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Topical and Peripherally Acting Analgesics

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***Abstract*——Acute nociceptive, inflammatory, and neuropathic pain all depend to some degree on the peripheral activation of primary sensory afferent neurons. The localized peripheral administration of drugs, such as by topical application, can potentially optimize drug concentrations at the site of origin of the pain, while leading to lower systemic levels and fewer adverse systemic effects, fewer drug interactions, and no need to titrate doses into a therapeutic range compared with systemic administration. Primary sensory afferent neurons can be activated by a range of inflammatory mediators such as prostanoids, bradykinin, ATP, histamine, and serotonin, and inhibiting their actions represents a strategy for the development of analgesics. Peripheral nerve endings also express a variety of inhibitory neuroreceptors such as opioid, α-adrenergic, cholinergic, adenosine and cannabinoid receptors, and agonists for these receptors also represent viable targets for drug development. At present, topical and other forms of peripheral administration of nonsteroidal anti-inflammatory drugs, opioids, capsaicin, local anesthetics, and α-adrenoceptor agonists are being used in a variety of clinical states. There also are some clinical data on the use of topical antidepressants and glutamate receptor antagonists. There are preclinical data supporting the potential for development of local formulations of adenosine agonists, cannabinoid agonists, cholinergic ligands, cytokine antagonists, bradykinin antagonists, ATP antagonists, biogenic amine antagonists, neuropeptide antagonists, and agents that alter the availability of nerve growth factor. Given that activation of sensory neurons involves multiple mediators, combinations of agents targeting different mechanisms may be particularly useful. Topical analgesics represent a promising area for future drug development.**

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I. Introduction

Analgesic therapies for acute and chronic pain conditions currently rely on three major classes of drugs: nonsteroidal anti-inflammatory drugs (NSAIDs[1]), opioids, and a group of drugs with diverse pharmacological actions collectively known as adjuvants (e.g., antidepressants, anticonvulsants, local anesthetics, α_2-adrenoceptor agonists). Both NSAIDs and opioids exhibit a variety of adverse actions, and many chronic pain states, particularly those involving nerve injury, are not adequately controlled by these agents. With adjuvants, it is often necessary to titrate the dosage until adequate pain relief or intolerable side effects develop. Unfortunately, the latter outcome often occurs, and the degree of pain relief that results is only partial. The pharmacotherapy of chronic and neuropathic pain states has been described extensively in several recent reviews (Kingery, 1997; MacFarlane et al., 1997; Sindrup and Jensen, 1999; Watson and Watt-Watson, 1999; MacPherson, 2000).

An alternative approach to pain control is to apply drugs locally to the peripheral site of origin of the pain. This can be attained by the topical application of a cream, lotion, gel, aerosol, or patch to somatic sites or by injections directly into joints. With orofacial pain conditions, lozenges and mouthwashes also may be of use. These application methods allow for a higher local concentration of the drug at the site of initiation of the pain and lower or negligible systemic drug levels producing fewer or no adverse drug effects. Other potential advantages of localized applications are the lack of drug interactions, the lack of need to titrate doses to tolerability, and importantly, the ease of use. However, some degree of systemic absorption will occur following localized delivery methods, expecially with lipid soluble drugs, and the degree of systemic absorption needs to be assessed during the development of formulations. It is also important that potential local adverse effects be monitored carefully, both after topical delivery methods (e.g., cutaneous reactions), and following direct injections into joints (cf. Buerkle, 1999).

By definition, topical drugs used to control pain will act locally on damaged or dysfunctional soft tissues or peripheral nerves. Topical delivery systems differ from transdermal delivery systems in that they target a site immediately adjacent to the site of delivery rather than using the skin as an alternate systemic delivery system. Their actions may be on the inflammatory response itself (e.g., decreased production of inflammatory mediators, block of action of inflammatory mediators) or on sensory neurons (e.g., altered impulse generation through actions on up-regulated sodium channels, actions at specific receptors on the sensory neuron to attenuate activation of that neuron). Both acute and chronic pain conditions are likely to be amenable to this approach. In chronic pain states, the effectiveness of the approach may depend on the degree of inflammation, the degree of alteration in peripheral sensory processing, and the degree of central sensitization involved. Thus, chronic pain involves changes in both peripheral and central elements (Attal and Bouhassira, 1999; Raja et al., 1999; Baron, 2000; Bridges et al., 2001), and this approach is more likely to be effective where there is a prominent peripheral component. Recently, a mechanism-based classification of pain has been proposed as an alternative approach to prior taxonomies (Woolf et al., 1998; Woolf and Decosterd, 1999; Woolf and Mannion, 1999). Within this scheme, there is a prominent group of conditions in which primary afferents are involved, and these are the conditions that could exhibit the most benefit with this approach.

To date, there are only a limited number of topical therapies available for the relief of somatic pain (NSAIDs, capsaicin, lidocaine). With certain other local delivery methods (intra-articular injections), there is promising clinical data (morphine, clonidine). There is, however, considerable interest in the preclinical literature in identifying novel peripheral targets, and the development and formulation of this approach as a viable alternative to systemic therapies (e.g., Jones, 2000; Padilla et al., 2000). It is likely that in the next few years, several alternative modalities will become available for clinical use. The present review will consider both currently used topical analgesic therapies as well as emerging classes of agents. This is not an exhaustive review of the literature available on each of these modalities but rather a highlighting of the approach and a consideration of the potential for development.

II. Peripheral Pain Signaling

Significant advances in understanding pain signaling mechanisms and the pathophysiology of pain have occurred in the past decades. This has involved an appreciation of the diversity of the agents and the mechanisms that can modulate the pain signal in peripheral and central compartments, as well as an appreciation of the neurobiological changes that can occur in chronic pain states involving inflammation and nerve injury. Under normal physiological conditions, nociceptive signals are produced by intense stimulation of primary afferent sensory Aδ and C nerve fiber terminals by chemicals, heat, and pressure (Besson and Chaouch, 1987; Treede et al., 1992; Bevan, 1999; Millan, 1999; Raja et al., 1999). Sensory neurons can be divided into subgroups based on anatomical (fiber size, degree of

[1] Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; 5-HT, 5-hydroxytryptamine; IL, interleukin; NGF, nerve growth factor; COX, cyclooxygenase; DAMGO, [D-Ala^2,N-Me-Phe^4,Gly^5-ol]-enkephalin; NMDA, N-methyl-D-aspartate; VGSC, voltage-gated sodium channel; NA, noradrenaline; AMPA, α-amino-3-hydroxy-5-ethylisoxazole-4-propionic acid; CB, cannabinoid; KA, kainic acid; ACh, acetylcholine; OFQ/N, orphinan FQ/nociceptin; VR, vanilloid receptor.

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myelination, postsynaptic connections in the spinal cord), histochemical (presence of peptides and other neurotransmitters, presence of ion channels and receptors, regulation by growth factors), and physiological (responsiveness to sensory modalities, conduction velocity) properties (Lawson, 1996; Snider and McMahon, 1998; Caterina and Julius, 1999). Nociceptive signals are transmitted to the superficial layers of the dorsal spinal cord where they undergo substantial modulation by local mechanisms, as well as by projections from supraspinal structures, which can provide both inhibitory and facilitatory influences; further transmission to brainstem and thalamic sites, and subsequently to the cerebral cortex, then occurs (Basbaum and Fields, 1984; Besson and Chaouch, 1987; Fields and Basbaum, 1994; Millan, 1999). Chronic inflammation or nerve injury produce 1) alterations in the excitability of peripheral nerves and in the expression of neurotransmitters, enzymes, receptors, and ion channels in these nerves; 2) changes in blood flow and vascular permeability, in the activation and migration of immune cells, and in the release of growth and trophic factors from tissues surrounding the nerve; and 3) alterations in the spinal processing of pain (Woolf and Doubell, 1994; Doubell et al., 1999; Levine and Reichling, 1999; McMahon and Bennett, 1999; Raja et al., 1999; Woolf and Salter, 2000).

A diversity of chemical mediators that are produced or released locally following tissue injury or inflammation can activate peripheral sensory nerve endings (Fig. 1). These can directly activate the sensory nerve [e.g., H^+, ATP, glutamate, 5-hydroxytryptamine (5-HT), histamine, bradykinin], sensitize the nerve ending to the action of other stimuli [e.g., prostaglandins and prostacyclin, cytokines such as interleukin-1β (IL-1β), IL-2, IL-6, IL-8, tumor necrosis factor-α], or exert regulatory effects on the sensory neuron, adjacent inflammatory cells, and sympathetic nerves [e.g., bradykinin, tachykinins, nerve growth factor (NGF)]. Some agents that activate sensory neurons do so by acting directly on ion channels (e.g., H^+ via acid-sensitive ion channels, ATP via P2X receptors, glutamate via ionotropic glutamate receptors), whereas other agents sensitize sensory neurons by acting on G-protein-coupled metabotropic receptors to alter intracellular messengers (e.g., cyclic AMP, Ca^{2+}, inositol trisphosphate), and some of these activate protein kinases (e.g., protein kinase A, protein kinase C) that then phosphorylate ion channels and modulate their function. The diversity of chemical mediators and the mechanisms involved in peripheral pain signaling have been described in detail in recent reviews (Bevan, 1999; Levine and Reichling, 1999; Millan, 1999).

Sensory nerve endings also express a number of receptors for neurotransmitters that can inhibit pain transmission (Fig. 1). Many of these receptors were characterized initially in the dorsal spinal cord (Yaksh, 1999), but some receptors that are synthesized in the cell body of dorsal root ganglia cells and transported centrally to reside presynaptically on primary afferent neurons also are transported peripherally (Coggeshall and Carlton, 1997). Axonal transport of neuroreceptors

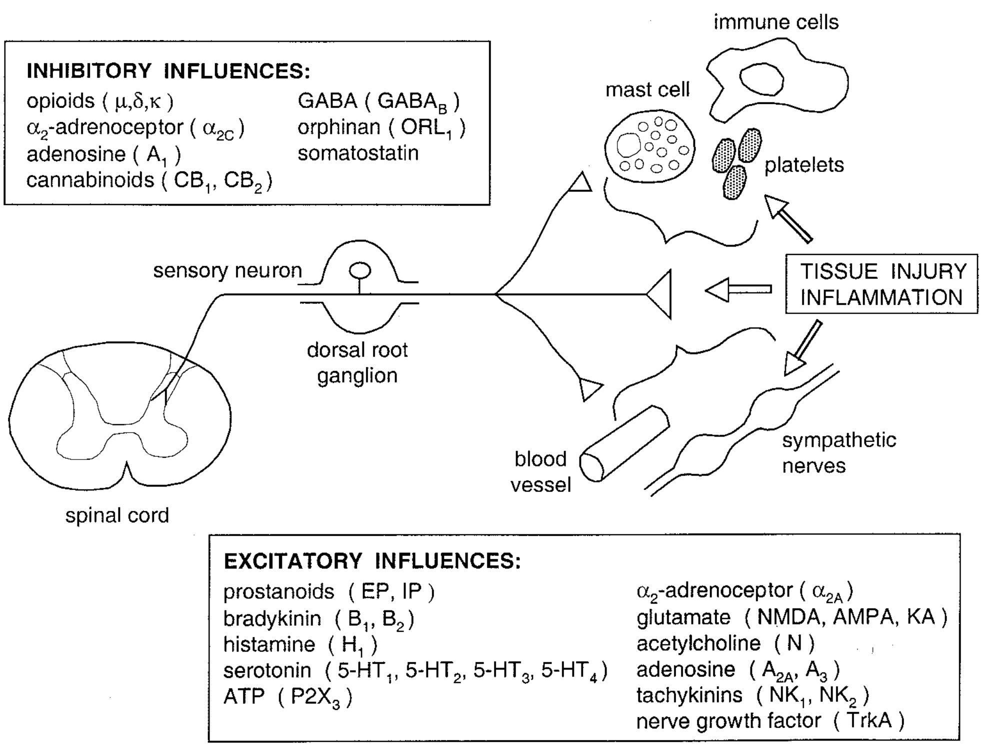

FIG. 1. Excitatory and inhibitory influences on peripheral nerve activity by mediators released by tissue injury and inflammation and by a variety of agents acting on neuroreceptors.

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can be demonstrated following ligation of the nerve and detection of an accumulation of receptors proximal and distal to the ligature. For example, μ-, δ-, κ-opioid (Young et al., 1980; Laudron, 1984; Stein et al., 1990; Hassan et al., 1993), and cannabinoid receptors (Hohmann and Herkenham, 1999b) have been detected in this manner. Other inhibitory receptors, such as γ-aminobutyric $acid_A$ ($GABA_A$) receptors (Carlton et al., 1999), have been visualized directly on peripheral nerve profiles. Although not all receptors that are transported centrally are necessarily also transported peripherally (Coggeshall and Carlton, 1997), it is likely that the peripheral receptor profile of sensory nerve terminals, as well as the alterations in these induced by inflammation and nerve injury, remains incompletely characterized. Regardless of whether there is direct evidence for a particular receptor to be localized on sensory afferents, there is a mounting body of evidence that many of these neurotransmitters have been well characterized in the spinal cord and exert significant peripheral effects on pain transmission by acting directly on sensory nerves. Such evidence will be considered in subsequent sections.

III. Topical and Peripherally Acting Analgesics

A. Nonsteroidal Anti-Inflammatory Drugs

The NSAIDs are among the most widely used of all therapeutic classes of drugs. These agents have been understood for many years to act peripherally to reduce the production of prostaglandins that sensitize nerve endings at the site of injury (Vane, 1971). This effect occurs due to inhibition of the cyclooxygenase (COX) enzyme that converts arachidonic acid liberated from the phospholipid membrane by phospholipases to prostanoids such as prostaglandins. Two forms of COX are well characterized, a constitutive form (COX1) that is normally expressed in tissues such as stomach and kidney and plays a physiological role in maintaining tissue integrity, and a form that is induced by inflammatory mediators (COX2) and plays a significant role in pain and inflammation (Vane et al., 1998). The analgesic actions of NSAIDs can be dissociated from anti-inflammatory effects, and this may reflect additional spinal and supraspinal actions of NSAIDs to inhibit various aspects of central pain processing (Yaksh et al., 1998). Both COX isoforms contribute to spinal and supraspinal prostanoid production following tissue injury or inflammation (Yaksh et al., 1998). A major recent drug development that has occurred in an attempt to minimize certain adverse effects with NSAIDs has been the development of selective COX2 inhibitors (Vane and Botting, 1998). This strategy targets the production of prostaglandins specifically involved in pain and inflammation while sparing constitutive prostaglandins that exert important physiological roles such as maintaining the integrity of the gastric lining and normal renal function. A further enzyme, COX3, has recently been described; this has a prominent central distribution, is selectively inhibited by acetaminophen, and is potently inhibited by NSAIDs (Chandrasekharan et al., 2002). Its identification has the potential to explain a number of unresolved issues regarding the pharmacology of NSAIDs as analgesics (Warner and Mitchell, 2002).

An additional strategy to try to minimize adverse effects has been the development of topical formulations of NSAIDs, as this can minimize plasma concentrations of drugs and lead to fewer adverse effects at sites remote from the area of application. Bioavailability and plasma concentrations following topical application are 5 to 15% of those achieved by systemic delivery (Heyneman et al., 2000). In human experimental pain paradigms, topical application of NSAIDs produces analgesia in models of cutaneous pain (Steen et al., 1995, 1996; Schmelz and Kress, 1996; McCormack et al., 2000) and muscle pain (Steen et al., 2001). In a clinical context, there have been three substantial reviews of the efficacy of topical NSAIDs (Moore et al., 1998; Vaile and Davis, 1998; Heyneman et al., 2000). One of these addressed applications in musculoskeletal and soft tissue injuries (e.g., sprains, strains, tendonitis) and rheumatic diseases (Vaile and Davis, 1998), another accessed a wider database including company trials (86 trials, >10,000 patients; Moore et al., 1998), and the third focused on efficacy and safety, primarily in chronic rheumatic diseases (Heyneman et al., 2000). Each overview concluded that there was clear evidence to support efficacy of topical NSAIDs given by gel, spray, or patch for such conditions. A multi-center trial of an NSAID patch for sports-related soft tissue injury found similar benefit (Galer et al., 2000).

When NSAIDs are administered topically, relatively high concentrations occur in the dermis, whereas levels in the muscle are at least equivalent to those following systemic administration (Heyneman et al., 2000). Topically applied NSAIDs do reach the synovial fluid, but it is not clear whether this reflects local penetration or results from systemic circulation (Vaile and Davis, 1998). In osteoarthritis and rheumatoid arthritis, the effects of topical NSAIDs may be modest, and efficacy can be quite variable ranging from 18 to 92% (Heyneman et al., 2000). This may be due to high placebo rates in rheumatic diseases, use of rescue medications, and significant variability in percutaneous absorption rates.

Adverse effects with topical NSAIDs can generally be divided into cutaneous and systemic reactions. Adverse drug reactions occur in up to 10 to 15% of patients, and cutaneous reactions (rash, pruritis at site of application) account for most of these (Moore et al., 1998; Heyneman et al., 2000). Adverse systemic effects, such as gastrointestinal effects, occur less frequently but are more likely in patients who have previously demonstrated such responses to oral preparations (Vaile and Davis, 1998).

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B. Opioids

The central effects of opioids on pain transmission by actions within the dorsal horn of the spinal cord and at brainstem and other supraspinal sites have been recognized for some time. It is known now that opioid receptors also are present on the peripheral terminals of thinly myelinated and unmyelinated cutaneous sensory fibers (Coggeshall et al., 1997). Dorsal root ganglia contain mRNA for opioid receptors (Maekawa et al., 1994; Minami et al., 1995), and when synthesized, these receptors are transported both centrally (Coggeshall and Carlton, 1997) and peripherally (Stein et al., 1990; Hassan et al., 1993). Peripheral opioid actions are not prominent in normal tissue but appear early after the induction of inflammation (Stein, 1993; Schäfer et al., 1995; Zhou et al., 1998). Although inflammation enhances opioid receptor expression and transport to peripheral nerve terminals (Hassan et al., 1993), this process takes days and the initial expression of analgesia precedes these changes (minutes to hours). The early effect is due to inflammation disrupting the perineurial barrier that normally limits the access for drugs to the nerve (Antonijevic et al., 1995). Thus, following such disruption, opioids have access to the nerve terminal and the receptors that are normally present (Dado et al., 1993; Coggeshall et al., 1997). The lowered pH at inflammatory sites may also enhance opioid receptor coupling to G-proteins (Selley et al., 1993).

There are a large number of behavioral studies that have examined peripheral antinociceptive effects of exogenous opioids, and these effects have been demonstrated primarily using models of inflammation (Stein, 1993, 1995; Machelska et al., 1999). μ-Opioid receptor agonists are generally the most potent at producing peripheral analgesia, with δ- and κ-opioid receptor agonists being less active. However, effects can depend on the nature of the noxious stimulus and the type of inflammation (i.e., differences manifest depending on whether an acute model such as intraplantar prostaglandin E_2 is used or whether a more chronic model such as Freund's adjuvant is used).

Opioid receptors are present on several distinct peripheral targets including sensory nerves, sympathetic postganglionic neurons, and immune cells. Antinociception by μ-, δ-, and κ-opioid agonists in inflammation results from actions on sensory nerves rather than sympathetic neurons (Zhou et al., 1998). Although opioid receptors are present on a variety of immune cells and activation can modulate proliferation and several of their functions (e.g., chemotaxis, superoxide production, mast cell degranulation), these immunomodulatory actions can be stimulatory as well as inhibitory, and their significance in relation to antinociception has not been determined (Stein et al., 1997). Activation of peripheral opioid receptors on sensory nerve terminals results in interactions with G-proteins (G_i and/or G_o), a decrease in cyclic AMP in the sensory nerve terminal, an increased K^+ efflux, and a decreased Ca^{2+} entry, and these attenuate the excitability of the peripheral nerve terminal, the propagation of action potentials, and release of neuropeptides (Stein et al., 1997; Machelska et al., 1999). A recent study also reports analgesia following peripheral administration of morphine in a model of nerve injury where inflammation is not prominent (Pertovaara and Wei, 2001). This particular action may reflect an involvement of the sympathetic nervous system as chemical sympathectomy augments such analgesia.

A number of studies have addressed the issue of whether peripheral opioid mechanisms are of significance in a clinical setting. Some studies have examined experimental pain, but the largest number of studies have examined the intra-articular application of morphine (0.5–10 mg) during knee surgery (Stein and Schäfer, 1997; Stein et al., 1997; Kalso et al., 2002). The majority of studies report significant effects by at least one pain measure (visual analog scale, numerical scales, verbal scales, supplementary analgesia consumption, or time to first supplementary analgesic), provided adequate doses are used (3–5 mg). Effects are reversible by naloxone, similar in magnitude to conventional local anesthetics, and can last up to 48 h after injection. Peripheral analgesia with morphine also has been observed in dental surgery (Likar et al., 1998, 2001). Local analgesic actions of morphine also have been examined in arthritis, a condition involving more chronic inflammation. In such studies, the intra-articular injection of morphine (1–3 mg) produced a long-lasting analgesia (up to 6 days) (Likar et al., 1997; Stein et al., 1999). Morphine also reduced synovial leukocyte counts indicating that a possible anti-inflammatory effect also may have contributed to the pain relief (Martinez et al., 1996; Wilson et al., 1996, 1998). No adverse effects of morphine were noted, and it was concluded that opioids may be a promising novel class of intra-articular agents for chronic arthritis that is devoid of central side effects such as respiratory depression, sedation, dependence, or addiction when given by this method.

In addition to the peripheral delivery of opioids by localized injection, opioids may also produce benefits following topical application to somatic sites. In preclinical studies using a model of thermal injury-induced hyperalgesia, loperamide (an opioid not systemically absorbed following oral administration) was shown to produce an antihyperalgesic effect following topical application to the rat hindpaw (Nozaki-Taguchi and Yaksh, 1999). Another model, that of immersing the tail of a mouse into a solution containing dimethyl sulfoxide with morphine or DAMGO (another μ-opioid receptor agonist), also reveals a local peripheral action by μ-opioids (Kolesnikov and Pasternak, 1999a,b). Interestingly, repeated administration of the opioid produced tolerance to the peripheral analgesia, and this was both reversed and prevented by N-methyl-D-aspartate (NMDA) recep-

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tor antagonists (Kolesnikov and Pasternak, 1999a,b). Earlier studies had demonstrated that repeated peripheral injection of morphine could produce a peripheral analgesia and tolerance (Aley et al., 1995; Aley and Levine, 1997a), and the latter involved nitric oxide (Aley and Levine, 1997b). Peripheral opioid analgesia thus exhibits tolerance just as when opioids are administered by other routes, such as via spinal routes, where the mechanism of tolerance also involves NMDA receptors and nitric oxide (Mao, 1999).

The topical route of opioid administration has recently been employed in clinical contexts as well, and there are several case reports attesting to its effectiveness. Thus, topical opioids produce analgesia when applied to painful ulcers and skin lesions (Back and Finlay, 1995; Twillman et al., 1999; Ballas, 2002), following burns (Long et al., 2001), and in cutaneous pain in a palliative care setting (Krajnik et al., 1999). Given that side effects resulting from these applications are minimal, this approach represents a mode of delivery of opioids that warrants further clinical attention. Factors determining bioavailability following such application (e.g., specific formulations, degree of absorption from healthy versus inflamed or lesioned skin), as well as the potential for cutaneous side effects (e.g., via histamine release) will need to be evaluated systematically.

C. Capsaicin

Capsaicin is a natural constituent in pungent red chili peppers. Depending on the concentration used and the mode of application, capsaicin can selectively activate, desensitize, or exert a neurotoxic effect on small diameter sensory afferent nerves while leaving larger diameter afferents unaffected (Holzer, 1991; Winter et al., 1995). Sensory neuron activation occurs due to interaction with a ligand-gated nonselective cation channel termed the vanilloid receptor (VR-1) (Caterina et al., 1997), and receptor occupancy triggers Na^+ and Ca^{2+} ion influx, action potential firing, and the consequent burning sensation associated with spicy food or capsaicin-induced pain. VR1 receptors are present on both C and Aδ fibers, and can be activated by capsaicin and its analogs, heat, acidification, and lipid metabolites (Tominaga et al., 1998; Caterina and Julius, 2001). Desensitization occurs with repeated administration of capsaicin, is a receptor-mediated process, and involves Ca^{2+}- and calmodulin-dependent processes and phosphorylation of the cation channel (Winter et al., 1995; Wood and Docherty, 1997). Capsaicin induces release of substance P and calcitonin gene-related peptide from both peripheral and central terminals of sensory neurons, and desensitization inhibits such release (Holzer, 1991); such inhibition may result from inhibition of voltage-gated Ca^{2+}-currents (Docherty et al., 1991; Winter et al., 1995). Neurotoxicity is partially osmotic and partially due to Ca^{2+} entry with activation of Ca^{2+}-sensitive proteases (Wood et al., 1989; Winter et al., 1995). In neonates, neurotoxicity can be lifelong (Janscó et al., 1977), whereas in adult animals receiving a localized dose, a reversible injury may occur as cell bodies capable of regeneration are left intact (Holzer, 1991). Both desensitization and neurotoxicity lead to analgesia in rodent paradigms, with specific characteristics of analgesia depending on the dose of capsaicin, route of administration, treatment paradigm (i.e., acute or repeated administration), and age of the animal (Holzer, 1991; Winter et al., 1995). The topical skin application of capsaicin to rodents produces analgesia (Kenins, 1982; Lynn et al., 1992), but variability in outcome can occur due to the concentration, the number of applications, and the different vehicles used that can affect the rate and extent of skin penetration (Carter and Francis, 1991; McMahon et al., 1991).

Acute intradermal injection of capsaicin to the skin in humans produces a burning sensation and flare response; the area of application becomes insensitive to mechanical and thermal stimulation, the area of flare exhibits a primary hyperalgesia to mechanical and thermal stimuli, and an area beyond the flare exhibits secondary allodynia (Simone et al., 1989; LaMotte et al., 1991). Repeated application to normal skin produces desensitization to this response and thus forms the basis of the therapeutic use of topical capsaicin in humans. Desensitization involves both physiological changes in the terminals of the sensory neuron noted above, as well as a degree of loss of sensory fiber terminals within the epidermis (Simone et al., 1998; Nolano et al., 1999).

Topical capsaicin preparations of 0.025 and 0.075% are available for human use, and these produce analgesia in randomized double-blind placebo-controlled studies, open label trials, and clinical reports (Watson, 1994; Rains and Bryson, 1995). Topical capsaicin produces benefit in postherpetic neuralgia (Bernstein et al., 1989; Watson et al., 1993), diabetic neuropathy (Capsaicin Study Group, 1992), postmastectomy pain syndrome (Watson and Evans, 1992; Dini et al., 1993), oral neuropathic pain, trigeminal neuralgia, and temperomandibular joint disorders (Epstein and Marcoe, 1994; Hersh et al., 1994), cluster headache (following intranasal application) (Marks et al., 1993), osteoarthritis (McCarthy and McCarthy, 1992), and dermatological and cutaneous conditions (Hautkappe et al., 1998). Whereas pain relief is widely observed in these studies, the degree of relief is usually modest, although some patients have a very good result. Topical capsaicin is generally not considered a satisfactory sole therapy for chronic pain conditions and is often considered an adjuvant to other approaches (Watson, 1994). No significant benefit was reported in chronic distal painful neuropathy (Low et al., 1995) or with human immunodeficiency virus-neuropathy (Paice et al., 2000).

The most frequently encountered adverse effect with capsaicin is burning pain at the site of application, particularly in the first week of application. This can make

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it impossible to blind trials and can lead to dropout rates ranging from 33 to 67% (Watson et al., 1993; Paice et al., 2000). Another factor in compliance is the time delay before therapeutic effect is observed (at least a week, but sometimes several weeks). One approach toward minimizing adverse effects and accelerating the rate of analgesia has been to deliver a higher capsaicin concentration (5–10%) under regional anesthesia, and this produced sustained analgesia lasting 1 to 8 weeks in cases of complex regional pain syndrome and neuropathic pain (Robbins et al., 1998). When topical local anesthetics were applied with 1% topical capsaicin, no alteration in pain produced by the capsaicin was observed in healthy subjects (Fuchs et al., 1999) indicating that this cotreatment was not sufficient to block the pain induced by capsaicin.

D. Local Anesthetics

Voltage-gated sodium channels (VGSCs) play a fundamental role in the control of neuronal excitability, and a family of genes encoding α-subunits of the channel have been identified (Catterall, 2000). Sensory neurons contain both classical VGSCs that are sensitive to inhibition by tetrodotoxin, as well as several atypical VGSCs that are relatively resistant to tetrodotoxin, and some tetrodotoxin-resistant subtypes are selectively expressed in sensory afferent neurons (McClesky and Gold, 1999; Waxman et al., 1999). Alterations in the expression, distribution, and function of VGSCs that occur following nerve injury or chronic inflammation have a profound effect on the firing of primary afferent neurons and contribute to the expression of pain behaviors (Devor and Seltzer, 1999; McCleskey and Gold, 1999; Raja et al., 1999).

In neuropathic pain, a major factor that contributes to the initiation and maintenance of ectopic repetitive firing of primary afferents following injury appears to be redistribution of VGSCs along injured axons, and this causes an abnormal accumulation and increased membrane density of sodium channels at focal sites of injury, which then contributes to a lower threshold for activation and ectopic impulse generation (Devor and Seltzer, 1999; Raja et al., 1999). Local anesthetics that block VGSCs have long been used to abolish pain temporarily by blocking nerve conduction, but local anesthetics are now used as an effective treatment for many chronic pain conditions. Thus, the increased sensitivity of ectopic activity to local anesthetics and the use-dependent nature of channel block allow for the block of spontaneous and evoked activity (impulse generation) without affecting nerve conduction (impulse propagation) (Fields et al., 1997; Hunter, 1999). Systemically administered local anesthetics such as i.v. lidocaine, oral mexilitine, and oral tocainamide are effective in a number of chronic pain conditions (Fields et al., 1997; Kingery, 1997; MacFarlane et al., 1997). Such regimens produce analgesia in diabetic neuropathy (Dejgard et al., 1988; Bach et al., 1990), neuralgias (Rowbotham et al., 1991; Marchettini et al., 1992), peripheral nerve injury (Chabal et al., 1992; Galer et al., 1996), and reflex sympathetic dystrophy (Edwards et al., 1985; Galer et al., 1993). However, despite this efficacy in different clinical pain conditions, systemic local anesthetics are limited by their adverse central nervous system (dizziness, lightheadedness, somnolence) and cardiac effects.

Topical formulations of local anesthetics may be an effective alternative to systemic delivery systems for chronic pain. Such formulations are widely used as topical anesthetics for minor acute surgical procedures (Lener et al., 1997), and there are some reports of use in chronic pain conditions such as postherpetic neuralgia (Stow et al., 1989; Attal et al., 1999; but see Devers and Galer, 2000). Clinical attention has focused recently on topical formulations of lidocaine. Thus, topical lidocaine as a 5% gel (Rowbotham et al., 1995) or patch (Rowbotham et al., 1996) provides effective pain relief in postherpetic neuralgia with no systemic adverse effects. The patch itself provided some pain relief, likely due to the protection afforded to allodynic skin (Rowbotham et al., 1996). A subsequent study used a novel time-to-study-exit criterion and an enriched enrolment design, and the lidocaine patch produced a significantly prolonged time to exit without systemic side effects (Galer et al., 1999). An open label study noted clinically meaningful pain relief in a variety of neuropathic pain conditions (Devers and Galer, 2000). This delivery method was regarded as effective, safe, and convenient and was proposed as a first line therapy for postherpetic neuralgia, especially in the elderly who are more susceptible to systemic side effects.

In addition to VGSCs, voltage-gated Ca^{2+} channels play an important role in primary afferent function by regulating transmitter release, second messenger signal transduction pathways, and gene expression. Whereas multiple types of Ca^{2+} channels are localized on sensory neurons, *N*-type channels have a high density in laminae I and II of the dorsal spinal cord (Gohil et al., 1994), and the spinal application of blockers of these channels produces analgesia in several models of acute and chronic pain (Malmberg and Yaksh, 1994, 1995). In models of nerve injury pain, the local administration of N-type Ca^{2+} channel blockers to the spinal cord (Chaplan et al., 1994; Bowersox et al., 1996), the site of injury (Xiao and Bennett, 1995), and peripheral sites in the receptive field (White and Cousins, 1998) can alleviate manifestations of nerve injury pain. Interestingly, altered functioning of G-protein-coupled Ca^{2+} currents in sensory neurons is implicated in diabetic neuropathy (Hall et al., 2001), and Ca^{2+} channels may represent a further target in neuropathic pain states.

E. Antidepressants

Antidepressants given systemically have been used to treat chronic pain for 40 years (Sindrup, 1997). Initially,

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efficacy in this condition was attributed to central actions within the spinal cord and at supraspinal sites (Sindrup, 1997; Eschalier et al., 1999). Recently, the local peripheral administration of antidepressants was demonstrated to produce analgesia in the formalin model of tonic pain (Sawynok et al., 1999a,b) and a model of neuropathic pain (Esser and Sawynok, 1999). Peripheral activity also was noted in a visceral pain model (Su and Gebhart, 1998). Several antidepressants are active in the formalin test including desipramine, imipramine, nortriptyline, doxepin, and fluoxetine (Sawynok et al., 2000a). Local release of adenosine and activation of adenosine A_1 receptors is involved in the action of amitriptyline, as analgesia is reduced by adenosine receptor antagonists (Sawynok et al., 1999a; Esser and Sawynok, 2000), and local administration of amitriptyline enhances the peripheral availability of adenosine (Liu et al., 2000b). However, antidepressants produce a range of acute pharmacological actions including inhibition of noradrenaline (NA) and 5-HT reuptake, inhibition of NMDA, nicotinic, histamine, and 5-HT receptors, and block of ion channels (Sindrup, 1997; Eschalier et al., 1999), and a number of these actions, and even combinations of these actions, may contribute to the local peripheral efficacy of antidepressants (Sawynok et al., 2000a). Additional actions of antidepressants are expressed following chronic administration (Leonard, 1996; Duman et al., 1997; Skolnick, 1999), but the contribution of these actions to analgesia by antidepressants, following either systemic or local administration, remains to be determined.

The antidepressant doxepin is available as a cream for the treatment of eczema (Drake et al., 1995; Smith and Corelli, 1997). Topical doxepin cream has been reported to produce analgesia in two randomized double-blind placebo-controlled studies with chronic neuropathic pain (McCleane, 2000a,b). In the first study, doxepin (5%) was applied for 4 weeks, and produced significant analgesia in the last 10 days of treatment, but not in the 1st week. In the larger study, topical doxepin (3.3%) was compared with topical capsaicin (0.025%) and a combination of doxepin with capsaicin. Significant reductions in overall pain scores were observed for all treatment groups from week 2 to 4, but the combination group had a faster onset of action with analgesia at 1 week. A burning discomfort after cream application was noted by 81% in the capsaicin group, 61% in the doxepin/capsaicin group, and 17% in the doxepin group. Interestingly, a recent study reported that doxepin, formulated as a mouthwash, produces analgesic actions in patients with oral mucosal pain due to cancer or cancer therapy (Epstein et al., 2001). Antidepressants exhibit promise as a useful class of agents to be used as analgesics following topical application and other methods of local delivery.

F. Glutamate Receptor Antagonists

Within the dorsal spinal cord, both ionotropic glutamate receptors [NMDA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), kainic acid (KA)] and metabotropic glutamate receptors are involved in nociceptive signaling and central sensitization in conditions of chronic pain (Coderre et al., 1993; Dickenson, 1994; Price et al., 1994; Dickenson et al., 1997). Both the systemic and spinal administration of multiple classes of glutamate receptor antagonists have been observed to produce analgesia in a variety of persistent pain models, and although their potential for development as a novel class of analgesics has been considered, this may be hampered by the presence of adverse motor and other effects (Coderre, 1999; Fisher et al., 2000).

More recently, it has been appreciated that multiple glutamate receptors also are expressed on peripheral nerve terminals, and these may contribute to peripheral nociceptive signaling. Ionotropic and metabotropic glutamate receptors are present on membranes of unmyelinated peripheral axons and axon terminals in the skin (Carlton et al., 1995; Zhou et al., 2001b), and peripheral inflammation increases the proportions of both unmyelinated and myelinated nerves expressing ionotropic glutamate receptors (Carlton and Coggeshall, 1999). Local injections of NMDA and non-NMDA glutamate receptor agonists to the rat hindpaw (Jackson et al., 1995; Zhou et al., 1996) or knee joint cavity (Lawland et al., 1997) enhance pain behaviors generating hyperalgesia and allodynia. Intraplantar injection of metabotropic glutamate receptor agonists produces similar actions (Walker et al., 2001; Zhou et al., 2001b). On the other hand, local administration of antagonists for both ionotropic (Davidson et al., 1997; Davidson and Carlton, 1998) and metabotropic receptors (Bhave et al., 2001; Zhou et al., 2001b) inhibits pain behavior evoked by formalin, as well as hyperalgesia produced by kaolin and carrageenan injected into the knee joint (Lawland et al., 1997). Inflammation of the hindpaw (Omote et al., 1998) or the knee joint produces a local release of glutamate (Lawland et al., 2000) that appears to originate from A and C fibers (deGroot et al., 2000). An additional indirect mechanism, via activation of glutamate receptors on sympathetic afferents to release NA and other substances from postganglionic efferents (e.g., ATP, neuropeptide Y), could occur as NMDA, AMPA, and KA receptors also are present on postganglionic sympathetic efferents, and inflammation enhances the expression of such receptors (Coggeshall and Carlton, 1999). Collectively, these results suggest the involvement of local release of glutamate and activation of both ionotropic and metabotropic glutamate receptors in inflammatory pain in particular, and raises the possibility that topical formulations of such agents might be a useful strategy to develop for such conditions (Carlton, 2001). It is also possible that peripheral glutamate receptors play a significant role in peripheral pain signaling in neuropathic pain (as occurs at spinal sites), but direct data regarding this are not yet available.

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There is some evidence in humans to support a peripheral site of action for ketamine, a noncompetitive NMDA receptor antagonist, in reducing pain responses. In a study of acute postoperative pain, ketamine enhanced local anesthetic and analgesic effects of bupivacaine by a peripheral mechanism (Tverskoy et al., 1996). In a thermal injury model in healthy volunteers, subcutaneous injection of ketamine produced a long-lasting reduction in hyperalgesia in one study (Warncke et al., 1997) but only produced a brief analgesia with no effect on hyperalgesia in another such study (Pedersen et al., 1998). Following intradermal injection of capsaicin to healthy volunteers, peripheral ketamine had no effect on any pain outcome measures whereas peripheral lidocaine reduced all such measures (Gottrup et al., 2000). It appears that analgesic effects following peripheral administration of ketamine are variable and may be condition-dependent. It should be noted that ketamine also produces local anesthetic actions, blocks voltage-sensitive Ca^{2+} channels, alters cholinergic and monoaminergic actions and interacts with opioid mechanisms, and these actions also may contribute to its analgesic profile (Hirota and Lambert, 1996; Meller, 1996; Sawynok and Reid, 2002). The peripheral contribution of glutamate receptors to pain may be more pronounced in conditions involving chronic inflammation where up-regulation of receptors occurs (see above), or in conditions of nerve injury. In humans, a recent report has demonstrated that in the synovial fluid of arthritis patients, concentrations of both glutamate and aspartate are elevated (McNearney et al., 2000). There are also some case reports regarding the efficacy of ketamine administered topically for sympathetically maintained pain (Crowley et al., 1998) and for pain in a palliative setting (Wood, 2000). These observations support the notion that targeting peripheral glutamate receptors in inflammatory and chronic pain states may represent a useful option to explore for pain treatment.

G. α-Adrenoceptor Agonists

There is evidence from both clinical and preclinical studies that the sympathetic nervous system contributes to pain following nerve injury (Jänig et al., 1996; Perl, 1999; Michaelis, 2000). Clinically, when hyperalgesia and allodynia resulting from nerve injury are relieved by sympathetic or adrenergic blockers, it is termed sympathetically maintained pain, and such disorders are now regarded as complex regional pain syndromes (Stanton-Hicks et al., 1995). Normally, sympathetic mechanisms do not cause excitation of primary afferent neurons. However, following experimentally induced nerve injury, the following may be observed: 1) coupling occurs between sympathetic fibers and afferent terminals in the neuroma following nerve cut or ligation, and sympathetic stimulation or NA can cause excitation of unmyelinated nerves; 2) coupling occurs between unlesioned postganglionic and afferent nerve terminals following partial nerve lesions; and 3) sympathetic nerve terminals enter the dorsal root ganglia and form basket-like structures around dorsal root ganglia cell bodies, particularly larger diameter cells, providing a collateral innervation from sympathetic terminals that normally supply blood vessels (Jänig et al., 1996; Perl, 1999; Michaelis, 2000). Thus, sympathetic-afferent coupling occurs at three distinct sites; at the site of injury, at the sensory terminal, and within dorsal root ganglia. The relative contributions of these mechanisms to sympathetic-afferent coupling in the different nerve injury conditions is highly dependent on the location and nature of the lesion, as well as on the time following the injury; as a consequence, sympathectomy can relieve the different manifestations of neuropathic pain (hyperalgesia and allodynia) in various nerve injury models to varying degrees (Kim et al., 1997; Lee et al., 1998; Ramer and Bisby, 1999).

Both behavioral and electrophysiological studies indicate that α_2-adrenoceptors are primarily mediators of sympathetic-afferent coupling following nerve injury (Sato and Perl, 1991, 1999; Tracey et al., 1995a; Chen et al., 1996; Moon et al., 1999). Multiple α_2-adrenoceptors have been detected in rat dorsal root ganglia, with α_{2C} on most, α_{2A} on some, and α_{2B} on few neurons (Cho et al., 1997; Shi et al., 2000). Nerve ligation or transection results in an up-regulation of α_{2A}-adrenoceptors, and a decrease or no change in α_{2C}-adrenoceptors in rat dorsal root ganglia (Cho et al., 1997; Birder and Perl, 1999; Shi et al., 2000). Afferent excitation following nerve injury is thought to result from α_{2A}-adrenoceptor activation (Perl, 1999; Kingery et al., 2000). α_1-Adrenoceptors also are involved in such activation in some conditions (Chen et al., 1996; Lee et al., 1999).

The sympathetic nervous system also contributes to hyperalgesia following tissue injury and inflammation, but the nature of the involvement in this case differs from that in nerve injury (Jänig et al., 1996). Inflammation does not lead to up-regulation of α_{2A}-adrenoceptors in dorsal root ganglia (Birder and Perl, 1999), and in this case, the enhancing effects of NA on the sensitivity of primary afferents may be mediated indirectly by actions on sympathetic postganglionic nerves (Levine et al., 1986; Jänig et al., 1996). α_2-Adrenoceptor activation also can produce analgesia following localized administration in an inflammation model (Khasar et al., 1995; Aley and Levine, 1997a). Hyperalgesia is proposed to be mediated by α_{2B}-adrenoceptors located on sympathetic postganglionic neurons, and analgesia by α_{2C}-adrenoceptors on primary afferent terminals (Khasar et al., 1995). The α_{2C}-receptor on primary afferents may exist as part of a trireceptor complex along with μ-opioid and adenosine A_1 receptors (Aley and Levine, 1997a).

Clonidine, an α_2-adrenoceptor agonist commonly used in the treatment of hypertension, is available as a patch for transdermal administration and has been used in chronic pain conditions. Transdermal clonidine relieved

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symptoms of neuropathic pain in a subset of patients with diabetic neuropathy through a systemic action (Bayas-Smith et al., 1995). Clonidine patches also relieved hyperalgesia in some patients with sympathetically maintained pain due to a localized action, but had no effect on hyperalgesia in cases of sympathetically independent pain (Davis et al., 1991). Clonidine applied as a cream relieved orofacial neuralgia-like pain but was less effective against orofacial neuropathic pain (Epstein et al., 1997). Other studies reveal that local application of NA into symptomatic skin aggravates pain and mechanical or thermal hyperalgesia in some patients with sympathetically maintained pain (Torebjörk et al., 1995; Ali et al., 2000), peripheral nerve injury (Chabal et al., 1992), and postherpetic neuralgia (Choi and Rowbotham, 1997). The efficacy of local clonidine in sympathetically maintained pain may result from presynaptic inhibition of NA released from sympathetic nerves as well as actions directly on primary afferent nerve terminals (see above).

Peripheral analgesic actions of clonidine also have been examined following intra-articular injection of clonidine following arthroscopic knee surgery. Both an intrinsic analgesia (Gentili et al., 1996; 1997) and augmentation of analgesia produced by bupivacaine (Reuben and Connelly, 1999; Joshi et al., 2000) and morphine (Buerkle et al., 2000) have been reported. Clonidine has been injected into the inflamed knee joint of rodents in preclinical trials, and analgesia was observed to be enhanced by inflammation (Buerkle et al., 1999). The mechanisms underlying enhanced activity with inflammation are not clear.

H. Adenosine

Both the systemic and spinal administration of adenosine analogs produce antinociception in a range of nociceptive, inflammatory, and neuropathic pain tests in rodents (Sawynok, 1998; Dickenson et al., 2000). In humans, the intravenous infusion of adenosine produces analgesia in experimental pain models in volunteers as well as in acute perioperative pain and chronic neuropathic pain (Segerdahl and Sollevi, 1998). When administered locally to the hindpaw of rats, adenosine A_1 receptor agonists produce analgesia in models of nociceptive pain (Taiwo and Levine, 1990; Aley et al., 1995), inflammatory pain (Karlsten et al., 1992), and neuropathic pain (Liu and Sawynok, 2000). Similarly, local administration of inhibitors of adenosine kinase (that augment local tissue levels of adenosine; Liu et al., 2000a) also produces analgesia in models of inflammatory (Sawynok et al., 1998; McGaraughty et al., 2001) and neuropathic pain (Liu and Sawynok, 2000). The demonstration of a peripheral site of analgesia with adenosine raises the possibility of developing topical formulations of either adenosine A_1 receptor agonists or inhibitors of adenosine kinase as analgesics. Systemic administration of inhibitors of adenosine kinase can also produce anti-inflammatory actions via adenosine A_{2A} receptors (Kowaluk and Jarvis, 2000), and this occurs due to effects on a variety of peripheral immune cells (Cronstein, 1998). Thus, peripheral adenosine kinase inhibitors might produce a direct effect on pain by actions on the sensory nerve terminal (via A_1 receptors) as well as an indirect effect on the inflammatory process itself (via A_2 receptors). Although potential actions of adenosine on A_{2B} and A_3 receptors on mast cells that produce pain facilitatory effects (Sawynok et al., 1997) could be a limiting factor for inhibitors of adenosine metabolism, these receptors have a lower affinity for adenosine than do adenosine A_1 receptors.

Although peripheral adenosine A_1 receptors hold some appeal as a target for analgesia, several issues need to be resolved regarding their actions. Thus, whereas in rodents adenosine A_1 receptors are implicated in analgesia (see above), in humans pain-initiating actions of adenosine have been attributed to adenosine A_1 receptors (Pappagallo et al., 1993; Gaspardone et al., 1995). In addition, adenosine A_1 receptor agonists increase the firing of sensory afferent nerves (Dowd et al., 1998; Hong et al., 1998; Kirkup et al., 1998), and can cause neurogenic edema following local application in rodents (Sawynok et al., 2000b; Esquisatto et al., 2001).

I. Cannabinoids

Systemic, spinal, and supraspinal administration of cannabinoids can produce analgesia in a variety of nociceptive test systems, and the potential for development of cannabinoids as an alternative class of analgesics is being considered (Rice, 2000; Richardson, 2000; Rice et al., 2002). Cannabinoids can act at peripheral sites to produce analgesia via cannabinoid (CB) CB_1 or CB_2 receptors. Dorsal root ganglia cells that express neuropeptide markers found in nociceptive primary afferents contain mRNA for CB_1 cannabinoid receptors (Hohmann and Herkenham, 1999a), and these receptors are transported both centrally (Hohmann et al., 1999) and peripherally (Hohmann and Herkenham, 1999b). In behavioral experiments, the peripheral administration of agents selective for CB_1 receptors produces a local analgesia in the formalin test (Calignano et al., 1998), the carrageenan hyperalgesia model (Richardson et al., 1998), and the partial nerve injury model (Fox et al., 2001). The peripheral actions of CB_1 receptor agonists are attributed to an effect on the sensory nerve terminal itself to inhibit release of calcitonin gene-related peptide (Richardson et al., 1998) or inhibit sensitizing effects of NGF (Rice et al., 2002). Local analgesic actions of directly and indirectly acting agonists for CB_2 receptors, that are expressed on mast cells and inhibit mast cell function, also have been demonstrated (Calignano et al., 1998; Malan et al., 2001), and CB_2 receptor mechanisms may play a particularly prominent role in inflammatory pain (Rice et al., 2002). Interestingly, coadministration of agonists for both CB_1 and CB_2 receptors produced a

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dramatically potentiated analgesia (Calignano et al., 1998). Collectively, such observations raise the possibility of developing local peripheral formulations of cannabinoid derivatives (either alone or as combinations) for pain relief that would be devoid of central actions that currently are of concern for this class of agents.

J. Cholinergic Receptors Agonists

Acetylcholine (ACh) has been known to be a peripheral algogen for some time, but ACh was hardly ever implicated in peripheral pain mechanisms since there was no histological relationship between possible sources of ACh and sensory nerve endings, and extrajunctional ACh levels are low due to choline esterases. However, it now is recognized that peripheral sources of ACh could include sensory neurons themselves (Tata et al., 1994) or keratinocytes and fibroblasts (Grando et al., 1993), and these may release ACh following cutaneous injury. Nicotinic receptors are present on sensory afferent neurons (Boyd et al., 1991; Roberts et al., 1995), and multiple nicotinic receptor subtypes are expressed (Flores et al., 1996; Genzen et al., 2001). ACh can activate sensory afferents through nicotinic receptors (Steen and Reeh, 1993; Jinks and Carstens, 1999; Bernardini et al., 2001), and nicotinic agonists produce sensations of irritation or pain when delivered to skin or the oral mucosa (Dessirier et al., 1997, 1998). Such actions are blocked by specific antagonists and exhibit desensitization with replacement application. Sensory neurons also express multiple muscarinic receptors (Bernardini et al., 1999; Tata et al., 2000), and muscarinic receptor activation, particularly via M2 receptors, results in sensory neuron desensitization (Bernardini et al., 2001, 2002). Thus, selective ligands for certain cholinergic receptors could represent potential peripheral analgesics.

The cholinesterase inhibitor, neostigmine, has been injected directly into the knee joint, and such an approach also provides evidence for a cholinergic peripheral analgesia. Thus, intra-articular neostigmine partially suppresses mechanical hyperalgesia in the rat inflamed knee joint model (Buerkle et al., 1998) and produces some postoperative analgesia in patients undergoing knee surgery (Yang et al., 1998). Although the mechanisms involved in such analgesia were not defined, it could involve desensitization of nociceptors (Bernardini et al., 2001).

K. GABA Agonists

GABA receptors also can modulate peripheral pain signaling. Endogenous peripheral GABA could arise from primary afferent fibers that contain glutamate (which can be converted to GABA by glutamate decarboxylase), and $GABA_A$ receptors are present on some unmyelinated afferent axons (Carlton et al., 1999). In behavioral experiments, local peripheral administration of the $GABA_A$ agonist, muscimol, can initially suppress then, at higher doses, augment the actions of formalin (Carlton et al., 1999). This is thought to reflect an initial modest primary afferent depolarization that decreases the size of peripheral action potentials and the consequent release of algesic substances, with a subsequent pronounced depolarization of the nerve terminal and initiation of action potentials. On the other hand, activation of $GABA_B$ receptors by local administration of baclofen results in a uniform reduction in formalin-evoked behaviors (Zhou et al., 1998), and these receptors may represent a more promising target than $GABA_A$ receptors.

Gabapentin was originally introduced as a GABA analog, but its action as an anticonvulsant is unrelated to GABA mechanisms (Taylor et al., 1998). Gabapentin, given systemically, is clinically effective in chronic neuropathic pain conditions (Morello et al., 1999; Mao and Chen, 2000). In preclinical studies, systemic and spinal administration of gabapentin produce analgesia in both inflammatory (Field et al., 1997; Shimoyama et al., 1997) and neuropathic pain models (Hunter et al., 1997; Field et al., 1999). The peripheral administration of gabapentin has been reported to produce analgesia by a local action in the formalin test (Carlton and Zhou, 1998). The actions of gabapentin on $GABA_B$ receptors (Bertrand et al., 2001) and on glutamate release (Maneuf et al., 2001) potentially may contribute to local effects.

L. Neuropeptides

Substance P has long been considered an important peptide for the transmission of noxious sensory information, particularly in the dorsal spinal cord. In the periphery, substance P contributes to local axon reflexes and inflammation following release from sensory nerve endings and subsequent mediator release from mast cells, and is a prominent contributor to neurogenic inflammation (Holzer, 1988). Earlier studies noted that substance P did not activate C-fibers to any great extent or sensitize C-fibers to other stimuli using in vitro approaches (Cohen and Perl, 1990; Kessler et al., 1992). Substance P receptors, however, are present on sensory afferent nerve terminals (Carlton et al., 1996), and local injection of substance P into the hindpaw produces hyperalgesia, allodynia and augmentation of the pain-facilitating actions of glutamate (Nakamura-Craig and Gill, 1991; Carlton et al., 1998), which does suggest a contribution to afferent pain signaling by actions on nerve terminals. Substance P also increases vascular permeability, attracts white blood cells, activates phagocytic activity, and increases production and release of inflammatory mediators in neutrophils and macrophages (Levine et al., 1993; Brain, 1996). The peripheral release of substance P may play a role in inflammatory conditions such as arthritis (Levine et al., 1984, 1985). However, clinical trials with nonpeptide neurokinin antagonists have not revealed significant effects on joint pain in arthritis (Rupniak and Hill, 1999; Boyce and Hill, 2000;

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Hill, 2000). Given that there is concern about the degree of penetration to central sites of action with neurokinin antagonists, a direct evaluation of the local peripheral actions of substance P antagonists (e.g., by direct injection into the knee joint) may be worthwhile.

Indirect evidence also suggests a significant role of peripheral substance P in nociceptive signaling. Orphinan FQ/nociceptin (OFQ/N) is a recently described peptide that is the endogenous ligand for a cloned orphan opioid receptor (Pasternak, 1998). Local intraplantar administration of low doses of OFQ/N is profoundly nociceptive, and this action is blocked by intraplantar tachykinin antagonists (Inoue et al., 1998). This observation suggests a marked effect of substance P on peripheral pain signaling and a peripheral site for the OFQ/N-substance P interaction, and raises the possibility that antagonists at this receptor may represent a novel peripheral drug target. As at central sites, there is also evidence for dual effects of OFQ/N on sensory neuron function. Thus, like opioids, OFQ/N decreases Ca^{2+} currents in dorsal root ganglion neurons (Abdulla and Smith, 1998) and, given systemically, can inhibit neurogenic inflammation by decreasing the release of substance P and calcitonin gene-related peptide (Helyes et al., 1997; Németh et al., 1998). Such actions could form the basis of a peripherally mediated antinociceptive action for OFQ/N at certain doses and in some conditions, although this has not been demonstrated directly in functional studies.

Other peptides also play a significant role in peripheral pain processing. For example, receptors for somatostatin, which is present in some sensory afferent neurons, are present on peripheral primary afferent sensory fibers, and local peripheral administration of somatostatin reduces nociceptive behaviors induced by formalin and electrophysiological activation of sensory afferents by heat and chemicals (Carlton et al., 2001a). Somatostatin appears to provide a tonic inhibitory effect, as local administration of somatostatin antagonists augments behaviors elicited by formalin and increases nociceptor activity (Carlton et al., 2001b). On the other hand, neuropeptide Y, which is co-released with NA and ATP from sympathetic nerves, can exacerbate hyperalgesia when applied locally to peripheral nerve terminals in a nerve injury model (Tracey et al., 1995b). This effect may be secondary to an action on postganglionic sympathetic nerves. It is likely that the peripheral modulatory influences of neuropeptides on pain signaling are only partially understood at present.

M. Antagonists for Inflammatory Mediators

1. Prostanoids. Inhibition of the production of prostaglandins is a well recognized therapeutic approach, and this forms the basis of the NSAID class of analgesics (*Section III.A.*). An additional strategy involving this class of mediators could be to develop specific antagonists for particular prostanoid receptors. All members of the prostanoid receptor family have been cloned; all are coupled to G-proteins and the pattern of coupling determines the consequences of receptor activation (Coleman et al., 1994). In situ hybridization studies reveal the presence of mRNA for multiple prostanoid receptors in dorsal root ganglion neurons (Sugimoto et al., 1994; Oida et al., 1995). The major effect of prostanoids on sensory afferents is to sensitize these to the actions of chemicals, heat, and mechanical stimuli, and prostaglandin E_2, prostacyclin I_2, leukotriene B_4, and leukotriene D_4 exhibit the more prominent roles in this regard (Bevan, 1999; Raja et al., 1999). Whereas antagonism of prostanoid receptors remains a potential therapeutic strategy, only a limited number of such agents are presently available (Rang et al., 1999).

2. Bradykinin. Activation of bradykinin B_2 receptors on sensory nerves produces pain and hyperalgesia by depolarization and sensitization of nerve fibers to physical stimuli (heat and mechanical), whereas activation of B_2 receptors on other tissues such as sympathetic nerves and inflammatory cells stimulates the production of proinflammatory mediators such as prostanoids and cytokines (Dray, 1997). The B_1 receptor, for which the major metabolite of bradykinin des-Arg^9-bradykinin has a greater affinity than the parent peptide, is expressed under inflammatory conditions and plays a prominent role in inflammatory hyperalgesia by actions on targets other than sensory nerves (Dray and Perkins, 1993; Davis et al., 1996). The involvement of both B_1 and B_2 receptors in inflammatory hyperalgesia suggests that kinin antagonists might be useful analgesics in such conditons. Both peptidic and nonpeptidic B_1 and B_2 antagonists have been developed (Hall, 1992; Dray and Urban, 1996). Peptidic antagonists have been available for some time, but the focus for drug development primarily has been on the development of orally active nonpeptide antagonists (e.g., Asano et al., 1997). Given that central activation of B_2 receptors also may contribute to pain (Dray, 1997), systemic antagonists may have the advantage of multiple sites of action. However, the possibility of topical application of nonpeptidic B_1 and B_2 antagonists could be considered, because such preparations could potentially avoid adverse effects at central sites or in tissues other than the one in which the pain primarily originates.

3. ATP. The ability of local peripheral administration of ATP to elicit pain in humans has been known for some time (Bleehen and Keele, 1977), but it is only in the last few years that the receptors and mechanisms underlying this response have been understood. The excitatory effects of ATP on sensory neurons are now known to be mediated by $P2X_3$ ligand-gated cation channels (Chen et al., 1995; Lewis et al., 1995). This receptor is selectively expressed in capsaicin-sensitive C-fibers, and heteromeric forms ($P2X_2/P2X_3$) can mimic the action of the native receptor (Jarvis and Kowaluk, 2001). ATP may play an important role in pain signaling in inflam-

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mation and following nerve injury (Bland-Ward and Humphrey, 2000; Burnstock, 2000; Hamilton and McMahon, 2000). In behavioral studies, local administration of ATP and its analogs produces overt pain behaviors (Bland-Ward and Humphrey, 1997) that are enhanced by inflammation (Sawynok and Reid, 1997; Hamilton et al., 1999, 2000), as well as mechanical allodynia (Tsuda et al., 2000). Following nerve injury, $P2X_3$ receptors are up-regulated in dorsal root ganglia and the dorsal spinal cord (Novakovic et al., 1999; Tsuzuki et al., 2001). ATP increases firing of Aβ-afferent fibers (Chen et al., 2001), enhances the activity of units showing ectopic activity (Zhou et al., 2001a), and interacts with the sympathetic nervous system following nerve injury (Park et al., 2000). Collectively, the above observations indicate that peripheral ATP receptors on both capsaicin-sensitive and capsaicin-insensitive neurons may mediate elements of inflammatory and neuropathic pain by actions on $P2X_3$ and $P2X_{2/3}$ heteromers. This raises the possibility that antagonists selective for these receptors might be useful as peripherally acting or topical analgesics (Jarvis and Kowaluk, 2001).

4. Biogenic Amines. 5-HT is contained in platelets, and in several species (although not humans), in cutaneous mast cells. 5-HT produces pain when applied to the human blister base and is a well recognized algogen (Richardson et al., 1985). Applied peripherally to rodents, 5-HT produces spontaneous pain behaviors and hyperalgesia, particularly when combined with other inflammatory mediators such as prostaglandin E_2, bradykinin, NA, and histamine (Taiwo and Levine, 1992; Hong and Abbott, 1994; Abbott et al., 1996) or injected in combination with a low concentration of formalin (Doak and Sawynok, 1997). There is considerable electrophysiological data supporting both excitation and sensitization of nociceptive afferents by 5-HT (Kress and Reeh, 1996). Peripheral 5-HT actions are due to activation of ligand-gated cation channels via 5-HT_3 receptors (Richardson et al., 1985) as well as via 5-HT_1, 5-HT_2, and 5-HT_4 receptors that exert effects through G-protein-coupled receptors (Taiwo and Levine, 1992; Abbott et al., 1996; Doak and Sawynok, 1997). The local peripheral administration of antagonists selective for several of these receptors reduces pain elicited by inflammatory mediators and inflammation (Giordano and Roberts, 1989; Abbott et al., 1996, 1997; Doak and Sawynok, 1997; Parada et al., 2001). Such observations indicate that local formulations of 5-HT antagonists may be a potentially useful approach for inflammatory pain. In humans, topical odansetron, a selective 5-HT_3 receptor antagonist, reduces pain elicited by intradermal capsaicin (Giordano et al., 1998) providing direct support for this concept. Peripheral analgesia by 5-HT_3 receptor antagonists can be augmented by combination with other 5-HT receptor antagonists (Espejo and Gil, 1998), or subanesthetic doses of local anesthetics (Giordano and Sacks, 1997), indicating that combination strategies involving this class of agents might be worthy of further attention.

Histamine originates from storage granules in mast cells and basophilic leukocytes that infiltrate inflamed tissue from blood. The most prominent local action of histamine in skin is itch, reflecting a direct action on sensory nerves, as well as wheal, reddening, and extravasation due to vasodilation; there is a further and more widespread flare response due to an axon reflex or neurogenic inflammation (Simone et al., 1987). Histamine alone produces some activation of sensory afferents, but more prominently, it sensitizes the nerve terminal to the action of other inflammatory mediators (Hong and Abbott, 1994; Carstens, 1997). These stimulatory actions are due to activation of histamine H_1 receptors on the sensory nerve, which produces an increase in membrane Ca^{2+} permeability (Ninkovic and Hunt, 1985); further actions may occur secondarily to the release of peptides from sensory afferent terminals (Saria et al., 1988). In rodent models, the local peripheral application of antagonists for histamine H_1 receptors produces analgesic responses in the formalin test (Sawynok et al., 2000a; Parada et al., 2001).

In humans, when itch is a prominent complaint, topical antihistamine preparations such as doxepin (a tricyclic antidepressant with prominent histamine blocking actions) have been used to control the itch (Drake et al., 1995; Smith and Corelli, 1997). As noted above (*Section III.E.*), topical doxepin can also relieve neuropathic pain (McCleane, 2000a,b). This raises the possibility that antihistaminic actions of antidepressants may contribute to analgesia by this class of agents. However, itch and pain appear to be distinct sensations (McMahon and Koltzenburg, 1992; Carstens, 1997), such that the extent to which antihistaminic actions account for the peripheral analgesic action of antidepressants is not clear (Sawynok et al., 2000a).

5. Nerve growth factor. NGF is a target-derived survival factor that plays an important role in development and plays a critical role in the regulation of sensory neuron properties in inflammatory and neuropathic states in adult animals (Lewin, 1995; McMahon and Priestley, 1995; McMahon and Bennett, 1999). NGF sensitivity can distinguish particular subsets of sensory neurons, regulate peptide, ion channel, and growth factor expression in such neurons (McMahon and Bennett, 1999; Gould et al., 2000). NGF involvement in inflammatory and neuropathic pain differs, and deficits can result not only from a neurotropin excess but also from a deficiency.

During inflammation, tissue levels of NGF are increased, and the administration of anti-NGF antibodies reduces inflammatory hypersensitivity (Donnerer et al., 1992; Woolf et al., 1994). Peripheral actions of NGF on sensory neurons, mast cells, and sympathetic efferents (transiently) contribute to the hyperalgesia (Woolf et al., 1996). Central actions, mediated by changes in the ex-

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pression of neuropeptides, ion channels, and growth factors in the sensory neurons, contribute to later manifestations (Donnerer et al., 1992; Leslie et al., 1995; Michael et al., 1997). Although drugs that inhibit the actions of NGF (e.g., antibodies, fusion proteins) may be useful for the treatment of chronic inflammatory pain, large proteins are likely to be of limited use systemically (Rang et al., 1999). Whereas topical or local delivery forms of simpler molecules that inhibit NGF actions (e.g., ALE-0540; Owolabi et al., 1999) may selectively target peripheral components of action and minimize actions at central sites, NGF exerts actions at multiple peripheral targets (e.g., mast cells, eosinophils, T-, and B-cells; McMahon and Bennett, 1999). It is unclear if such an agent would have the required target specificity to be an effective analgesic agent.

In contrast to inflammatory pain, neuropathic pain may benefit from the augmentation of NGF. Thus, following nerve injury, sensory neurons become disconnected from their targets and the supply of NGF is reduced; this leads to a compensatory response in which non-neuronal cells now produce NGF, and the NGF now exerts neuroprotective effects on the sensory neuron (McMahon and Bennett, 1999). In functional studies, NGF can ameliorate adverse effects on neural function induced by streptozotocin and cytostatic drugs and nerve injury in rodent models (McMahon and Priestley, 1995; Ren et al., 1995). In humans, recombinant human NGF has been demonstrated to improve chemotherapy-induced neuropathies (Apfel et al., 1992), diabetic neuropathy (Apfel et al., 1998), and human immunodeficiency virus-associated sensory neuropathy (McArthur et al., 2000). On the other hand, there are reports that NGF regulates sympathetic sprouting into dorsal root ganglia and contributes to sympathetically maintained pain (Ramer et al., 1999) and, when applied to dorsal root ganglia, triggers a persistent allodynia (Zhou et al., 2000b). In addition, a novel nonpeptide NGF antagonist has an anti-allodynic action in a spinal nerve ligation model (Owolabi et al., 1999). Such observations suggest that *block* of NGF activity might be useful in alleviating manifestations of neuropathic pain. Further study is required, particularly because it is recognized that actions of NGF on behaviors can be complex, reflecting both central and peripheral actions (Lewin et al., 1994; Lewin, 1995), early and delayed responses (Ro et al., 1999), and can depend on the location of the nerve injury (Ramer and Bisby, 1999). Similarly, the role of regulation of NGF actions that remain limited to peripheral actions by localized delivery methods remains to be determined.

IV. Conclusions

Peripheral pain signaling in conditions of chronic pain involving inflammation and nerve injury can involve the actions of a complex array of chemical mediators that impinge upon the sensory nerve. This can reflect direct actions on the sensory nerve, or indirect actions on sites adjacent to the sensory nerve. Inflammatory pain, in particular, involves the actions of multiple peripheral mediators that frequently interact with each other to produce a more pronounced activation of the sensory nerve terminal (sensitization, facilitation). The success of a strategy that targets a particular mediator will depend on the overall contribution of that mediator to pain signaling in relation to other mediators. Thus, the success of the therapeutic strategy of inhibiting the production of prostaglandins, which are only one class of pain facilitators, may reside in their ability to sensitize nerve endings to multiple mediators, as well as to actions at multiple steps in the complex cascade of inflammatory pain (e.g., release from adjacent structures by other mediators). For neuropathic pain, peripheral pain signaling mechanisms involving hyperexcitability/spontaneous activity of afferents is also an important contributor to pain. In this instance, there may be a differential involvement of particular peripheral mediators compared with chronic inflammation, with certain elements that have been perturbed playing a particularly prominent role. Considerations in the body of this review indicate that both inflammation and nerve injury pain are amenable to modulation by the peripheral application of drugs, such that both conditions potentially can benefit from the topical application or localized application of appropriate agents for the relief of pain. The success of a particular strategy in a particular condition may reflect the degree of involvement of inflammatory versus neurogenic components. Although these are not mutually exclusive categories, it may be that some treatments are more effective for certain conditions than others. For example, NSAIDs or other strategies that primarily target inflammation may have limited efficacy in nerve injury pain, and the latter condition may be more amenable to drugs that act directly on the sensory nerve to dampen down sensory afferent nerve activity.

The above review has focused on specific targets and classes of drugs. In recognizing the chemical complexity of pain signaling, it is important to appreciate that optimal pain relief may require combinations of more than one agent. Thus, although individual treatment strategies may give significant pain relief, this still may be only partial and require the addition of another ingredient for a more complete effect. With inflammatory pain, combinations could include any number of multiple targets for inflammatory mediators. With neuropathic pain, there are again examples of agents that can act peripherally to regulate pain expression. An interesting aspect of such combinations would be agents that target mechanisms on C-fibers as well as Aβ-fibers, because this would provide a more complete spectrum of pain relief. Finally, if tolerance occurs to repeated peripheral application of analgesics (as shown for opioids), then combination strategies might target a suppression of

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mechanisms involved in tolerance (e.g., NMDA receptor antagonists with opioids). Thus, as topical formulations of drugs are developed, it is clear that certain combinations may be useful to develop as well. With the potential for fewer systemic adverse drug effects and drug interactions, topical formulations of analgesics for chronic pain conditions represent a promising area for future drug development.

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