca\textsuperscript{2+}-dependent protein kinase C (PKC), resulting in phosphorylation of TRPV1 and radically lowering its thermal threshold (from approximately 42°C to 35°C).\textsuperscript{5,31}

Bradykinin is an example of a direct-acting mediator capable of nociceptor activation and sensitization. Like PGE\textsubscript{2}, the TRPV1 receptor seems to be responsible for most bradykinin-induced nociceptive activity.\textsuperscript{32} Bradykinin seems to work through multiple signaling pathways to reduce TRPV1 thermal thresholds, including phospholipase C (PLC), PKC, phospholipase A (PLA), and, downstream of this, lipoxygenase (LOX).\textsuperscript{33} In addition to its ability to reduce TRPV1 thermal thresholds dramatically, bradykinin can also activate TRPA1 in a PLC-dependent manner to enhance noxious cold sensitivity.\textsuperscript{11}

A relatively new discovery is the importance of neurotrophic factors as key players in the process of peripheral sensitization. Traditionally, the role of neurotrophic factors, such as NGF, was thought to be regulation of neuronal survival in the developing nervous system. As its contribution to the pain response continues to be unraveled, however, it seems that NGF may soon be recognized primarily for its role as a pain mediator.

NGF is the founding member of the neurotrophin family of proteins, which includes brain-derived neurotrophic factor (BDNF), neurotropin 3 (NT-3), and neurotropin 4 (NT-4).\textsuperscript{34} The receptor tyrosine kinase known as TrkA and the receptor p75 NTR bind NGF.\textsuperscript{35,36} Evidence indicates that TrkA receptors are mandatory for the nociceptive actions of NGF but that p75 NTR may also play a role.\textsuperscript{37}

Induction of expression of NGF is an early event in injured and inflamed tissues, and elevated levels are sustained throughout chronic inflammation. Increased levels of NGF may contribute to peripheral sensitization directly or indirectly. First, NGF can sensitize TRPV1 channels directly through PKC signaling. Second, retrograde NGF signaling from nociceptor peripheral terminals triggers altered gene expression in the cell bodies to produce substance P, the Na\textsubscript{+}1.8 channel, the ASIC3 channel, the TRPV1 channel, and BDNF. These proteins further sensitize the primary afferents and contribute to the phenomenon of primary hyperalgesia.\textsuperscript{35,36} Finally, NGF released under conditions of tissue injury and inflammation can also sensitize nociceptors indirectly by activating mast cells.\textsuperscript{38}

**Analgesic Drugs that Inhibit Peripheral Sensitization**

The NSAIDs, through their antiprostaglandin effects, are the classic group of drugs with efficacy at inhibiting peripheral sensitization. NSAIDs are widely used in veterinary medicine for the management of acute perioperative pain and various types of chronic pain. Because they focus on COX pathways only, numerous other sensitizers, such as bradykinin and NGF, are still able to alter nociceptor function significantly during tissue injury and inflammation. Thus, the currently available NSAIDs always have a ceiling effect that limits their analgesic potential.

Opioids have traditionally been considered the prototype class of centrally acting analgesics, although evidence has emerged over the past decade suggesting that these drugs have peripheral effects as well. Opioid receptors of all three major types have been identified on the processes of sensory neurons, and they respond to peripherally applied opioids and locally released endogenous opioid peptides when upregulated during inflammation.\textsuperscript{39,40} Currently available opioid analgesics bind central and peripheral opioid receptors nonselectively; however, there is the theoretic potential to develop selective ligands for peripheral opioid receptors, which would offer the possibility of analgesia without centrally mediated adverse side effects.
Other future drug discovery approaches to inhibit peripheral sensitization include the following: (1) drugs that reduce bradykinin production, (2) drugs that block binding of bradykinin or one or more of its signaling pathways (eg, PKC), (3) NGF-capturing drugs that could effectively remove free NGF, (4) drugs that prevent NGF binding to TrkA, and (5) drugs that inhibit TrkA signaling.32,34

Central Sensitization

In the same way that the peripheral terminal of the nociceptor can become sensitized, dorsal horn nociceptive neurons can also exhibit increased excitability. Initially, central sensitization is considered to depend on activity; that is, it is triggered by nociceptor input into the spinal cord.5 Later, it is sustained beyond the initiating stimulus by transcriptional changes in the molecular machinery of the cell and is referred to as transcription dependent.41 Within seconds of major nociceptive inputs, dorsal horn neurons begin to exhibit hyperresponsiveness and the ensuing clinical manifestations become evident. Exaggerated pain responses are noted within the injured area (called primary hyperalgesia) and also well outside the site of injury (called secondary hyperalgesia). As well, low-threshold Aβ fibers that, under normal circumstances, do not respond to noxious inputs are recruited and contribute to the pain response. This means that normally innocuous stimuli, such as a light touch to the skin, now elicit pain (called tactile allodynia).

In general, many of the alterations underlying central sensitization are similar to those that produce peripheral sensitization. Mechanistically, numerous intracellular signaling pathways are activated in the dorsal horn by the neurotransmitter glutamate in addition to other neuromodulators, including substance P and BDNF. Increased synaptic efficacy seems to result from two primary mechanisms: (1) alterations in ion channel or receptor activity arising from posttranslational processing and (2) mobilization of receptors to neuronal membranes. One key receptor involved in these changes is the glutamate-activated NMDA receptor. Phosphorylation of this receptor stimulates its mobilization from intracellular stores to the synaptic membrane and increases its responsiveness to glutamate by removal of the voltage-dependent Mg2+ ion block, thereby favoring the open-state configuration.5

Recent investigations into the basis of central sensitization have revealed the central neuroimmune response as a driving force, with particular relevance in chronic pain states after peripheral nerve injury.42 Traditionally, nonneuronal glial cells were thought to function mainly as “housekeepers,” whose role was to provide support and nutrition to neurons while acting as passive bystanders of neuronal transmission. Within the past decade, considerable evidence has accrued to support the notion that glial cells are in fact key players in the creation and maintenance of pathologic pain states.43 Glial cell activation occurs secondary to nerve trauma or inflammation, which results in the production of numerous proinflammatory mediators.43,44 Important proinflammatory cytokines include interleukin (IL)-1β, tumor necrosis factor-α (TNFα), and IL-6.44 Chemokines (ie, chemoattractant cytokines), such as macrophage inflammatory protein-2 and monocyte chemoattractant protein-1, recruit macrophages and neutrophils from the circulation into nerves.43 Together, these neuroexcitatory substances released after glial cell activation can create and maintain the state of augmented pain facilitation known as central sensitization.

Furthermore, these immune cells also seem to compromise opioid efficacy for management of clinical pain.45,46 It is now clear that glial cells regulate morphine analgesia, tolerance, and dependence and withdrawal.47 Although it is also clear that such effects are not limited to morphine, it is as yet unknown how pervasive this glial regulation may turn out to be.
Analgesic Drugs that Inhibit Central Sensitization

Because of the importance of the NMDA receptor in central sensitization, inhibition of this receptor is a rational analgesic strategy. Ketamine has NMDA antagonistic properties and is a drug well known to veterinary medicine, wherein it has been used traditionally as a short-acting anesthetic. Ketamine has been shown to reduce the early phase of central sensitization and the resultant hypersensitivity to pain.48,49 Unfortunately, because of the widespread distribution of the NMDA receptor throughout the brain, psychomimetic side effects may accompany ketamine’s analgesic effects, which limits its clinical utility. Amantadine is another drug with anti-NMDA effects that has been shown to produce analgesia. Because amantadine’s predominant inhibitory mechanism is stabilization of NMDA channels in the closed state50 rather than blockade of current flow through open channels like ketamine, amantadine seems to have a more favorable clinical safety profile. Development of new anti-NMDA drugs that are able to block central sensitization without other central nervous system side effects is being actively pursued at this time.

The anticonvulsant gabapentin is another drug used increasingly by veterinarians as an adjunctive and occasionally primary analgesic agent. Evidence suggests that this drug works by binding to the \( \alpha_2-\delta_1 \) subunit of presynaptic voltage-gated calcium channels that are upregulated during central sensitization.51 The intensity of the analgesic effect achieved with gabapentin seems to be proportional to the magnitude of sensitization within the dorsal horn.52,53

The NSAIDs, as discussed previously, have effects at numerous locations along nociceptive pathways, peripherally and centrally. COX-2 begins to be expressed by neurons in many areas of the central nervous system several hours after localized peripheral tissue injury.54 The resultant COX-2–mediated increase in PGE2 production contributes to a late-onset, prolonged, and diffuse phase of central sensitization.54 Thus, COX-2–specific NSAIDs are likely to continue to be important components of multimodal pain management strategies because of their ability to dampen central sensitization.

The new appreciation of the importance of immune glial cells in the pain response is currently driving the search for antiglial drugs, or drugs with anticytokine or antichemokine effects, as novel analgesic agents. Such agents have significant potential to reduce opioid tolerance and improve analgesic efficacy in chronic neuropathic pain states.

NEW DIRECTIONS IN UNDERSTANDING THE BIOCHEMICAL BASIS OF PAIN

A group of investigators has recently proposed an interesting theory that the origin of all pain is inflammation and the inflammatory response.55 Furthermore, they suggest that pain syndromes should be reclassified and treated based on their inflammatory profiles. Specifically, they recommend following four general principles for the treatment of all types of pain: (1) determination of the inflammatory profile of the pain syndrome, (2) inhibition or suppression of production of the appropriate inflammatory mediators, (3) inhibition or suppression of neuronal afferent and efferent (motor) transmission, and (4) modulation of neuronal transmission.55,56 This theory is appealing in that it supports development of rational multimodal analgesic strategies tailored to the individual patient rather than empiric trial-and-error approaches. Whether this theory proves to be true or not, a transition to mechanism-specific pharmacologic management of pain seems to be the way of the future.
REFERENCES