Perspectives in Pharmacology

Pharmacology of Opioid and Nonopioid Analgesics in Chronic Pain States

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Received March 26, 2001; accepted July 6, 2001 This paper is available online at http://jpet.aspetjournals.org

ABSTRACT
Chronic pain represents a mixture of pathophysiologic mechanisms, a complex assortment of spontaneous and elicited pain states, and a somewhat unpredictable response to analgesics. Opioids remain the mainstay of treatment of moderate to severe chronic pain, although there is little systematic examination to guide drug selection. Cyclooxygenase inhibitors play primarily an adjunctive role in chronic pain treatment. Agents with little activity in the treatment of acute pain, such as antidepressants, antiepileptics, and i.v. administered local anesthetics, are initiated in many patients and have significant long-term efficacy in some patients with chronic pain. The N-methyl-D-aspartate antagonist ketamine and the /H2-adrenergic agonist clonidine exhibit activity in patients with acute or chronic pain and reduce opioid consumption, but are often poorly tolerated due to side effects. Topical treatment with capsaicin or lidocaine exhibits efficacy in a subset of patients, and invasive intrathecal treatment with opioids as well as clonidine, neostigmine, and adenosine may have advantages in some patients. Several laboratory models have been developed to mimic chronic pain states found in humans. Nerve injury has been induced in rats by a variety of means, resulting in mechanical allodynia and thermal hyperalgesia. A number of arthritic states have also been produced by means of chronic joint inflammation in rats. The pharmacology of these neuropathic and arthritic pain models generally resembles that found in the respective human conditions. Additional models of chronic pain, particularly visceral pain, have been developed; however, the pharmacology of these models is not well established at this time.

Heterogeneity of Chronic Pain
Although pain is part of our daily experience, the vast majority of the time it is trivial, transient, or easily treated with simple over the counter drugs. Some people experience more severe and recurring pain from various etiologies, often from peripheral tissue inflammation or destruction. Some of these individuals, and others for whom no peripheral pathophysiology is evident, experience stimulus-independent and/or -dependent pain, reflecting presumably abnormal spontaneous afferent activity, alterations in central processing, and/or increased afferent sensitivity. This leads to a clinical syndrome of neuropathic pain, including persistent pain, typically of a shooting or burning nature, and hypersensitivity to mechanical or thermal stimuli. This type of pain is often resistant to treatment with simple analgesics or with traditional agents but may be sensitive to other classes of drugs that normally produce no effect on pain transmission, such as antidepressants. The generation of this shift in neurotransmission and in plasticity of pharmacologic response is the subject of considerable preclinical work, and animal models reveal a complex underlying array of shifting peripheral and central anatomic and neurophysiologic changes, many of which are model-specific (Woolf and Salter, 2000).

Clinical classification and diagnosis of chronic pain remain controversial. Although chronic pain has often been classified according to an associated disease (alcoholic or diabetic neuropathy, postherpetic neuralgia, cancer, arthritis) or symptom complex (complex regional pain syndrome, fibromyalgia), neither of these classifications reliably predicts response to pharmacotherapy. This may reflect a mixture within each disease classification of pathophysiology, as exemplified by the recent observation that some patients with postherpetic neuralgia exhibit evidence of peripheral denervation, whereas others have hyperexcitability peripherally mediated responses (Petersen et al., 2000). Additionally, more than one

ABBREVIATIONS: NMDA, N-methyl-D-aspartate; CCI, chronic constriction injury; COX, cyclooxygenase; GABA, /H2-aminobutyric acid; PSL, partial sciatic ligation; SCN, sciatic cryoneurolysis; SNL, spinal nerve ligation; SNS, sciatic nerve section.
pathologic process may coexist simultaneously in one patient, or the pathophysiology of pain and hypersensitivity may change over time in a poorly predictable manner within patients with the same disease. This has led some to suggest that associated diseases and symptom complex be replaced with evaluation of ongoing and elicited pain phenomena to classify patients for the purpose of clinical trials (Wooll and Mannion, 1999). At any rate, the treatment of chronic pain remains empiric.

**Clinical Opioid Pharmacology**

Aside from butorphanol and nalbuphine, all clinically available opioids are \( \mu \)-opioid receptor preferring agents. The \( \kappa \)-opioid agonists, butorphanol and nalbuphine, are limited by partial agonist activity as well as central side effects, primarily dysphoria, sedation, and hallucinations, and are little used in the treatment of chronic pain. Oxycodone has only recently been suggested to be a \( \kappa \)-opioid preferring agonist (Ross and Smith, 1997), and has not been systematically examined in the treatment of chronic pain. Thus, although there is strong preclinical evidence for efficacy of \( \kappa \)-opioid agonists in chronic pain treatment, current agents are inadequate, and novel agents are under experimental study in humans.

Barriers to effective treatment of chronic pain with \( \mu \)-opioid agonists are primarily regulatory and related to unsubstantiated fears. These concerns include the development of dependence and addiction as well as side effects such as sedation, dysphoria, and constipation from this class of agents. Clinical research in the use of these agents for chronic pain has focused on relative efficacy, side effects, and development of tolerance. As regards efficacy, choice of opioid reflects economic or convenience factors, with a focus on long-acting, orally available, and inexpensive drugs. There is little systematic study to support efficacy of one drug over another. The recent observations that methadone may exhibit important NMDA antagonist as well as opioid agonist properties (Ebert et al., 1995) and that it is a more efficacious agent than morphine in in vitro assays (Selley et al., 1998) has led to renewed interest in this long-acting, inexpensive opioid treatment for chronic pain. Indeed, recent anecdotal clinical data support a greater efficacy of methadone than other \( \mu \)-opioid agonists in patients with chronic pain (Mercadante et al., 1999). As regards side effects, all clinically available opioids appear to have similar incidences of side effects at equianalgesic plasma concentrations with subacute administration, although an individual may experience side effects from one agent and not another, leading to an empiric approach to therapy.

Tolerance to opioids and responsiveness of chronic pain to opioids remain controversial. Dose escalation commonly occurs with chronic opioid treatment for analgesia (Mercadante, 1999) but varies considerably among individuals, is usually gradual and of a much lesser extent than observed in animals, and is often accompanied by tolerance to bothersome side effects. The cause of dose escalation is uncertain, as it may reflect tolerance, disease progression, or change in pathophysiologic mechanism of pain. Thus, although tolerance undoubtedly occurs with the use of opioids for chronic pain, the importance of this factor compared with others remains unclear.

Publication of a report that neuropathic pain, regardless of etiology, is unresponsive to opioids (Arner and Meyerson, 1988) led to a decade-long debate on the use of opioids in this and, by extension, all types of chronic pain. Most clinicians believe that opioids are effective and rely on them as a central component in the pharmacologic treatment of chronic pain, whether the primary symptoms can be characterized as neuropathic or otherwise. There is also a consensus that larger doses of opioids may be necessary to treat hypersensitivity phenomena associated with neuropathic pain than acute pain (Benedetti et al., 1998), and these larger doses may limit therapy.

**Clinical Nonopioid Pharmacology**

Because of the side effects, dose escalation, and regulatory and psychological issues surrounding chronic opioid treatment, there has been a large preclinical effort to develop nonopioid therapies in the treatment of chronic pain. A description of the many targets implicated in nociception or in neuronal plasticity in various animal models of chronic pain is beyond the scope of this review. Below is a brief summary of drug classes exhibiting enough apparent efficacy that they are routinely administered in the clinic.

**COX inhibitors** are the first step in the World Health Organization scheme for the treatment of chronic pain, and the majority of patients with chronic pain receive these agents as a base throughout their treatment. Evidence that these agents exert some of their analgesic effects via actions in the spinal cord (Malmberg and Yaksh, 1992) and that these agents prevent development of tolerance to opiates at this site has led to an interest in intrathecal therapy with COX inhibitors for chronic pain treatment. Similarly, development of COX2-specific inhibitors has led to use of this target in patients who have treatment-limiting side effects from nonselective agents.

**NMDA antagonists** exhibit powerful inhibition of both production and maintenance of hypersensitivity states in various preclinical models of chronic pain, and have demonstrated efficacy in patients with chronic pain. The most potent and efficacious of clinically available agents, ketamine, produces unacceptable side effects, primarily sedation, dysphoria, and hallucinations, and is not routinely used for this purpose. The less efficacious drugs dextromethorphan, memantine, and amantadine have demonstrated analgesic activity in some, but not all clinical trials, and have similarly resulted in therapy-limiting side effects. Thus, although the NMDA receptor may play a key role in plasticity associated with many causes of chronic pain, it has been difficult to separate the wanted effect of antagonism of this receptor for analgesia from side effects.

**Antidepressants**, usually in doses much lower than those required to treat depression, are effective as adjunctive agents in a large minority of patients with chronic pain, including those with neuropathic pain (McQuay and Moore, 1997). The mechanisms by which these agents act are uncertain and have been hypothesized to include inhibition of monoamine reuptake, NMDA antagonism, \( \mathrm{Na}^+ \) channel blockade, and stimulation of adenosine release. Structure-activity relationship suggests that agents with primarily norepinephrine or mixed monoamine reuptake inhibition are
more effective than serotonin-specific reuptake inhibitors (Onghena and Houdenhove, 1992).

**Antiepileptics**, traditionally carbamazepine and phenytoin, are commonly administered for chronic pain. The high incidence of therapy-limiting side effects with these agents and the antidepressants probably explains the rapid and widespread use of a newer antiepileptic, gabapentin. The clear efficacy of this agent in patients with hypersensitivity and chronic pain, as well as its tolerability (Backonja et al., 1998), has led to multiple preclinical studies of the mechanism of action of gabapentin. Inhibition of calcium channels, excitatory amino acid release, and modulation of GABA receptor activity or GABA release have been postulated.

**Local anesthetics**, administered in relatively low doses i.v., reduce hypersensitivity and reduce pain in patients with neuropathic pain (Wallace et al., 1996). Presumably this reflects actions on novel or up-regulated Na⁺ channels on primary afferents, as well as silencing abnormal spontaneous activity in these afferents, which provides a constant drive to maintain the hypersensitivity state. Although these effects can be demonstrated clinically, therapy with local anesthetics is limited by the need to give agents such as lidocaine via the i.v. route, and by the high incidence of intolerable side effects with the orally acting agent, mexilitine.

**Topically applied agents** are also utilized in clinical practice to treat chronic pain. The opioid agonist, fentanyl, is applied in a transdermal preparation, but this is merely a convenient method of systemic administration. Topical capsaicin cream is approved for the treatment of postherpetic neuralgia and acts presumably by causing temporary degeneration of C fiber terminals in the skin of the treated area. Its use is limited by selection of patients with appropriate pathology (as noted above, some patients with postherpetic neuralgia have evidence of peripheral denervation, not hyperactivity), pain on application, and identification and size of affected area for application. Transdermal lidocaine was recently approved for the treatment of pain. Although it is not limited by pain on application, similar problems with identifying appropriate patients, areas, and sizes of application will likely limit this therapy.

**Epidural clonidine** is approved in the treatment of neuropathic cancer pain and is effective in approximately 50% of patients refractory to epidural opioids (Eisenach et al., 1995). Clonidine reduces hypersensitivity and alleviates chronic pain by its action on α₂-adrenergic receptors. Animal models of neuropathic pain often exhibit complete loss or reduced activity of opioid receptors (as noted above, often observed clinically), whereas the potency and efficacy of α₂-adrenergic agonists increases in these models. The reasons for this pharmacologic plasticity are uncertain; however, both anatomic and neurophysiologic changes have been postulated. Clonidine is only effective when administered near its site of action in the spinal cord. Although it is the second most commonly administered agent epidurally or intrathecally in the setting of chronic pain, its use may be limited by cardiovascular depression and sedation. Other agents that exhibit activity in preclinical models have undergone neurotoxicity screening, and are under clinical investigation, including neostigmine, which inhibits acetylcholinesterase activity and results in analgesia in animals mediated by both muscarinic and nicotinic systems; adenosine, which results in analgesia in animals mediated by A1 adenosine receptor mechanisms, and SNX-111, which acts through calcium channel blockade.

### Neuropathic Pain Models in Laboratory Animals

The neuropathic pain models that have been developed to date generally involve surgical manipulation of the sciatic nerve, surgically induced damage to spinal nerves related to the sciatic nerve, or induction of pathological states within the spinal cord itself by a variety of chemical or surgical manipulations. Although this review is focused primarily upon the pharmacology of these various models, an overview of what is known in regard to the pathophysiology resulting from these experimental manipulations is provided as a basis for understanding the rationale for the pharmacological studies. The pharmacology has not been well developed for certain of these models, and therefore the model itself is presented primarily for comparison with the other models for which more pharmacological data are available.

A number of neuropathic pain models have been developed in laboratory animals within the last several years that involve direct manipulation of the sciatic nerve. These include sciatic cryoneuromyelosis (SCN); sciatic nerve section, ligation, or crush (SNS); partial sciatic ligation (PSL); and chronic constriction injury (CCI). Each of these models of neuropathic pain seeks to cause at least somewhat selective damage to the sensory component of the sciatic nerve while leaving the motor component largely intact. These models display numerous common features with a few salient differences that are highlighted below.

**Sciatic Cryoneurolysis (SCN).** Cryoneurolysis or cryoblation is a surgical procedure that involves destroying nerves by rapid freezing and has been used for the treatment of neuropathic pain in some instances, albeit with limited success (Evans, 1981). In several cases, this procedure can exacerbate rather than alleviate chronic pain syndromes (Conacher et al., 1986). In laboratory animals, sciatic cryoneurolysis is achieved by rapid freeze-thaw-freeze cycles with the sciatic nerve using a cryoprobe (DeLeo et al., 1994). This procedure produces hypoesthesia in the ipsilateral hind paw in the first few days due to direct damage to the sciatic nerve (DeLeo et al., 1994). However, as the nerve begins to recover from injury, mechanical allodynia develops that persists for up to 10 weeks (Willenbring et al., 1994). The development of allodynia is accompanied by an increase in both the incidence and severity of autotomy, self-injurious behavior to the affected hindlimb, which is a measure that has been associated with ongoing pain in animals (Willenbring et al., 1994). An increase in the inflammatory cytokine interleukin-6 occurs in both the ipsilateral and contralateral dorsal horn following SCN and is correlated temporally with the development of allodynia in this model (DeLeo et al., 1996). This suggests that inflammatory processes may underlie the developing pathology as the sciatic nerve recovers partially from freeze injury.

Some patients with chronic pain conditions receive significant pain relief following reduction of sympathetic nervous system activity in the region of their pain, a condition commonly referred to as “sympathetically maintained pain”. It has been suggested that such pain is maintained by increased activity of sympathetic efferents, abnormal sprouting...
of sympathetic efferents, especially those surrounding dorsal root ganglion cells, or novel expression of excitatory adrenergic receptors on afferent terminals or cell bodies. Sympathectomy prior to SCN does not attenuate or retard the development of allostynia, suggesting that SCN is a model of sympathetically independent neuropathic pain (Willenbring et al., 1995a). There is a relative paucity of pharmacological information available with this model; however, the \( \mu \)-opioid agonist fentanyl and kainate receptor antagonists display relatively weak antiallodynic effects in rats following sciatic cryoneurolysis (Ta et al., 2000). Consistent with the findings of sympathectomy, \( \alpha_1 \)-adrenergic antagonists and \( \alpha_2 \)-adrenergic agonists produce little, if any, effects on allostynia produced by SCN (Willenbring et al., 1995b).

**Partial Sciatic Nerve Ligation (PSL).** Another technique for producing neuropathic pain in animals is to ligate the dorsal one-half to one-third of the sciatic nerve, a model first described by Seltzer et al. (1990). The dorsal aspect of the sciatic nerve contains primarily sensory fibers and therefore tight ligatures placed around this portion of the nerve will result in neuronal death while sparing motoneurons that are contained in the more ventral aspects of the sciatic nerve. Allostynia and hyperalgesia develop rapidly following PSL and persist for approximately 2 weeks following nerve injury. Female rats have been reported to be more susceptible than males to the production of mechanical allostynia following PSL (Coyle et al., 1995). The behavioral consequences of this technique are reasonably similar to those of SCN, namely, abnormal posturing of the ipsilateral hindlimb in a guarded position and hypolocomotion. Although PSL decreases latency to withdrawal from a mild heat stimulus (40–42°C) and decreases paw withdrawal threshold, the strength of the withdrawal response is not affected, nor are the receptive fields altered for thermal or mechanical stimuli (Takaishi et al., 1996). The mechanical allostynia produced by partial sciatic nerve ligation is responsive to nicotinic agonists (+)-epibatidine and ABT-594 (Kesingland et al., 2000) as well as the antiepileptic drug gabapentin (Pan et al., 1999).

**Sciatic Nerve Section (SNS).** Others have induced neuropathic by ligating, severing, or crushing a part of or the entire sciatic nerve. Crush injury of the sciatic nerve results in development of thermal cold allostynia within 7 to 12 days that is responsive to i.t. opioids and \( \alpha_2 \) agonists (Przewlocka et al., 1999). Ligation of or severing the sciatic nerve results in loss of motor function within the affected hindlimb and generally leads to the development of autotomy that increases in severity and frequency over the month following nerve section. Pretreatment with opioids prior to sciatic ligation retards the development of autotomy; however, after 3 to 4 weeks, autotomy develops to a similar extent regardless of opioid pretreatment (Puke and Weisenfeld-Hallin, 1993). The effect of morphine pretreatment has been linked to its ability to prevent the development of spinal reflex hyperexcitability following SNS (Luo et al., 1994). Chronic treatment with \( \alpha_2 \)-agonists after nerve section produces similar results, and pretreatment with clonidine prior to SNS is ineffective at preventing the development of autotomy (Puke and Weisenfeld-Hallin, 1993). Pretreatment intrathecally with local anesthetics also has no effect on the development of autotomy following SNS (Luo and Weisenfeld-Hallin, 1995). As with the above two models, pharmacological data available with SNS are relatively scarce.

**Chronic Constriction Injury (CCI).** This model was first described by Bennett and Xie (1988) and involves placing four loose ligatures around the sciatic nerve at the mid-thigh level. Mechanical allodynia and thermal hyperalgesia develop, usually within 1 week or less and persist for 2 to 3 weeks. Behavioral signs consist of abnormal posturing or guarding of the affected hindlimb and elongation of nails due to lack of attention to and use of the ipsilateral hindlimb. A closely related model has been developed involving placement of a polyethylene cuff around the sciatic nerve, which results in similar pathophysiology and behavioral symptoms (Mosconi and Kruger, 1996). Numerous physiological and neurochemical changes have been documented in animals following CCI. Both calcitonin gene-related peptide and substance P immunoreactivity decrease from 1 to 4 weeks following CCI, whereas met-enkephalin immunoreactivity increases in the dorsal horn during the later recovery phase (Sommer and Myers, 1995). Similar alterations were found in mRNA levels for calbindin gene-related peptide and substance P in dorsal root ganglia following CCI, with an up-regulation in the expression of mRNA for neuropeptide Y and vasoactive intestinal peptide (Nahin et al., 1994). Lumbar neurons in the dorsal horn of the spinal cord on the ipsilateral side to the injured nerve display spontaneous firing at approximately 5 times the rate of those on the contralateral side following CCI, and this rate is suppressed by electrical stimulation of the nucleus raphe magnus (Sotggi, 1993). Dorsal root ganglia also display increased spontaneous firing following CCI (Study and Kral, 1996). CCI results in an increase in the metabolic activity of numerous brain regions measured by 2-deoxyglucose uptake, including numerous somatosensory cortical areas, thalamic regions, limbic areas, and brainstem regions known to be involved in pain transmission (Mao et al., 1993). The explicit role of these physiological and neurochemical changes remains to be elucidated.

Following CCI, thermal hyperalgesia and mechanical allostynia develop that are responsive to both systemic (Desmeules et al., 1993) and spinal (Levy et al., 1994) injections of opiates. Intrathecal administration of \( \alpha_2 \)-adrenergic agonists also reverses the mechanical allodynia and thermal hyperalgesia that develop following CCI (Levy et al., 1994). Intrathecal administration of the cyclooxygenase inhibitor ketorolac decreases mechanical and thermal allostynia following CCI, although it is less effective than morphine (Parris et al., 1996). Subchronic i.v. infusion of morphine for 7 days will reverse the effects of CCI on latency and duration of withdrawal from mechanical, and thermal stimuli and no evidence was found for the development of tolerance after 7 days of treatment (Backonja et al., 1995). In contrast, s.c. administration of 10 mg/kg morphine twice daily has been found to produce tolerance to the effects of i.v. morphine on vocalization threshold after only 4 days of treatment (Idänpää-Heikkilä et al., 1997). Intrathecal administration of morphine increases ambulation in animals following CCI injury; however, chronic treatment results in the development of tolerance to this effect after only 4 days (Levy et al., 1994). Chronic i.t. administration of tizanidine, an \( \alpha_2 \)-agonist, produces effects similar to those of morphine in this model, and tolerance also develops over 4 days of treatment (Levy et al., 1994). Therefore, although the allodynia and hyperalgesia that develop following CCI in rats are responsive to opioids, there appears to be some discrepancy regarding the develop-
ment of opioid tolerance depending upon the behavioral measure that is used and the opioid dosing regimen.

L5/L6 Spinal Nerve Ligation (SNL). One other model that is similar to the above-mentioned models has been developed by Kim and Chung (1992). This model involves tight ligation of the L5 and L6 spinal nerves just distal to the dorsal root ganglion and prior to joining with the L4 nerve to form the sciatic nerve. This procedure results in the development of mechanical allodynia and, to a lesser extent, thermal hyperalgesia that develop within 7 to 10 days and persist for up to several months (Kim and Chung, 1992). The allodynia and hyperalgesia are more robust when the procedure is performed in young (40- to 50-day-old) compared with mature (100- to 120-day-old) or aged (15-month-old) Sprague-Dawley rats (Chung et al., 1995). In addition to mechanical allodynia and thermal hyperalgesia following SNL, rats display ventroflexion of the toes and foot eversion (posturing outward from the body), postures thought to be related to the presence of ongoing pain. Animals also display a guarding behavior, in which the foot is elevated and contact with any surface is avoided. This postural effect has been attributed to both the presence of ongoing pain and an effect on motor neurons, in that rhizotomy of the ventral roots of the L5 and L6 nerves will produce this abnormal foot posture in the absence of mechanical allodynia or thermal hyperalgesia (Na et al., 1996). Abnormal mechanoreceptors arise in innervations of the plantar surface of the affected hind paw following SNL that display a prolonged response to a mechanical stimulus on the hind paw (Na et al., 1993). These abnormal mechanoreceptors are thought to mediate the allodynia and hyperalgesia observed in this model, and α2-adrenergic agonists inhibit their prolonged response to mechanical stimulation (Na et al., 1993). It has been postulated by some that this model displays sympathetically maintained chronic pain in that sympathetic nerve fiber sprouting is significantly greater in the dorsal root ganglia of the L5 and L6 spinal nerves following ligation, and the increase in sympathetic innervation of the dorsal root ganglion persists for up to 20 weeks (Chung et al., 1996). However, there are discrepancies in the literature regarding the effect of sympathetic denervation on the allodynia resulting from SNL (Lavand’homme et al., 1998). It has also been postulated that dynorphin may be a mediator of the chronic pain resulting from SNL in that spinal dynorphin levels are elevated following this procedure with a time course that is consistent with behavioral symptoms (Malan et al., 2000). Spinal application of dynorphin-related peptides will produce allodynia and hyperalgesia, an effect that is blocked by NMDA antagonists but not opioid antagonists (Vanderah et al., 1996). Others have demonstrated that NMDA receptor activation is important for both the induction and maintenance of mechanical allodynia and thermal hyperalgesia following partial denervation of the tail in rats (Kim et al., 1997).

There also appear to be supraspinal influences in the establishment and maintenance of allodynia and hyperalgesia associated with SNL. The rostroventral medulla contains both inhibitory and facilitatory fibers with respect to pain transmission (Fields et al., 1991). It is thought that spontaneous firing of facilitatory fibers within the rostroventral medulla may contribute to the effects of SNL, as infusion of lidocaine into this region following SNL results in a loss of mechanical allodynia and thermal hyperalgesia (Kovelowski et al., 2000; Pertovaara et al., 1996). Therefore, numerous changes are documented along the neuraxis from the foot to the brainstem that contribute to the development and maintenance of mechanical allodynia and thermal hyperalgesia following SNL. The influence of specific neuronal changes at higher brain centers as well as changes related to the development and maintenance of ongoing pain, if indeed it exists, are less clear following SNL.

The pharmacological investigations that have been conducted in the SNL model focus primarily on opioids, cyclooxygenase inhibitors, adrenergic agonists, cholinergics, and antiepileptic compounds. As with clinical neuropathic pain, opioids have only marginal efficacy in the SNL model, particularly following i.t. administration (Bian et al., 1995). Systemic administration of morphine is more effective than i.t. administration, displaying relatively modest antiallodynic effects at sedating doses (Bian et al., 1995; Martin et al., 1998). As with spinal administration, i.v. administration of opioid agonists that have greater efficacy than morphine, such as heroin and dihydroetorphine, display greater efficacy against the allodynia produced following SNL with a greater separation between the antiallodynic and sedative effects (Martin et al., 1998). The antinociceptive potency of opioids is diminished following SNL as well, as measured by the tail-flick assay, and this effect has been postulated to be due to a loss in spinal/supraspinal synergy that occurs as a result of peripheral nerve ligation and a remodeling of nociceptive circuitry within the dorsal horn of the spinal cord (Ossipov et al., 1995). There does not appear to be a loss in either opioid receptor number or second messenger coupling efficiency following SNL, but it may result from a change in the transmission of nociceptive input from C-fibers to Aβ fibers (Porreca et al., 1998). The ability of morphine applied spinally to reverse the allodynia resulting from SNL is enhanced by administration of antisera to dynorphin A(1-13) or the NMDA antagonist MK-801, suggesting that spontaneous dynorphin release may contribute to morphine’s loss of efficacy in this model (Nichols et al., 1997). Administration of dynorphin antisera or MK-801 also restores the antinociceptive potency and efficacy of morphine in inhibiting the tail-flick response following SNL (Nichols et al., 1997). Therefore, tonic stimulation of afferents by dynorphin through NMDA receptors may contribute to the lack of efficacy of opiates given spinally in this model.

Cyclooxygenase inhibitors display marginal effects in the SNL model of neuropathic pain. Inhibitors of either cyclooxygenase 1 (COX1) or cyclooxygenase 2 (COX2) do not produce significant antiallodynic effects when given either i.t. or systemically (Lashbrook et al., 1999). However, both COX1 and COX2 inhibitors potentiate the antiallodynic actions of i.t. morphine following SNL when administered i.v. or spinally (Lashbrook et al., 1999; Ossipov et al., 2000). Supra-additive effects are found when both COX1 and COX2 inhibitors are coadministered in conjunction with i.t. morphine (Lashbrook et al., 1999).

A number of other agents have been studied in the SNL model of neuropathic pain, including α2-adrenergics, NMDA antagonists, and neostigmine. Clonidine has recently been approved for use in patients with neuropathic pain, and this compound has been studied in the SNL model of neuropathic pain in laboratory animals. Intrathecal injection of a number of α2- but not α2-adrenergic agonists attenuates tactile allo-
dynia following SNL (Yakhsh et al., 1995). Clonidine given i.t. produces a robust antiallodynic effect in rats following SNL at dosages that are mildly sedating, and this effect is potentiated by coadministration of MK-501 (Lee and Yaksh, 1995). Clonidine administration i.t. also restores the potency of morphine’s antinociceptive effect, which is diminished in animals following SNL (Ossipov et al., 1995). Neostigmine given intrathecally produces antiallodynic effects and also enhances the actions of i.t. morphine in rats following SNL (Hwang et al., 2000). These agents in various combinations appear to potentiate the antiallodynic actions of each other while producing less sedation.

A number of antiepileptic drugs have also been studied in the SNL model of neuropathic pain. Of these, gabapentin (Neurontin) has recently received the most attention. Gabapentin produces robust antiallodynic effects following SNL, with both systemic or i.t. administration (Chapman et al., 1998; Chen et al., 2000; Hunter et al., 1997). Gabapentin also attenuates cold allodynia following SNL, an effect not shared by other antiepileptic agents such as carbamazepine and phenytoin (Hunter et al., 1997). Gabapentin reduces both spontaneous and evoked (mechanically, thermally, and electrically induced) responses in spinal neurones in both SNL and sham-operated animals (Chapman et al., 1998). The antiallodynic effects of i.t. administration of gabapentin are potentiated by coadministration of a non-NMDA antagonist (Chen et al., 2000). The relative lack of sedative effects following administration of doses effective in the SNL model make gabapentin a promising candidate for clinical studies.

Summary

Treatment of nonmalignant chronic pain continues to be a troublesome clinical problem. Issues such as side effects of long-term administration of analgesics, efficacy of treatment alternatives, and both tolerance to and physical dependence on opioids plague both clinicians and patients. The development of relevant laboratory animal models, particularly for the study of neuropathic pain and arthralgia, has greatly increased the systematic study of these issues and has identified various pharmacological classes as candidates for drug development. Issues such as abuse liability of opioids in the presence of persistent pain, as well as behavioral and biological consequences of chronic drug treatment in the presence of pain areas that are desirable continued attention. Hopefully, development of other models to address these issues for chronic pain syndromes other than neuropathic and arthritic pain will continue to evolve as well. Effective new treatments will hopefully arise for chronic pain management as both clinicians and basic scientists from multiple disciplines, particularly physiologists, pharmacologists, and psychologists focus on finding solutions to these problems.

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