■ MEDICAL INTELLIGENCE ARTICLE

Intrathecal Drug Therapy for Chronic Pain

From Basic Science to Clinical Practice

Patrick M. Dougherty, Ph.D.,* Peter S. Staats, M.D.†

SYSTEMIC analgesics and conservative therapies are effective in controlling chronic pain for the majority of patients. However, many other patients, such as those with advanced head and neck carcinoma and those with neuropathic pain, require more aggressive therapy to directly modulate pain transmission in the central nervous system. Reversible methods of aggressive therapy in the spinal cord include electrical stimulation procedures and intrathecal delivery of analgesics by implanted pumps, both of which are finding ever-expanding roles in pain control. Of these, long-term intrathecal drug therapy is likely to show the largest near-term expansion because the numbers of agents approved for this route of administration are likely soon to increase substantially. Moreover, drug therapy itself will change as treatments using microsome drug encapsulation and novel suspension media are introduced. Further on the clinical horizon is intrathecal cell implantation for the relief of chronic pain. The goal of this review is to update the reader regarding each of these pending advances in intrathecal drug therapy for chronic pain.

* Associate Professor, Departments of Neuroscience and Neurosurgery.

† Associate Professor, Department of Anesthesiology and Critical Care Medicine.

Address reprint requests to Dr. Dougherty: Department of Neurosurgery, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Meyer 5-109, Baltimore, Maryland 21287-5354. Address electronic mail to: pmd@research.med.jhu.edu

Present and Future Intrathecal Analgesics

Morphine is the only drug presently approved for long-term intrathecal treatment of pain by the United States Food and Drug Administration and by the major manufacturers of infusion pumps for use in their devices. Nevertheless, chronic pain conditions are not always adequately treated by intrathecal opioids alone. Opioids have many unwanted side effects and a significant stigma. Therefore, extensive basic animal and clinical research has focused on identifying alternative classes of analgesics and adjuvants to manage pain.[1] Many receptors and compounds that modulate pain transmission have been identified (Fig. 1).[2] The analgesic properties of drugs active at a variety of these targets are being investigated, both alone and in combination, in humans (table 1).[3] Herein, we review the basic and clinical science of many of these compounds organized on the basis of their function in the spinal dorsal horn. Agents that nonspecifically alter transmission in the dorsal horn by interacting with the ion channels and second-messenger systems that generate action potentials, release synaptic neurotransmitters, and regulate cell excitability are discussed first. We progress to compounds that act on neurotransmitter receptor systems. Finally, we discuss compounds that act on peptide neuromodulator and novel trans-synaptic signal molecule receptor systems.

Various animal models of nociception are used to approximate specific pain conditions in humans. For example, hot plate, tail flick, tail–paw pinch, and shock titration experiments assess analgesic effects on acute cutaneous thermal and mechanical pain. Intraplantar injections of formalin, zymosan, carrageenan or Freund's adjuvant are models of acute and sustained inflammatory pain. Intraperitoneal hypertonic saline, acetic acid, and colorectal distension model acute visceral pain. There are also a number of nerve injury models of human
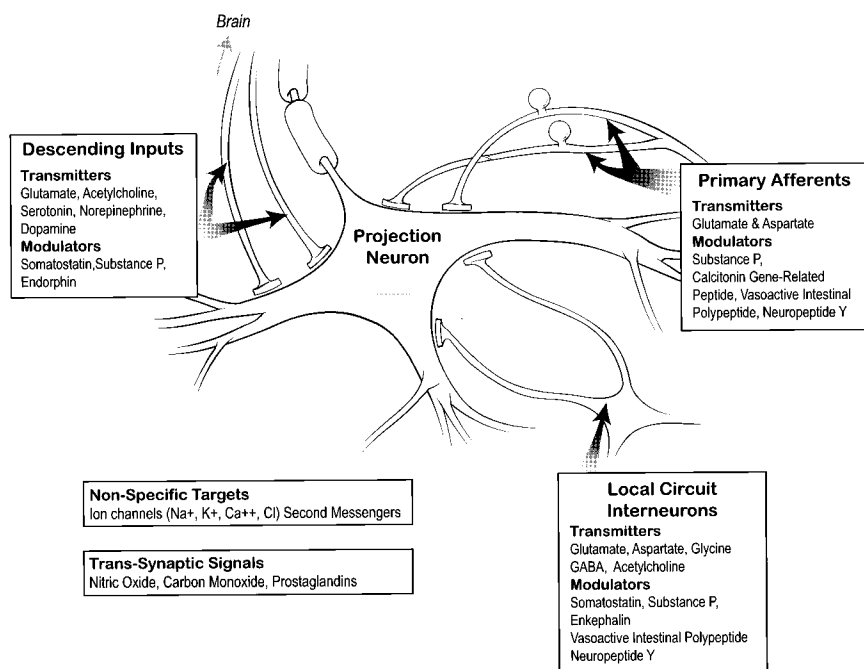
Fig. 1. Schematic diagram of the major neurochemicals involved in somatosensory transmission and processing in the spinal dorsal horn. The figure is organized with the pain signaling output neurons of the dorsal horn, the dorsal horn projection neurons, as the central cellular component. These cells are the source of all inputs for pain and temperature to the rostral central nervous system structures, such as the thalamus, brain stem, and hypothalamus, that in turn influence cortical and limbic brain structures necessary for conscious perception and appreciation of pain. The primary afferents that convey input from peripheral tissues to spinal interneurons and projection cells are shown entering at the right of the figure. The local circuit interneurons that influence the processing of sensory inputs to projection cells are represented by the cell profile at the bottom right. Meanwhile, the inputs to the spinal cord that have come from rostral central nervous system sensory modulatory sites are shown in the cellular component at the top of the figure, alongside the departing axon of the projection cell. The chemicals involved as neurotransmitters (transmitters) and neuromodulators (modulators) associated with each compartment are indicated in the boxes associated with each profile. Boxes at the bottom left list the nonspecific and trans-synaptic signals that provide additional sites for intervention.

neuropathic pain. Despite these models, it is impossible to directly assess the effects of drugs in animals on the complex cognitive experience that humans know and can communicate as pain. Although we refer to certain drugs as showing "analgesic" properties in animals, it is more appropriate to state that these studies assess "antinociceptive" properties. This is because we know that particular stimuli activate nociceptors or produce nociceptive responses and that certain drugs block these activities. The effect of analgesics in animal studies therefore needs validation in humans before a given compound can enter widespread clinical use. Preclinical studies not only need to be designed as thorough, blinded, placebo-controlled studies, but also should evaluate drug toxicity and drug interaction effects. Therefore, our review is intended to update readers regarding the future of intrathecal drug therapy and not as an explicit charge to alter current therapies to include unproven experimental compounds.

Blockade of Ion Channels and Second-messenger Systems

Propagation of bioelectric signals in the nervous system is crucially dependent on the movement of various ions and the activity of cellular enzymes and metabolites.

The proteins that form ion channels and function as second-messenger enzymes can be blocked by numerous agents, and many of these have been studied as putative analgesics. However, because ion channels and second messengers are found in all neural elements, the effects of compounds acting at these sites are not specific to pain circuitry. Therefore, side effects are often encountered with these drugs that limit their usefulness when given alone. Nevertheless, many compounds in this category will be successful as analgesic adjuvants. The four ion channels involved in pain transmission, those for sodium, calcium, potassium, and chloride, are discussed individually. In contrast, the eight second-messenger enzymes involved in pain transmission (including adenylate and guanylate cyclase; phospholipases A_3, D, and C; and protein kinases C, A, and G) have complex biochemical interrelations and therefore are discussed as a set.

Sodium Channels. Local anesthetics such as lidocaine and bupivacaine inactivate voltage-sensitive sodium channels (fig. 2). The opening of these channels is the primary event underlying the depolarization of nerve membranes and therefore is the key to propagation of neural impulses throughout the nervous system. Dorsal root ganglion neurons have multiple types of sodium

Table 1. Human Intrathecal Analgesics

Class	Drug	Chronic Infusion	Bolus Infusion
Sodium channel antagonists (local anesthetics*)			
	Bupivacaine	Y	Y
	Lidocaine	Y	Y
	Tetracaine	Y	Y
Calcium channel antagonists			
	Verapamil		Y
	Conotoxin		Y
NMDA antagonists			
	Ketamine		Y
	CPP		Y
GABA agonists			
	Midazolam		Y
	Baclofen†	Y	Y
α_2-Adrenergic agonists			
	Clonidine	Y	Y
Acetylcholinesterase inhibitors			
	Physostigmine		Y
	Neostigmine		Y
Adenosine agonists			
	Adenosine		Y
Opioid agonists			
	Morphine	Y	Y
	Hydromorphone	Y	Y
	Fentanyl	Y	Y
	Meperidine	Y	Y
	Sufentanil	Y	Y
	D-ala-D-leu-enkephalin	Y	Y
	Dynorphin		Y
	β-Endorphin		Y
Somatostatin			
	Somatostain		Y
	Octreotide	Y	Y

Y = those compounds that have been tested as analgesics by chronic or acute intrathecal administration.

* Compounds have been tested both alone and in combination with opiates.

† Baclofen has been infused chronically for the treatment of spasticity but not for the treatment of pain.

currents that are mediated by at least one class of tetrodotoxin-sensitive channel and by as many as four tetrodotoxin-resistant sodium channels.[4] Sodium currents in dorsal horn neurons are mediated by at least three types of tetrodotoxin sensitive channels.[5]

The effects of spinally delivered local anesthetics for short-term pain management have been studied in animals and humans for many years.[6] However, use of long-term intrathecal infusion of local anesthetics for pain relief in animals was first investigated in the early 1980s.[7] Since then, these compounds have been used in numerous experimental studies for long-term relief of

somatic, visceral,[8] and neuropathic pain.[9-12] Although relief of experimental measures of pain was often profound in each of these studies, many side effects, including somatic and visceral motor impairment, were encountered.

Prolonged infusion of local anesthetics for postoperative pain in humans became widespread in the 1990s.[13-16] Many patients with cancer and chronic nonmalignant pain receive continuous infusions of intrathecal local anesthetics outside of the hospital.[17-20] Intrathecal local anesthetics combined with intrathecal opiates have provided pain relief in each of these conditions, but side effects are common.[17-20] These include delayed urinary retention, paresthesia, paresis–gait impairment, periods of orthostatic hypotension, bradypnea, and dyspnea. The percentages of patients affected by one or more of these side effects varied among studies, ranging from one third to two thirds of all subjects.[17-21] Additionally, tolerance often increased drug requirements to such a large extent that increases in drug concentration (limited by solubility) and increases in drug infusion rate (limited by pump design) did not permit administration of sufficient doses to produce pain relief.[22] Externalized epidural and intrathecal catheters were therefore necessary to maintain analgesia, increasing the risk of infection.

Future local anesthetics for treatment of chronic pain will probably be compounds active at C-fiber–specific

Tetrodotoxin Sensitive   Tetrodotoxin Resistant

Bupivacaine, lidocaine*   *Phenytoin* Carbamazepine* 4030W92*

3 types in dorsal horn 1 in dorsal root ganglion cells

3 in dorsal root ganglion C-fibers only
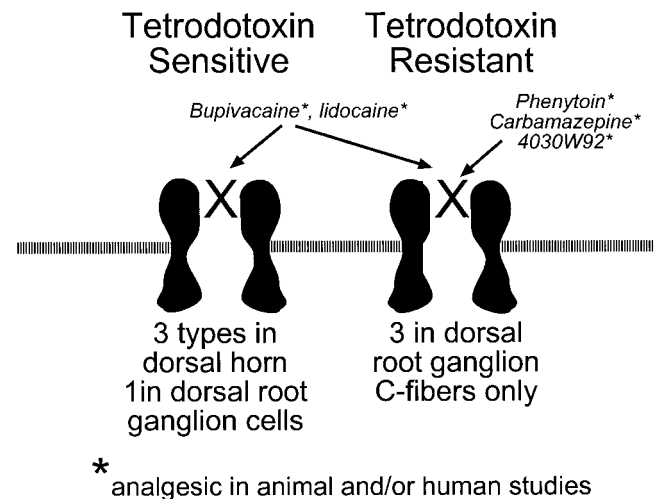
* analgesic in animal and/or human studies

Fig. 2. Summary of the two major classes of sodium channels involved in somatosensory transmission at spinal levels. Drugs that modify each channel are listed, with arrows indicating sites of action. The "X" indicates blockade of the channel. 4030W92 = 2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethylpyrimidine.[34]
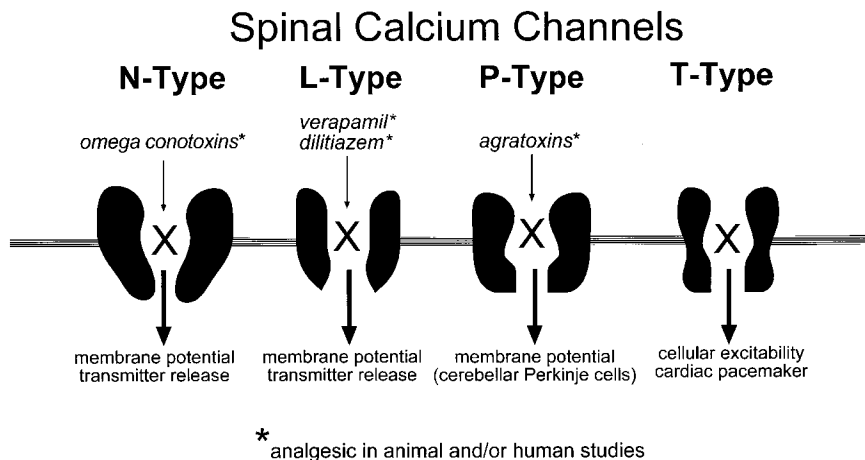
Spinal Calcium Channels

Fig. 3. Summary of the four classes of calcium channels involved in sensory transmission at spinal levels. Drugs that modify each channel are listed, with arrows indicating the sites of action. The "X" indicates blockade of the channel. Some conotoxins block "P"-type channels, but these may not be involved in transmission of sensory information at spinal levels.

sodium channels.[23,24] Tetrodotoxin-resistant sodium channels are concentrated in primary afferent C fibers of the mouse, the rat, and humans and present only at much lower concentrations in other dorsal root and autonomic ganglion neurons.[23-27] Tetrodotoxin-resistant sodium channels are the chief mediators of action potentials in nociceptive C primary afferents,[28] and algesic compounds, such as prostaglandins, specifically increase sodium currents through these channels.[29] Expression of tetrodotoxin-resistant channels increases during the development of nociceptive (inflammatory) pain but undergo down-regulation with development of neuropathic pain.[30-33] Finally, the usefulness and specificity of antagonists at these channels to pain signaling has been substantiated in an animal study with one recently developed compound.[34] Extension of these findings should soon follow, with novel antagonists to these channels based on the chemical structure of the anticonvulsants.[35]

Calcium Channels. Calcium ions are essential for regulation of neuronal excitability and for the release of neurotransmitter with synaptic depolarization.[36] At least four types of calcium channels, the L, N, T, and P types, have been identified in dorsal root ganglion and dorsal horn neurons (fig. 3). There are numerous chemical antagonists of L-type calcium channels,[36] whereas N-type calcium channels are blocked using toxins of *Conus magnus*.[37] P channels are especially prevalent in Purkinje cells and are sensitive to venom toxins of the funnel-web spider (*Agelenopsis aperta*).[36] T channels are involved in the regulation of neuronal excitability and pacemaker activity.[38] T channels in dorsal root ganglia are also blocked by some conotoxins.[39]

Mixed antinociceptive effects of intrathecal L-type cal-

cium channel antagonists have been observed in animals. In one series, verapamil alone had little effect on tail-flick latency of rats, although it potentiated the effects of small doses of morphine.[38,40] In contrast, verapamil and diltiazem produced analgesia in the tail-flick and colorectal distension tests[41]; and nifedipine prevented capsaicin-induced mechanical hyperalgesia.[42] N-type calcium channel antagonists have shown a clearer antinociceptive profile in animal studies. Intrathecal administration of conopeptides in rats relieved neuropathic pain,[37,43] attenuated both phases of the formalin test,[37] produced short-term thermal antinociception,[38] and prevented capsaicin-induced hyperalgesia.[42] However, pronounced motor disturbances persisted for 2 or 3 days after administration of high-dose conotoxin in rats.[43]

The analgesic properties of P-type calcium channel antagonists have been evaluated after intraspinal infusion of agatoxins.[42,44] Agatoxin did not affect the responses of rats to short-term noxious mechanical or heat stimuli or to spontaneous pain behaviors after intradermal injection of capsaicin or after joint inflammation. However, agatoxin prevented development of mechanical hyperalgesia after capsaicin and thermal hyperalgesia after joint inflammation.[42,44] Similar effects were reported on dorsal horn neurons after application of agatoxin to the surface of the spinal cord.[45] There was little effect on the responses of single dorsal horn neurons to pressure applied to the knee joint in normal animals. However, agatoxin markedly decreased the response to pressure in neurons from animals with inflamed knee joints.[45]

Both L- and N-type calcium channel antagonists have clinical analgesic properties. Patients who received epi-

dural verapamil (in combination with bupivacaine) consumed smaller doses of analgesics postoperatively than patients treated with bupivacaine alone.[46] Similarly, an N-channel antagonist, conotoxin, was analgesic after intrathecal administration to patients with uncontrolled pain caused by malignant disease.[47] Verapamil did not produce any major side effects, whereas side effects similar to those of excessive lidocaine limited the usefulness of conotoxin.[47]

In summary, combinations of L-type calcium channel antagonists with standard analgesics such as morphine will probably find increasing clinical use in the near term. However, the future of calcium channel analgesics will probably follow the course observed in sodium channel research, with efforts to identify C-fiber–specific channel subtypes.

Potassium Channels. Potassium is the second main cation of the neuronal action potential. There are two large families of potassium channels: the voltage-gated channels and the inwardly rectifying channels.[48] The voltage-gated channels include the "A" fast-transient conductances sensitive to 4-aminopyridine, barium, and cobalt and the calcium-activated potassium channels sensitive to cobalt, manganese, and cadmium.[49] Dorsal root ganglion neurons are believed to have one to three types of voltage-gated channels and three or four types of delayed rectifier channels.[50,51] Opening of voltage-gated potassium channels allows outward positive current flow from neurons, such as during repolarization after an action potential. Blockade of these channels initially prolongs generation of action potentials.[52] Continued application, however, prevents repolarization and, therefore, ultimately produces a failure to generate action potentials.[52]

Although intrathecal administration of potassium channel antagonists has not been used to treat pain in either animals or humans, 4-aminopyridine is used for long-term intrathecal treatment of spasticity in multiple sclerosis.[53] One side effect of this treatment, paresthesia, is suggested to be caused by preferential blockade of nonmyelinated fibers,[54,55] which in turn suggests analgesic potential. However, a number of patients have also reported abdominal pain with these treatments that may relate to abnormal discharge patterns in primary afferent fibers.[55] Potassium channel agonists–antagonists are not likely to be used soon for the treatment of pain.

Chloride Channels. Three major classes of chloride channels have been identified.[56] The first class identified was the ligand-gated chloride channels, including those of the γ-aminobutyric acid type A (GABA$_A$) and glycine receptors. The ligand-gated chloride channels are common in dorsal root ganglia and dorsal horn neurons.[57] The second class, also probably common at spinal levels, is the voltage-gated chloride channel.[58] The final chloride channel class is activated by cyclic adenosine monophosphate (cAMP) and may include only the cystic fibrosis transmembrane regulator.[59] Activation of chloride currents usually produces inward movement of chloride to cells that hyperpolarize neurons; facilitation of these hyperpolarizing currents underlies the mechanisms of many depressant drugs. An important exception at spinal levels, however, is that GABA$_A$ receptors on primary afferent terminals gate a chloride channel that allows efflux of chloride,[60,61] with a net effect therefore of depolarizing primary afferent terminals.

Chloride channel antagonists, such as bicuculline and strychnine, have not been administered to relieve pain, but instead to produce an experimental pain state characterized by a pronounced opiate refractory allodynia.[62-64] These compounds were also used to exacerbate the anatomic consequences of nerve constriction injury.[65] Nevertheless, chloride channels may have paradoxic effects in some pain conditions.[66] As mentioned previously, C-fiber volleys depolarize primary afferent A fibers by activating outward chloride currents through GABA$_A$ receptor channels.[60,61] This primary afferent depolarization was proposed as a means of limiting painful input to the dorsal horn, consistent with the gate-control theory of pain transmission.[67] However, new evidence suggests that the allodynia produced by intradermal injection of capsaicin is caused by an increased effectiveness of chloride currents evoked by A-fiber "touch"-type afferents on C-fiber nociceptors.[66] If substantiated, chloride channel antagonists may prove to be useful for treatment of chronic pain conditions that have touch-evoked nociceptive components.

Second-messenger Systems. Surface receptors affect neuronal activity either by direct gating of an ion channel or by activating biochemical cascades and, therefore, are often classified as either ionotropic or metabotropic, respectively (fig. 4). The transduction of metabotropic receptor activation to biochemical processes involves interactions with a family of so-called G-binding (guanosine triphosphate) proteins.[68-71] G proteins assemble as trimeric complexes composed of α, β, and γ subunits that associate physically to surface receptors. The β and γ subunits are constant in all complexes, whereas one of three differing isoforms of the α subunit confers functional specificity.[68-71] The α subunit is activated after ligand-receptor interaction by the addition of
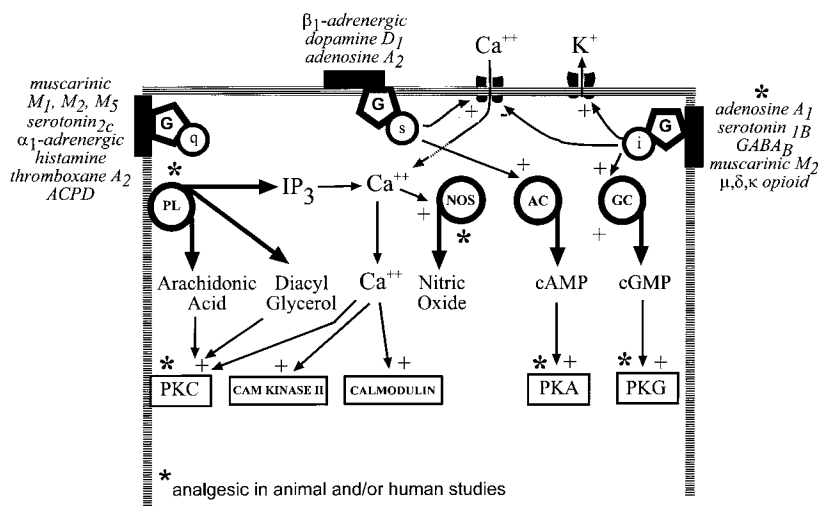
Second Messenger Systems and Pain Signaling

Fig. 4. Schematic summary of the spinal second-messenger systems involved in pain transmission. The figure is organized in columns and rows. Filled rectangles represent surface drug receptors. Compounds that activate each receptor are listed at the side. G-labeled pentagons represent the G-protein β and γ subunits, whereas the circles labeled "q", "s," and "i" represent the three functionally distinct isoforms of the α subunit. Circles with arrows represent enzymes that generate secondary metabolites as a direct consequence of activity of the G-protein subunits. The products of these enzymes are listed in the center of the figure. Rectangles represent the final tier of enzymes activated in the cascade. The "+" indicates activation or positive modulation, whereas the "-" indicates inactivation or inhibition. *Indicates those targets for which antagonists were shown to produce antinociception. AC = adenylate cyclase; CamKII = calcium-calmodulin dependent protein kinase II; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; GC = guanylate cyclase; IP$_3$ = inositol triphosphate; NOS = nitric oxide synthase; PKA = protein kinase A; PKC = protein kinase C; PKG = protein kinase G; PL = phospholipase.

guanosine triphosphate, dissociates from the complex, and interacts with and modulates the function of numerous intracellular targets until the bound guanosine triphosphate is autohydrolyzed.[68–71] The α_S subunit increases conductance at L-type calcium channels, inactivates guanylate cyclase, and activates adenylate cyclase, thereby increasing cellular concentrations of cAMP.[68–70] The α_I subunit, in contrast, inactivates adenylate cyclase, thereby decreasing levels of cAMP; negatively modulates calcium channels; activates outward potassium currents; and activates guanylate cyclase, thereby increasing cellular cyclic guanosine monophosphate (cGMP). Finally, the $\alpha_{q,12}$ subunits activate one of several phospholipase enzymes (e.g., phospholipase C, D, or A$_3$), resulting in release of membrane phospholipid metabolites, including arachidonic acid, diacyl-glycerol, and inositol triphosphate.

The metabolites generated by each of the G proteins, in turn, activate one of three types of protein kinases or increase intracellular calcium. Increases in diacylglycerol or arachidonic acid activate the protein kinase C family of enzymes.[72] There are at least 12 isoforms of protein kinase C, although three (α, β, and γ) subtypes predominate in the spinal cord.[70,72] Protein kinases A and G are those families of enzymes activated by cAMP and cyclic guanosine monophosphate (cGMP), respectively. The functions of protein kinases at the spinal level include regulation of tetrodotoxin-sensitive sodium channels in

primary afferent fibers,[28] release of neurotransmitter,[72] and control of excitatory neurotransmitter currents in dorsal horn cells.[73] Intracellular calcium is released from internal stores by binding inositol triphosphate and is stimulated by the action of α_S on L-type calcium channels. Increases of intracellular calcium activate the enzymes calmodulin, cam kinase II, and nitric oxide synthase.

The role of second-messenger systems on pain sensitivity has been evaluated in a number of studies. Levels of membrane-bound protein kinase C increase after nerve injury[74] and intraplantar injection of formalin.[75] Spinal infusion of phorbol esters to activate protein kinase C increases the behavioral response to intraplantar formalin[76] and increases the spontaneous and evoked activity of primate spinothalamic tract neurons.[77] In contrast, antagonists for protein kinase C decrease pain behavior after nerve injury,[74] intraplantar formalin,[75,76] intraspinal N-methyl-D-aspartate (NMDA)[78] and intradermal capsaicin.[79] Similarly, inhibition of phospholipase C[76] or phospholipase A[80] (needed for release of cofactors to protein kinase C) reduced hyperalgesia after intraplantar formalin and zymosan, respectively. Antagonists of protein kinases A and G[79] also decreased capsaicin-induced pain. Finally, animals engineered with defects in protein kinase C had less pain after nerve injury,[81] whereas those engineered with defects in pro-

Spinal Glutamate Receptors

Fig. 5. Schematic summary of the spinal excitatory amino acid (glutamate) receptors that participate in pain transmission. Excitatory amino acid receptor antagonists that modulate each receptor are listed, with arrows indicating the site of action. The boldface names and solid lines indicate the two classification schemes for these receptors. The "-" indicates antagonist effect.
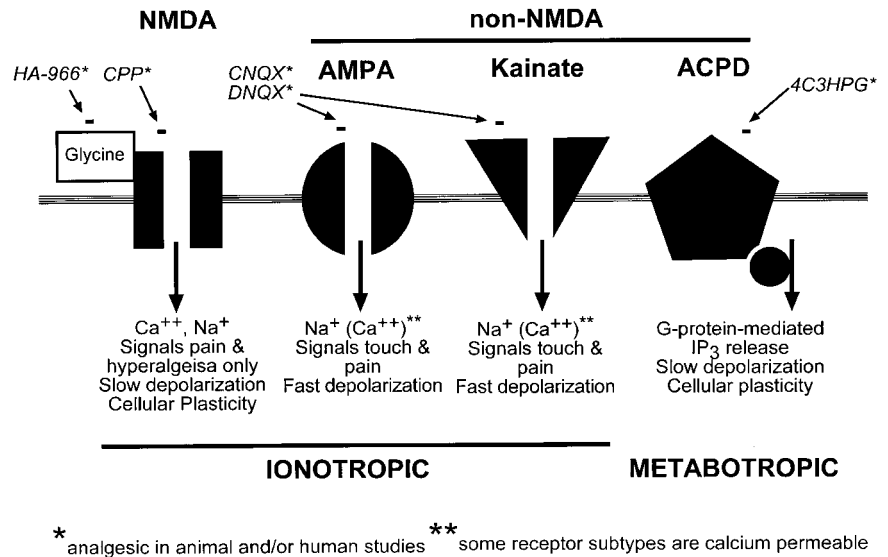
tein kinase A had decreased responses to formalin, capsaicin, and hind-paw inflammation.[82]

In summary, many second-messenger systems may ultimately become targets for clinical pain treatment. However, the role of these systems in pain management is indirect through the action of various drugs that interact with surface receptors linked to G proteins. Receptors linked to G_S (receptors associated with $\beta\gamma\alpha_S$ subunits) include the β_1-adrenergic, dopaminergic type 1, and adenosine type 2 receptors. Those that activate $G_{q,12}$ ($\beta\gamma\alpha_{q,12}$) include the serotonin 2c, α_1-adrenergic; histamine; thromboxane A2; metabotropic glutamate; and muscarinic types 1, 3, and 5 receptors. Finally, G_i- ($\beta\gamma\alpha_i$)–linked receptors include adenosine 1; serotonin 1B; $GABA_B$; muscarinic type 2; and μ-, δ-, and κ-opioid receptors.[68] As reviewed in the after-sections, neurotransmitter receptors linked to G_S and $G_{q,12}$ generally increase pain transmission, whereas G_i-linked receptors inhibit pain signaling.[68–70,83]

Blockade or Facilitation of Neurotransmitter Function

Neurotransmitters are the chemicals that mediate transmission of action potentials at synaptic junctions between neurons. There are four major groups of neurotransmitters in the spinal dorsal horn: excitatory amino acids, inhibitory amino acids, monoamines, and purines. All are relatively small molecular-weight compounds. Their rapid release and reuptake (degradation)

yields a corresponding rapid time course in effects, usually measured in the range of milliseconds. Most pharmacologic agents act by either blocking or mimicking neurotransmitter actions.

Excitatory Amino Acids. The amino acids glutamate and aspartate are the main excitatory neurotransmitters of somatosensory transmission pathways. Glutamate and aspartate are present in peripheral nerves, dorsal root ganglia and axons, and cells of the dorsal horn.[2,84–87]

There are at least four distinct types of excitatory amino acid receptors named for the selective synthetic agonists that bind to them[88] (fig. 5). The sites that bind NMDA define the NMDA receptors. These have the highest affinity for the natural ligand aspartate and form an ion channel that is permeable to calcium (and sodium and potassium).[88] NMDA receptors are selectively blocked by a number of chemical antagonists, such as CPP. Ketamine and dextromethorphan are also NMDA antagonists; however, both act on nonexcitatory amino acid receptors.[88] Ketamine, for example, binds to σ opioid and serotonin receptors.[88] NMDA receptors are blocked at resting membrane potentials by magnesium. Relief of this blockade requires depolarization of the cell by other synaptic inputs, which means NMDA receptors function as detectors of temporally coincident synaptic events.[89] The combined features of calcium permeability and coincidence detection are thought to be the keys to NMDA-receptor mediation of heterosynaptic (Hebbian) plasticity in neural pathways, such as that underlying

hippocampal long-term potentiation and dorsal horn neuron sensitization.[89,90]

Non-NMDA excitatory amino acid receptors include three distinct sites. The first of these selectively binds AMPA and the second selectively binds kainate. Glutamate has its highest affinity for AMPA and kainate receptors.[91-93] Most AMPA and kainate receptors form monovalent cationic channels, although subtypes of each have been identified that are also permeable to calcium.[94,95] Although antagonists for these receptors, such as CNQX and DNQX, do not select between the AMPA and kainate binding sites, the receptors have differential sensitivity to antagonists of receptor desensitization.[96,97] Finally, the third non-NMDA site selectively binds ACPD and is blocked by 4C3HPG. The ACPD receptor, in contrast to the NMDA, AMPA, and kainte receptors, is a G-protein–linked complex that initiates inositol phospholipid metabolism when activated. This feature results in a second partitioning of excitatory amino acid receptors into ionotropic (NMDA, AMPA, kainate) and metabotropic (ACPD) subtypes.

All four excitatory amino acid receptors mediate somatosensory transmission in the dorsal horn. Intrathecal injection of NMDA, AMPA, and kainate produced nocifensive biting and scratching behavior,[98] whereas injection of ACPD increased the behavioral responses to intraplantar formalin.[99] Intrathecal injection of NMDA antagonists has little effect on the responses to acute nociceptive stimuli in normal animals but markedly decreases touch and heat hyperalgesia after peripheral inflammation or nerve injury.[100-103] Similar effects have been observed after intrathecal injection of magnesium sulfate.[104] In contrast, intrathecally administered AMPA and kainate receptor antagonists reduce behavioral responses to short-term nociceptive stimuli and after induction of hyperalgesia.[103,105,106] However, AMPA and kainate antagonists, unlike NMDA antagonists, impair motor function at analgesic doses.[103,105,106] Finally, metabotropic receptor antagonists had no effect in a model of postoperative pain[107] but reduced the behavioral responses to intraplantar formalin,[99] and treatment with metabotropic receptor antisense oligonucleotide increased tail-flick latency.[108]

Neurophysiology studies confirm the roles of excitatory amino acids in pain transmission. Ionotropic glutamate receptor agonists increase[109-114] and antagonists decrease the responses of dorsal horn neurons to somatosensory stimuli.[91,93,115-124] Non-NMDA–receptor antagonists decreased the transmission of both noxious and non-noxious information, whereas NMDA-recep-

tor antagonists selectively attenuated responses to sustained noxious stimuli.[92,93] ACPD produced excitation of nociceptive neurons in monkeys and rats and a selective increase in responses to innocuous cutaneous stimuli.[125,126] The majority of synapses activated by primary afferent fibers on arrival to the dorsal horn are mediated by the "fast" ionotropic non-NMDA (AMPA and kainate) receptors. NMDA receptors are recruited with polysynaptic activation of intrinsic dorsal horn neurons and are essential for induction of hypersensitivity of dorsal horn cells after injury. Influx of calcium through the NMDA receptor is the crucial first step in initiation of hypersensitivity.[101] In turn, increased intracellular calcium increases resting membrane potential and membrane resistance and initiates changes in gene expression. Long-term maintenance of hypersensitivity requires coincident activation of neuropeptide receptors involving either G_S- or G_Q-mediated biochemical cascades.[127] Finally, ACPD receptors appear to affect global sensitivity of multireceptive dorsal horn neurons to innocuous and noxious stimuli and, therefore, function to control the gain of these neurons to peripheral inputs.[126]

Clinical analgesia trials have been begun with NMDA antagonists.[128-130] Intrathecal ketamine has consistently produced analgesia at dosages of 50 mg and more, although this dosage is also analgesic when given systemically.[131-133] Limitations to intrathecal use of ketamine include its well-described psychotropic effects.[128] Additionally, vacuolar myelopathy has been reported in a patient who received intrathecal ketamine.[129] Although this neurotoxicity might be attributed to preservative in the preparation,[129] similar toxicity was observed in animals administered preservative-free ketamine.[134] Finally, a "pure" NMDA antagonist, CPP, relieved intractable neurogenic pain in a single patient trial, although psychotropic side effects were encountered.[135] In summary, studies in animals suggest that excitatory amino acid receptor antagonists have promise as future analgesics. However, preliminary clinical studies with these compounds indicate limitations.

Inhibitory Amino Acids. γ-Aminobutyric acid and glycine are the inhibitory amino acid neurotransmitters of the spinal dorsal horn.[136,137] Three types of GABA receptors and two glycine receptors have been identified,[138-140] although a fourth distinct GABA receptor may be expressed by human dorsal root ganglion neurons[141] (fig. 6). The $GABA_A$ receptor is part of a chloride ionophore complex.[142,143] Selective $GABA_A$ agonists include muscimol; selective antagonists include gabazine. Barbiturates and alcohol modulate activity at this recep-

Spinal GABA Receptors

A-Receptors   B-Receptors   C-Receptors
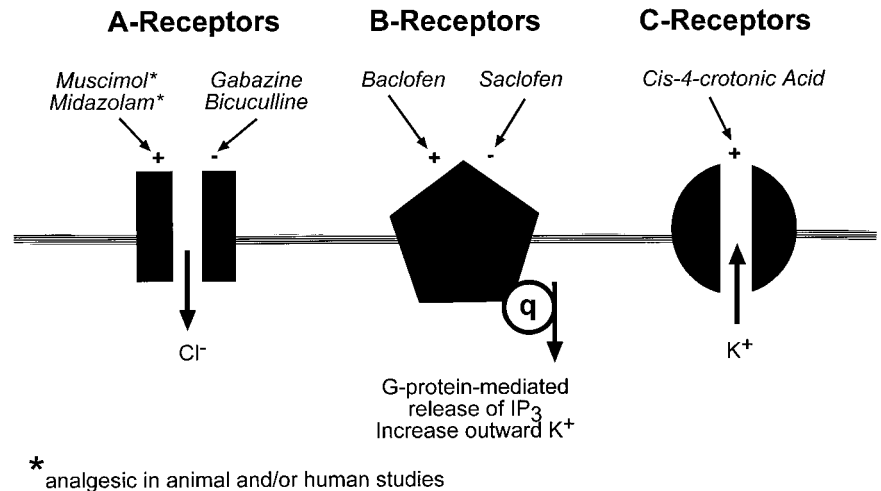

Fig. 6. Summary of the spinal GABA receptors involved in pain transmission. Agonists and antagonists active at each receptor are listed, with arrows indicating the site of action. The "+" indicates agonist function and the "-" indicates antagonist function.

Muscimol* Midazolam*   Gabazine Bicuculline   Baclofen   Saclofen   Cis-4-crotonic Acid

Cl⁻

q

G-protein-mediated
release of IP_3
Increase outward K^+

K^+

* analgesic in animal and/or human studies

tor by direct facilitation of inward chloride currents.[142,143] Benzodiazepines bind to a unique site on the $GABA_A$ receptor complex that facilitates GABA receptor–agonist binding and, therefore, increases channel open time.[136,138,140] The $GABA_B$ receptor is a G-protein–linked complex that, when activated, typically increases outward potassium currents.[144] Baclofen is a selective $GABA_B$ receptor agonist and phaclofen is a selective antagonist. It has been suggested that the newly described $GABA_C$ receptor is directly associated with a potassium channel ionophore. Cis-4-aminocrotonic acid is a selective $GABA_C$ receptor agonist, but there is no selective antagonist for these receptors.

Glycine receptors include one subtype linked to a chloride ionophore and sensitive to the antagonist strychnine. The second is a strychnine-insensitive modulatory site on the NMDA-receptor complex antagonized by HA-966.[139,140]

Both $GABA_A$ and $GABA_B$ agonists have analgesic properties after intrathecal administration in a number of pain models in animals. Muscimol and baclofen blocked both the allodynia produced by a long-term nerve constriction injury[145] and the biting and scratching behavior elicited by intrathecal injection of substance P.[146] Similarly, muscimol and baclofen each produced antinociception in phases 1 and 2 of the formalin model[147] and in the electrical current threshold test in rats[148] and monkeys.[149] Midazolam, similar to muscimol and baclofen, produced antinociception in the hot plate, tail-flick and electric current threshold test in rats.[150-154] Of note, the baclofen-induced increase of tail-flick latency and inhibi-

tion of hot plate responses were attenuated by pretreatment with pertussis toxin,[155] and the effects of midazolam were additive with that of morphine.[151] Therefore, $GABA_B$ receptors and opioid receptors probably access complementary G-protein systems (G_I) in the dorsal horn.

$GABA_A$ and $GABA_B$ receptor antagonists enhance nociceptive behaviors after intrathecal injection in rats.[156] However, a long-term facilitation of the flexor withdrawal reflex was produced by intrathecal injection of the $GABA_A$ receptor antagonist bicuculline but not by a $GABA_B$ antagonist.[64] These results indicate that $GABA_A$ receptors mediate a tonic inhibition, whereas $GABA_B$ receptors mediate a stimulus-driven inhibition of spinal pain-signaling (somatosensory) pathways.

Intrathecal administration of glycine in awake animals decreased responses to noxious heat[157] and inhibited substance P-induced biting and scratching.[146] Similarly, iontophoresis of glycine profoundly inhibited the responses of spinal neurons to all peripheral stimuli,[158,159] probably by a direct membrane hyperpolarization.[158] Strychnine facilitates flexor withdrawal[64] and produces morphine-insensitive allodynia in rats.[62,63] Finally, administration of the strychnine-insensitive glycine receptor antagonist HA-966 predictably results in effects similar to those of NMDA antagonists, including reduction of responses to noxious, but not non-noxious, stimuli.[160]

Although antinociception is well-demonstrated with intrathecal GABA agonists in animal studies, similar analgesic effects in humans have not been produced consistently. Intrathecal injection of the $GABA_A$ agonist mi-

dazolam was effective in treating chronic mechanical low back and postoperative pain.[161,162] Long-term midazolam treatment also successfully relieved chronic non-malignant musculoskeletal and neurogenic pain without evidence of toxicity.[163] However, midazolam did not have an independent effect on pain of peripheral arteriopathy or in malignant disease.[163]

Intrathecally administered GABA$_B$ agonists have also shown mixed results for pain relief. Intrathecal baclofen is approved by the Food and Drug Administration of the United States and is widely used for the relief of spasm in spinal cord injury, cerebral palsy, and multiple sclerosis.[164–171] Baclofen has also been used to relieve central poststroke and musculoskeletal pain[164,172] However, in other studies, baclofen was ineffective for neurogenic pain in patients with spinal cord injury[173] and had no effect on pinch-evoked or musculoskeletal pain.[174]

In summary, the usefulness of intrathecal GABA receptor analgesics in humans remains open to question. Basic science studies have emphasized that GABA$_A$ and GABA$_B$ agonists have analgesic effects that are very modality specific. For example, muscimol, but not baclofen, antagonized the biting and scratching behavior elicited by intrathecal injection of the excitatory amino acid agonists NMDA, quisqualic acid, and kainate.[175] In contrast, baclofen, but not midazolam, attenuated formalin-evoked pain behaviors.[151] Future clinical studies with these compounds may show more consistent effects as the conditions most appropriate for each agonist subtype in humans are clarified.

The effects of intrathecally administered glycine or glycine antagonists, such as HA-966, in humans have not been reported.

Monoamine. *Norepinephrine.* Norepinephrine was first detected in fibers of the dorsal lateral spinal funiculus in the late 1960s.[176] Potential analgesic effects were not considered, however, until inhibition of dorsal horn neurons by microstimulation of norepinephrine-containing brain stem nuclei was shown in the late 1970s.[177] The native receptors for norepinephrine include two broad classes, the α- and β-adrenergic receptors, of which there are multiple subtypes (*e.g.*, α_{1a}, $\alpha_{1b}, \alpha_{2a}, \alpha_{2b}, \beta_1, \beta_2$).

α-Adrenergic receptors, in particular α_2 receptors, have antinociceptive properties in many models of acute pain in rats, cats, and monkeys.[178] This includes an increase in shock titration assay,[149] suppression of the flexion withdrawal reflex,[179] increase in tail-flick and hot plate latencies,[151,155,180–183] and inhibition of responses to colorectal distension[184] and noxious compression of skin.[185,186] α_2 Agonists also have antinociceptive properties in animal models of prolonged and chronic pain, including the formalin test,[187] experimental neuropathy,[188] spinal cord ischemia,[179] and autotomy.[189]

Epidural clonidine recently was approved for treatment of intractable pain, and intrathecal clinical trials are now being conducted. Intrathecal infusion of clonidine with hydromorphone or other opiates provided relief of intractable cancer pain.[190,191] Intrathecal clonidine was also effective for management of reflex sympathetic dystrophy and postoperative pain,[191,192,193] and prolonged the effects of local anesthetics and potentiated the effectiveness of other agents used in neuraxial delivery.[194] The interactions of clonidine with morphine and other opiates may be a result of combined effects of both agents in reducing calcium currents in presynaptic terminals. Alternatively, the effects of clonidine may be mediated, in part, by local release of acetylcholine.[191]

Although intrathecal clonidine has promise as an adjunctive analgesic compound, clinical use has been limited by a number of side effects, most particularly, hypotension and bradycardia.[195,196] Thus, α_2-adrenergic compounds need further improvement before they can be used widely.

Dopamine. Dopamine is found in axon terminals in the superficial laminae of the dorsal horn. These terminals arise from cells at supraspinal levels that send axons to the spinal cord *via* the dorsal lateral spinal funiculus.[197] Intrathecal injection of dopamine and dopamine receptor agonists increased tail-flick latency[198,199] and decreased hot plate and acetic acid writhing.[200] This effect was blocked by a type 2 dopamine but not by a type 1 receptor antagonist.[198,199] Interestingly, the analgesia of spinal apomorphine is reduced by naloxone[201] and dopamine-2 receptor agonists facilitated the motor effects of morphine,[202] suggesting reciprocal interactions between spinal opioid and dopamine receptor systems.

Patients with dysfunction of endogenous dopamine systems, such as Parkinson's disease, often have an accompanying pain syndrome.[203] However, no studies have evaluated the possible analgesic effects of dopamine in these or other patients.

Serotonin. Increases in serotonin, or 5-hydroxytryptamine, in the spinal dorsal horn after microstimulation of brain stem pain inhibitory nuclei suggest antinociceptive activity for this monoamine.[177,180,204] Serotonin is present in terminals in the dorsal horn, primarily in laminae I and II, the intermediolateral cell column, and the ventral horn. Serotonin colocalizes with several peptides, including enkephalin, somatostatin,

calcitonin gene-related peptide, substance P, and the neurotransmitter GABA. There are at least three serotonin receptor classes in the dorsal horn termed 1, 2, and 3, each of which has multiple subtypes.[205] The effect of these receptors in control of pain remains unclear. Intrathecal serotonin produced antinociception in tail-flick, hot plate, paw pressure, intraplantar formalin, and shock titration experiments in mice and rats.[180;206–209] Yet, in other studies, serotonin facilitated input to dorsal horn cells from primary afferent C fibers and facilitated paw pressure and tail-flick responses.[205,209,210] Intrathecal studies with more selective serotonin receptor agonists have not clarified these discrepancies. For example, one group reported serotonin-1a receptor agonists inhibit hot plate responses,[211] whereas others reported a facilitation of tail flick.[210,212] Intrathecal-1b receptor agonists were analgesic in tail-flick and colorectal distension tests[210,212-214] but without effects on hot plate responses.[211] Similarly, serotonin type 2 receptors enhanced nociceptive responses in some studies[215,216] and reduced responses in others[213,214] Intrathecal type 3 agonists were also pro-[217] and antinociceptive.[208] Thus, serotonin modulates pain transmission; however the receptor mechanisms that govern these effects are poorly defined. Possible confounding factors in previous studies are that serotonin differentially regulates nociceptive stimuli of varying modality,[209] the distribution of serotonin receptor subtypes varies between spinal regions,[215] and the drugs available have been inadequately selective. Further study with more selective pharmacologic tools will be needed to resolve these issues before initiation of clinical studies.

Acetylcholine. Another potentially analgesic member of the monoamine family is acetylcholine. Cholinergic terminals are abundant in the dorsal horn, arising from brain stem raphe nuclei,[218] the nucleus ambiguous, the dorsal motor nucleus of the vagus,[177] and local dorsal horn neurons.[219] Spinal cholinergic receptors include nicotinic and muscarinic 1 and 2 subtypes.[220] Although intrathecal injections of acetylcholine had no effect on nociceptive responses of animals, injection of synthetic cholinergic agonists were antinociceptive in a number of behavioral paradigms. For example, carbachol and oxotremorine produced antinociception in tail-flick, hot plate, and acetic acid writhing tests.[183] These effects were additive to that of morphine,[151,221,222] were prevented by atropine and pirenzepine[223] but not by *d*-tubocurarine, and were not reproduced with nicotine.[222] These results suggest that spinal muscarinic-1 and -2 receptors are antinociceptive but nicotinic recep-

tors are not. This conclusion, however, may be premature based on recent studies with a novel nicotinic cholinergic agonist that had an excellent antinociceptive profile after systemic administration.[224]

Intrathecal injection of acetylcholinesterase inhibitors also produced analgesia in animal studies.[225] Although the analgesic effects of the cholinesterase inhibitors were transient, the effects were synergistic to those of clonidine and morphine, resulting in a profound and long-lasting analgesia. Side effects described as "abnormal behavior" were observed in these studies that were reduced with clonidine.[225]

Clinical studies of acetylcholinesterase inhibitors have begun.[226] Intrathecal administration of neostigmine produced antinociception to a cold stimulus in normal human volunteers[226,227] and relieved visceral and somatic postsurgical pain.[228,229] However, side effects included nausea, emesis, reversible lower extremity paresis,[226-230] tachycardia, hypertension, sedation, and anxiety.[226,227] Application of cholinesterase inhibitors with opiates did not increase the incidence of nausea or emesis, although postsurgical analgesia was produced at lower doses of each drug than when either was given alone.[231] In summary, cholinesterase inhibitors have promise as novel independent analgesics and as adjuvants to established analgesics such as morphine. However, a solution to the side effects of nausea and emesis may be needed before widespread use of these compounds.

Tricyclic Antidepressants. Tricyclic antidepressants have long been known to modulate pain transmission. This effect is believed to be a result of inhibition of reuptake and consequent increases in norepinephrine and serotonin. However, there is uncertainty regarding the mechanism of analgesia of tricyclics. For example, *in vitro* studies have shown that tricyclics bind to the NMDA-receptor complex,[232,233] suggesting that the hyperalgesia and allodynia treated by tricyclics is caused by NMDA-receptor inhibition, rather than by increases in levels of serotonin or norepinephrine. Intrathecal injection of desiprimine or amitriptyline decreased NMDA-induced pain behaviors in a dose-dependent fashion.[234,235] These effects were unaffected by coadministration of phentolamine or methysergide, suggesting that monoamines were not involved.[235] Clinical application of intrathecal tricyclic antidepressants is not possible because preservative-free preparations are not available, toxicology has not been assessed, and motor weakness developed at high doses in rat experiments.[235] In that tricyclics are synergistic with opiates[236] and po-

Adenosine* Receptors and Pain Signalling

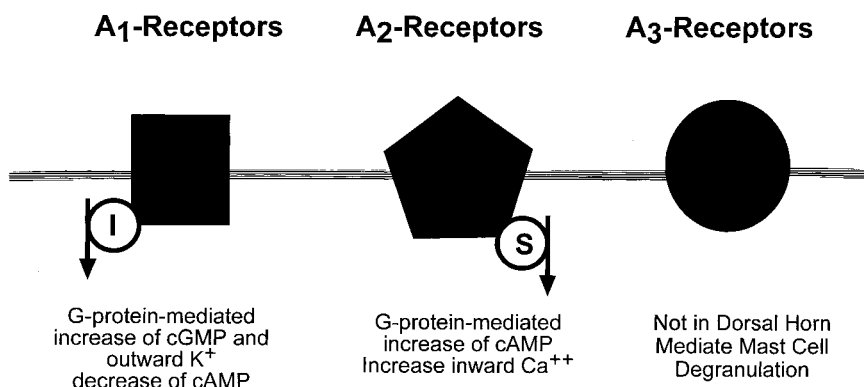### A₁-Receptors ### A₂-Receptors ### A₃-Receptors

Fig. 7. Schematic summary of the spinal adenosine receptors involved in pain transmission. Subtype-selective agonists–antagonists have not yet been studied and therefore are not listed.

G-protein-mediated increase of cGMP and outward K⁺ decrease of cAMP

G-protein-mediated increase of cAMP Increase inward Ca⁺⁺

Not in Dorsal Horn Mediate Mast Cell Degranulation

* analgesic in animal and/or human studies

tently decrease inflammatory hyperalgesia,[235] further attention should be devoted to this potentially effective mode of pain control.

Purines. Evidence has accumulated during the past several years that adenosine and adenosine triphosphate are somatosensory neurotransmitters.[237] There are at least three types of adenosine receptors, termed 1–3, each with differing effects on target cells (fig. 7). Adenosine 1 receptors link to the G_i-protein subunit and therefore inhibit target cells by decreasing cAMP[238,239] and facilitating currents at adenosine triphosphate–sensitive potassium channels.[240] In contrast, adenosine 2 receptors link to the G_s-protein subunit and therefore excite target cells by increasing the activity of adenyl cyclase.[238] Type 3 adenosine receptors are not present in the dorsal horn, but rather are expressed in dermal mast cells.[237] Activation of adenosine 3 receptors provokes pain as a result of mast cell degranulation and the release of serotonin and histamine.[241]

Adenosine produces pain when administered peripherally but produces analgesia when administered spinally.[237] For example, intrathecal adenosine produced antinociception in the rat tail-flick test. This effect was enhanced by supplemental calcium.[242] The mixed type1–type 2 receptor agonist 5′-N-ethylcarboxamide adenosine produced analgesia in rats that was enhanced by clonidine.[243] Adenosine produced antinociception in the hot plate test in mice.[180] Intrathecal administration of type 1 receptor agonists decreased the discharges of deep dorsal horn cells to C-fiber volleys.[244] The antinociception produced by adenosine was inhibited by methylxanthines, confirming that adenylate cyclase is involved in these effects. Many reports

cite a role for adenosine in morphine-produced antinociception that may be a result of a shared action on adenylate cyclase.[244–248] Adenosine and opiate-like substances may also mediate norepinephrine-produced antinociception.[246]

Four studies have addressed the role of adenosine in pain transmission in humans. Intravenous and subcutaneous administration of adenosine caused pain in healthy subjects,[237] but intravenous adenosine relieved neuropathic pain in one study.[249] Adenosine decreased spontaneous and touch-evoked pain in healthy volunteers after application of mustard oil[250] and relieved neuropathic allodynia.[251] No significant complications or side effects were reported, although one volunteer experienced transient lumbar pain with drug injection.[251,252] Further study with intrathecal adenosine and adenosine-receptor selective agonists should be of interest.

Blockade or Facilitation of Neuromodulator Receptors

Neuromodulators are substances that adapt the action of neurotransmitters to varying biologic conditions.[49,253] Similar to transmitters, modulators are released at synapses and act on specific membrane receptor sites. Unlike transmitters, the time course of neuromodulator effects is long, with effects measured in seconds to minutes. The sites of action for neuromodulators are not necessarily confined to a single synapse. Modulators often spread from their site of release and through tissue after high-intensity stimulation to affect synapses at a distance.[254] The majority of neuromodulators are relatively large-molecular-weight peptides.

Opioid Receptors. The natural opioids include the peptides β-endorphin, leuenkephalin, and met-enkephalin and dynorphin derived from the *proopiomelanocortin, proenkephalin,* and *prodynorphin* genes, respectively.[255] The opioid peptides are found in axon terminals and cell bodies throughout the spinal dorsal horn, although mostly in the superficial laminae.[177] The nerve terminals containing opioid peptides arise from dorsal root ganglia, cells intrinsic to the dorsal horn, and cells of various brain stem nuclei that descend *via* the dorsal lateral funiculus.

Opioid agonists exert their effects at μ, δ, and κ receptors. All three consist of seven transmembrane spanning G-protein–coupled complexes.[256,257] Dorsal horn opioid receptors are located presynaptically on capsaicin-sensitive small-diameter primary afferent nerve endings[258–260] and postsynaptically on dendrites and somata of intrinsic neurons.[177] Inhibition of transmitter release from primary afferent nerve terminals by suppression of voltage-gated calcium currents is one widely recognized mechanism for opioid-induced analgesia.[256,257] A second is direct inhibition of dorsal horn neurons by inhibition of adenyl cyclase and activation of outward potassium currents.[177,261] Synthetic opioid receptor–selective agonists include the nonpeptide compounds morphine (μ-agonist) and trans-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)- cyclohexyl] benzeneacetamide (U50488, κ-agonist) and peptide analogs such as D-Pen^2-D-Pen^5-enkephalin (δ-agonist).

A number of studies in animals have established the analgesic effects of intrathecal morphine to short-term noxious stimuli. For example, intrathecal morphine increases shock-titration threshold in monkeys,[149] suppresses the responses of rats to colorectal distension,[262] decreases hyperalgesia in a model of postoperative pain,[263] and increases tail-flick and hot plate latencies in rat.[155] Intrathecal morphine also decreases the discharge of deep dorsal horn cells to C-fiber volleys.[244,264] These effects of morphine are mimicked by the natural μ-agonist β-endorphin.[265–267] Pertussis toxin blocks the effects of morphine and β-endorphin, confirming the role of G proteins in transduction after receptor activation.[155]

Intrathecal morphine also has analgesic effects in prolonged models of nociception, such as experimental arthritis[268] and intraplantar formalin.[269] However, intrathecal morphine is less effective in animal models of chronic neuropathic pain. For example, morphine had no effect on the onset of thermal hyperalgesia in sciatic experimental peripheral neuropathy.[270] Relief of neuropathic pain in rats has been observed only when morphine is coadministered with other compounds.[271]

Although intrathecal δ- and κ-opioid receptor agonists decreased the response to short-term noxious thermal stimuli,[264] these usually produce antinociception only in specific models of acute pain in animals. For example, δ-agonists produced marked analgesia in the colorectal distension and intraplantar formalin models,[272,262] whereas κ-agonists had only marginal effects.[262] Conversely, κ-agonists markedly reduced arthritis-induced pressure pain, whereas δ-agonists were ineffective.[268] Toxicity has not been reported after intrathecal enkephalin, but the κ-agonist dynorphin produced hindlimb paralysis in some studies.[273,274] A long-lasting tactile allodynia has also been reported after intrathecal dynorphin.[275] Interestingly, NMDA-receptor antagonists prevented dynorphin-induced paralysis and allodynia. This suggests not only that dynorphin may be neurotoxic when administered in the intrathecal space, but also that there are important functional interactions between dynorphin and the excitatory amino acids that contribute to this toxicity.

Intraspinal delivery of opioids for pain management in humans is relatively new; nevertheless, morphine is the gold standard for intrathecal analgesics.[276] Epidural and intrathecal opiates usually produce excellent analgesia,[277,278] and infusion pumps have been developed to provide continuous delivery of spinal opioids in patients with chronic pain. Intrathecal morphine has fewer side effects than do systemic opioids.[279–286] Only minor neurohistopathologic changes, including focal foreign body giant cells and small aggregates of lymphocytes and reactive microglia near the catheter site, have been observed after long-term infusion of morphine to cancer patients.[287] Nevertheless, complications are common, most notably, pruritis, respiratory depression, somnolence, and gastrointestinal and urinary dysfunction.[279–285,288] Additionally, development of tolerance often necessitates continued escalation of dose until the capacity of current infusion pumps is exceeded. Furthermore, some authors reported that continuous morphine infusion is ineffective for long-term management of chronic pain from nonmalignant causes[289] and that accumulation of morphine metabolites provokes development of a paradoxic hyperalgesia, allodynia and myoclonus.[290]

Other opioids have also been tested as intrathecal analgesics. Lipophilic agents, such as fentanyl, dilaudid, and sufentanil, that diffuse poorly in cerebrospinal fluid may have a role in well-localized pain syndromes when delivered by catheters to spinal levels corresponding to

the affected areas. δ-Opioid and κ-opioid receptor agonists may be useful in pain syndromes that are little affected by μ-agonists such as morphine. Intrathecal β-endorphin produced postsurgical analgesia[291] and relief of intractable pain caused by disseminated cancer.[292,293] Intrathecal dynorphin produced analgesia for cancer pain patients without obvious toxicity.[294] Therefore, future studies with opioids will probably focus on improving effectiveness for neuropathic-related pains, perhaps with a focus on the usefulness of δ- and κ-agonists in these conditions, and to limit unwanted effects, such as tolerance.

Neurokinin Receptors. The neurokinin peptides include substance P and neurokinins A and B.[295–297] Substance P and neurokinin A are involved in transmission and modulation of nociceptive inputs, whereas a role for neurokinin B is poorly defined. Neurokinin peptides are located in primary afferents, dorsal roots, and cells and axon terminals in the spinal cord. The majority of neurokinin-containing terminals are from primary afferent fibers, whereas the remainders are from axons descending from various brain stem nuclei.[2]

There are at least three neurokinin receptors (1, 2, and 3) expressed in the dorsal horn[295] and on dorsal root ganglion neurons.[298] Although each peptide binds to all three receptors, substance P binds preferentially to the neurokinin-1 receptor, whereas neurokinin A and neurokinin B prefer type 2 and type 3 receptors, respectively. Neurokinin-1, and perhaps neurokinin-2, receptors are important in transmission of short-term nociceptive stimuli and induction of hypersensitivity after peripheral injury.[127,299–303] The transduction mechanisms of neurokinin-1 and -2 receptors involve metabolism of phosphatidyl inositol and increases of intracellular calcium levels.[2]

Evidence for substance P as a transmitter for nociceptive afferents was initially based on its excitation of nociceptive neurons in the dorsal horn of experimental animals in the late 1970s.[304,305] Subsequently, intrathecal administration of substance P was shown to produce a "caudally directed biting and scratching syndrome," presumed to reflect nocifensive behavior.[306–308] Smaller intrathecal doses of substance P reduced thresholds to noxious heat stimuli.[306–308] The tachykinin peptides produce small but prolonged depolarizations of many dorsal horn neurons *in vitro*[309–311] and excite many nociceptive dorsal horn cells *in vivo*.[304,305,312–316] Tachykinin receptor antagonists decrease nociceptive responses in behavioral paradigms[317–321] and the responses of dorsal horn neurons to noxious stimuli.[301,315,322,323] Finally, animals with bioengineered disruptions of the *tachykinin-1* gene, the source of substance P and neurokinin A, have increased baseline nociceptive thresholds and decreased responses to formalin and capsaicin,[324,325] whereas animals with bioengineered alterations of the neurokinin-1 receptor showed decreased 'wind-up'.[326] Interestingly, animals given intrathecal injections of neurokinin-1 receptor antisense oligonucleotide did not show a decrease in receptor level or change in behavioral responses to formalin until also treated with intrathecal substance P.[327]

Human studies with intrathecal neurokinin receptor antagonists have not been reported, possibly because of the potential toxicity and rapid degradation of the peptide analog antagonists that were available. Newer nonpeptide antagonists have alleviated these previous concerns, and clinical trials for relief of depression[328] and postoperative pain have begun for orally active antagonists.[329] Intrathecal studies should follow soon.

Calcitonin Gene-related Peptide Receptors. Calcitonin gene-related peptide is found in many small dorsal root ganglion cells, in thinly myelinated (A-δ) and unmyelinated (C) axons, in axons of Lissauer's tract, and in terminals of these primary afferents in spinal laminae I, II, and V.[330] Although two types of calcitonin gene-related peptide, α and β, are present in dorsal root ganglion cells and as many as four types of G-protein–coupled receptors are present in the dorsal horn, the function of this neuropeptide is unknown.[330,331] The coexistence of calcitonin gene-related peptide and substance P within spinal cord terminals[332,333] and dorsal root ganglion neurons[334] suggests a functional relation between the two. The levels of calcitonin gene-related peptide in the dorsal horn change in parallel with those of substance P after acute knee joint inflammation[335] and after injury to peripheral nerve.[336] Noxious thermal, mechanical, and chemical stimuli provoke the corelease of calcitonin gene-related peptide with substance P in the substantia gelatinosa.[332,337,338] However, intrathecal administration of calcitonin gene-related peptide has mixed effects in models of nociception. Calcitonin gene-related peptide had no effect on nociceptive reflexes in one series of studies[333,339] but facilitated tail-flick reflex in another series.[340] Similarly, calcitonin gene-related peptide antagonized the effects of substance P in one series[341] but enhanced the effects of substance P by preventing degradation or increasing peptide release in others.[333,342] The effects of intrathecal injection of calcitonin gene-related peptide $_{8-37}$, a receptor antagonist,

have been clearer. This compound produced a dose-dependent increase in paw-withdrawal latency of normal rats to paw pressure and radiant heat.[339] Additionally, calcitonin gene-related peptide $_{8-37}$ reversed hyperalgesia produced by thermal[343] and nerve injury.[344] These effects were suggested to be a result of antagonism at endogenous opioid receptors.[344,345] In summary, the role of calcitonin gene-related peptide in dorsal horn somatosensory processing necessitates further definition before its usefulness for treatment of human pain can be evaluated.

Somatostatin Receptors. Terenius[346] first suggested an antinociceptive role for somatostatin in the spinal cord. Somatostatin is detected in primary afferent axons terminating in the dorsal horn, spinal interneurons, and terminals of axons from descending pathways.[347] There are at least five distinct somatostatin receptors, designated by numbers 1–5, encoded by separate genes.[348] This may be an underestimate, however, because subtypes of the somatostatin-2 receptor (A and B) have been identified. All receptors identified to date are G-protein coupled and widely expressed throughout the central nervous system.[348] Somatostatin is specifically increased in the dorsal horn after noxious thermal but not after noxious mechanical stimulation.[349,350] Similarly, intrathecal injection of somatostatin, or somatostatin analogs, produced analgesia to thermal but not mechanical stimuli.[351-357] Evidence of neurotoxicity, including gait disturbance, paralysis, pyknotic dorsal horn neurons, and posterior column demyelination, are common after intrathecal somatostatin in cats and rats.[358-360]

Despite the neurotoxicity observed in animals, two clinical trials with intrathecal somatostatin have been conducted in cancer patients[361,362] In the first study, six of eight patients had good-to-excellent pain relief, although tachyphylaxis or short-term tolerance after a short period of infusion necessitated increased dosing. Postmortem observations revealed histopathologic changes in two of eight patients.[361] Although these changes were attributed to progression of disease, a direct neurotoxic effect of somatostatin cannot be discounted because of the animal data.[358] Another similar study used octreotide, a synthetic analogue of somatostatin, because of its longer half-life and lack of associated neurodegenerative effects.[362] Two patients with nonmalignant pain were treated successfully with continuous intrathecal infusion of octreotide for 5 yr, although additional opioids were necessary. When blinded to the drug, each patient preferred octreotide to placebo.[362] Thus, although a number of factors limit the use of somatostatin, derivatives of this peptide may ultimately have clinical usefulness.

Other Neuromodulators. A large number of neuropeptides and neuropeptide receptors have been identified in the dorsal horn of animals and humans for which a clear role in nociceptive processing has yet to be established. Neuropeptide Y, for example, is colocalized in GABA-containing cells of the dorsal horn.[363] The peptide and its receptors concentrate in the superficial layers of the dorsal horn, where afferent information is modulated,[364] and neuropeptide Y decreases transmitter release from primary afferent fibers.[365] Galanin and its binding sites also concentrate in the superficial layers of the dorsal horn.[366] Galanin antagonizes many effects of substance P and calcitonin gene-related peptide.[341,367] The levels of neuropeptide Y and galanin substantially increase after peripheral nerve injury.[368]

Other neuropeptides and neuropeptide receptors found in the dorsal horn include angiotensin II,[369,370] bombesin,[371] corticotropin releasing hormone,[370] vasopressin, oxytocin,[372] vasoactive intestinal polypeptide,[373] and cholecystokinin. Of this group, bombesin produces a caudally directed biting and scratching behavior similar to that of substance P after intrathecal injection[374]; vasoactive intestinal polypeptide is directly excitatory to dorsal horn neurons[375]; and cholecystokinin may act as a natural opiate-receptor antagonist.

In summary, there are many peptides in the dorsal horn for which function is poorly defined. However, it appears that several of these limit the signaling of nociceptive information, whereas others promote this signaling. Eventually, agonists for some, such as neuropeptide Y and galanin, and antagonists for others, such as bombesin and vasoactive intestinal polypeptide, may prove useful for the clinical treatment of pain.

Modulation of Trans-synaptic Signal Molecules. The trans-synaptic signal molecules are the newest class of substances to be identified. Similar to neuromodulators, these substances have relatively slow onset and a prolonged duration of effect. In addition, these substances often have effects that are remote from their site of release. The trans-synaptic molecules differ from neuromodulators, however, in that they do not necessarily have either a discrete neuronal locus for release or a specific neuronal target site of action, but rather may also have non-neuronal (glial) sites of release and effect.[376-379] Members of this family include the prostaglandins, leukotrienes, nitric oxide, and carbon monoxide.

Prostaglandins and Leukotrienes. Prostaglandins and leukotrienes are synthesized from arachidonic acid by the fatty acid cyclooxygenase and lipoxygenase pathways.[380] Prostaglandins and leukotrienes both have important roles in the sensitization of peripheral primary afferent fibers[381-383] and the generation of primary hyperalgesia.[384] It is the prostaglandins, however, that play the more important role in dorsal horn (central) mechanisms of pain transmission.[385] Influx of calcium to neurons and glia through NMDA and voltage-gated ion channels activated by nociceptive inputs activates phospholipase A_2 and releases arachidonic acid.[379,386,387] Arachidonic acid is then metabolized in the central nervous system by the enzyme cyclooxygenase type 2 and in peripheral tissues by cyclooxygenase type 1 to form prostaglandins.[378,385] Effects of prostaglandins on pain transmission are mediated by increases in neuronal levels of calcium and cAMP,[386] thereby increasing excitability and the release of excitatory neurotransmitters and neuromodulators.[388,389]

Effectiveness of intraspinal cyclooxygenase inhibitors has been evaluated in two animal models of sustained pain.[390-392] Intrathecal ketorolac, aspirin, and indomethacin had limited effects on the short-term phase reaction to formalin, but markedly attenuated the delayed second phase.[390,392] Interestingly, ketorolac produced a synergistic antinociceptive effect with morphine and an α_2-adrenergic agonist, suggesting complementary but unshared cellular mechanisms between these receptor systems.[390] Ketorolac probably decreases activation of G_S by prostaglandins, whereas the opioids and α_2-adrenergic agonists activate G_I, resulting in inhibition of spinal adenylate cyclase.[386] Finally, intrathecal administration of a cyclooxygenase type 2 antagonist decreased thermal hyperalgesia after paw inflammation.[391] In summary, intrathecal cyclooxygenase inhibitors are effective in reducing moderate levels of pain but not completely effective against more severe pain. This reduced effectiveness compared with analgesics, such as morphine, may reflect the observation that not all prostaglandins provoke pain, but rather some prostaglandins appear to limit pain.[393] Future directions in prostanoid research will probably focus on the design of antagonists that selectively reduce synthesis of pain-provoking prostanoids, such as the prostaglandin E_2, while sparing formation of pain-limiting prostanoids, such as prostaglandin F_2.[393,394]

Nitric Oxide and Carbon Monoxide. Nitric oxide and carbon monoxide have recently been recognized as novel neurotransmitter substances.[71,395-397] Nitric oxide is synthesized from L-arginine by activation of the enzyme nitric oxide synthase. Nitric oxide synthase is activated by increases in intracellular calcium after opening of NMDA receptors and neurokinin-1 receptor-mediated release of inositol triphosphate.[398] Free nitric oxide diffuses to nearby and distant cells, penetrates the cell membranes, and increases the function of guanylate cyclase and protein kinase G, thereby influencing gene regulation.[395,396] Although less studied, carbon monoxide appears to function identically to nitric oxide in many neural systems.[397]

The role of nitric oxide in nociceptive transmission has been tested in several animal studies. Levels of nitric oxide synthase increase in the dorsal root ganglion and dorsal horn of rats with paw inflammation and neuropathic pain.[399,400] Nitric oxide is involved in the development of wind-up and several models of hyperalgesia.[78,399,401-403] Intrathecal administration of arginine analogs, which inhibit nitric oxide synthesis as false substrates, produced a dose-dependent reduction in hyperalgesia as a result of intraplantar formalin and nerve injury.[401-403] Recently, a possible role of carbon monoxide in nociceptive transmission was evaluated. Intrathecal zinc protoporphyrin IX, which binds and neutralizes carbon monoxide, produced a blockade of spinal nociceptive transmission.[404] Thus, both substances may have future roles in the management of pain. However, no clinical trials have assessed the analgesic or potential neurotoxic effects[395,397] of nitric oxide or carbon monoxide inhibitors.

Future Methods of Drug Delivery

Many of the compounds reviewed herein may have more widespread clinical use in the near future. Further on the treatment horizon will be the introduction of novel drug delivery strategies. For example, analgesics encapsulated in liposomes for prolongation of pharmacologic effects will become available. Two compounds, tetracaine and meperidine, produce prolonged analgesia in the mouse after liposome encapsulation.[405,406] Initial attempts have been made to develop slowly degradable polymers that contain local anesthetics or opioids to provide prolonged, sustained release of analgesics.[407] For example, epidurally implanted biodegradable polymers that contain local anesthetics yielded an 8- to 10-fold increase in duration of neural blockade.[408] Similarly, a hydromorphone-containing polymer delivered a constant amount of drug over 30–90 days both *in vitro* and

in animal models, without an early drug spike.[409] Although these preparations have not been studied extensively with intrathecal administration, the implications are obvious.

Still further on the horizon looms the possibility of long-term pain relief using intrathecal cell implantation. Antinociceptive effects were produced in rats by intrathecal transplantation of catecholamine-producing B16 melanoma cells.[410] Analgesia has also been produced by intrathecal transplantation of adrenal medullary chromaffin cells that secrete opioid peptides and catecholamines 411.

Conclusion

We are entering an exciting era in the therapy of chronic pain conditions as basic science provides many new intrathecal compounds and drug delivery systems to meet the needs of clinical practice. The only compound approved by the Food and Drug Administration for long-term intrathecal treatment of pain is morphine. All other compounds that we discussed are experimental, and issues regarding long-term toxicity and drug interactions are not resolved. Nevertheless, it is likely that many new compounds and treatment approaches will ultimately have a clinical niche and, as a consequence, alter and improve the treatment of chronic pain.

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