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Intrathecal Ziconotide for use in the Treatment of Pain

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ABSTRACT: Ziconotide is a powerful analgesic drug that has a unique mechanism of action involving potent and selective block of N-type calcium channels, which control neurotransmission at many synapses. The analgesic efficacy of ziconotide likely results from its ability to interrupt pain signaling at the level of the spinal cord. Ziconotide is a peptidic drug and has been approved for the treatment of severe chronic pain in patients only when administered by the intrathecal route. Importantly, prolonged administration of ziconotide does not lead to the development of addiction or tolerance. The current review discusses the various studies that have addressed the in vitro biochemical and electrophysiological actions of ziconotide as well as the numerous pre-clinical studies that were conducted to elucidate its antinociceptive mechanism of action in animals. In addition, this review considers the pivotal Phase 3 (and other) clinical trials that were conducted in support of ziconotide's approval for the treatment of severe chronic pain and tries to offer some insights regarding the future discovery and development of newer analgesic drugs that would act by a similar mechanism to ziconotide but which might offer improved safety, tolerability and ease of use.

KEYWORDS: Ziconotide, Prialt, Analgesic Drug, N-type Calcium Channel Blocker, Severe Chronic Pain

INTRODUCTION

Ziconotide, which is also known as SNX-111, is a novel non-opioid analgesic drug. It is a synthetic version of ω-conotoxin MVIIA (ω-MVIIA), which is a peptide that is found in the venom of the fish-eating marine snail, Conus magus. Ziconotide has only limited ability to cross the blood–brain barrier and so in order to achieve optimal analgesic efficacy with reduced potential for serious side-effects, it must be administered intrathecally to patients. This spinal route of administration permits ziconotide to reach its maximum local concentration in a short time, which encourages a rapid onset of analgesia. Following the successful completion of three pivotal double-blind, placebo-controlled trials, intrathecal infusion of ziconotide was recently approved by regulatory bodies worldwide as a therapeutic approach for the symptomatic management of severe chronic pain, particularly in patients who are refractory to treatment with morphine and for whom intrathecal therapy is a viable option. The "Ziconotide Intrathecal Infusion" product is marketed by Elan Pharmaceuticals as Prialt® and is intended for continuous delivery via a programmable surgically implanted variable rate infusion device such as the Medtronic SynchroMed® EL, the SynchroMed® II Infusion System, or the CADD-Micro® Ambulatory Infusion Pump. Alternatively, an external microinfusion device can be used temporarily. The use of an infusion pump allows the dose of ziconotide to be titrated incrementally according to patients' personal needs and comfort in order to achieve an optimal balance of analgesic efficacy and side-effects.

Ziconotide's pharmacological effects have been investigated extensively in pre-clinical in vivo and in vitro models. Briefly, intrathecal ziconotide is a powerful antinociceptive drug in several animal models of chronic pain and it appears to have a completely novel mechanism of action that involves potent and selective block of pre-synaptic neuronal N-type calcium channels in the spinal cord. In fact, it is the only selective N-type channel blocker that is currently approved for clinical use. Evidence suggests that ziconotide delivers its antinociceptive efficacy by reducing the release of pronociceptive neurotransmitters in the dorsal horn of the spinal cord, thereby inhibiting pain signal transmission. Intrathecal ziconotide's clinical efficacy is consistent with the hypothesis that spinal N-type calcium channels are key regulators

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of nociceptive signaling in humans, although it is fair to say that its precise analgesic mechanism in humans remains unconfirmed at this time. There are several recent publications that are relevant to the topics in this review and they will be cited where appropriate.

Acute and chronic pain

Pain has been defined as "an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage" (International Association for the Study of Pain and can be classified according to a variety of characteristics including its duration (acute or chronic) and intensity (mild, moderate, or severe). Acute pain is a normal experience that is usually short-lasting and serves to alert the body about ongoing tissue damage so that protective or evasive measures can be taken. Acute pain usually lessens over time as a consequence of the healing process. In contrast, chronic pain represents an abnormal experience that is long-lasting and persists in the absence of any apparent tissue damage. Chronic pain is not equivalent to long-lasting acute pain; it appears to serve no useful purpose and is often associated with diseases involving tissue inflammation (leading to chronic inflammatory pain) or damage to peripheral or central neurons (leading to chronic neuropathic pain). More complex chronic pain syndromes may exhibit signs of both inflammatory and neuropathic pain.

Pain is experienced through a complex neural network that has two anatomically defined and functionally interacting systems that control pain perception and pain modulation. During normal pain sensation, components of the pain perception system are activated first and subsequently the pain modulation system may contribute inhibitory and/or facilitatory input to alter the strength and duration of the pain. During pain perception, the peripheral nerve endings of high-threshold mechanosensitive and polymodal nociceptive neurons, whose cell bodies are located in the dorsal root ganglia (DRG), are excited by noxious stimuli, leading to the generation and propagation of sodium channel-dependent action potentials along small diameter finely myelinated (Aδ fiber) or unmyelinated (C fiber) axons. The Aδ and C fibers project mainly to the superficial laminae of the dorsal horn in the spinal cord, where they make synaptic connections with secondary sensory neurons. In contrast, large diameter low-threshold mechanosensitive Aβ fibers, which encode ordinary tactile information, project mainly to the deeper laminae of the dorsal horn. When the action potentials reach the central terminals of the primary afferent neurons, calcium influx through pre-synaptic voltage-gated calcium channels triggers the release of pronociceptive neurotransmitters and neuromodulators such as substance P, calcitonin gene related peptide (CGRP), and glutamate. Under conditions of chronic pain, plastic changes in the nervous system may occur, possibly leading to overactivity in the pain perception system and/or an imbalance in the inhibitory and facilitatory components of the pain modulation system. Both peripheral and central maladaptive mechanisms may contribute to the generation of sensory deficits. Peripheral mechanisms include sensitization of Aδ and C fibers, phenotypic switching of Aβ fibers, and awakening of silent nociceptors. Central mechanisms include sensitization of secondary and tertiary sensory neurons, as well as spinal and cortical circuit reorganization.

Many medications are available to treat acute and chronic inflammatory pain, but options for treating chronic neuropathic pain are more limited. Mild to moderate acute pain often can be managed effectively by over-the-counter medications, such as acetaminophen, whereas severe acute pain requires stronger analgesics such as opioid drugs. The exact mechanism of action of acetaminophen is unknown and although it is a very safe drug with few side-effects, a recent study suggests that it may increase the serum levels of liver enzymes when taken at high doses. The opioid drugs are very effective pain relievers and exert their analgesic effects by agonizing μ, δ, and κ opioid receptors located at spinal and supraspinal sites in the central nervous system. Unfortunately, the opioids can produce serious side-effects, are prone to addiction and promote the development of tolerance with prolonged or repeated use. Drugs that have been used to treat pain associated with inflammation include non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen. These drugs are non-selective inhibitors of the two major isoforms of cyclo-oxygenase (COX), ie, constitutive COX-1 and inducible COX-2. The COX inhibitors work by decreasing the production of prostaglandins, which are endogenous agents that are known to sensitize peripheral and central sensory neurons. However, these non-selective drugs are associated with the development of gastric ulcers, probably as a result of COX-1 inhibition. In contrast, COX-2 selective inhibitors produce fewer gastrointestinal problems and were prescribed widely for several years, but

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following controversial revelations regarding potential cardiovascular risks, some COX-2 inhibitors have been withdrawn from the market and others now carry warnings about the potential dangers. Drugs that have been approved for the treatment of neuropathic pain include carbamazepine, gabapentin, pregabalin and duloxetine. In addition, several tricyclic antidepressant, antiepileptic, and antiarrhythmic drugs are commonly used off-label for the symptomatic relief of neuropathic pain. The majority of these drugs appear to act by inhibiting non-selectively the activity of neuronal voltage-gated sodium and calcium channels. However, these drugs usually require high doses, have a high incidence of non-responders and deliver suboptimal efficacy. Consequently, there are significant opportunities for the discovery and development of novel drugs for the treatment of severe and chronic pain conditions although it must be remembered that regulatory agencies will insist that drugs are very safe before granting market approval.

Voltage-gated Calcium Channels, Neuro ransmission, and Pain Signalling :

Various subtypes of voltage-activated calcium-permeable ion channels, including L-type, N-type, P/Q-type, and T-type channels have been identified throughout the mammalian nervous system. Most neuronal voltage-activated calcium channels are believed to exist as a complex of proteins **(see Figure 1),**comprising a large α_1 subunit, which forms the pore of the channel and is responsible for defining the majority of its biophysical and pharmacological properties, as well as smaller auxiliary disulphide-linked $\alpha_2\delta$ and cytosolic β subunits, which regulate membrane insertion of the channel complex and modulate its functional properties. So far 10 architecturally similar α_1 subunits have been identified and structural elements have been identified that correlate with certain functions of the channel. The α_1 subunit is organized into four homologous domains (DI-DIV), each of which contains six membrane-spanning segments (S1–S6). Membrane depolarization is sensed by positively charged amino acids in the so-called voltage-sensors that are located in the S4 transmembrane segment of each domain. The selectivity of the channel for calcium and the process of ion permeation are governed by four critical glutamate residues, one in each of the pore loops (P-loops) that are located between the S5 and S6 segments in each domain of the α_1 subunit. Of relevance to the current review, the molecular target of ziconotide appears to be the N-type calcium channel, which is a high-voltage-activated channel that contains the α_{1B} subunit (also known as $Ca_V2.2$). The α_{1B} subunit is subject to extensive splice variation, which enhances not only the molecular diversity of the N-type calcium channel but also its functional diversity, since there is the potential for altered biophysical and pharmacological properties. Perhaps with the exception of the $\alpha_2\delta$ subunit, which binds gabapentin and pregabalin, the α_{1B} subunit contains most of the pharmacologically relevant binding sites on the N-type calcium channel. Calcium permeation can be modulated by agents that directly block the pore of the channel, such as divalent cations and peptides derived from venomous species, as well as by small molecule drugs that block the channel in a use-dependent manner, as a result of preferential interactions with activated and/or inactivated states of the channel.

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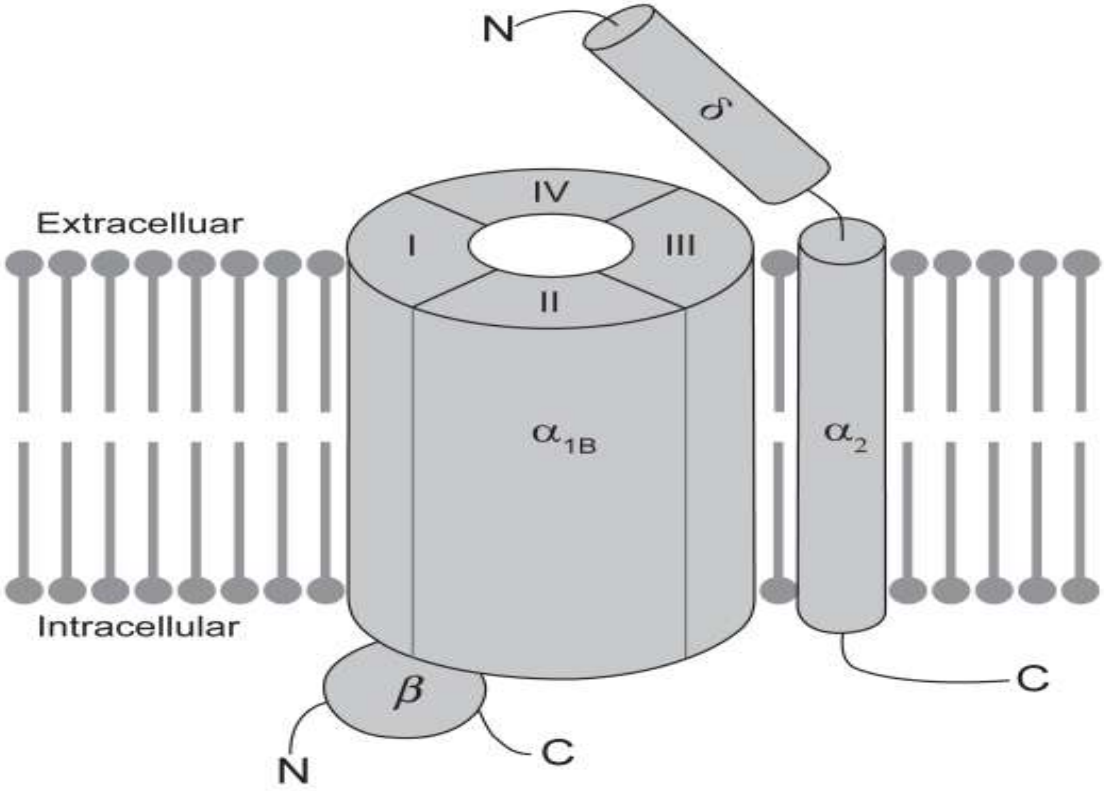

Figure 1

Schematic representation of the putative structure of the voltage-gated N-type calcium channel. N-type calcium channels are made up of a large pore-forming a_{1B} subunit in association with one or more auxiliary subunits. The a_{1B} subunit contains most determinants of channel function, including its biophysical and pharmacological properties. The proposed membrane topology of the a_{1B} subunit is believed to involve four homologous domains (DI-DIV), each of which contains six transmembrane segments (S1–S6; not shown). The auxiliary subunits include the disulphide-linked a_2d subunit, which is anchored in the membrane by a single membrane-spanning segment and the cytosolic b subunit, which interacts with the intracellular loop connecting DI to DII in the a_{1B} subunit.

Voltage-activated calcium channels exhibit subtype-specific cellular and subcellular distributions in the nervous system and play distinct roles in controlling neuronal physiology. For instance, pre-synaptic calcium channels play a critical role in the biochemical cascade of events that leads to the exocytotic release of neurotransmitters via fusion of synaptic vesicles with the plasma membrane. Immunocytochemical approaches have revealed that N-type and P/Q-type calcium channels are localized predominantly on pre-synaptic nerve terminals throughout the nervous system, where they associate with and are regulated by other components of the cellular machinery involved in synaptic transmission. Although both subtypes are found pre-synaptically on the terminals of primary sensory neurons in the dorsal horn, only occasionally are they co-localized on the same nerve terminal . The N-type channels are evenly distributed throughout all the laminae of the dorsal horn and are in fact the predominant subtype in the superficial laminae (1 and 2), which is consistent with an involvement in Aδ and Cfiber-mediated pain signalling. Furthermore, N-type channels are exclusively co-localized with substance P in presumptive C fibre terminals. In contrast, the P/Q-type channels are not found in lamina 1 of the dorsal horn, although their presence in lamina 2 suggests that they may also play a role in pain signal processing.

In accordance with these distribution data, the use of subtype-selective calcium channel blockers has confirmed that synaptic transmission in the peripheral and central nervous systems is triggered mainly by calcium influx through N-type and P/Q-type channels, although additional subtypes may also contribute but to a lesser degree.

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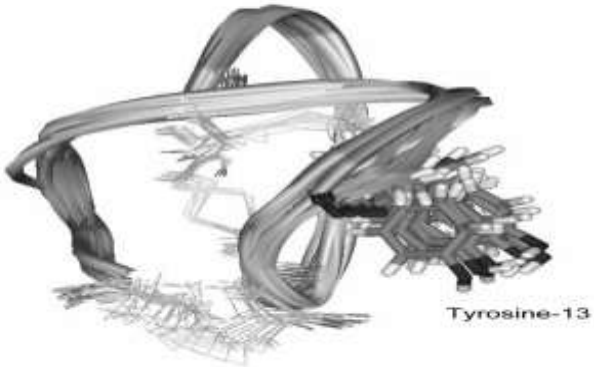
In the spinal cord, N-type and P/Q-type calcium channels contribute to both excitatory and inhibitory synaptic transmission. Interestingly, the N-type calcium channel is subject to direct regulation by G-protein βγ subunits and a component of the spinal analgesic action of opioid drugs likely involves reduced release of pronociceptive neurotransmitters in the dorsal horn as a consequence of μ-opioid receptor activation and G-protein-dependent inhibition of N-type channels. The importance of both N-type and P/Q-type calcium channels in the transmission and modulation of nociceptive signaling at the level of the spinal cord is further supported by in vivo pharmacological experiments with subtype-selective blockers, which will be discussed in more depth later. In addition, the reader is directed to several recent reviews that have discussed the relative contributions of N-type and other calcium channel subtypes to pain signalling.

Ziconotide: structural considerations and in vitro biochemical and electrophysiological studies

The ω-conotoxins, such as ω-GVIA, ω-MVIIA, ω-MVIIC, and ω-CVID, constitute a structurally related group of polypeptidic molecules that are found naturally in the venom of certain species of marine snail. In general, the ω-conotoxins bind with high affinity to voltage-gated calcium channels and potently block calcium flux. Despite structural conservation not only among the various ω-conotoxins but also among their binding sites on voltage-activated calcium channels, individual peptides actually exhibit distinguishing specificities for different channels.

ω-MVIIA contains 25 amino acids, 6 of which are cysteine residues that are linked in pairs by 3 disulphide bonds. The disulphide bond linkage pattern is a characteristic feature of ω-conotoxins and serves to ensure correct folding of the peptide and stabilization of its structure in a compact, well-defined, native conformation. Disruption of any one of the disulphide bridges greatly destabilizes the structure of ω-MVIIA and renders the remaining disulphide bonds more prone to reduction. Interestingly, the naturally occurring ω-MVIIA is synthesized by Conus magus as a precursor peptide that includes a C-terminally located glycine residue that becomes post-translationally converted to an amide group. This glycine appears to enhance the folding efficiency of the peptide in vivo by promoting molecular interactions that stabilize the native conformation with respect to other disulphide-bonded forms. The high resolution three dimensional structure of w-MVIIA has been determined by nuclear magnetic resonance (NMR) spectroscopy. The molecule displays a short triple-stranded anti-parallel β-sheet structure containing four loops, as illustrated in Figure 2B.

A. Amino acid sequence of ω-MVIIA, illustrating the characteristic disulphide linkage pattern between the six cysteine residues. The three disulphide bridges serve to stabilize the native conformation of the toxin and cause the peptide to display 4 loops, some of which contain important structural determinants of N-type calcium channel blocking activity, eg, tyrosine-13 (in bold).



B. Representation of the 3-dimensional structure of ω-MVIIA. The coordinates of ω-MVIIA were obtained from the Protein Data Bank (http://www.rcsb.org/) entry 1OMG. The position of the critical residue tyrosine-13 is indicated. (The assistance of Les Miranda, Peptide Research & Discovery, Amgen Inc. is gratefully acknowledged in generating Figure 2B.)

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As already mentioned, the molecular target of ziconotide (ω-MVIIA) appears to be the N-type calcium channel. In support of this hypothesis, radioligand binding experiments have demonstrated that ziconotide binds rapidly, reversibly, and with high affinity (see Table 1A) to N-type calcium channels in membrane and synaptosome preparations of rat brain. Ziconotide displays a high degree of binding and functional selectivity (>1000-fold) for the N-type calcium channel, whereas in contrast ω-MVIIC is more selective for the P/Q-type calcium channel. It is believed that the differential potencies of the toxins are determined largely by the relative positions of amino acid side chains on the exposed surface of the toxin peptides. In the case of ω-MVIIA, it is the non-cysteine amino acids in the loops that determine its binding affinity and calcium-channel-blocking activity. In particular, the second loop located between cysteine-8 and cysteine-15 appears to be most important in directing the selectivity of ω-MVIIA towards N-type channels and away from P/Q-type channels, although the fourth loop also contributes to a lesser degree. Alanine substitution experiments have revealed that tyrosine-13 in ω-MVIIA is a critical determinant of binding to N-type calcium channels. As one would expect, correct folding of the ω-MVIIA peptide is necessary to ensure appropriate positioning of tyrosine-13 and permit toxin binding to the N-type calcium channel. Furthermore, altering the chirality of tyrosine-13 appears to affect the positions of key residues in the second loop of ω-MVIIA, leading to a reduction in its ability to recognize the N-type calcium channel in a radioligand binding assay. In addition, individual amino acid substitutions and chimeric-toxin approaches have revealed the importance of other amino acids such as lysine-2 and arginine-21 as well as those residues in positions 9 through 12 in d

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