Peripheral and Spinal Actions of Opioids in the Blockade of the Autonomic Response Evoked by Compression of the Inflamed Knee Joint

Hiroshi Nagasaka, M.D.*, Hamdy Awad, M.D.*, Tony L. Yaksh, Ph.D.†

Background: Three types of opioid receptors, μ, δ, and κ, are present in the periphery and in the central nervous system. In contrast to the effects in the central nervous system, the antinociceptive action of opioids in the periphery is not as well characterized. The effects of intraarticular, spinal, and intramuscular injections of μ, δ, and κ opioid agonists on the autonomic response evoked by compression of an inflamed knee joint were evaluated.

Methods: In halothane-anesthetized rats, arthritis was induced by injecting kaolin and carrageenan into the right knee joint. Standardized compression of the knee joint by inflation of a pediatric blood pressure cuff to 200 mmHg for 2 min produced a reliable stimulus-dependent hypertension (Δ = 13 mmHg). Drugs were delivered intramuscularly, intrathecally through a chronic catheter, or intraarticularly into the right knee joint. The drug injection was performed 4 hr after induction of the inflammation.

Results: The intrathecal administration of μ, δ, and κ agonists resulted in a dose-dependent blockade of the cuff-evoked increase in blood pressure. The order of intrathecal drug activity on the compression-evoked blood pressure responses with median effective dose (ED50) was sufentanil (0.02 nmol); PD117302 (0.5 nmol); δ; morphine (2.4 nmol); κ; DPDPE (1.5 nmol); κ; morphine (2.4 nmol); μ; DADL (15 nmol); δ; PDPE (18 nmol); κ; naloxone = 0. The intrathecal activity of μ and κ, but not δ agonists, produced a dose-dependent blockade of a compression-evoked increase in blood pressure, with the order of drug activity (ED50) as follows: sufentanil (0.04 μmol) > PD117302 (0.3 μmol); δ; morphine (0.8 μmol); κ; morphine (0.9 μmol) > U-50,488H (0.9 μmol) > DPDPE (>5 μmol); DADL (>18 μmol) > naloxone = 0. Intramuscular injection of these agonists caused suppression of the autonomic drug activity (ED50) as follows: sufentanil (0.2 μmol) > PD117302 (2 μmol); δ; morphine (11 μmol); κ; morphine (9 μmol) > DPDPE (>5 μmol); DADL (18 μmol) > U-50,488H (22 μmol) = naloxone = 0. All intraarticular effects were reversible by injecting naloxone intramuscularly, with the ordering of naloxone potency against equieffective doses of morphine > U-50,488H.

Conclusions: The activity of the respective agonists and the intrathecally > intramuscularly ordered systemic potency in this model indicate that opioids, by an action at μ and κ, can exert a direct antihyperalgesic action at the terminals of primary afferents projecting to a region of inflammation. These observations offer strong support for a peripheral action of opioids in certain states of inflammation-induced hyperalgesia. (Key words: Opioid receptors, morphine, peripheral, U-50,488H, spinal, spiradoline, knee joint inflammation, D-Pen2, D-Pen2 enkephalin [DPDPE], Pain and autonomic response, D-alanyl2-D-leucine2-enkephalin [DADL]).

DURING knee joint inflammation, a cascade of events occurs, including synthesis and release of inflammatory mediators in the joint, release of neuropeptides from afferent fibers in the joint cavity, and increased primary afferent outflow from the sensory fibers of groups II, III, and IV.1 An important result of this cascade is that the responses of small, lightly myelinated and unmyelinated afferents to low-intensity stimuli are augmented. In this manner, the peripheral nerve innervating inflamed tissue can evoke an exaggerated behavioral response to otherwise innocuous stimuli (i.e., a state of hyperalgesia). This scenario has been well documented in the knee joint. Thus inflammation of the knee joint will increase spontaneous afferent activity and produce the appearance of an exaggerated discharge with joint flexion and extension2 and signs of a pain-associated autonomic reaction.3 Three types of opioid receptors, μ, δ, and κ, are present in the periphery and in the central nervous system.4,5 Their presence in the periphery led to the hypothesis that these peripheral receptors may modulate afferent nociceptive transmission. Thus inflammation of the skin was shown to induce hyperalgesia, and researchers have reported that such hyperalgesia can be reduced by injecting opioid agonists locally.6 The pharmacologic action of this effect is not well charac-

*Research Fellow.
†Professor of Anesthesiology, and Vice Chairman for Research.

Received from the Anesthesiology Research Laboratory, University of California, San Diego. Received for publication June 22, 1994. Accepted for publication May 5, 1996. Supported by Saitama Medical School (H.N.) and grant DA02110 (Tony L. Yaksh).

Address reprint requests to Dr. Yaksh, Department of Anesthesiology, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92037-4818.

Anesthesiology. V 85, No 4, Oct 1996
terized. There is some general agreement about the antinociceptive action of local \( \mu \) agonists under certain inflammatory conditions, but there are conflicting data for agonists acting at \( \delta \) and \( \kappa \) receptors.\(^7\) More recently, several reports indicated that after arthroscopic surgery in humans, morphine administered intraarticularly can diminish postoperative pain.\(^8\)–\(^10\) As noted, previous preclinical work showed that local inflammation of the knee results in a state in which otherwise innocuous stimuli cause a prominent autonomic response, including increased blood pressure and heart rate.\(^3\) In the present study, we evaluated the effects of the intraarticular, intrathecal, and intramuscular injections of \( \mu \), \( \delta \), and \( \kappa \) opioid agonists on the blood pressure response evoked by compression of the inflamed knee joint in rats anesthetized with halothane. This novel model can show the efficacy of peripherally delivered \( \mu \) and \( \kappa \) opioids.

**Materials and Methods**

This study was performed with approval of the Institutional Animal Care and Use Committee of the University of California, San Diego.

**Preparation**

To induce inflammation, each animal (male Sprague-Dawley rats weighing 300 to 340 g) was anesthetized in a Plexiglas acrylic plastic induction chamber with 2% halothane in oxygen-enriched room air. During halothane anesthesia, 0.2 ml of a mixture of 4% kaolin and 4% carrageenan (Sigma Chemical Co., St. Louis, MO) was slowly injected into the right knee joint cavity through the patellar ligament using a 21-gauge needle. After inflammation was induced, the rat was allowed to recover from anesthesia. Three and a half hours later, the rat was anesthetized again with halothane (2%) in a 50% oxygen-and-air mixture delivered through a face mask. The tail artery was cannulated to monitor blood pressure. When surgical preparation was completed, halothane anesthesia was continued at 1% inspired halothane. Blood pressure was recorded continuously (Grass model 7 polygraph, Grass Instrument, Quincy, MA), and body temperature (rectal) was monitored and maintained at 37°C by a servo-controlled heating blanket. For intrathecal injection, rats were prepared with long-term lumbar intrathecal catheters.\(^11\) After 5 to 7 days, they were entered into the study.

To produce a reliable compression of the knee joint, a pediatric blood pressure cuff was placed around the inflamed knee. For stimulation, the cuff was inflated rapidly to 200 mmHg using a syringe pump. Each inflation was sustained for 2 min. Typically testing was done at -5 min and at 15, 30, 60, 90, and 120 min.

**Measure of Joint Volume and Circumference**

To assure a standard state of inflammation, the volume and circumference of the inflamed and uninflamed knee joints were measured 3.5 hr after kaolin and carrageenan injection. Volume was assessed by displacing fluid after the hindquarter of the rat was immersed to the groin. Circumference was measured by a flexible cord placed around the knee joint at the level of the knee joint flexure. After the first 85 rats, inflammation was found to be sufficiently reliable and did not require further screening in this manner.

**Drug Delivery**

The routes of drug injection were intramuscular into the left hamstring muscle, intrathecal through the long-term catheter, or intraarticular into the right knee joint using a 30-gauge needle. We initially discovered that the simple intraarticular injection of saline (vehicle) into the already-inflamed knee joint at 4 hr would prompt an additional facilitated response. Thus, to compare the potency of the intrathecal and intramuscular routes of delivery with the intraarticular route, all intrathecal and intramuscular treatments used a concurrent intraarticular injection of saline, in addition to the intrathecal or intramuscular injection. Intrathecal and intramuscular vehicle injection had no effect on the response, and thus it was not necessary to give parallel intrathecal or intramuscular vehicle injections with intraarticular drugs. The volume of all intramuscular and intraarticular drug injections was 0.2 ml, except for intramuscular injection of 10 mg U-50,488H, which was in 0.6 ml. All drugs administered intrathecally were injected in a volume of 10 \( \mu \)l followed by 10 \( \mu \)l of physiologic saline to clear the catheter.

**Drugs**

The drugs used for injection were \( \mu \) agonists: morphine sulfate (molecular weight, 334; Merck, Sharpe and Dohme, West Point, PA) and sufentanil citrate (molecular weight, = 571; Janssen Pharmaceuticals, Titusville, NJ); \( \kappa \) agonists: PD117302 (((\pm)-trans-N-methyl-N-2-(1-pyrrolidinyl)-cyclohexyl)-benzo-[b]-thiophene-4-acetamide); molecular weight, 412; Parke Davis, Ann

Anesthesiology. V 85, No 4. Oct 1996
Arbor, MI) and U-50,488H (trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide; molecular weight, 465; Upjohn, Kalamazoo, MI); spironolactone mesylate (molecular weight, 522; Research Biochemicals International, Natick, MA); δ agonists: DADL (D-alad-L-leu⁵-enkephalin; molecular weight, 556, courtesy of Dr. Murray Goodman, University of California, San Diego), DPDPE (D-Pen², D-Pen⁵) enkephalin; molecular weight, 646; courtesy of Dr. Victor Hruby, University of Arizona Health Science Center, Tucson, AZ), and naloxone HCl (molecular weight, 364; Endo Labs, Garden City, NJ).

**Naloxone Antagonism**

To define the potency of naloxone to reverse the effects of intraarticular morphine and U-50,488H, rats received an injection of naloxone (intraperitoneal injection measured in milligrams per kilogram) given 10 min before 1 mg intraarticular morphine or 1 mg intraarticular U-50,488H. This time interval was based on preliminary observations. If the naloxone dose completely reversed the effects of the agonist, it was scored as an antagonism. In sequential rats, the naloxone dose was increased or decreased by a factor of 3 (approximately one-half log unit: 0.01, 0.03, 0.1, 0.3, 1, 3, or 10 mg/kg) if the preceding naloxone dose was either ineffective or effective (e.g., the Dixon up-down method) for potency determination.12

**Statistics**

Blood pressure was evaluated as a mean, (systolic − diastolic)/5 + diastolic pressure. For dose-response analysis, the blood pressure was expressed as a percentage change of the baseline before drugs were administered. Data are presented as mean ± SE of the percentage of the preinjection change induced by compression: % Δ of blood pressure = (Δ of blood pressure post-drug/Δ of blood pressure pre-drug) × 100. Statistical comparisons were performed using Student's t test, paired or unpaired as required. For statistical analysis and graphic presentation, blood pressure dose-response curves were generated using the maximum reduction in the evoked response (% Δ of blood pressure) observed within 60 min after drug injection. These dose-response data were analyzed by calculating a least-squares linear regression. Median effective dose and slopes with a 95% confidence interval (CI) were calculated.13

**Results**

**General Observations**

In all experiments, the injection of kaolin and carrageenan induced inflammation, with swelling and edem-
Peripheral Opioid Receptors and Hyperalgesia

Atinous deformation of the joint. The volume of the right injected hindlimb was measured in the first 85 rats and found to be 6.6 ± 0.1 versus 14.6 ± 0.5 ml, respectively, before and after kaolin and carrageenan injection (n = 85; Δ = +1.8 ± 0.1 ml, P < 0.01, paired t test). Injection of saline alone resulted in a small but not significant increase in the circumference of the injected knee joint. The left, uninjected knee was no different from the right knee before kaolin and carrageenan and did not change during the study (P > 0.10, paired t test data not shown). Before blood pressure response testing, all rats tended to keep the injected limb from weight bearing. Unstimulated rats (n = 193), which were maintained in an anesthetic state with inspired 1% halothane, displayed a stable resting blood pressure (121 ± 6 mmHg). As indicated in figure 1, inflation of the cuff on the inflamed knee joint resulted in a reliable stimulation-dependent increase in blood pressure during the 2-min interval of inflation (Δ = 14.6 ± 0.2 mmHg, P < 0.01, paired t test). With knee joint compression, the time course of the increasing blood pressure evoked by compression was uniform, reaching the maximum response approximately 20 to 30 seconds after the onset of stimulation. The blood pressure changes persisted throughout the 2-min period of stimulation and gradually returned to the control level within 1 to 2 min after the end of the stimulus.

In the absence of drug treatment, the response to compression was stable during the 2-hr interval of testing (sec figures 1 and 2).

Intrathecal Opioid Agonists

Intrathecal administration of the μ, δ, and κ agonists at the doses used had no statistically significant effect on resting blood pressure (data not shown) but resulted in an early blockade of the cuff-evoked increase in blood pressure. The antinociceptive effects were dose dependent (fig. 3). The order of drug activity on the cuff-evoked blood pressure responses was sufentanil > PD117302, spiradoline, morphine > DADL, DPDPE > U-50,488H = naltrexone = 0. Table 1 presents the median effective dose values in nanomoles, with a 95% CI of the opioid agonists.

Cardiovascular Response of Intraarticular Opioid Agonists

The intraarticular administration of the agents at the largest dose had no effect on resting blood pressure for any of the agents delivered (data not shown). However, the μ and κ, but not δ, agonists produced a dose-depen-

Fig. 2. Maximum evoked change in blood pressure (expressed as the mean ± SEM) as a percentage of the change in blood pressure measured before drug injection at time zero. The response at each time point was evoked by compressing the knee joint to 200 mmHg for 2 min in rats that received an intraarticular injection of kaolin and carrageenan 3.5 hr before treatment. The bottom panel indicates the control response associated with kaolin and carrageenan alone (IA CAR) or carrageenan plus intraarticular saline at time zero. In the two panels show the effects of U-50,488H (3 mg, middle) or morphine (3 mg, top) given at time zero. Because the intraarticular injection alone exaggerates the response, all intramuscular injections of drug were accompanied by a concurrent injection of saline into the knee joint (e.g., intraarticular saline). Each line presents the mean ± SEM of four to eight rats. The reduction in the compression-evoked increase in blood pressure. The rank ordering of drug activity on a molar basis was sufentanil > PD117302, spiradoline, morphine, U-50,488H > DADL, DPDPE > = naltrexone = 0. Table 1 presents the median effective dose measured in micromoles with a 95% CI of the opioid agonists.

Anesthesiology, V 85, No 4, Oct 1996

Downloaded from anesthesiology.pubs.asahq.org by guest on 03/17/2019
agonists resulted in a blockade of the compression-evoked increase in blood pressure. The ordering of activity was sufentanil > PD117302, spiradoline, morphine > DADL, DPDPE > U-50,488H = naloxone = 0. Table 1 presents the median effective dose values, with a 95% CI of the morphine effect.

**Naloxone Antagonism**

Figure 4 shows the effects of intramuscular naloxone on the depressive effects of intrarticular morphine (1 mg) and intra-articular U-50,488H on the compression-evoked increase in blood pressure depression. The antagonistic potency of naloxone for morphine was approximately four times greater than for an approximately equally effective dose of U-50,488H. Intramuscular naloxone alone had no effect on a compression-evoked change in blood pressure (prenaloxone blood pressure response, $\Delta = 14.6 \pm 0.2$ mmHg versus postnaloxone blood pressure response, $\Delta = 16.6 \pm 0.3$ mmHg; $P > 0.2$, paired $t$ test). To determine if the effects of naloxone were local, within the articular space, naloxone (30 $\mu$g) was administered with morphine in four rats. This injection attenuated the antihyperalgesic effects of morphine otherwise observed 30 min after agonist injection (control blood pressure response, $\Delta = 16.2 \pm 0.4$ mmHg versus post-intraarticular morphine + naloxone blood pressure response, $\Delta = 14.9 \pm 0.5$ mmHg; $P > 0.2$, paired $t$ test).

**Discussion**

**Blood Pressure Response to Compression of the Inflamed Knee Joint**

Joint inflammation is associated with hyperalgesia (pain during normal flexion and extension) and during application of gentle innocuous pressure or persistent pain (resting pain). In the present study, this treatment was characterized by a reliable increase in joint volume and circumference. In the unanesthetized rat, these joint changes were accompanied by a tendency to avoid weight bearing, suggesting an ongoing pain state. C and A$\delta$ units normally responding only to extreme joint distortion become activated by slight movement after initiation of inflammation, and deep dorsal horn neurons of the spinal cord show hyperexcitability. This sensitization of groups III and IV fibers was observed 2 to 3 hr after injection of kaolin and carrageenan into the knee joint, a time course that closely

---

**Cardiovascular Response of Intramuscular Opioid Agonists**

To determine if the intrarticular effects could be similarly achieved through "systemic" delivery, intramuscular administration of these agents was also studied. As shown in figure 3, intramuscular $\mu$ opioid

---

Anesthesiology, V 85, No 4, Oct 1996

---

---
PERIPHERAL OPIOID RECEPTORS AND HYPERALGESIA

Table 1. Summary Showing EDso Values with 95% CI for Depression of the BP Response Evoked by Compression of the Inflamed Knee Joint in the Halothane-anaesthetized Rats

<table>
<thead>
<tr>
<th>Route</th>
<th>IT (nmol)</th>
<th>IA (μmol)</th>
<th>IM (μmol)</th>
<th>IM/IA Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ opioid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.02 (0.01–0.04)</td>
<td>0.04 (0.02–0.06)</td>
<td>0.16 (0.04–0.26)</td>
<td>4</td>
</tr>
<tr>
<td>Morphine</td>
<td>2.4 (0.3–4.2)</td>
<td>0.9 (0.3–1.8)</td>
<td>9.3 (1.5–22.3)</td>
<td>10.3</td>
</tr>
<tr>
<td>K opioid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U50488*</td>
<td>620</td>
<td>0.9 (0.2–1.9)</td>
<td>&gt;22</td>
<td>&gt;24</td>
</tr>
<tr>
<td>Spiradoline</td>
<td>1.5 (0.1–1.3)</td>
<td>0.8 (0.14–0.81)</td>
<td>11.1 (0.9–13.2)</td>
<td>11.1</td>
</tr>
<tr>
<td>PD117302</td>
<td>0.5 (0.07–0.91)</td>
<td>0.3 (0.8–0.59)</td>
<td>1.8 (0.3–5.2)</td>
<td>6.0</td>
</tr>
<tr>
<td>δ opioid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPDPE</td>
<td>18 (5–48)</td>
<td>&gt;4.9*</td>
<td>–4.7†</td>
<td>–</td>
</tr>
<tr>
<td>DADL</td>
<td>15 (4–52)</td>
<td>&gt;18†</td>
<td>&gt;18†</td>
<td>–</td>
</tr>
<tr>
<td>Naloxone</td>
<td>&gt;82†</td>
<td>-2.8†</td>
<td>-2.8†</td>
<td>–</td>
</tr>
</tbody>
</table>

CI = confidence interval; BP = blood pressure; IT = intrathecal; IA = intrarterial; IM = intramuscular.

Values in parentheses are confidence intervals.

* U50488 is limited to a 2-point dose–response curve and confidence limits were not calculated.

† Dose represents the highest dose examined. As noted in Figure 3, the effect produced by this highest dose fell within the confidence interval of the saline vehicle. Accordingly, EDso values could not be computed.

Fig. 4. To determine the potency of naloxone to reverse the effects of intraarticular opiates, rats received an injection of naloxone (IP) (mg/kg) 1 min before intraarticular morphine (1 mg) or intraarticular U50488 (1 mg). If the naloxone dose completely reversed the effects of the agonists, it was scored as an antagonism (black dot). In sequential rats, the naloxone dose was elevated by 0.5 log units (e.g., 0.01, 0.03, 0.1, 0.3, 1, 3, or 10 mg/kg) if the preceding naloxone dose was ineffective, or it was decreased by a 0.5 log unit if the naloxone dose was effective. The graph plots the results observed in sequential rats against the dose of naloxone (on the Y axis). Median effective dose values, shown with 95% confidence intervals, were calculated using Dixon tables.

Anesthesiology, V 85, No 4, Oct 1996

matches the time course of the development of hyperalgesia in the rat knee joint compression model. These observations indicate that both spinal cord neurons and joint primary afferent fibers become sensitized and may underlie the hyperalgesia observed in this arthritic state. Such afferent input may drive autonomic responses that are typically associated with the processing of input from afferents typically activated by stimuli generated by the local inflammatory state. In addition to the previously noted inflamed knee joint mechanism, blood pressure changes also may be evoked reflexively by afferent neural activity from receptors located in the skeletal muscle. This response depends on both the changes in intramuscular pressure and the quantity of muscle mass compressed. This particular mechanical reflex, however, appears to operate independently of the pain response and played a minor role in our experiment, as inflation of the cuff on the left normal knee joint had no effect on blood pressure (data not shown). In any case, overflow of the carrageenan from the joint capsule might render surrounding tissue inflamed as well. Sensitization of C and Aβ units was observed in the rat gastrocnemius muscle by infiltration with carrageenan. We thus believe that compression of the inflamed knee joint yields a noxious stimulus and this in turn activates a sympathetic response, resulting in an increase in blood pressure. As previously noted, manipulation of an inflamed knee joint increases autonomic outflow, as evidenced by ac-
tivity in autonomic efferents and by the release of circulating stress hormones.\textsuperscript{3,17,18} This interpretation is consistent with results from previous studies in which the immersion of the tail in 52 to 60°C water evoked similar autonomic response in rats anesthetized with halothane.\textsuperscript{19,20}

**Spinal Opioid Agonists and Antinociception**

The compression-evoked increase in blood pressure was blocked by the intrathecal delivery of morphine sufentanil (μ) and DPDPE/DADL (δ). PD117304, spiradalone and U50488 (κ). Spinally delivered opioid μ and δ agonists depress behavioral and electrophysiologic responses evoked by noxious stimulation.\textsuperscript{1,5} In contrast, κ agonists frequently appear to have modest effects in behavioral models of acute nociception (such as the tail flick or hot plate)\textsuperscript{21,22} but are more efficacious in models of protracted pain (typically induced by inflammatory stimuli, as in the present model).\textsuperscript{21,22} Given the lack of significant changes in resting blood pressure with the spinal agent, we conclude that these agents are blocking the response through small afferent input generated by compression of the inflamed knee.

**Intraarticular Opioid Agonists and Antinociception**

In the present work, intraarticular administration of μ and κ, but not δ-prefering agonists, resulted in a dose-dependent blockade of the hyperalgesia produced by the inflammation of the knee. Importantly, as defined by the dose-response curves, the effects produced by injection at the site are more robust and potent than when the respective agent is delivered intramuscularly. This observation indicates that the effect of intraarticular μ and κ agonists are probably mediated by a local action at the site of injection. This local action is further supported by the observation that local naloxone could attenuate the effects of intraarticular morphine at a very low dose. Importantly, the local agonist dose required to induce this antihyperalgesic effect considerably exceeds that dose required after spinal delivery. This difference in potency by the two "local" routes may reflect the accessibility of the joint to the drug. Alternately, the high dose may reflect the fact that a high level of occupancy is required to block the transduction. Further studies with noncompetitive antagonists are needed to address this possibility.

Antagonism of the effect of intraarticular morphine and U50,488H by systemic naloxone emphasizes the role of opioid receptors in this action. The difference in systemic naloxone potency against an equally potent dose of morphine and U50,488H is consistent with the fact that the affinity of naloxone for the κ receptor is less than for the μ receptor\textsuperscript{23} and supports the hypothesis that both classes of receptors are involved in this action.

The limited activity of U50488 compared with spiradalone and PD 117302 was unexpected after intrathecal delivery, particularly because they appeared to possess similar activity after intraarticular delivery. This might reflect κ receptors with different agonist profiles in cord versus the knee joint. Multiple populations of κ receptors have been proposed,\textsuperscript{24} but whether that explanation is relevant to the present model is not known. Further work with other κ agonists and antagonists is warranted.

At the highest dose used, DPDPE and DADL failed to induce a comparable antihyperalgesic action. Higher doses of DADL were limited by drug availability, whereas doses of DPDPE were limited by availability and solubility. The apparently limited effect may be due to the absence of δ receptors at this site or to differences in bioavailability. Because DPDPE and DADL are peptides, they may be more rapidly metabolized than the other agents despite their protected structures. However, rapid inactivation is unlikely. We have shown that DPDPE is cleared from plasma after intravenous delivery with a half-life of 15 to 30 min, suggesting some degree of stability (P. J. Tiso, M. B. Sabbe, and T. L. Yaksh, unpublished observations). Although the inflammatory exudates in the knee joint would be expected to show elevated enzymatic activity, the cyclic structures and D-amino acid substitutions are consistent with the relatively long period of plasma clearance. These issues, coupled with the high drug doses used, thus suggest that peptide clearance is not the defining variable.

Our observations in the inflamed knee joint correlate with the hypothesis that peripherally mediated antinociceptive effects observed during inflammation may be mediated by μ and κ opioids.\textsuperscript{25} There are, however, conflicting reports regarding the pharmacology of the antinociceptive effects of peripheral opioids. Not only μ and κ but also δ receptors appear able to mediate the antinociceptive effects in peripherally inflamed tissue.\textsuperscript{27} On the other hand, intradermal injection of DAMGO (μ opioid), but not DPDPE or U50,488H (κ opioid), inhibited the hyperalgesia induced by peripheral prostaglandin E\textsubscript{2}.\textsuperscript{28} These results suggest the possibility that different peripheral inflammatory states may
PERIPHERAL OPIOID RECEPTORS AND HYPERALGESIA

lead to the development of different patterns of opiate receptor expression and coupling. Systematic comparisons of the pharmacology across models will be particularly important in defining these variables.

Mechanism of Peripheral Opioid Action

Despite difference in models and results, the behavioral studies, including the present one, all show that the actions of peripheral opioids are characterized by two properties: (1) the effects are naloxone-reversible, emphasizing that the drug actions are mediated by an opioid receptor and do not indicate a local anesthetic effect that is not naloxone sensitive, and (2) the peripheral actions are most clearly manifested in the inflamed state when a well-defined hyperalggesia is present. Consistent with behavioral observations that peripheral opioids may not change normal thresholds, electrophysiologic studies have shown that opioids do not depress the discharges of nociceptors in normal skin or their responses to noxious stimuli. Although peripheral afferents are typically silent under normal conditions, with inflammation these afferents will develop substantial spontaneous activity (see Schaible and Grubb). In this state, previous work showed that local morphine will depress the spontaneous firing of peripheral nociceptors induced by carrageenan inflammation. In addition, repetitive exposure of skin to ultraviolet light produces an injury state that yields a spontaneous discharge of small afferents. In this model, local DAGOL ([D-Ala², MePhe³Gly(ol)⁶]) (μ receptor) and U-69593 (κ receptor), but not DPDPE, depressed this discharge of ultraviolet irradiation. These observations suggest that at the level of the local terminal, changes that occur in the peritenninal milieu during inflammation and result in spontaneous discharges are sensitive to μ and κ (but not δ) opioids.

Several observations support the hypothesis that at least a component of this local opioid effect on spontaneous afferent activity may be mediated by a direct reduction in terminal excitation. First, opioids can reduce the release of peptides from the peripheral C fiber terminal. Thus μ opioids depress the release evoked by antidromic stimulation of substance P or calcitonin gene-related peptide from the knee joint or skin (T. H. M. Mirzai and T. L. Yaksh, unpublished observations). Recent research has shown that release of calcitonin gene-related peptide from the trachea is reduced by the local action of κ agonists (X-Y Hua, personal communication). Second, μ and κ receptor opioids can inhibit plasma extravasation and peripheral vasodilation induced by antidiromic C-fiber stimulation in healthy skin. Aside from a direct opioid effect on afferent terminals, opioid receptors have been found in inflammatory cells, and these sites might regulate the secretion of a product that regulates terminal excitability and is turned over rapidly, accounting for the early onset of intraarticular opioid effects. Future studies are required to address these issues. Nevertheless, elucidation of this action may yield important targets for future drug development in specific pain states.

References


Anesthesiology, V 85, No 4, Oct 1996
NAGASAKA, AWAD, AND YAKSH


Anesthesiology, V 85, No 4, Oct 1996