
REVIEW ARTICLE

Spinal Mechanisms of Pain and Analgesia

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■ **Abstract:** Chronic pain—especially that which is refractory to conventional treatment—presents particular challenges to physicians and patients. Examination of the molecular and cellular mechanisms involved in this pathophysiology suggests that spinal instillation of therapeutic agents may offer an effective treatment option through the modification of the processing and sensation of chronic pain. Intrathecal therapy, used alone or in combination with other analgesic agents, may reduce chronic pain by attenuating both pre- and postsynaptic activities. This article reviews chronic pain pathophysiology and the mechanisms whereby spinally administered analgesics may modify chronic pain. Available treatment options are also considered, including recommendations from the 2007 Polyanalgesic Consensus Conference (PACC) guidelines on the use of intrathecal agents for nociceptive, neuropathic, and mixed pain. ■

Key Words: intrathecal analgesia, review, pain mechanisms

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INTRODUCTION

Chronic pain is a common condition that confers a substantial burden—physical, psychologic, and economic—on individuals and society.^{1–3} Chronic pain that is refractory to conventional treatment remains a challenge to physicians and patients alike. Interventional techniques, especially neuromodulation, can be effective in patients whose pain does not respond to oral or other systemic analgesics.

Given the prominent role of neural activity within the spinal cord in the pathophysiology of chronic pain, the instillation of therapeutic agents within the central nervous system (CNS), particularly to the intrathecal (IT) space, is a well-established therapeutic modality for treating chronic pain. Not only does the agent gain intimate access to the spinal pain pathways, but it largely bypasses peripheral receptors that may be responsible for many untoward side effects. Two analgesic agents have been approved by the US Food and Drug Administration (FDA) for IT administration in patients with chronic pain: morphine and ziconotide. Many other medications have a history of IT use, but this approach is considered off-label and largely based on clinical experience with minimal evidence from controlled clinical trials.

A group of expert pain physicians, the Polyanalgesic Consensus Conference (PACC), meets every few years to review relevant literature and update their guidelines for the use of IT agents in chronic pain. In the

most recent PACC consensus report,⁴ morphine, ziconotide, and hydromorphone were recommended as first-line agents for nociceptive, neuropathic, and mixed pain. Second-line strategies included fentanyl monotherapy and combination therapy of hydromorphone or morphine with ziconotide, clonidine, or bupivacaine. Third-line options were 2-drug combinations with fentanyl plus ziconotide, clonidine, or bupivacaine, or 1 of the following 3-drug combinations: morphine (or hydromorphone) + bupivacaine + clonidine; morphine (or hydromorphone) + ziconotide + clonidine; morphine (or hydromorphone) + ziconotide + bupivacaine. In part, these recommendations take into account the fact that ziconotide, clonidine, and bupivacaine attenuate pain by different mechanisms compared with opioids. The purpose of this article is to review chronic pain pathophysiology and the molecular and cellular mechanisms whereby spinally administered analgesics may modify the processing and sensation of chronic pain.

PATHOPHYSIOLOGY OF PAIN AND OPPORTUNITIES FOR ANALGESIA

Nociceptive Input

Chronic pain can involve aberrant activity at any point along the pain processing pathways (Figure 1). When primary afferent neurons (nociceptors) are activated in the periphery by stimuli (inflammation, tissue damage, pressure, or temperature), action potentials are generated in these neurons. This leads to the transmission of a signal, mediated by the release of neurotransmitter, to second-order neurons in the dor-

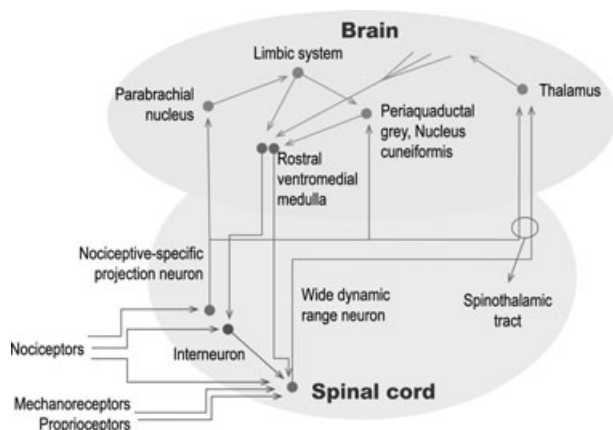


Figure 1. Schematic of neural pain pathways involved in pain processing.

sal horn. The probability of neurotransmitter release from primary nociceptors is affected by the relative activity of various presynaptic ion channels. Excitability of nociceptors depends on the nature and strength of the stimulus, expression of receptors, availability of ion channels, and content/readiness of synaptic vesicles. Chemokines, cytokines, and neurotrophins, among other modulators, bind specific receptors on nociceptors and influence directly their excitability in the periphery and in the CNS.⁵ Induction by a host of factors including post-translational modifications and altered gene expression can also indirectly alter the probability of neurotransmitter release. Other aberrant phenomena include spontaneous ectopic activity and peripheral sprouting, which can increase the signal being passed on from the primary afferents to the dorsal horn.⁶

At the level of the spinal cord, the aspect of nociceptive input most amenable to analgesic influence is ion conductance in presynaptic neurons. Once an action potential reaches the nociceptor terminal, the release of neurotransmitters depends first upon continued depolarization of the terminal membrane, which can be modulated by potassium efflux and/or the inactivation state of sodium channels. If the depolarization is sufficient, calcium influx mediated by voltage-gated calcium channels is triggered (Figure 2). Both N-type and P-type⁷ calcium channels have been found in axon terminals of dorsal root ganglion (DRG) neurons. The localization of N-type calcium channels specifically to nociceptor terminals has been confirmed in rodents by immunofluorescence⁸ and autoradiography.⁹ P-type channels, on the other hand, have a somewhat wider subcellular distribution in spinal neurons.¹⁰

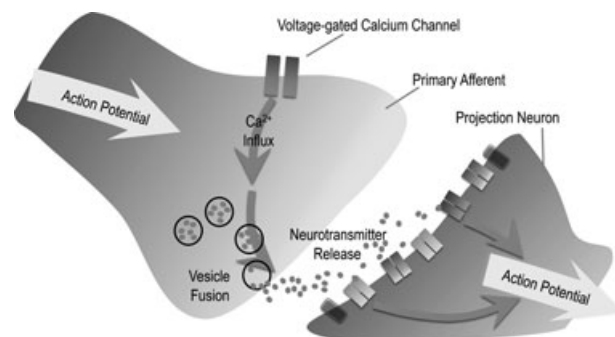


Figure 2. Normal synaptic transmission from nociceptor to projection neuron depends upon the activation of voltage-gated calcium channels.

Multiple subtypes of voltage-gated calcium channels are involved in nociceptive neurotransmission. In animal models, blocking spinal N-type calcium channels with 1 of the ω -conotoxins (calcium channel-blocking neurotoxins first identified in marine snail venoms) partially reduces acute pain,^{11–13} substantially reduces allodynia following nerve injury,^{11,14} and reduces the thermal hyperalgesia induced by intraplantar formalin injection.^{11,12} Similarly, blocking P-type channels with ω -agatoxin IV (a neurotoxin found in spider venoms) diminishes the response to acute pain and second-phase hyperalgesia,¹² while not affecting allodynia.¹⁴ Potentially, P-type calcium channels may be more important for the development of hyperalgesia, while N-type calcium channels are involved in both the development and maintenance of secondary hyperalgesia.¹⁵ P-type channel blockers are not clinically practical because their LD50s are too close to their EC50s for analgesia. In contrast to P-channel blockers (and opioids, as well), ω -conotoxin N-channel blockers, including ziconotide, have a very large safety margin in animals and humans.

These findings are supported by phenotypes observed in mice lacking functional N-type calcium channels. When the $Ca_v2.2$ gene (which underlies the expression of N-type calcium channels) is knocked out, responses to acute noxious stimuli are inconsistently affected,^{16–18} while the early phase 2 responses to formalin-induced inflammation showed complete dependence upon N-type calcium channels. Moreover, the allodynia and hyperalgesia associated with neuropathic pain are abolished in the absence of N-type calcium channels;¹⁸ notably, there is no compensatory functional upregulation of other voltage-gated calcium channels in these mice.^{16–18} The relatively exclusive localization of N-type calcium channels to nociceptor terminals within the spinal cord (supraspinal distribution is less restricted), as well as their demonstrated roles in nociceptive and neuropathic pain, makes them an attractive target for IT analgesic therapy.¹⁹

Excitability of Projection Neurons. Although persistent aberrant peripheral events may initiate the chronic pain signals by way of primary nociceptors, those signals must be relayed to the brain to be perceived as pain. Projection neurons are primarily responsible for this task. The response of the postsynaptic projection neuron is partly dependent upon receptor expression and recent excitation, as well as input from interneurons and descending modulatory

neurons. The activity of projection neurons can be dampened at nociceptor–projection neuron synapses presynaptically by reducing nociceptor input and/or postsynaptically by reducing intrinsic excitability. Changes in descending modulation (disinhibition and enhanced facilitation) can also increase the excitability of the projection neurons.⁶

In chronic pain, glutamate released from the nociceptor activates all 3 types of glutamate receptors: metabotropic, α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), and N-methyl D-aspartate (NMDA) receptors. Substance P (SP) and calcitonin gene-related peptide (CGRP), also released from nociceptors, activate G-protein-coupled receptors, the neurokinin 1 receptor, and the calcitonin receptor-like receptor, respectively. Reduced inhibition by local GABAergic and glycinergic interneurons, coupled with depolarizing responses to SP or CGRP receptors, provides sufficient depolarization to permit calcium influx to the postsynaptic neuron through the NMDA channel.²⁰ The entry of calcium can lead to long-term potentiation (LTP)—long-lasting increased postsynaptic excitatory response. There is evidence supporting the involvement of LTP in the development of chronic pain, particularly in hyperalgesia associated with inflammation.²¹ LTP can be induced in certain spinal pain synapses by tetanic stimulation at physiologically relevant frequencies and by the injection of capsaicin or formalin in animal models.²² Although not seen in all synapses, this phenomenon is known to occur in neurons receiving input from C fibers in lamina I and projecting to the periaqueductal gray. LTP is probably in part responsible for central sensitization—that is, changes occurring within the CNS that enhance the longer-term sensitivity to or perception of pain. Central sensitization, in turn, is thought to be an important, underlying feature of chronic pain.

MECHANISMS OF SPINAL ANALGESICS

Opioids

One mechanism for the therapeutic activity of opioids involves action at opioid receptors on neurons within the pain pathway. Specificity for the various receptor subtypes determines in part the analgesic efficacy and side effects of opioids. The receptor subtype most closely associated with analgesia is the μ -opioid receptor (MOR), while there is evidence that δ -opioid receptors

(DOR) and κ -opioid receptors (KOR) can also inhibit pain transmission in the CNS.²³

In addition to the peripheral nervous system, descending modulatory pathways, the midbrain, and other areas of the CNS,^{24,25} MORs are found in the spinal dorsal horn, both pre- and postsynaptically. About 6% of terminals in the dorsal horn that contain SP also express MORs.²⁶ There is a preponderance of MORs on C fibers.²⁷ A substantial portion of MORs in the dorsal horn, however, appears to be localized to postsynaptic sites on interneurons and projection neurons.²⁵ In contrast to MORs, DORs within the spinal dorsal horn are found primarily on presynaptic terminals in laminae I, II, and V, where wide dynamic range neurons receive input from A δ fibers and descending serotonergic neurons.²⁸ Although KORs are present on neurons in spinal pain pathways,²⁹ their involvement in opioid-mediated IT analgesia is less clear and will not be discussed here. These data indicate that the net effect of spinally delivered opioids is probably mediated by concurrent pre- and postsynaptic actions, particularly via MORs.²⁴

The binding of an opioid receptor agonist activates the G-protein complex, which then acts on various channels or second messengers to affect neuronal function (Figure 3). The MOR is known to couple with G_i and G_{i/o}. Typically, presynaptic MORs, including those localized to axon terminals of DRG neurons, inhibit calcium influx through voltage-gated calcium channels, resulting in reduced synaptic transmission, reduced depolarization, and possibly, reduced release of calcium from intracellular stores. On the postsynaptic side, the binding of an opioid to its receptor is more likely to lead to G-protein-mediated inhibition of adenylyl cyclase.³² Postsynaptic MORs and DORs, via the G $\beta\gamma$ complex, also appear to produce analgesia by inducing inward-rectifying potassium current to dampen membrane excitability.³³ Sodium current may also be inhibited after postsynaptic MOR activation, downstream of protein kinase A and protein kinase C activation.³⁴ All of the above mechanisms would reduce the transmission of pain signals to the brain.

Clinical Picture. Morphine was the first analgesic approved by the FDA for continuous IT administration via an implantable pump. IT efficacy in severe chronic pain has since been demonstrated for morphine, as well as other opioids, in uncontrolled retrospective and

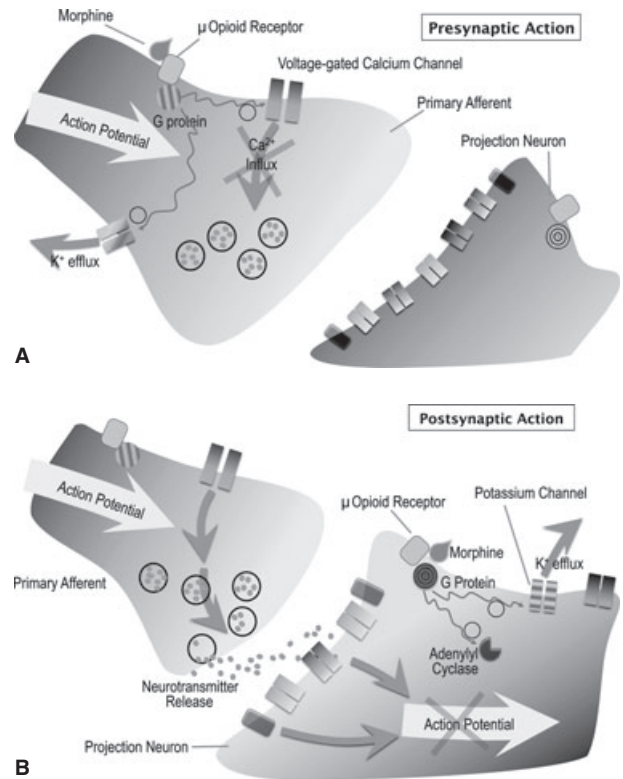


Figure 3. Activation of μ -opioid receptors has pre- and postsynaptic effects in dorsal horn synapses.

prospective cohort studies.^{35–43} Typically, patients were selected to have IT pumps implanted after a successful bolus or continuous infusion trial of IT opioid. Most studies found substantial pain relief with IT opioids (mean 25% to 70% decrease in visual analog scale [VAS] pain score) in 30% to 70% of patients, and this level of pain relief was relatively consistent across nociceptive, neuropathic, and mixed pain, although, at least in 1 study, visceral nociceptive pain appeared to respond best to IT opioids.³⁶ Interestingly, most patients included in the various studies had received systemic opioids prior to the initiation of IT opioids,^{35–38,40,41} suggesting that, at least in some patients, spinal opioid receptors had not become completely desensitized to opioids in spite of previous exposure. In most studies, the efficacy of the IT opioid was maintained for the duration of the study period, although the mean or median IT opioid dose increased over time.^{35–37,42,44,45} However, in 1 prospective study, efficacy diminished after the first few months of treatment, despite opioid dose increases.³⁸ These studies strongly suggest that in chronic pain patients, spinal opioids can provide additional pain relief beyond that achieved with systemic analgesics. In addition, because

of the reduced peripheral and supraspinal side effects, higher spinal concentrations can be achieved with IT than with systemic administration.

During continuous IT administration of opioids, supraspinal exposure can occur by redistribution through blood vessels (for more lipophilic agents) and by cerebrospinal fluid (CSF) flow (for more hydrophilic agents), allowing interaction of opioids with receptors in brain stem, midbrain, and above. The supraspinal opioid receptors are widely dispersed, and actions at these sites are involved in the addiction/reward system, in addition to other specific parts of the pain processing systems. For instance, there are opioid receptors located in the descending modulatory pain system, and binding of an opioid there may account for some of the analgesia associated with IT opioids.⁴⁶ Action at opioid receptors beyond the pain system may also affect pain perception. For example, activation of opioid receptors on dopaminergic neurons of the midbrain can produce euphoria, which may alter the subjective experience of pain.

The proposed mechanisms of opioid action may also explain physiologic tolerance. The effects of opioids on cellular physiology are all indirect, requiring G-proteins and second messengers. It is known that prolonged exposure to opioids can lead to decoupling of opioid receptors from their effector molecules.^{47–51} In addition, prolonged or repeated binding of opioids to their receptors can lead to internalization and degradation of the receptors and/or their downstream targets,^{47,49} although the relationship of internalization with the development of tolerance is unclear.⁵⁰ Thus, chronic exposure to opioids can lead to desensitization that requires dose escalation for continued analgesic effect.

Although peripherally mediated side effects should theoretically be reduced by IT administration, many opioid side effects are nonetheless observed, including sedation, constipation, urinary dysfunction, nausea, sexual dysfunction, and pruritus.^{35–43} Reduction in gastrointestinal motility, for instance, is not just a consequence of opioid receptor activation in the gut but can be induced by MOR and DOR activation in the spinal cord.⁵² Supraspinal exposure may account for other side effects, such as nausea and vomiting, which are thought to arise from opioid receptor activation in the chemoreceptor trigger zone within the area postrema⁵³ and from induction of endocrinopathy by the suppression of the hypothalamic–pituitary–adrenal axis.⁵⁴

Ziconotide

Ziconotide was the second analgesic approved by the FDA for IT administration to treat chronic, severe pain and was recommended as a first-line agent by the 2007 PACC.⁴ Ziconotide is a synthetic version of the naturally occurring ω -conopeptide, MVIIA, a direct and selective antagonist of the N-type calcium channel.⁵⁵ It was first synthesized in the early 1990s and designated as SNX-111 and underwent extensive nonclinical investigation in neuroprotection and antinociception.⁵⁶ Because conopeptides and other neurotoxins were widely used to define the roles of various calcium channels in neuronal physiology, it became clear that N-type calcium channels play a central role in the generation and maintenance of chronic pain, leading to the clinical investigation of ziconotide.

As noted above, N-type calcium channels in the spinal cord are localized to the superficial dorsal horn, where they mediate neurotransmitter release from nociceptors. Upon binding to the N-type calcium channel, ω -conopeptide reduces calcium current⁵⁷ and inhibits transmitter release from presynaptic nerve terminals.^{58,59} Ziconotide and the ω -conopeptides have been shown to block the release of glutamate, SP, and CGRP from DRG neurons (Figure 4).^{60–63}

Clinical Picture. The efficacy of ziconotide in severe chronic nociceptive, neuropathic, and mixed pain of malignant and nonmalignant etiology has been investigated in controlled and open-label clinical trials as well as retrospective cohort studies. Thus, it is the best characterized IT analgesic. In 2 short-term (5- to 6-day) randomized, double-blind, placebo-controlled trials, IT ziconotide significantly reduced pain intensity.^{64,65} Mean reduction in the VAS pain intensity

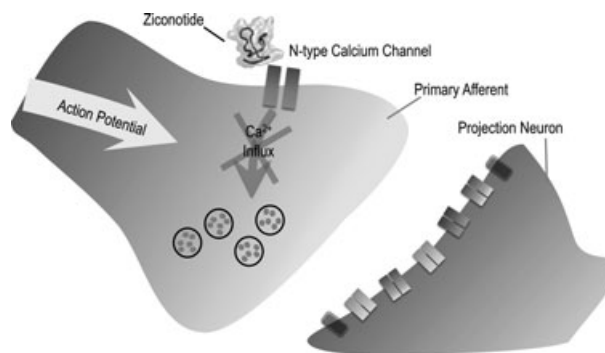


Figure 4. Binding of ziconotide to N-type calcium channels in dorsal horn synapses reduces calcium current.

(VASPI) score was 25% to 35% greater for patients receiving ziconotide ($n = 237$) than for those receiving placebo ($n = 126$). In a third double-blind, placebo-controlled trial in which the ziconotide dose was titrated more conservatively over 3 weeks, patients receiving ziconotide ($n = 112$) experienced a 7.5% greater mean VASPI reduction relative to patients who received placebo ($n = 108$)—2.4-fold the VASPI reduction seen with placebo—and reported improvements in sleep duration and quality.⁶⁶ In a large retrospective cohort study ($n = 104$), about 70% of patients experienced at least a 30% decrease in VASPI after a month of IT ziconotide therapy (0.5 to 11.2 mcg/day), and the level of pain relief was independent of pain type or etiology.⁶⁷ Among the 45 patients who were followed for 6 months or more, efficacy was maintained (mean VAS 5.5 at 2 months, 5.9 at 6 months, NS), and ziconotide doses remained steady (mean 4.1 mcg/day at 2 months, 4.5 mcg/day at 6 months, NS). Over the long term (up to 3.5 years), ziconotide efficacy in prospective open-label trials also persisted without the need for dose increases, consistent with a lack of physiologic tolerance.^{68,69}

In the clinical context, the use of ziconotide, like that of morphine, is frequently initiated following a trialing procedure to evaluate the safety and effectiveness. Some insurance payers require the demonstration of success in an intrathecal trial before approving reimbursement for pump implantation. Aside from this requirement, some clinicians consider IT trialing of ziconotide helpful to assess patient response to spinal analgesia before implanting an IT pump, while others do not. Burton and colleagues reviewed the literature on ziconotide trialing published or presented through December 2008 and distinguished 3 trialing methods: continuous infusion, limited-duration infusion, and bolus trialing. Comparing the results of 8 clinical reports and 1 expert opinion paper, the clinical pain experts who authored this review conclude that the small study sample sizes and lack of controlled trials make it impossible to determine whether effectiveness and safety of long-term IT ziconotide use can be predicted by trialing and if so, which method(s) may be superior. Although additional studies have been published since December 2008, definitive evidence about the value of trialing remains a need for research.⁷⁰

As discussed earlier, functional N-type calcium channels are essential for certain features of pain in

animal models. However, experience in animal models may not directly translate to clinical efficacy in human chronic pain, especially because most models test acute nociception, or hyperalgesia or allodynia after nerve injury or inflammation, rather than recreating a state akin to chronic pain of years' duration. Therefore, the involvement of N-type calcium channels in severe chronic pain is partially defined by human response to blockade of these channels. Empirical evidence from clinical trials suggests that most types of chronic pain, regardless of etiology, are at least partially dependent upon spinal neurotransmission mediated by N-type calcium currents.

Whereas opioids and gabapentin/pregabalin indirectly inhibit N-type calcium channel currents, ziconotide binds directly to the channel to inhibit its function.⁵⁵ This direct and reversible inhibition does not lead to adaptation or tolerance and avoids potential withdrawal effects. Unlike the binding of ziconotide to the N-type calcium channel, G-protein decoupling from MORs after chronic opioid exposure can lessen the effect of opioids on N-type calcium channels and lead therefore to tolerance.

IT ziconotide that distributes to the periphery is cleaved by endo- and exopeptidases and does not accumulate in plasma during continuous IT infusion (Azur Pharmaceuticals Inc 2010). For example, after a single hour-long IT infusion, low levels of ziconotide were rarely detected in the plasma, and systemic exposure is not thought to play a role in the generation of side effects.^{71,72} CSF flow is responsible for the spread and clearance of ziconotide after IT administration⁷¹ and may expose supraspinal N-type calcium channels to ziconotide. N-type calcium channels are present throughout the brain; in rodents, strong labeling was observed in the olfactory bulb, forebrain, thalamus, hippocampus, striatum, cerebellum, and substantia nigra.^{8,9,73} Binding of ziconotide in these areas may underlie some known side effects in humans. The most frequent adverse events (AEs) observed in clinical trials were dizziness, nausea, headache, confusion, nystagmus, somnolence, and asthenia.⁷⁴ Additional cognitive and psychiatric side effects included memory impairment, speech disorder, aphasia, abnormal thinking, and hallucinations.⁷² Vestibular effects such as dizziness, nystagmus, and possibly nausea could be attributed to the inhibition of N-type calcium channels in the cerebellum, while effects on memory and cognition may well be related to ziconotide actions in the hippocampus and forebrain.

Ziconotide Plus Opioid Combination Therapy. The N-channel-mediated effects of the approved agents for IT pain therapy, ziconotide and morphine or hydromorphone, should overlap substantially (Figure 5). However, an opioid should also act on postsynaptic neurons (Figure 3) and other molecular targets in non-overlapping subsets of neurons. Postsynaptic or descending modulation by the opioids may underlie the therapeutic benefit observed when an opioid is added to ziconotide. On the other hand, the association between opioid receptors and N-type calcium channels on presynaptic neurons (Figure 3) is both incomplete and transitory, especially as a consequence of opiate tolerance. In contrast, ziconotide directly and fully inhibits all N-type calcium channels it encounters (Figure 4). Thus, the addition of ziconotide to an IT opioid would result in more complete blockade of synaptic transmission from cells bearing N-type calcium channels. It should be noted that these circumstances may also apply to side effects (Figure 5). For example, both morphine and ziconotide cause side effects of dizziness, nausea, somnolence, confusion, and the like, whereas only opioids but not ziconotide cause pruritus, constipation, euphoria, and dependence.

The safety and effectiveness of ziconotide in combination with other drugs have been investigated in pre-clinical, clinical, and observational studies, which were critically reviewed by Wallace and colleagues.⁷⁵ In the animal studies reviewed, ziconotide did not exacerbate morphine-induced respiratory depression or clonidine-induced hypotension or bradycardia but did potentiate morphine-induced hypotension and inhibition of gastrointestinal tract motility. Results meeting current criteria for strong evidence of effectiveness are still

needed, but limited studies provided some support for the use of ziconotide in combination with morphine, hydromorphone, clonidine, or baclofen. Reductions in pain intensity were reported when IT morphine was added to the pumps of patients with suboptimal pain relief on stable IT ziconotide doses⁷⁶ and when ziconotide was added in patients receiving stable IT morphine doses.⁷⁷

Gabapentin and Pregabalin

Originally developed as antiepileptic drugs, gabapentin and pregabalin are synthetic analogs of GABA but have no interaction with GABA targets. Both have been shown to bind the calcium channel $\alpha 2\delta 1$ subunit of the same N-type channel that is blocked by ziconotide and indirectly modulated by opioids and clonidine.^{78,79} It is this interaction that is thought to be responsible for analgesic efficacy in animal pain models.⁷⁹ $\alpha 2\delta 1$ is expressed widely throughout the nervous system, but especially dense expression is noted in the spinal dorsal horn, anterior olfactory nucleus, anterior amygdala, basolateral (ventral) amygdala and cortical amygdala, and the piriform, perirhinal, insular, and entorhinal cortices.⁸⁰ $\alpha 2\delta 1$ expression augments currents through recombinant L-type calcium channels in cell culture,⁸¹ supporting the observation that specific binding of $\alpha 2\delta 1$ to $Ca_v1\alpha 1$ and $\alpha 2$ plays an important role in membrane expression of functional calcium channels.⁸²

It is currently proposed that the $\alpha 2\delta 1$ subunit is essential for upregulating the expression of calcium channels in chronic pain but is not as critically important in maintaining basal levels of N-channels. This may explain why gabapentin is quite safe, but also is not as efficacious as opioids and ziconotide. The $\alpha 2\delta 1$ subunit appears to play a role in the development and maintenance of neuropathic pain. In animal models, neuropathic pain is associated with increased detection of $\alpha 2\delta 1$ in DRG neurons after peripheral nerve injury⁸³⁻⁸⁵ or spinal cord injury.⁸⁶ It is unclear whether this only involves increased $\alpha 2\delta 1$ trafficking from the nucleus⁸⁷ or also involves increased expression.^{85,88,89} However, blocking upregulation of $\alpha 2\delta 1$ blocks the induction of neuropathic pain after nerve injury^{86,90} or reverses it.⁸⁴ Interestingly, overexpression of $\alpha 2\delta 1$ results in allodynia in the absence of nerve injury.⁹¹

Analgesic efficacy of the $\alpha 2\delta 1$ ligands is uniformly observed in animal models in which central sensitiza-

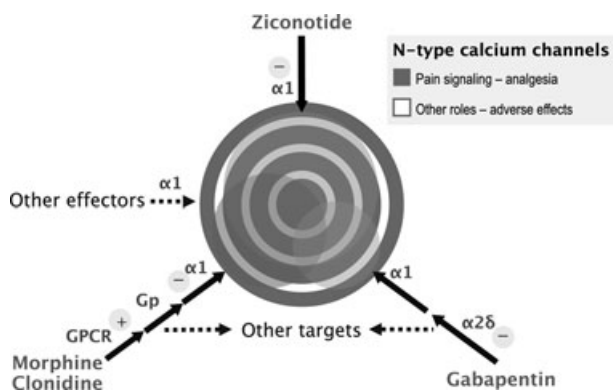


Figure 5. Convergence of analgesic presynaptic actions on spinal N-type calcium channels. GPCR, G-protein-coupled receptor; Gp, G-protein.

tion is thought to play an important role in pain generation and maintenance.⁹² There is debate as to whether the analgesic effects of gabapentin and pregabalin result from direct inhibition of the calcium channels at the presynaptic membrane, or whether their primary effect is to reduce functional expression of calcium channels at synaptic terminals. Gabapentin reduces calcium channel activity in dissociated neurons,⁹³ and both gabapentin and pregabalin acutely and dose dependently reduce N-type⁹⁴ and P/Q-type⁹⁵ calcium currents. Spinally administered gabapentin acutely inhibits SP release from primary afferents⁹⁶; however, it has also been demonstrated that binding of gabapentin to $\alpha 2\delta 1$ inhibits its trafficking from proximal-to-distal portions of neurons (Figure 6).⁸⁷ Accordingly, treatment with gabapentin or pregabalin has been shown to reduce the expression of $Ca_v 1$ and $Ca_v 2$ on presynaptic membrane (Figure 7).⁹⁷ Support for the

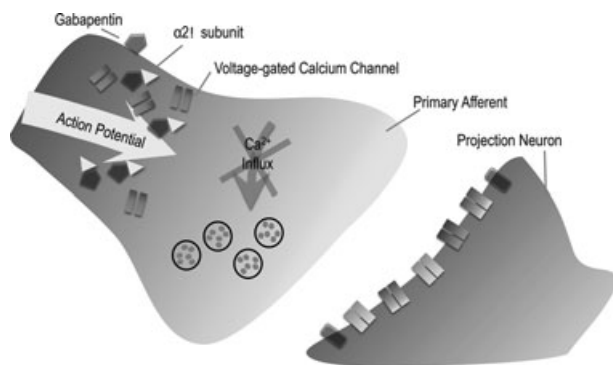


Figure 6. Interaction of gabapentin with the calcium channel accessory subunit reduces functional expression of voltage-gated calcium channels in dorsal horn synapses. (This action mainly blocks the recruitment of additional N-channels, but not the basal level of N-channels.)

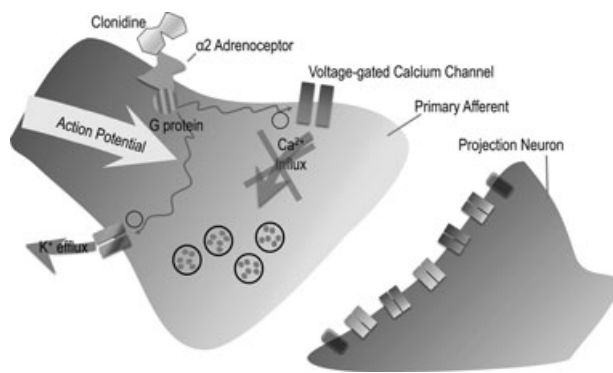


Figure 7. Action of clonidine at the $\alpha 2$ adrenoceptor reduces calcium current and increases potassium current.

importance of the trafficking theory derives from the timing of analgesic onset after the administration of gabapentin or pregabalin and the fact that even if both mechanisms play a role, the trafficking of calcium channel $\alpha 1$ subunits precedes functional expression in the axon terminals. Moreover, as discussed above, the proximal-to-distal movement of $\alpha 2\delta 1$ is upregulated in and essential for the expression of neuropathic pain. Gabapentin also inhibits recycling of the $\alpha 2\delta 2$ calcium channel subunit, reducing the expression of voltage-gated calcium channels at the membrane.⁹⁸ Whether through direct inhibition of calcium currents or reduction in functional calcium channel expression at the synapse, it has been shown that gabapentin and pregabalin attenuate the release of glutamate, SP, and CGRP in spinal cord after sensitization.^{96,99–101}

Both have also been shown to interfere with enhanced descending serotonergic facilitation^{102–105} that is involved in some chronic pain,¹⁰⁶ while possibly also altering noradrenergic modulation of dorsal horn excitability.^{107–109}

Clinical Picture. Neither gabapentin nor pregabalin has been approved by the FDA for IT administration, although clinical trials have been conducted to investigate the efficacy and safety of IT gabapentin. Data from clinical trials are not yet available, although there are considerable data on the efficacy and safety of oral gabapentinoids in chronic pain. In a systematic meta-analysis, about a third of participants in clinical trials—most of whom had neuropathic pain—experienced substantial pain relief with oral gabapentin.¹¹⁰ Based on efficacy observed with oral and IT administration in animal models,^{96,111} it may be expected that neuropathic pain in particular will respond to IT gabapentin. Although calcium channels are essential for most neurotransmission from nociceptors, the role of gabapentin and pregabalin in regulating the transport of these channels may or may not limit their usefulness in chronic pain that is accompanied by the upregulation of $\alpha 2\delta 1$ -mediated calcium channel trafficking.

It has been demonstrated in animal models that blocking upregulation of $\alpha 2\delta 1$ can block the development of allodynia.^{84,86,90} Because $\alpha 2\delta 1$ ligands can interrupt trafficking by $\alpha 2\delta 1$,^{87,97} it will be interesting to determine whether IT administration in humans attenuates the development of chronic neuropathic pain after nerve injury or inflammation. Such an effect has been observed with IT gabapentin in the rat peripheral nerve ligation model.¹¹¹

Based on a meta-analysis of randomized, double-blind studies, 66% of patients taking oral gabapentin for neuropathic pain experienced an AE, although serious AEs were no more common with gabapentin than with placebo.¹¹⁰ The most common AEs included dizziness, somnolence, peripheral edema, and gait disturbance. These, as well as the typical AEs seen with oral pregabalin,¹¹² resemble AEs also seen with IT opioids and ziconotide and may thus be partially dependent upon the inhibition of calcium currents in supraspinal regions, again implicating the cerebellum and hippocampus. Because most of these AEs are neurologic, it is reasonable to suggest that AEs observed with IT administration of gabapentin would be similar.

Clonidine

Clonidine is an agonist of the α_2 adrenoceptor, a G-protein-coupled receptor for epinephrine and norepinephrine.^{113,114} The antinociceptive properties of clonidine in animal models relative to the other clinically available α_2 adrenoceptor agonists, tizanidine and dexmedetomidine, correlate with their competitive binding to spinal α_2 -adrenoceptors, leading to the deduction that clonidine analgesia is mediated primarily through its actions at α_2 adrenoceptors.¹¹³ These α_2 adrenoceptors have been detected by immunofluorescence on primary nociceptor terminals in superficial dorsal horn neurons, but not on secondary projection neurons, interneurons, or descending noradrenergic neurons.¹¹⁵ Both G_o and G_i are known to be coupled with presynaptic α_2 adrenoceptors; thus, activation in the nociceptor terminal inhibits adenylyl cyclase, thereby reducing the activation of protein kinase A and diminishing protein phosphorylation, and/or inhibits voltage-gated calcium channels and enhances voltage-gated potassium channels.¹¹⁶ All of these effects would in turn reduce the likelihood of synaptic transmission from the nociceptor. Clonidine may act directly on postsynaptic dorsal horn neurons as well, although it is unclear if this effect is mediated by α_2 adrenoceptors or by direct interaction with ion channels.¹¹⁷

Accumulated evidence strongly suggests that α_2 adrenoceptors affect pain signaling presynaptically in the dorsal horn. Animal studies indicate that norepinephrine from descending modulatory neurons is the endogenous ligand for α_2 adrenoceptors in the spinal dorsal horn.¹¹⁶ Further elucidation of the role of α_2 adrenoceptors in pain has mainly been derived from studies using clonidine itself, occasionally another ago-

nist such as tizanidine or dexmedetomidine, and/or the α_2 adrenoceptor antagonist yohimbine. There is evidence that nerve injury may strengthen the coupling between α_2 adrenergic receptors and inhibitory G-proteins, leading to a reduction in synaptic transmission.¹¹⁸ Activating the α_2 adrenoceptor with clonidine, dexmedetomidine, or norepinephrine can reduce glutamate release from DRG neurons in response to capsaicin, an effect that was reversed by an α_2 adrenoceptor antagonist.¹¹⁹ Blocking C fiber signaling by activating α_2 adrenoceptors can suppress LTP in postsynaptic projection neurons.¹²⁰ Likewise, activation of these receptors reduces the phosphorylation of NMDA receptors in spinal projection neurons.¹²¹ In general, it seems likely that α_2 adrenoceptor activation reduces the excitability of spinal projection neurons primarily by reducing transmission from the primary nociceptors.

Clonidine has demonstrated antiallodynic and antihyperalgesic activities in animal models of inflammatory and neuropathic pain. Clonidine alone produced a dose-dependent antinociception in the rat inflamed knee joint model.¹²² IT administration of clonidine or tizanidine (another α_2 -adrenergic agonist) abolished allodynia associated with nerve ligation in rats.¹²³ Also in the nerve ligation model, IT clonidine acted additively with adenosine to reduce neuropathic allodynia.¹²⁴ In another study of rats subjected to nerve ligation, IT administration of ω -conotoxin CVID or dexmedetomidine completely inhibited allodynia; the combination of these 2 agents synergistically decreased mechanical hypersensitivity.¹²⁵

Clinical Picture. Clonidine is approved in the United States for epidural administration in patients with cancer for whom IT morphine is ineffective or has failed. Although not currently approved for long-term IT infusion in chronic pain, clonidine has shown analgesic efficacy in patients with chronic pain. Clinical evidence supporting the use of IT clonidine for chronic pain includes mainly case reports and retrospective cohort studies. Combination therapy, especially with opioids, appears to be typical for IT use of clonidine. There is a perception among clinicians that clonidine is efficacious in chronic pain that has a neuropathic component.¹²⁶ In a double-blind, placebo-controlled trial of morphine plus clonidine, patients with neuropathic pain following spinal cord injury were given IT bolus or infusion trials of clonidine, morphine, or a combination of clonidine and morphine.¹²⁷ Although neither morphine nor

clonidine alone produced analgesia superior to saline for these patients, the combination of clonidine and morphine was significantly more effective than saline 4 hours after administration. In chronic pain, multiple case reviews report analgesia with IT clonidine in combination with midazolam in 4 patients with nonmalignant neuropathic and nociceptive pain¹²⁸ and in combination with baclofen in a patient with spinal cord injury-related neuropathic pain and spasticity.¹²⁹ Clonidine in combination with an opioid has shown efficacy in both malignant¹³⁰ and nonmalignant chronic pain.¹³¹

Continuous IT infusion of clonidine appears to sustain efficacy over a long period. One retrospective cohort study reported 16 patients with degenerative lumbar spinal disease receiving IT clonidine in combination with morphine, with or without bupivacaine and/or midazolam, for up to 2 years.¹³² All but 1 patient reported sufficient, good, or excellent outcomes over the observation period, although it should be noted that morphine dose increased steadily over the same period. Another questionnaire-based study of 36 patients with failed back surgery syndrome or chronic mechanical low back pain who received IT diamorphine (27 in combination with clonidine) for an average of more than 4 years found improvements in pain relief and quality of life without opioid or clonidine dose escalation.¹³³

Although there have been no formal studies examining the safety and tolerability of IT clonidine in chronic pain, known side effects of IT clonidine include hypotension, bradycardia, and sedation.¹³⁴ Oral administration of clonidine in humans has also led to impaired cognitive function, presumably through an action in the CNS.¹³⁵ There is 1 report of a patient who experienced night terrors, depression, and insomnia upon receiving IT clonidine for neuropathic pain.¹³⁶

The α_2 adrenoceptors are found throughout the body, including in the periphery and in the CNS.¹¹⁶ Yaksh and colleagues have shown that spinal actions of clonidine and other α_2 adrenoceptor agonists in animal models are responsible for their analgesic properties.^{137,138} Likewise, in humans, analgesia to cold-induced acute pain has been correlated with spinal CSF levels of clonidine rather than plasma levels upon IT administration, implicating a CNS site of action.¹³⁹ The spinal cord appears to be an important site of action for clonidine in chronic pain as well, given that epidural administration was almost as effective as IT administration for reducing hyperalgesia and

allodynia associated with inflammation,¹⁴⁰ whereas intravenous administration had no effect on hyperalgesia and allodynia.¹⁴¹ There is very little evidence to support a supraspinal component to IT clonidine analgesia.¹¹⁶

Studies in dogs with another α_2 adrenoceptor agonist, dexmedetomidine, suggest that the sedative and cardiorespiratory effects associated with this class of drugs are because of supraspinal action at α_2 adrenoceptors, possibly in the locus coeruleus, as the drug is redistributed throughout the CSF.¹³⁷

Bupivacaine and Local Anesthetics

The local anesthetics, including bupivacaine, have been used intrathecally since the 1980s for long-term treatment of chronic pain, albeit without FDA approval. It has been demonstrated that local anesthetics primarily block voltage-gated sodium channels on C and A δ fibers in a state-dependent fashion.¹⁴² With variable selectivity and potency, local anesthetics inhibit both tetrodotoxin (TTX)-sensitive and TTX-resistant sodium channels in primary afferents,¹⁴³ disrupting propagation of the action potential from the periphery into the DRG and dorsal horn.¹⁴⁴ Based on relative inhibition at these 2 types of sodium channels and their differential effects on various neuronal processes, there is reason to believe that the action of local anesthetics, particularly at TTX-resistant channels on C and A δ fibers, underlies their analgesic properties.¹⁴⁵ However, in addition to inhibiting voltage-gated sodium channels, low concentrations of local anesthetics may enhance voltage-gated potassium channels, leading to hyperpolarization of the axon terminal.¹⁴⁶ In vitro evidence also suggests that bupivacaine may directly inhibit NMDA and nicotinic acetylcholine receptors on the postsynaptic dorsal horn neurons and 3-HT_{3A} receptors on inhibitory interneurons.^{146,147}

Clinical Picture. Although long-acting local anesthetics are most commonly used to treat or prevent acute pain, their utility in treating chronic pain by continuous IT infusion has been reported in multiple case reports and case series and at least 1 randomized double-blind trial. Like clonidine, IT local anesthetics are used most often in combination with another agent, usually an opioid, to manage chronic pain.

IT bupivacaine has demonstrated analgesic activity in chronic malignant and nonmalignant pain of both neuropathic and nociceptive origin.¹⁴⁸ In a retrospective

review of charts from 109 consecutive patients with chronic malignant and nonmalignant pain, those who received bupivacaine in addition to an opioid had greater pain relief, used fewer oral nonopioid adjuvants, visited physicians and pain clinics less frequently, and were more satisfied than those who received an IT opioid without bupivacaine.¹⁴⁹ In another retrospective study following 17 patients for an average of more than 2 years, the addition of bupivacaine to a constant dose of IT opioids improved pain control, daily functioning, and quality of life while allowing a reduction in oral/transdermal opioid use.¹⁵⁰ However, no benefit was seen when bupivacaine (4 to 8 mg/day) was added in a double-blind fashion to an IT opioid in 24 patients with chronic nonmalignant pain.⁴⁴

In a randomized, controlled trial in 60 patients following lower limb surgery, the addition of dexmedetomidine to ropivacaine intrathecally extended the duration of the motor and sensory block.¹⁵¹

CLINICAL IMPLICATIONS OF THE MECHANISMS OF ACTIONS OF IT ANALGESICS

Voltage- and ligand-gated ion channels that mediate neuronal excitability and signal propagation play a central role in the pathophysiology of pain and the spinal mechanisms of analgesia. In general, the more restricted these targeted channels are to pain pathways, the narrower the potential side-effect profiles of the analgesics will be. Because N-type calcium channels control signaling at the first synapse in the pain pathway and their localization within the spinal cord is restricted to nociceptor terminals, it is not surprising that the mechanisms of many useful IT analgesics converge on N-type calcium channel activity. Some analgesics affect the calcium channels indirectly through G-protein-coupled inhibition (eg, opioids and clonidine) or by reducing functional channel expression in the membrane (gabapentin), while at least 1 (ziconotide) directly binds to the N-type channels themselves. These analgesics also differ in the state dependence/state independence of their action at N-type calcium channels. For instance, GPCR agonists require the receptor to be present in the membrane and associated with the appropriate G-protein. Gabapentin may be most effective when trafficking of the $\alpha 2\delta$ subunit is upregulated. Ziconotide, on the other hand, directly blocks N-type calcium channels regardless of the channel state. These alternative routes to N-type calcium

channel inhibition affect the degrees of channel inhibition and analgesia as well as the nature and severity of AEs (Figure 5). These differences may also account for the efficacy of 1 analgesic when another has not worked in the same patient, although both agents converge on N-type calcium channel activity. Finally, the prevalence of the N-type channel as a target of G-protein activation opens the possibility of other GPCR agonists as potential IT analgesics.

All the agents discussed here—except perhaps gabapentin—attenuate LTP in animals and have effects on memory in humans. However, ziconotide appears to be the most potent at inhibiting memory, while morphine and clonidine are somewhat less potent and gabapentin has no effect or may actually be proamnesic. Can these gradations be explained by the extent of N-channel blockade? This may be an oversimplification, but it might be postulated that ziconotide blocks essentially all N-channels, morphine and clonidine inhibit a fraction of N-channels, and gabapentin inhibits only those N-channels induced in chronic pain. This model might suggest why ziconotide may be effective in cases where morphine, clonidine, and gabapentin are not, why morphine and clonidine may be effective when gabapentin is not, and why gabapentin has a more benign side-effect profile than ziconotide, morphine, and clonidine. That is, by affecting LTP and central sensitization, all these agents should have disease-modifying effects to varying degrees on chronic pain.

The degrees of efficacy and adverse effects are also heavily dependent upon the site of IT administration relative to the site of pathological activity and the distribution and perseverance of the active drug within the CSF. Indeed, substantial drug concentration gradients appear to radiate from the catheter tip during long-term infusion, resulting in very high concentrations near the catheter tip and much lower concentrations farther away from the tip.^{152,153} Concentration gradients can be affected by the ambulatory status of the patient¹⁵⁴ and the basicity of the drug solution relative to CSF.¹⁵⁵ Interestingly, the incidence and severity of AEs may increase with increasing infusion rate, while analgesic effect may diminish, potentially due to broader drug distribution and reduced drug concentration at the site of analgesic action with higher infusion rates.¹⁵⁶ Other AEs, such as granuloma formation, may correlate with slower infusion and consequent high local drug concentrations.¹⁵⁴

The data presented herein provide a strong rationale for using IT analgesic combinations in chronic pain

when a single agent is insufficient. While many of these analgesics are believed to act on the primary nociceptor to reduce neurotransmission, others influence the activity of descending modulatory pathways or the excitability of projection neurons. Combining ziconotide with an opioid, for example, could provide for additive inhibition of nociceptive neurotransmission and also dampen postsynaptic response in nociceptors that are not sensitive to N-type channel inhibition. Even when 2 analgesics have the same downstream target (eg, the N-type calcium channel), their combined action may more fully inhibit channel activity than either agent alone, especially for agents that have indirect or state-dependent effects on the channels. It is also possible that the primary targets for drugs that converge on N-type calcium channel inhibition are expressed in different populations of neurons.

CONCLUSIONS

IT administration provides analgesics with access to the first synapse in the pain pathway, where they can attenuate both pre- and postsynaptic activities to reduce chronic pain. Many effective IT analgesics directly (eg, ziconotide) or indirectly (eg, opioids and clonidine) inhibit the activity of the N-type calcium channel, demonstrating the importance of this channel in pain transmission. Although unimpeded access to the spinal pain pathways may account for efficacy, the presence of an analgesic in the CSF may also lead to off-target and supraspinal actions that result in adverse effects.

As more is learned about the molecular and cellular characteristics of neurons, their organization within the spinal pain pathways, and their roles in various types of pain, the choice of an IT therapy may become more directed and personalized.

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