The Peripheral Analgesic Effects of Opioids

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Results from numerous studies indicate that opioids produce effects through activation of receptors located in the central nervous system at spinal and supraspinal levels. However, opioids may also possess peripheral analgesic activity. Behavioral studies conducted in animals indicate that mu, kappa, and delta selective opioids possess significant antinociceptive activity after injection into hyperalgesic tissue by activation of a peripheral mechanism(s). These effects appear to be predominantly receptor-selective since they are dose-related, stereospecific, and blocked by administration of receptor antagonists. Recent clinical trials suggest that opioids activate a peripherally mediated analgesic mechanism in clinical models of pain due to inflammation. These results suggest that peripherally administered opioids or development of peripherally selective opioids may provide clinical analgesia without the development of traditional central nervous system mediated side effects. **Key words:** *analgesia, opioids, pharmacology, pain, inflammation*

The analgesic efficacy of opioids has been well established in numerous clinical and animal studies. Less clear, however, are their precise mechanisms of action and loci of activity. It is well recognized that opioids produce analgesia through activation of receptors located in the central nervous system (CNS) at both spinal and supraspinal levels.[6,95] However, recent studies suggest that opioids also may activate targets in inflamed tissue, resulting in a peripherally mediated suppression of sensitized nociceptors.

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PERIPHERAL EFFECTS OF OPIOIDS: ANIMAL AND CLINICAL STUDIES

The hypothesis for a peripheral site of opioid action was received initially with caution, because classical studies suggested that opioids are active only in the CNS. For example, Lim et al. used a cross-perfused spleen preparation in which the splenic blood supply was isolated from the rest of the dog's blood supply via splenic cannulas attached to another dog.[59] This type of surgical preparation allowed drugs to be injected into either the "periphery" (via injection into the isolated splenic circulation) or "centrally" (via injection into the rest of the dog's circulation). The paradigm used electrical or chemical stimulation of the spleen to elicit nocifensive behavior and recorded vocalization or splenic nerve activity as the dependent measure. Inspection of their data indicates that propoxyphene had substantial peripheral activity, while morphine appeared to have some peripheral effects. However, the major component of morphine antinociception was observed following "central" injection and, based on these results, the authors concluded that opioids are "centrally acting analgesics." The concept of opioids having only a CNS site of action was not seriously challenged for the next 10–15 years.

In the mid-1970s, Collier and Roy published a series of papers indicating that prostaglandins increase cyclic adenosine monophosphate (cAMP) in various CNS tissues, and that opioids suppress cAMP levels; these findings led to their suggestion that the mechanism for opioid analgesia is inhibition of adenylate cyclase.[22,23] Based on these findings, and on other studies demonstrating that prostanoids induce

hyperalgesia, Ferreira and Nakamura evaluated whether opioids have peripheral effects for suppressing prostaglandin-induced mechanical hyperalgesia.[25–27] In their experimental design, the test opioid was injected either into the hyperalgesic paw or into the contralateral control paw. A peripheral opioid effect was interpreted to be present if the antinociception was observed following an ipsilateral but not a contralateral injection. Using this approach, morphine was shown to have a peripheral site of action for blocking hyperalgesia due to intraplantar injection of PGE_2, prostacyclin, isoprenaline, $BaCa_2$, and A23187 (a calcium ionophore), but the opioid had no effect on hyperalgesia due to injection of dibutyrl cAMP.[26] Additional studies demonstrated that morphine, pentazocine, [Met]enkephalin, [Leu]enkephalin, nalorphine, and naloxone all produced dose-dependent peripherally mediated antinociception in hyperalgesic tissue with doses of 3–30 nmol/paw. In contrast, lidocaine required doses of about 1,000 nmol/paw to produce a peripheral effect.[26] Collectively, these results indicate that peripheral opioid analgesia has the following characteristics: (1) it is present when opioids are injected into hyperalgesic tissue; (2) it is not evident when opioids are injected into "normal" tissue; and (3) it may be due, in part, to inhibition of the adenylate cyclase system. This last conclusion was supported by the finding that opioids blocked hyperalgesia due to injection of agents that elevate cAMP (e.g., PGE_2, prostacyclin, isoprenaline), but had no effect on hyperalgesia due to administration of dibutyrl cAMP.[26]

Numerous studies have since extended these findings of peripheral opioid-induced antinociception (Table 1). An important observation was that peripheral opioid antinociception was not restricted to PGE_2-induced hyperalgesia, but was also evident in actual models of tissue inflammation. For example, the rat carrageenan model of inflammation[38] has been used to evaluate peripheral opioid antinociception to thermal stimuli.[46] In these studies, both hindpaws were injected with carrageenan; 90 minutes later one paw was injected with the test opioid, while the contralateral paw was injected with saline, using a randomized, double-blind, counterbalanced experimental design. This type of within-animal control permits interpretation of drug effects as due to activation of a peripheral target (i.e., analgesia in the opioid injected paw only) or to a systemic target (i.e., analgesia in both inflamed hind paws). These studies demonstrated that both fentanyl and ethylketocyclazocine had prolonged peripheral antinociceptive effects in blocking carrageenan-induced hyperalgesia to thermal stimuli. In addition, levorphanol produced a dose-related antinociception that was stereospecific (i.e., dextrorphan had no effect).[46] Additional behavioral studies indicate that opioids act peripherally to block the hyperalgesia that accompanies PGE_2 injection,[26,28,58] bradykinin injection,[89] abdominal writhing,[8,84] or actual tissue inflammation due to injection of carrageenan[27,28,46,76] or complete Freund's adjuvant.[85–87]

But is peripherally located opioid antinociception due to activation of a receptor-selective mechanism? The generally accepted criteria for evaluating a receptor-selective mechanism is demonstration of a dose-related, stereospecific, antagonist reversible effect. Although these criteria have not been evaluated in all peripheral opioid studies, they have been generally satisfied when tested (Table 1). Stein et al.[87] conducted an elegant series of studies evaluating the receptor selectivity of peripherally injected opioids. They demonstrated that dose-related, peripheral opioid antinociception was evident following intraplantar injection of mu (DAGO), kappa (U50,488H), and delta (DPDPE) selective agonists, and that the antinociception for each agonist was blocked only by administration of the respective mu (CTAP), kappa (nor-BNI), or delta (ICI 174,864) antagonist.

However, not all data supports a receptor-selective mechanism. For example, dextrorphan, an inactive stereoisomer, has activity in the writhing test,[8] but not in carrageenan-induced thermal hyperalgesia.[46] In addition, peripheral administration of the opioid antagonist naloxone has been reported to produce antinociception in some,[26,76,84] but not all studies.[8,85,86] Although it has been suggested that the peripheral naloxone-induced antinociception may be due to metabolic conversion of the antagonist to an agonist,[76] there is currently little biochemical data to support this hypothesis. It appears unlikely, however, that peripheral opioid antinociception is due to a nonselective local anesthetic-like action since peripherally administered opioids have little to no activity when injected into normal tissue.[58,85–87] Taken together, the majority of reported studies indicate that peripheral opioid antinociception is due to activation of a receptor-selective mechanism (Table 1), although the possibility exists that a concurrent nonselective or unique peripheral mechanism (i.e., metabolic conversion) contributes to the effect.

Collectively, these animal studies indicate that opioids have a peripheral site of action for blocking behavioral hyperalgesia. In contrast to this wealth of animal data, there is a relative paucity of data collected in clinical models of inflammation. A review of the clinical literature reveals several anecdotal re-

Table 1. Summary of behavioral studies evaluating peripheral antinociceptive effects of opioids

Opioid	Animal	Hyperalgesia Model*	Stimulus	Dependent Measure	Dose Response?†	Receptor Antagonist?	Stereo-specific?	Ref.
MU opioids								
Codeine	Mouse	AAW	Spontaneous	Stretch reflex	1.9 nmol/kg	—	—	7
DAMGO	Rat	CFA	Mechanical	Paw withdrawal	‡	Yes	—	80
DAMGO	Rat	Bradykinin	Mechanical	Paw withdrawal	‡	Yes	—	82
DAMGO	Rat	PGE_2	Mechanical	Paw withdrawal	‡	—	—	52
Dextrorphan	Mouse	AAW	Spontaneous	Stretch reflex	1.8 nmol/kg	—	No	7
Dextrorphan	Rat	Carrageenan	Thermal	Paw withdrawal	IA	—	Yes	40
Fentanyl	Rat	Carrageenan	Thermal	Paw withdrawal	—	—	—	40
Fentanyl	Rat	CFA	Mechanical	Paw withdrawal	‡	Yes	—	78
Levorphanol	Rat	Carrageenan	Thermal	Paw withdrawal	—	—	Yes	40
Levorphanol	Mouse	AAW	Spontaneous	Stretch reflex	2.1 nmol/kg			7
Morphiceptin	Rat	PGE_2	Mechanical	Paw withdrawal	‡	—	—	52
Morphine	Mouse	AAW	Spontaneous	Stretch reflex	5.9 nmol/kg	Yes	—	7
Morphine	Mouse	CW	Spontaneous	Stretch reflex	0.2 mg/kg	—	—	77
Morphine	Rat	CFA	Mechanical	Paw withdrawal	‡	Yes	—	79
Morphine	Rat	CFA	Mechanical	Paw withdrawal	‡	—	Yes	80
Morphine	Rat	PGE_2	Mechanical	Freezing behavior	14.2 nmol/paw	No	—	21
Morphine	Rat	PGE_2	Mechanical	Paw withdrawal	‡	Yes	—	52
N-methyl morphine	Mouse	CW	Spontaneous	Stretch reflex	12.4 mg/kg	—	—	77
N-methyl morphine	Rat	Carrageenan	Mechanical	Freezing behavior	—	—	—	23
N-methyl morphine	Rat	PGE_2	Mechanical	Freezing behavior	—	—	—	23
N-methyl nalorphine	Mouse	CW	Spontaneous	Stretch reflex	2.7 mg/kg	—	—	77
N-methyl nalorphine	Rat	Carrageenan	Mechanical	Freezing behavior	—	—	—	23
N-methyl nalorphine	Rat	PGE_2	Mechanical	Freezing behavior	—	—	—	23
Normorphine	Mouse	AAW	Spontaneous	Stretch reflex	1.3 nmol/kg	—	—	7
Oxymorphone	Mouse	AAW	Spontaneous	Stretch reflex	2.6 nmol/kg	—	—	7
Propoxyphene	Mouse	CW	Spontaneous	Stretch reflex	1.8 mg/kg	—	—	77
Propoxyphene	Dog	Spleen	Electrical	Vocalization	—	—	—	53
Tifluadom	Rat	CFA	Mechanical	Paw withdrawal	‡	—	Yes	80
Delta opioids								
BW180c	Rat	PGE_2	Mechanical	Freezing behavior	—	—	—	22
BW180c	Rat	Carrageenan	Mechanical	Freezing behavior	—	—	—	22
DPDPE	Rat	Bradykinin	Mechanical	Paw withdrawal	‡	Yes	—	82
DPDPE	Rat	CFA	Mechanical	Paw withdrawal	‡	Yes	—	80
DPDPE	Rat	PGE_2	Mechanical	Paw withdrawal	IA	—	—	52
DSLET	Rat	PGE_2	Mechanical	Paw withdrawal	IA	—	—	52
[Leu]enkephalin	Rat	PGE_2	Mechanical	Freezing behavior	266 nmol/paw	—	—	21
[Leu]enkephalin	Mouse	AAW	Spontaneous	Stretch reflex	—	No	—	7
[Met]enkephalin	Rat	PGE_2	Mechanical	Freezing behavior	74.5 nmol/paw	—	—	21
[Met]enkephalin	Mouse	AAW	Spontaneous	Stretch reflex	—	Yes	—	7
Kappa opioids								
Ethylketocyclazocine	Rat	Carrageenan	Thermal	Paw withdrawal	—	—	—	40
Ketocyclazocine	Mouse	AAW	Spontaneous	Stretch reflex	0.1 nmol/kg	No	—	7
U50,488H	Rat	Bradykinin	Mechanical	Paw withdrawal	‡	Yes	—	82
U50,488H	Rat	CFA	Mechanical	Paw withdrawal	‡	Yes	—	79
U50,488H	Rat	CFA	Mechanical	Paw withdrawal	‡	Yes	—	80
U50,488H	Rat	PGE_2	Mechanical	Paw withdrawal	IA	—	—	52
Mixed agonist-antagonists								
Nalorphine	Rat	PGE_2	Mechanical	Freezing behavior	17.8 nmol/paw	—	—	20
Pentazocine	Mouse	AAW	Spontaneous	Stretch reflex	229 nmol/kg	—	—	7
Pentazocine	Rat	PGE_2	Mechanical	Freezing behavior	22.4 nmol/paw	—	—	21
Pentazocine	Rat	PGE_2	Mechanical	Freezing behavoir	—	—	—	21
Opioid antagonists								
CTAP	Rat	CFA	Mechanical	Paw withdrawal	IA	—	—	80
ICI 174,864	Rat	CFA	Mechanical	Paw withdrawal	IA	—	—	80
Naloxone	Mouse	CW	Spontaneous	Stretch reflex	23.2 mg/kg	—	—	77
Naloxone	Rat	Carrageenan	Mechanical	Paw withdrawal	—	—	—	69
Naloxone	Rat	PGE_2	Mechanical	Freezing behavior	20.4 nmol/paw	—	—	21
Naloxone	Rat	Carrageenan	Mechanical	Paw withdrawal	IA	—	—	77
Naloxone	Mouse	AAW	Spontaneous	Stretch reflex	IA	—	—	7
Naltrexone	Mouse	CW	Spontaneous	Stretch reflex	20.6 mg/kg	—	—	77
Naltrexone	Mouse	PBQ	Spontaneous	Stretch reflex	IA	—	—	77
Nor-BNI	Rat	CFA	Mechanical	Paw withdrawal	IA	—	—	80

* Model to produce behavioral hyperalgesia. AAW, acetic acid writhing test; CFA, complete Freund's adjuvant; CW, carbacyclin writhing test; PBQ, phenyl-b-benzoquinone writhing test.

† ED50 values are given for dose response studies; ‡, dose response studies conducted but ED50 values not provided. IA, inactive drug under examined experimental conditions.

—, parameter not examined.

ports suggesting a peripheral site of action for opioid analgesia. For example, in the mid-1800s, local administration of relatively small doses of morphine was reported to have analgesic effects in dental pulp,[19] blisters,[93] and other painful lesions.[20] More recent studies suggest that peripheral opioids produce analgesia for acute pain after application to exposed dental pulp[70] and for chronic sympathetically maintained pain via stellate blocks.[31,63,64] However, these studies are limited since they did not exclude systemic sites of action, were not double-blinded, or did not demonstrate opioid specificity.

Several recent randomized, double-blind clinical trials have tested the clinical utility of the peripheral opiate analgesia hypothesis. Stein et al. have demonstrated peripheral morphine analgesia in a double-blind experimental design using patients following arthroscopic knee surgery.[88] Patients were permitted to receive concurrent analgesic medication in addition to the test drugs. Patients receiving peripheral (intraarticular) injection of morphine (1 mg) reported significantly less pain and consumed significantly less concurrent analgesics than patients receiving systemic (intravenous) injection of the same dose of morphine. The peripheral opiate analgesia was at least transiently blocked by naloxone administration. However, not all studies have detected peripheral morphine analgesia after arthroscopic knee surgery,[73] suggesting that other experimental parameters may influence the ability to detect peripheral opioid analgesia. Another recently published clinical trial tested the peripheral opioid hypothesis in endodontic patients who were diagnosed as having moderate to severe pain due to acute dental infection.[40] Patients were randomly administered, on a double-blind basis, either morphine sulfate (0.4 mg), a positive control (0.4 mL of 2% lidocaine with 1:100,000 epinephrine), or a placebo control (0.4 mL of saline) via peripheral injections into the periodontal ligament space (intraligamentary injections). Patients did not receive any concurrent medication. Bioassay sensitivity was demonstrated by a significant separation of the positive control from the placebo control for pain relief over the 30-minute test period. Importantly, patients given a peripheral injection of morphine sulfate also reported significant amounts of pain relief over the observation period. The opiate analgesia was most probably peripherally mediated since the 0.4 mg dose is only 1/10 of a threshold systemic dose of morphine for relieving dental pain.[51] Together, these preliminary clinical trials suggest that peripheral opioid analgesia may have clinical utility for managing pain due to inflammation.

POSSIBLE MECHANISMS OF ACTION FOR PERIPHERAL EFFECTS OF OPIOIDS

In contrast to their effects when administered into inflamed tissue, opioids injected into uninjured tissue or administered perineurally produce little to no behavioral[16,85,86] or electrophysiological[81,100] effects. This finding is consistent with the observation that opioids possess greater antinociceptive activity in rats having inflamed hindpaws as compared to uninjured controls.[45,48,86] The lack of peripherally mediated antinociception when opioids are injected into normal tissue suggests that the mechanism for peripheral opioid antinociception is due to blockade of some process related to the development of inflammation (e.g., sensitization of nociceptors, activation of leukocytes, release of inflammatory mediators, etc.). Several mechanisms have been proposed for mediating peripheral opioid-mediated antinociception.

One possible target site is opioid receptors located on peripheral terminals of primary afferent fibers. Mu, delta, and kappa opioid bindings sites have been reported on dorsal root ganglion cells and on peripheral axonal shafts.[30,50,69,98] Many of these receptors are located on capsaicin-sensitive afferent fibers where they undergo peripherally directed axonal transport.[50,98] These opioid receptors appear to be physiologically active, since opioids suppress calcium entry into dorsal root ganglion somata[92] and inhibit the peripheral release of immunoreactive substance P due to inflammation,[97] antidromic nerve stimulation,[14,95] or capsaicin administration.[95] In addition, local intraarterial injection of opioids reduces the spontaneous activity of sensitized small-diameter afferent fibers.[79] Following the classic studies by Collier and Roy,[22,23] it has been suggested that opioids produce peripheral antinociception by inhibiting cAMP-induced hyperalgesia. Although specific biochemical data from primary afferent terminals is still lacking, the results from recent behavioral studies are consistent with the hypothesis that peripheral mu opioid antinociception is due to activation of a G_i protein, leading to inhibition of the adenylate cyclase system and suppression of primary afferent sensitization.[58]

It is possible that these receptors could mediate the analgesic and antiinflammatory effects[37,45] of opioids since activation of primary nociceptive fibers appears capable of altering inflammation. In support of this point, interventions including capsaicin treatment, denervation and administration of substance P antagonists suppress the development of inflammation in several[29,32,41,44,55,61,66,75,80] but not all[33] an-

imal models. These afferent fibers are thought to peripherally secrete neuropeptides such as substance P and calcitonin gene-related peptide, leading to the development of plasma extravasation and other effects.[32,61]

A second potential site is opioid receptors reported to be located on leukocytes. Several studies have demonstrated that opioids can alter chemotactic and functional activity of leukocytes via activation of opioid receptors[60,77,82,90]; however, the selectivity of these effects has been questioned.[83] Although the great majority of these studies are conducted *in vitro*, recent *in vivo* studies are consistent with opioid alteration of leukocyte function.[11,24] For example, opioids such as morphine have been shown to inhibit the free radical production of stimulated neutrophils.[35] It is possible that opioid modulation of leukocyte function could contribute to their peripheral effects since interventions that either chemically (methotrexate) or surgically (cannulation of the thoracic duct) suppress immune function have profound effects on inhibiting the development of inflammation.[2,34,53,54,56]

A third potential target is opioid receptors located on sympathetic fibers; various tissues have been reported to contain delta, kappa, or mu opioid receptors located on postganglionic sympathetic fibers.[17,74] Moreover, activation of opioid receptors alters stimulation-evoked release of norepinephrine.[12,72,74] In support of this hypothesis, Taiwo and Levine have reported that kappa and delta opioids suppress sympathetically dependent hyperalgesia induced by bradykinin injection,[57,89] although the selectivity of this model has been questioned.[49,65]

The basis for sympathetic regulation of inflammation may be due to an alteration in the synthesis or release of inflammatory mediators since activation of the sympathetic nervous system (or administration of norepinephrine) stimulates the release of prostaglandins from vascular tissue[10,62,99] where they may activate nearby leukocytes or sensitize nociceptors.[57,67,71] In addition, chemical sympathectomy, by administration of either guanethidine or reserpine, reduces the magnitude of inflammation.[56,68]

In addition to peripherally mediated antinociception, opioids also suppress several peripheral vascular responses (i.e., plasma extravasation or edema) to antidromic nerve stimulation[5,52,84] or tissue injury.[15,38,78,97] These effects appear to be mediated by a receptor-specific mechanism since opioid suppression of carrageenan-induced edema and hyperthermia is dose-related, stereospecific, and naltrexone-reversible.[45] A reduction in plasma extravasation by a single injection of an opioid may reduce acute hyperalgesia by inhibiting bradykinin release (although chronic morphine administration may delay healing).[21] Plasma extravasation and the release of bradykinin from the vascular compartment are primarily due to increases in endothelial permeability and vascular tone. Opioids may modulate endothelial permeability either through direct actions on endothelium[96] or by indirect actions via inhibiting the release of inflammatory mediators that stimulate extravasation (e.g., substance P). In addition, opioids suppress the evoked release of bioactive bradykinin from both dental pulp[43] and cutaneous tissue.[42] Recent studies conducted have extended these observations by demonstrating the stereospecificity of opioid suppression of immunoreactive bradykinin release in the rat carrageenan model of inflammation using implanted microdialysis probes.[91] In these studies, administration of levorphanol, but not dextrorphan, suppressed carrageenan-induced release of immunoreactive bradykinin by nearly 50%.

However, not all peripheral opioid effects need be mediated by peripherally located receptors. For example, opioids administered intracerebroventricularly inhibit edema[9] as well as radiographic indices of arthritic joint lesions[55] in rats. It has been proposed that this centrally induced opioid effect may be due to inhibition of sympathetic outflow,[47] thereby altering the vascular response to inflammation. An additional alternative central mechanism is stimulation of the pituitary-adrenal axis. Opioids can stimulate the pituitary-adrenal axis in rats, and it has been reported that kappa agonists, evaluated 3.5 hours after administration, reduce edema via a corticosterone-dependent mechanism.[18]

It is important to note that these alternative mechanisms for peripheral opioid effects are not mutually exclusive. Additional research may well indicate that the relative contribution of these mechanisms is dependent upon the model of inflammation examined, the host tissue, and the stage of the inflammatory process.

CONCLUSIONS

The hypothesis of a peripheral analgesic mechanism for opioids has several scientific and therapeutic implications. The scientific issues relate to: (1) determining the biochemical mechanisms mediating this peripheral opioid effect; (2) determining whether endogenous opioids can activate these peripheral receptors[39,88]; and (3) evaluating whether a defect in this peripheral opioid system contributes to the development of chronic inflammation and pain.

The therapeutic issues relate to the observation that the clinical use of opioid drugs, especially in am-

bulatory outpatient settings, is dose-restricted due to CNS-mediated side effects such as respiratory depression, nausea, sedation, tolerance etc.[1,7] Thus selective activation of peripheral opioid receptors, either by route of injection or by drug design, may provide effective analgesia without the manifestation of traditional opioid-like side effects. Interestingly, several groups have reported recently on the development of peripherally selective opioids that are either quaternary[28,84] or hydrophilic analogs[3,4,13,36] of opioid compounds. Future studies are required to determine the ultimate clinical utility of peripherally selective opioid analgesics.

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