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THE PHYSIOLOGY AND PHARMACOLOGY OF SPINAL OPIATES

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INTRODUCTION

Opioid agonists with an action limited to the spinal cord produce powerful changes in an organism's response to otherwise painful stimuli. The effect is mediated by an action on opioid receptors located, we believe, on specific spinal elements that mediate the local processing of nociceptive information and its subsequent transmission to supraspinal centers. An extensive literature, reviewed elsewhere (1–2a), has made it abundantly clear that several classes of opioid receptors exist, including those with pharmacological profiles designated μ, δ, κ, σ and ϵ. In the following section we consider current thinking on the mechanism underlying the spinal action of opioids, the characteristics of the analgesia, and the characteristics of the receptor populations that mediate effect. Recently, it has become clear that spinal opioid receptors are also associated with a variety of systems in addition to those pertaining to sensory modulation. Thus, the spinal administration of opiates in the intact and unanesthetized animal has revealed powerful receptor-mediated effects on motor, cardiovascular, gastrointestinal, and bladder function. These subjects will also be briefly addressed.

OPIATES AND SPINAL FUNCTION

Several observations clearly demonstrate that opiates can exert a direct effect on spinal sensory and motor processing. The systemic administration of opiates in spinal-transected animals will at low doses selectively reduce the A-δ and C fiber and the thermally evoked ventral root reflex (3). Recording in the

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spinal-transected animal from wide dynamic-range neurons, a variety of systemically administered opiates have been shown to preferentially suppress the A-δ/C-evoked activity (4–7) as well as activity induced by a variety of somatic stimuli that evoke pain behavior in the unanesthetized animal [thermal >42°C (8, 9); cutaneous pinch, pressure (5)]. Although the effects are preferential for nociceptive input, less profound but measurable effects on receptive field size and the response to non-noxious stimuli have also been described (5, 8). An important question is whether the cells whose activity is affected by opiates project suprasegmentally or represent a population of local interneurons. Jurna & Grossmann (10) have demonstrated that lumbar neurons suppressed by systemically administered opiates can be antidromically fired from more rostral cord segments and thus do indeed represent "projection" neurons. These results on spinal nociceptors obtained with systemically administered opiates are probably mediated via an opioid receptor because: (*a*) the rank ordering of activity (the structure-activity relationship) bears a close correlation with the efficacy of these agents in opiate receptor bioassays: etorphine > fentanyl > levorphanol ≥ morphine ≥ d-1-methadone >> U-50488H ≥ meperidine >> dextrorphan = naloxone = 0 (4–13; T. L. Yaksh, unpublished data), and (*b*) their effects are antagonized by naloxone (see above) in a dose-dependent fashion (13).

The focal application of opiate alkaloids (morphine, levorphanol) and opioid peptides (e.g. met-enkephalin, leu-enkephalin, met-enkephalin amide) onto dorsal-horn neurons suppresses the activity evoked by noxious thermal or mechanical stimuli applied to the cutaneous receptive field (14–19). In the majority of these studies, naloxone given either systemically or iontophoretically can antagonize the suppression [but see (17)]. These results, suggesting that opiates act within the dorsal gray matter to suppress nociceptive activity, are supported by the observation that the effects of systemic opiates are reversed by naloxone iontophoresed into the dorsal gray (20).

Considerable skill and effort have been directed at understanding the mechanism whereby opiates in the spinal cord produce their particular effects. The ability of opiates to produce a powerful inhibition of small afferent fiber input with little effect on large afferent-evoked activity early led to speculation that opiates may act presynaptically. Alternately, the ability to suppress non-noxious activity in dorsal-horn neurons by high doses suggested that the selectivity is relative and depends on the temporal characteristics of the afferent input to the second-order neurons. This permits a postsynaptic effect to explain the observed events. The question of the substrate upon which opiates act to produce their physiological effects may be approached anatomically by noting the distribution of opioid ligand–binding sites and electrophysiologically by noting the spinal systems affected by opiates.

Binding Studies

Significant levels of μ, δ, and κ ligand binding have been demonstrated in the spinal cord, with the highest levels in the dorsal gray matter [see (2, 21)]. Ganglionectomies or rhizotomies result in a significant but clearly subtotal reduction in binding (22), suggesting that a proportion of these binding sites may be on primary afferents. The demonstration of binding in dorsal root ganglion cells (DRG) and in dorsal roots supports this association (23, 24). In fetal mouse spinal cord–ganglion preparations, opioid binding appears in the ganglion initially but does not appear in the cord until invasion by the ganglion cell neurites (25). Capsaicin, a neurotoxin that destroys small afferents (26), produces a significant reduction in the levels of markers for small primary afferents (27) and produces a reduction in ^{3}H-dihydromorphine binding in rat spinal cord comparable to that seen with rhizotomy (28). These observations jointly suggest that opiate binding sites may be found in primary afferents. Nevertheless, the subtotal loss of binding after neurotoxic and anatomical lesions argues that residual opioid binding exists on non-afferent elements.

The Primary Afferent Effects of Spinal Opiates

Evidence suggesting a presynaptic action for spinal opiates derives from studies examining the spinal release of neurotransmitters, the effects of opiates on primary afferent excitability, and the effects on dorsal root ganglion cell culture systems.

1. Substance P, a putative neurotransmitter found in small primary afferents, is released in vivo by A-δ/C fiber activity from spinal cord (29, 30). This evoked release is attenuated in vitro (31, 32) and in vivo (29, 30) by the local superfusion of opiates; the inhibition is antagonized by naloxone.

2. When current is applied by microelectrode in the dorsal-horn terminal field of a single primary afferent, the amount of change required to antidromically activate that axon permits assessment of the excitability of these terminals. Primary afferent depolarization, classically assumed to result in a decrease in neurotransmitter release, is reflected by a decrease in the threshold current required to evoke an antidromic discharge. Systemically administered opioid alkaloids in doses that result in behaviorally defined changes in pain in cats produce a significant decrease in terminal excitability (33). These effects of opiates appear to be mediated by an action on afferent terminals, because the focal iontophoretic delivery of morphine and met-enkephalin into the dorsal spinal gray also evokes a reliable decrease in the excitability of A-δ and C fiber but not of A-β terminals, which are naloxone antagonized (34).

3. Studies in chicken and mouse dorsal-root ganglion cultures have revealed that opiate alkaloids [morphine (32), etorphine (35)] and peptides [leu-

enkephalin (36), dynorphin (37), D-ala^2-met-enkephalin (32), morphiceptin (36)] have no effect on resting membrane potential or input resistance but do produce a shortening of the duration of the action potential antagonized by naloxone (32, 38, 39). This appears to occur by the attenuation of a voltage-dependent inward calcium current or by the enhancement of a voltage-dependent outward current. It must be stressed that all DRG cells do not respond to opiates, and those that do appear to have several populations of receptors (36, 40). This rather surprising finding has potential relevance for interpreting the physiological effects of opiates. In a cell culture system in which DRG cells synaptically drive spinal neurons, MacDonald & Nelson (35) demonstrated that etorphine iontophoretically applied to the spinal explant abolishes the EPSP evoked by stimulating the ganglion cell. This occurs in the absence of any change in either the membrane potential or the resistance of the second-order neuron. These data jointly suggest that opiates can diminish the depolarization-evoked release of a putative primary afferent neurotransmitter, perhaps by a local affect on the afferent terminals in the dorsal horn.

The Postsynaptic Effects of Spinal Opiates

To determine whether the observed effects of opiates on spinal nociceptive processing are pre- or postsynaptic, two ploys have been used: (*a*) to examine the ability of iontophoretically applied opioid to antagonize excitation evoked by glutamate, and (*b*) to apply the opiate near the terminals (in the substantia gelatinosa) and record from the cell body in the underlying nucleus proprious. Zieglgansberger and colleagues (15, 16) have noted that iontophoretic opiates applied in the vicinity of the cell body lead to a reduction in the rate of rise of the EPSP recorded intracellularly. This occurs in the absence of any evidence of hyperpolarization. Since spike initiation secondary to rapidly rising EPSP (generated, for example, by a synchronously arriving volley from rapidly conducting fibers) is less affected than the spike generated by slowly rising EPSP's (as generated by a dysynchronously arriving volley from small, slowly conducting afferents), the selective effects of opiates could be accounted for by this differential sensitivity to membrane conductance [but see (41) for a perceptive critique].

The majority of the studies that thus far have examined the response of neurons in the spinal cord to opiates have examined the neurons thought to lie within the nucleus proprious and whose dendrites lie more dorsally in the substantia gelatinosa. Duggan and colleagues, using multiple pipettes, examined the effect of opioids applied into the dorsal gray while recording from the vicinity of the more ventral cell body (42–44). In this work, morphine was observed to depress the responses evoked by thermal stimuli only when applied in the dorsal lamina; it was relatively inactive when given near the cell body. Peptides, in contrast, uniformly produce depression when administered along

the dorsal-ventral axis of the neuron. Importantly, naloxone reverses the depressive effects of both the alkaloids and the peptides.

Sastry & Goh (45) have observed that morphine and met-enkephalin amide excite gelatinosa neurons but suppress underlying cells. Such actions are not inconsistent with the effects of opiates on afferents, given the possible role of gelatinosa neurons in presynaptic inhibition.

The mechanism of the action of opiates on cell function has been investigated in in vitro studies. Zieglgansberger & Sutor (46) have observed slices in which activity evoked by stimulating an attached rootlet as well as by iontophoretically applied glutamate is suppressed by focally applied D-Ala^2-D-Leu^5-enkephalin (DADL); this effect is reversed by naloxone. Recording intracellularly, the application of morphine, met-enkephalin, and DADL (47, 48) results in hyperpolarization concentration dependent over ranges of 30 nmol–100 μmol. Naloxone results in a significant antagonism of the observed hyperpolarization. Importantly, this hyperpolarization has been observed in the presence of calcium-free, high-magnesium solutions and is associated with an increase in membrane conductance. The results of manipulating extracellular potassium suggest that this conductance increase is largely related to the potassium ion.

In short, persuasive anatomical and electrophysiological data argue that exogenously administered opiates can act in the dorsal horn at sites that are both pre- and postsynaptic to the primary afferent to suppress nociceptive processing.

THE BEHAVIORAL EFFECTS OF SPINAL OPIATES

The powerful selective effects of systemically administered opiates on dorsal-horn neurons and nociceptive reflexes in spinal-transected animals and the pharmacological characteristics of these effects clearly demonstrate beyond question the existence of spinal opioid receptors that regulate the spinal processing of A-δ/C fiber input. Such studies, however, provide no information about the relevance of these opiate–receptor linked systems to behavior.

The Spinal-Injection Preparation

The early studies (49) on the functional role of these spinal receptor systems in the intact and unanesthetized preparation were facilitated by the demonstration that a chronic spinal catheter could be passed to various levels of the intrathecal space in the spinal cord of the rat (50), rabbit (50), cat (51), and primate (52). After the initial description of this phenomenon in rats, several modifications have been presented (53, 54). This simple approach has found use in the majority of studies published thus far on this topic. Recently, a variation in the approach in the rodent has been described that incorporates a cervical (55) or a lumbar penetration (56, 57). The direct-puncture technique described by Hyl-

den & Wilcox (58) for the mouse must be considered an important contribution in view of the widespread use of this species. The use of osmotic minipumps to deliver opiates chronically through an intrathecal catheter in rats has been described (59).

Epidural animal preparations have been described for rat (56), cat (60), and primate (52). The present discussion will not deal with the results obtained using the epidural route, since these results are qualitatively comparable, although equipotent epidural doses generally exceed those observed after intrathecal administration and some drugs are comparatively inactive by the former route because it lies outside of the blood-brain barrier.

The question of the anatomical specificity of the intrathecal injection procedure has been discussed elsewhere (50, 61). The likelihood of a supraspinal redistribution of the drug can never be excluded and in fact increases with injection volumes, dose, lipid partition coefficient of drug (leading to increased blood levels), and time after injection. Failure to observe the effect associated with intrathecal action of the agent after intracisternal administration of an equal dose, or if such an injection produces a different behavioral syndrome, and if the effective intrathecal dose of the agent is inactive after intravenous injection, then the probability that the intrathecally administered drug is acting supraspinally is minimized. The intrathecal or epidural catheter preparation may cease functioning after an unpredictable period due to the formation of a fibrotic sheath that can prevent the drug from moving freely. A rightward shift in the dose response curve for intrathecal dynorphin has been reported in rats implanted more than a few days (62, 63). Durant & Yaksh (unpublished data) similarly have found a significant rightward shift in the dose response curve for morphine after epidural injection in rats, and this is associated with histologically defined fibrosis. Long-term studies must therefore build in controls to minimize the likelihood that loss of response to a particular agent is not simply due to a change in spinal drug distribution.

The Antinociceptive Effects of Spinal Opiates

Analgesia may be loosely considered the absence of an organized pain response in the presence of an otherwise adequate stimulus. Although complex, the central issue in assessing the effects of analgesic drugs is that somatic/visceral information must reach supraspinal centers to evoke the pain state. In animal models, the endpoint that signifies analgesia is the behavioral state in which the animal fails to respond with an organized behavioral response (hind paw lick, bar press) to escape an unconditioned stimulus that would otherwise evoke that behavior. Reliance on a task, the response components of which are spinally organized (e.g. the tail flick or skin twitch), makes it possible that drug effects that alter extensor/flexor tone (as with the Straub tail in the rat after morphine), or that postsynaptically alter the ability of flexor-reflex afferents to excite

motoneurons, can yield results that are reflective of motor dysfunction and not sensory processing. While supraspinally organized responses are not devoid of interpretational difficulty, if the spinally administered drug blocks the ability of a somatic stimulus to evoke an organized escape response and the animal has the demonstrated ability to make the response (i.e. ambulation, vocalization, bar press) one can be certain to some degree that the spinal drug has altered the text of the ascending message. Thus, while spinally mediated reflexes are convenient and reliable, the need to examine measures that require supraspinally organized responses cannot be underestimated.

Table 1 summarizes the activity of spinally administered opiates on a number of spinally or supraspinally organized pain models in man and animals. It also presents the dose of intrathecal (animal) or epidural morphine (man) that represents the ED_{50} or is the dose that significantly increases the response baseline. As shown, spinal morphine produces: (*a*) an increase in the latency to respond in spinally mediated reflexes (tail flick, skin twitch) and supraspinally mediated responses (hot plate) evoked by strong cutaneous thermal stimuli; (*b*) an increase in the shock intensity applied to the tail or the hind paws (but not the ear) required to evoke squeak or bar press response; (*c*) a decrease in the likelihood of an agitation response to pinches applied to the paws; and (*d*) a reduction in the incidence of behavioral sequelia secondary to the intraperitoneal injection of an irritant. In terms of relative activity, the approximate rank ordering of the efficacy of intrathecal morphine in the mouse is writhing > tail flick = hot plate, and in the rat is pinch = hot plate = tail flick > tail shock = shock titration. We want to stress that the comparison of efficacy across different tests is in part artifactual, because the apparent ED_{50} values can be shifted radically by altering the endpoints on the criteria for failure to respond. Nevertheless, comparability of doses in the several thermal nociceptive tests reflecting the ability to block the two end-points suggests comparable substrates. In dogs, spinal morphine blocks the rise in blood pressure secondary to exercise ischaemia induced by reversible ligation of the iliac artery during mild activity on a treadmill (88).

In man, experimental pain models have proven less useful than in animals; nevertheless, measurable effects on the ability to tolerate cold water immersion and a pressure tourniquet to the lower limbs (but not upper limbs) are significantly increased in volunteers receiving clinically useful doses of epidural morphine. The majority of work on the antinociceptive effects of spinal opiates in man has been carried out in postoperative pain patients and patients suffering from terminal malignancies. As shown in Table 1, following thoracic and/or abdominal surgery, epidural morphine produces a powerful analgesia, as measured by a variety of behavioral endpoints, such as the visual analogue scale, the McGill pain questionnaire, and the mobilization scale (indicating the relative activity of the patient during the postoperative course). One powerful

Table 1 Pain models in mouse, rat, cat, primate, and human sensitive to spinal morphine

Pain Model	Species	Spinal morphine dose (nmol)[a]	References
EXPERIMENTAL			
Temperature			
Thermal-spinal reflex			
Tail flick	Mouse	0.9–2.4[b]	64
	Rat	1.3–11.9	65
Skin twitch	Cat	120[b]	51
Thermal-supraspinal			
Hot plate	Mouse	1.5–5.7[b]	66
	Rat	0.9–12.7[b]	64
Cold-supraspinal			
Limb immersion	Human	~ 30,000[c]	67
Electrical			
Shock vocalization	Rat	90[c]	68
Shock titration	Rat	135[c]	69
	Primate	3000[d]	70
Pressure			
Pinch	Rat	0.8–3.5[b]	71
Tourniquet pressure	Human	~ 10,500[c]	72
Inflammatory			
Writhing	Mice	0.08–0.21[b]	77
	Rat	0.3–12.1[b]	65
CLINICAL			
Postoperative: Thoracic/upper abdominal		2–8 mg	
Visual analogue scale			74–76
Modified McGill pain questionnaire			74
Mobilization scale			77
Duration or time to first analgesic (> 10 hours)			78–80
Cumulative consumption of additional analgesics			78, 80
Respiratory function			
Peak expiratory flow rate			76, 77
Vital capacity			76, 81
Forced expiratory volume at 1 second			77, 80, 81
CO_2 response curves			82
Pulmonary X-ray changes			77, 81
Terminal Cancer			
Visual analogue			83, 84
McGill pain questionnaire			84
Consumption of additional analgesics			84–86
Time between doses			84, 85, 87

[a] Intrathecal in animals; epidural in man.
[b] 95% CI of ED_{50}.
[c] Dose that produces a significant increase over baseline.
[d] Dose that just produces the maximum increase in the shock titration response.

method of quantification is an examination of the pattern of analgesic consumption during the postoperative course, since this represents a clearly quantifiable operant response on the part of the patient during the occurrence of pain. Thus, among groups receiving spinal opiates, the time to administration of the first alternative analgesic is significantly increased and the cumulative consumption of alternative analgesics is reduced. A variety of physiological, particularly respiratory, indices generally compromised after thoracic or abdominal information have also been studied with spinal opiates. In all cases, there is a significant improvement in performance, which indicates a reduction in the pain stimulus evoked by the expansion of the chest wall.

In terminal cancer pain, difficulties arise by virtue of (*a*) possible day-to-day variation in pain, and (*b*) problems of tolerance associated with long-term use of systemic or spinal opiates. Nevertheless, spinal opiates have been shown to acutely produce pain relief as assessed by behavioral measures such as the visual analogue scale and the McGill pain questionnaire. During long-term administration, the adequacy of spinal drug therapy is reflected in the time between doses (or, in the case of chronic infusion, in the stability over time of the dose required to produce reports of analgesia) and the level of consumption of additional pain medication; long-term administration of spinal opiates, either by percutaneous catheters [see, for example, (85, 87)] or by chronic infusion [see, for example, (84, 86)], has indeed been reported to result in adequate analgesia, with minimum alternative drug consumption, without a need for significant spinal drug–dose escalation for periods of between three and six months.

In short, spinally administered opiates can produce a powerful increase in the tolerance to thermal, mechanical, and chemical stimuli, as well as postoperative states that otherwise evoke verbal and behavioral manifestations of pain.

The Locus of Action of Spinally Administered Opiates

What corollaries can be drawn between the effects of intrathecally administered opiates on behavior and the effects on single-unit activity in spinal cord? In view of the presence of opioid binding in the DRG and dorsal roots, and the observation that in vitro opiates can produce a significant effect on the activity of subpopulations of DRG cells in culture, it is reasonable to speculate that the spinally administered opiates may exert a direct effect on the afferents. This effect appears limited to the culture preparation, however, because in adult animals recording in situ from rat dorsal root ganglion cells and from vagus nerve opiates have failed to produce any effect on measured membrane properties (89, 90). Alternately, failure to observe opiate effects on adult ganglion cells may be due to limited sampling. As noted (36, 40), opiate sensitivity is found in a limited population of neurons.

To examine the correlation between intrathecally administered agents and

the effect on similar activity, drugs have been applied directly to the surface of the cat cord and the effect on the resting and evoked activity in the underlying neuronal pool has been examined. Doi & Jurna (91), in an outstanding series of experiments in the rat, observed that doses of intrathecal morphine that produce analgesia (69) result in a dose-dependent, naloxone-reversible suppression of activity in ascending axons evoked by A-δ and C, but not A-β, afferent stimulation. In other work, fentanyl (92), alftenanil (93), and morphine (94, 95) have been shown to produce a dose-dependent suppression of both resting activity and the activity evoked by the application of noxious thermal stimuli to the receptive field in anesthestized cats. These effects are also reversed by relatively low doses of intravenous naloxone. Importantly, the time course of the onset of the inhibition is shortest for fentanyl, longest for morphine. These time courses correspond closely with the time course reported for the onset of the block of the skin twitch response for these three agents in the cat (96) and the rat (69). Also of importance is that this ordering of the onset of activity corresponds closely with the lipid partition coefficient of these agents, which is known to correlate with the rate at which the material diffuses into the tissue (97). This close correspondence between time of onset of action in both single unit and behavioral studies, with lipid partition coefficients and the rate of drug diffusion, therefore is consistent with, but does not necessarily prove, that the effects on behavior are mediated by this particular population of wide dynamic-range neurons. As noted above, the possibility of a supraspinal movement of the drug cannot be discounted. The small amount of drug that does redistribute may account in part for the potent effects of spinally administered opiates. This is consistent with earlier speculations that there is a synergistic interaction between spinal and supraspinal opiate receptor–linked systems (98, 99). Nevertheless, the somatotopy of the antinociceptive effects of spinal opiates (51, 52, 69) in several species indicates that, at least acutely, the physiological effects of spinally administered opiates are mediated by an action on spinal receptors.

The Pharmacology of the Antinociceptive Effects of Spinal Opiates

As indicated in the preceding section, intrathecally or epidurally administered opiates will produce a significant attenuation in both experimental and clinical measures of assessing somatic or visceral pain in all species thus far examined, from mouse to man. What are the characteristics of the spinal receptor(s) through which these effects are mediated? An extensive literature based on in vivo and in vitro bioassays subsequently supported by ligand binding studies indicates the likelihood of discriminable populations of opioid receptors. Based on different structure-activity relationships viz different physiological measures, different affinities of the antagonists for the receptor acted upon by the

several agents in a given preparation, and differential cross tolerance, five distinguishable pharmacological profiles have been identified and named as μ, κ, σ (100), δ (101), and ε (102) receptors. A comparable analysis carried out with intrathecally administered drugs permits one to assess the characteristics of the spinal receptor systems that mediate the unconditioned response of the intact and unanesthetized animal to otherwise noxious stimuli. Such an approach has several inherent advantages: (*a*) it permits the use of agents that do not cross the blood-brain barrier or are otherwise inactivated by a peripheral route (metabolism or protein binding); (*b*) spinal application allows assessment of the characteristics of the *spinal* receptors in the intact animal, and as such permits one to determine whether those spinal receptors can alter a supraspinally mediated escape response, i.e. alter the rostrad transmission of nociceptive information.

THE STRUCTURE-ACTIVITY RELATIONSHIP OF INTRATHECALLY ADMINISTERED OPIOIDS Table 2 presents the structure-activity relationship for a series of opioid alkaloids and peptides given intrathecally in mice (tail flick, writhing), rat (hot plate, tail flick, writhing), and primate (shock titration). Where possible, the table is based on work from a single laboratory to permit examination of a variety of agents in comparable preparations. Where the full range of the dose response curves has been examined, it has been possible to produce a monotonic dose-dependent inhibition of the several endpoints, with maximum suppression achieved at doses that have no discriminable effect on the ability of the animal to make the response.

We want to emphasize several points made by the data presented in Tables 2 and 3.

1. In the rat, in spinal and/or supraspinally mediated responses to cutaneous thermal stimuli and in the primate in the shock titration test, μ and δ ligands produce a monotonic dose-dependent increase in the response latency or level of shock tolerated by the animal. Examination of the rank order of potency, in the rat in the two thermal response measures and between rat and primate, of opioids reported to have some degree of μ or δ selectivity indicates remarkable parallels between tests and between species. d-Stereoisomers of active agents are between 100–1,000 times less active than the l-isomer.

Examination of the rank order of potency in the rat and primate on thermal nociceptive measures and the shock titration indicates that among the more efficacious agents are those generally thought to possess significant mixed μ and δ affinity (e.g. β-endorphin, metkephamid). The spinal potency of β-endorphin has been noted by others (71). This observation is consistent with the finding that coactivation by intrathecal injection of μ and δ receptors results in an evident synergy (128). Whether this reflects the possibility that μ and δ receptors are allosterically coupled (129) is not known. In the mouse, intrathe-

Table 2 Potencies relative to morphine of intrathecally administered mu, delta, kappa, and sigma agonists in the mouse and primate

	Mouse		Rat[c]			Primate[d]
Ligand/putative receptor selectivity	Tail flick[a]	Writhing[b]	Tail flick	Hot plate	Writhing	Shock titration
Mu						
Morphine	1.0	1.0	1.0	1.0	1.0	1.0
Sufentanyl	—	—	15.0	27.7	—	—
Levorphanol	—	—	8.1	10.2	7.8	—
Fentanyl	—	—	2.0	1.7		—
Alfentanil	—	—	0.9	0.76	—	
D/L-methadone	—		0.1	0.6	—	1.0
Meperidine		—	0.07	0.05		0.2
Codeine	—	—	<0.01	<0.01	—	—
Delta						
DADL	150	2.5	1.5	1.0	<0.1	—
DPE_2	—	8.7	1.3	1.0	<0.06	
Met-enkephalin	0.07		0.03	0.02	<0.01	—
Leu-enkephalin	0.03	—	<0.01	<0.01	<0.01	—
DSTLE	—	—	—	—	<0.1	—
Mu/delta						
D-ala^2-MEA	17	—	42.0	33.0	0.04	2.3
Beta-endorphin	—	—	33.0	25.0	2.6	27.0
Metkephamid	—		21.0	21.0	1.4	35.0
Etorphine	—		18.1	22.3		
D-ala^2-met-enkephalin		—	0.7	0.9	–	—

Kappa						
U-50488H	32	—	<0.01	<0.01	0.03	—
Bremazocine	—	1.6	<0.01	0.05	0.09	—
EKC	1.1	0.4	<0.01	0.03	0.18	—
Dynorphin$_{1-10}$	38	0.4	<0.1	<0.1	1.1	—
Sigma						
SKF10047	—	—	<0.01	<0.01	<0.01	—
Partial agonists						
Nalbuphine	—	—	<0.01	<0.01	0.03	—
Buprenorphine	—		0.2		0.2	—
Nallorphine	—	—	<0.01	<0.01	—	—
Pentazocine			<0.01	<0.01	0.1	
D-isomer						
D-methadone		—	<0.01	<0.01	<0.01	<0.01
Dextrorphan	—	—	<0.01	<0.01	<0.01	—

[a] Taken from (103): morphine, DADL, met/leu-enkephalin, D-ala^2-MEA, EKC; taken from (66): dynorphin, U-50488H.
[b] Taken from (73)
[c] Taken from (65, 69, 104–111); T. L. Yaksh, unpublished observations
[d] Taken from (52, 70); T. L. Yaksh, unpublished observations
[e] (—) not tested

Table 3 Range of doses of epidurally administered opioids required to produce clinically acceptable analgesia in postoperative or terminal cancer patients

Drug	Clinical situation	Dose range (mg)	Reference
Morphine	Upper abdominal; thoracic	4–10	76, 78[b], 80, 112[b]
	C-section; gynecologic	4–8	75[b], 113, 114, 115[b]
	lower abdominal; orthopedic	2–4	116, 117[b]
	terminal cancer[a]		83, 84, 85, 87
Methadone	Upper abdominal; thoracic	9	80
Diamorphine	Lumbar laminectomy; major abdominal vascular surgery	5	118, 119
β-Endorphin	Terminal cancer pain	3	120
Meperidine	Upper abdominal; thoracic	50–60	79, 121
Alfentanil	Orthopedic; abdominal	0.015–0.3	122
Pentazocine	Gynecologic; abdominal	10–15	123, 124
Fentanyl	Upper abdominal; thoracic	0.06	125
Bupenorphine	Major abdominal; orthopedic	0.06–0.3	126

[a] Doses required are variable, depending upon state of tolerance. Doses as high as 175 mg have been reported (127).
[b] Dose response curves were generated.

cal μ and δ ligands block the tail-flick response. Hylden & Wilcox (130) have shown that the hindlimb scratching response evoked by intrathecal substance P (sP) is suppressed in a dose-dependent fashion by intrathecally administered μ and δ ligands.

2. Putative κ agonists (ethylketocyclazocine, bremazocine, and U-50488H), partial agonists (buprenorphine), and partial agonists/antagonists (nalbuphine) show limited activity in the cutaneous thermal tests when given spinally or systemically. Ethylketocyclazocine, which is weakly active on the hot plate and tail flick [(73, 105, 110), but see (131)], is known to possess μ receptor activity as defined by in vitro binding and bioassay analysis, indicating that some of its activity during these tests may be discriminable from its κ agonist activity [see (1, 2)]. Agents having reportedly high levels of κ specificity, such as U-50488H, show little if any effect on hot plate and tail flick in the rat when given intrathecally (65), although significant antireflexive activity has been reported after systemic and intrathecal administration in the mouse (66).

Recently, dynorphin-like peptides, endogenous peptides with putative κ receptor affinity, have been shown to be equal to (62, 63, 73, 77, 132) or considerably less potent than morphine (C. Stevens, G. Harty, T. L. Yaksh, unpublished observations) (Table 2) in blocking thermally evoked reflexes. Comparable results with dynorphin$_{1-13}$ have been reported after spinal administration in the mouse on the thermally evoked tail flick (see Table 2) (66).

3. In the rat, intrathecally administered μ and κ ligands, or agents classified as partial agonists and mixed agonist-antagonist, produce a monotonic dose-dependent reduction in the writhing response with no signs of an efficacy plateau. In the work summarized in Table 2, μ agonists displayed comparable activity on the visceral chemical and the two thermal response measures (see morphine ED_{50} values in Table 1). We want to stress that the quantitative similarity of the ED_{50} values on the writhing and thermal tests is a fortuitous function of the endpoint chosen in either class of test. In contrast, agents designated on the basis of in vitro bioassay and binding studies as being δ ligands (e.g. D-ala^2-D-leu^5-enkephalin, D-ser^2-thr^6-leu-enkephalin, leu-enkephalin-CH_2-leu-enkephalin) and that when given intrathecally in the rat display a rank order potency equal to or greater than morphine on the cutaneous thermal tests show little or no efficacy in the visceral chemical writhing measure at doses that (*a*) block the hot plate and tail flick responses or (*b*) do not produce evidence of motor dysfunction.

K ligands (U-50488H, dynorphin$_{1-13}$), which are minimally active on cutaneous thermal measures when given intrathecally in the rat, show an increase in activity on the writhing test. Consistent with the diminished efficacy of δ ligands in the rat writhing test, agents with significant μ and δ affinity, such as metkephamid and β-endorphin, display a marked reduction in their apparent potency in the writhing compared to the relatively selective μ agonist morphine, which shows little or no change in apparent efficacy. Przewlocki et al (73) reported that DADL produces a dose-dependent decrease in the writhing score but relative to morphine is less active than on the tail flick. With regard to dynorphin, these investigators observed blockade of the tail flick at doses above those that suppressed the writhing and in a range at which motor impairment could play a role (see below).

4. The low efficacy of met- and leu-enkephalin, putative δ receptor ligands, on the cutaneous thermal tests could be due to their lack of activity at the relevant receptor and/or to metabolism (133–136). Based on the half life of these peptides in brain tissue (134) and evidence suggesting that the magnitude of antinociceptive activity and metabolic stability do not appear to covary (135), it has been argued that the lack of activity is not related to their rapid turnover. Nevertheless, protecting an appropriate enkephalin from hydrolysis by the inhibition of enkephalinase A, by co-spinal administration of thiorphan, or by aminopeptidase inhibitors such as amastatin or bestatin (135) results in significant increases in the antinociceptive activity of intrathecally administered D-ala^2-met-enkephalin, met-, and leu-enkephalin (137, 138). When both terminals of the enkephalin molecule are protected either by the D-amino acid substitution and amidization (D-ala^2-D-met^5-enkephalin amide) or by D-alanine substitution along with enkephalinase A inhibition, the apparent potency after intrathecal injection or cutaneous thermal measures in the rat is in

excess of that observed with morphine (137). Significantly, neither met- nor leu-enkephalin in the presence of peptidase inhibitors in doses that block the tail flick had any detectable effect on the visceral chemical writhing responses (138). These observations are consistent with the previous findings that δ ligands have little effect on the visceral chemical response in the absence of motor deficit.

Recent studies have demonstrated that intrathecal opiates in the frog suppress the scratching response to acid applied to the skin. The phenomenon is characterized by a monotonic dose dependency, the rank ordering of potency being levorphanol > dynorphin > β-endorphin > morphine > met-enkephalin > naloxone = 0. The observed effects are antagonized by naloxone (139, 140). These results suggest the biological relevance of μ, δ and κ opioid binding sites previously described in amphibian brain (141).

NALOXONE ANTAGONISM The effects of intrathecally administered opiates that result in a significant elevation in the nociceptive thresholds with no detectable effect on motor function have uniformly been reversed by naloxone. Systematic studies on the ability of naloxone to reverse opioid effects have demonstrated (*a*) that the antagonism produced by either systemic or intrathecal administration of naloxone is dose-dependent, with the magnitude of the antagonism proportional to the log of the dose (69), (*b*) that the order of sensitivity to naloxone antagonism on the tail flick and hot plate is by ranking: morphine ≃ β-endorphin ≃ D-ala^2-met-enkephalin amide ≃ alfentanil ≃ sufentanil ≃ ethylketocyclazocine > DADL (69, 96, 105, 106, 107, 142). This calculation of the apparent pA_2 [see (143)] has provided values of around seven for the former and six for the latter group of intrathecally administered agents [see (2)]. These results indicate that on these behavioral endpoints the agents in the spinal cord may be grouped according to two classes of sites distinguishable on the basis of the efficacy of naloxone. Han and colleagues (132), examining the antagonistic potency of naloxone on a thermal tail withdrawal response, observed that the rank order of sensitivity to naloxone is: [N-Me-Phe^3, D-Pro^4]morphiceptin, dihydroetorphine, morphine, D-ala^2-leu-enkephalin, D-ala^2-D-leu^5-enkephalin, ethylketocyclazocine, dynorphin B, dynorphin A.

Results comparable to those in the rat have been observed in the primate on the shock titration task (70). Thus, the pA_2 for morphine and β-endorphin is around 6.7–6.8, while that for DADL and metkephamid is around 6.0–6.3. The congruency of this line of investigation in two species on two different classes of measures provides a validating consistency for this complex analysis.

In the visceral chemical test, the naloxone pA_2 measured in the presence of spinal morphine is comparable to that obtained in the cutaneous thermal measures, indicating that in the rat spinal cord the receptor intrathecal morphine acts on to block the cutaneous thermal and visceral chemical cannot be

distinguished. K ligands show lower sensitivity to naloxone antagonism (e.g. pA_2 values on the order of six) (65). Intrathecal ethylketocyclazocine thus displays complex characteristics such that, on cutaneous thermal tests, it behaves as if it is acting on a receptor acted on by morphine in the guinea pig ileum, for which naloxone has a relatively high affinity, while in the writhing model, at lower doses, the drug exerts its effects by a receptor in the ileum for which naloxone has a lower affinity [see (1, 2)].

TOLERANCE AND CROSS TOLERANCE Rats rendered tolerant to morphine by intrathecal or systemic injections show cross tolerance between the two routes, suggesting that at analgesic doses intrathecal morphine exerts its effects on receptors acted on by systemic opiates (144). Withdrawal phenomena secondary to systemic morphine can be induced by intrathecal opiate antagonists (144, 145). Intrathecal D-chlornaltrexamine, an irreversible opiate antagonist, antagonizes the effects of systemic morphine and attenuates the development of dependence, as evidenced by signs of precipitated withdrawal (145).

With regard to cross tolerance between intrathecally administered opioid ligands, rats and primates rendered tolerant to intrathecal morphine show a relative loss of activity such that morphine $\geqslant$ β-endorphin $>>$ metkephamid $\geqslant$ DADL = 0 (69, 70, 104, 146). In animals desensitized by intrathecal injections of morphine or ethylketocyclazocine given at short intervals, dynorphin B shows a significant loss of activity in animals receiving the former but not the latter alkaloid (132). Thus, agents that have a relative selectivity for the δ or κ receptor show little loss of effect in animals rendered tolerant to morphine, whereas animals desensitized to intrathecal ethylketocyclazocine show a significant reduction of the effect of dynorphin.

Several inconsistencies preclude any simple interpretation of cross tolerance experiments, however. First, β-endorphin is thought to have mixed μ/δ receptor activity, yet a loss of activity in morphine-tolerant rats and primates has been reported (104, 146). In contrast, metkephamid is relatively resistant to the loss of activity in morphine-tolerant animals (70), yet, according to the loss of intrathecal activity in the writhing test (Table 2), a significant proportion of its activity may originate from a synergistic interaction with μ and δ receptors. Second, animals rendered tolerant to intrathecal D-ala^2-D-leu^5-enkephalin (147; A. Tung, T. L. Yaksh, unpublished observations) or metkephamid (70) show a significant loss of response to intrathecal morphine. Cross-tolerance studies can provide information on whether two agents interact at comparable sites, but such studies are subject to variables such as the dose, the time of exposure to the tolerance-producing agents, and the selectivity of the respective agonists. Moreover, it is not clear, for example, that the tolerance observed after acute or chronic administration reflects the same phenomenon. High doses may give rise to actions not specific to the receptor under investigation. The asymmetric cross-tolerance data, for example, may reflect this difficulty. The

considerations of Rothman & Westfall (129, 148) regarding the allosteric coupling of the μ and δ receptors may also play a role in this observed asymmetry between μ and δ agonists.

The Pharmacology of Spinal Opioid Receptors in Man

Although adequate data do not exist to fully define the characteristics of the spinal receptors that modulate pain transmission in man, there is ample data to support distinct receptor interaction. First, patients tolerant to systemic morphine show cross-tolerance to spinally administered morphine (85). Second, although systematic studies have not been carried out, these effects of spinally administered opiates are antagonized by naloxone (149–151). Third, spinally administered agents produce analgesia with a structure-activity profile (see Tables 2 and 3) that can be roughly assessed. Although no systematic comparison is possible because of varying paradigms, the approximate rank order of potency seen in man resembles that observed after spinal injection in rat and primate animal models, i.e. on a molar basis: β-endorphin > fentanyl > morphine > pentazocine > meperidine (see Tables 2 and 3). Importantly, D-ala^2-D-leu^5-enkephalin given intrathecally in terminal cancer patients produces a powerful analgesia (152, 153). The reported activity of buprenorphine and pentazocine appears also to implicate a receptor-type interaction that resembles that displayed by the visceral chemical tests. Significantly, κ binding sites have been reported to predominate in human spinal cord (154), and some investigators have argued that κ binding sites predominate in other species as well [see (155)].

In summary, in the spinal cord, the different structure-activity profiles on different tests, the similarity of the profiles across species, the distinguishable pA_2 values, and the different degrees of cross-tolerance argue strongly for distinguishable populations of spinal opioid receptors that modulate spinal nociceptive processing. The particular pharmacological profiles observed in these models appear characteristic of the profiles observed in in vitro bioassay and binding studies designated μ, δ, and κ. Moreover, these observations suggest the likelihood that several classes of opioid receptors may be functionally associated with discrete sensory processing systems. Importantly, although limited data currently exist, the characteristics of the structure-activity relationship in man seem to resemble closely those obtained in rats and primates, suggesting parallels between these systems.

SPINAL OPIATES AND MOTOR FUNCTION

Early studies demonstrated that opiates in spinal-transected dogs did not influence monosynaptic stretch reflexes but suppressed crossed extensor reflexes and flexion reflexes [see (156)]. Such findings have been corroborated in

part by electrophysiological studies, which indicate that opiates suppress polysynaptic and to a lesser degree monosynaptic flexion reflexes (157–160) and the firing of α-motoneurons evoked by muscle stretch (159). Importantly, this inhibition, particularly on the monosynaptic reflexes, is most manifest on those reflexes evoked by high- but not low-frequency stimulation (158, 159). In rats, morphine has been reported to enhance firing of populations of extensors (161, 162). In paraplegic man, morphine in a naloxone-reversible fashion blocks the polysynaptic reflex evoked by sural nerve stimulation of the tibially anterior muscle but has little effect on the monosynaptic "H"-reflex (163).

The mechanisms of these effects are not clear. As discussed above, opiates can exert demonstrated presynaptic effects, although apparently not on large afferents. Opiates have been shown to have a direct effect on glutamate-evoked excitation of motoneurons (15, 16, 164). Both recurrent (mediated by Renshaw cells and activated by motoneuron collaterals) and to a lesser extent direct (mediated by interneurons activated by large primary afferents) inhibition is suppressed by opiates (165, 166). The complexity of opiate effects on motor function is illustrated by the clear excitatory effect opiates have on Renshaw cell activity. This phenomenon is stereospecific and antagonized by naloxone (167, 168). Comparable results have been observed with iontophoretically applied enkephalins (17).

In unanesthetized animals and man, spinal opiates at analgesic doses do not show any measurable effect on behaviorally assessed monosynaptic reflexes [see (61)]. In primates, systematic studies have shown that intrathecal morphine at analgesic doses has no effect on muscle strength (52). At high doses (> 100 nmol) intrathecally administered morphine in rats has been shown to produce two syndromes: (*a*) conclusive seizures of the hindquarters coupled with hyperreflexia secondary to cutaneous stimuli, and (*b*) intense motor rigidity. Neither phenomenon is antagonized by naloxone (68). The mechanism of these effects is not clear but may result from the ability of morphine to block the action of glycine (166). Intrathecal strychnine or bicuculline produces a comparable syndrome (T. L. Yaksh, unpublished observations). The rigidity may reflect the paradoxical effect in which morphine in rat has been shown to excite extensor motor neurons (161). Intrathecal δ-ligands, such as D-ala^2-D-leu^5-enkephalin at high doses (> 40 nmol), result in a loss of hindlimb placing and stepping reflexes, with the limb showing some degree of motor tone but no voluntary movement. This phenomenon is not antagonized by naloxone (109). In doses greater than 3–5 nmol, intrathecal dynorphin (dyn $_{1-13}$) has been observed to produce a comparable syndrome also not antagonized by high doses of naloxone (62, 169; C. Stevens, G. Harty, T. L. Yaksh, unpublished observations). Motor dysfunctions observed with high doses in animal models after intrathecal injection have not been reported in man after either intrathecal μ or δ agonists.

Several points should be stressed. First, detectable motor dysfunctions for μ agonists occur at doses generally at or above those classified as analgesic in all response measures. δ ligands block the cutaneous thermal responses and K ligands (dynorphin) readily block the visceral chemical at doses less than those that produce signs of motor dysfunction. If the dose of spinal drug required to block a response such as a tail withdrawal approaches that where evidence of motor impairment is observed, the likelihood of a nonspecific effect on spinal function must be considered before a selective inhibition of the pain response can be ascribed. Thus, intrathecal DADL has been reported not to block the writhing response and intrathecal dynorphin does not appear to totally block the tail flick in rats at doses that do not produce evidence of motor dysfunction (65, 169). After spinal injections, care must therefore be taken to carefully separate a motor dysfunction from a sensory inhibition. In the case of work utilizing only a tail response, this appears difficult at best. Second, several motor phenomena appear to have a pharmacology different from that associated with analgesia. The failure of naloxone to antagonize is the principle example of this hypothesis. Third, because after intrathecal injection these phenomena are often observed at higher doses, the possibility of supraspinal redistribution represents a very real concern. Thus, the syndrome observed after high intrathecal doses of morphine in which the rat shows extreme truncal rigidity (the banana rat syndrome) can be readily induced by injections into supraspinal structures.

At subtoxic doses, the reported effects of opiates on spinal motor function and the presence of opioid binding in the ventral horn suggest that the failure to see any detectable effect on motor function may simply reflect the role of spinal opioid systems not normally active or too subtle for the gross analysis to which they have been thus far subjected [see, for example, (170a)]. Struppler and colleagues (149) have noted that epidural morphine and fentanyl at analgesic doses diminish in a naloxone-reversible manner flexor-reflex spasm observed in a patient suffering from multiple sclerosis. This occurs in the absence of any change in oligosynaptic or voluntary motor functions or changes in the perception of touch or vibration.

Spinal Opiates and Cardiovascular Function

Spinal morphine given in the unanesthetized rat, cat (170), dog (172) and man (171) has no effect on resting heart rate or blood pressure. In dogs either anesthetized with halothane or unanesthetized, intrathecal morphine and DADL have no effect on cardiac output or peripheral resistance (172; R. Noueihed, T. L. Yaksh, unpublished observations). In man, spinal opiates have no effect on skin temperature and sudomotor activity and, unlike spinal anesthetic, do not diminish the magnitude of the Valsalva maneuver (171). In rats, spinal morphine has been shown to produce an elevation in body tempera-

ture associated with peripheral vasoconstriction (173). This, however, has been interpreted as the activation of coordinated thermoregulatory responses perhaps secondary to a reduction in warm receptor input.

During high-intensity stimuli of a visceral or somatic nature in anesthetized man and animals, there is a significant increase in autonomic outflow measured by markers of pituitary (e.g. prolactin, ADH, ACTH, ß-endorphin), adrenomedullary, and sympathetic (catecholamines, methionine enkephalin) activity. Similarly, physiologial measures such as heart rate, blood pressure, and cardiac output are elevated. In anesthetized preparations, spinal morphine [in man (174–178); in dogs (R. Noueihed, T. L. Yaksh, unpublished observations)] or intrathecal DADL [in dogs (R. Noueihed, T. L. Yaksh, unpublished observations)] produces a significant, but variable, reduction in the release evoked by high-intensity stimulation (intraoperative in man or stimulation of the sciatic nerve in dogs).

SPINAL OPIATES AND THEIR EFFECTS ON GASTROINTESTINAL FUNCTION

Systemic opiates are known to alter gastrointestinal (GI) motility. Intrathecally administered morphine in mice produces a dose-dependent slowing of the transit of a radioactive stomach load (179). δ receptor ligands (D-ala^2-D-leu^5-enkephalin, D-ser^2-leu-enkephalin-thr^6, and D-leu^2-L-cys^2-enkephalin) are also active. The suppressive effects of both intrathecal μ and δ agents remain in the presence of spinal transaction (179, 180). K ligands (ethylketocyclazocine, dynorphin$_{1-7}$, or dynorphin$_{1-13}$) are uniformly inactive (181). Intrathecal morphine does not suppress the migrating motor complex in unanesthetized dogs (G. Telford, M. Hashmonai, J. Szurzewski, T. L. Yaksh, unpublished observations), but does induce propagated bursts of motor activity in the small bowel during the fed state and suppress the fed pattern otherwise observed after a meal (J. Malagalada, M. Camilliera, T. L. Yaksh, unpublished observations). In man, no systematic studies have been carried out with spinal opiates on gastric motility, but ileus, a not-uncommon finding with local anesthetics, and constipation have not been reported.

SPINAL OPIATES AND BLADDER FUNCTION

Spinally administered morphine produces a naloxone-reversible inhibition of the volume-evoked micturition reflex in unanesthetized man (182) and animals (183, 184). Cystometrograms in man show an increase in bladder capacity with unchanged urethral pressures (185). Sphincter EMGs indicate that external sphincter tone is slightly increased (186). Intrathecal morphine in unanesthetized dogs increases the threshold pressure required to evoke the micturition

reflex (187). Dose-response curves carried out in unanesthetized rats with chronic indwelling bladder catheters reveal a clear structure-activity relationship: ß-endorphin ≥ DADL ≥ morphine > ethylketocyclazocine >> SKF10047. The effects of intrathecal agents on bladder function in man and animals are antagonized by naloxone. Animals rendered tolerant to the micturition-suppressing effects of intrathecal morphine show no change in the ED_{50} of intrathecal DADL (183). Comparable results have been observed in the anesthetized rat (187a), the unanesthetized cat, and the primate (T. L. Yaksh, unpublished observations). Intrathecal met-enkephalin, leu-enkephalin, and D-ala^2-met-enkephalin amide given in anesthetized cats reduce spontaneous bladder contractions (184). Although the mechanisms of this effect of opiates on bladder function are not clear, the observations suggest a vesico-sphincter dysynergia and are consistent with the inhibition of firing in vesico-postganglionic nerves (184). These findings represent a significant advance in understanding the central pharmacology of vesicle function. Although inhibition of micturition by spinal opiates is considered an undesirable side effect in their therapeutic use in pain management, it is likely that such observations may presage advances in the management of bladder disorders. Thus, the depressant effect of spinal morphine on spontaneous bladder tone has been used successfully to manage bladder spasm (188), while naloxone has been observed to augment the micturition reflex in spinal-transected animals (189).

SUMMARY

The use of the spinal-catheterized, unanesthetized animal in conjunction with systematic studies on the pharmacology of spinal drug action has provided a powerful tool by which complex functions mediated by spinal systems can be studied. The majority of work to date has focused on the spinal opioid–sensitive substrate that processes high-intensity stimulation. We want to emphasize two points, however. First, these methodological approaches have provided significant insights into the fact that non-opioid spinal receptor systems also play a role in pain modulation. Second, not only do the spinal systems modulate pain processing, they also play a precise role in the mediation of a variety of somatomotor and autonomic functions that are also amenable to investigation and manipulation using this methodology in the unanesthetized animal. The very complexity of the anatomy and biochemistry of the spinal gray emphasizes that the spinal cord substrates are not simply hard-wired systems and that spinal processing may be subject to very subtle alterations by the application of receptor-selective agents. Such insights clearly suggest the likelihood that such insights into spinal functioning possess significant clinical applicability. As indicated, such studies on basic spinal mechanisms have already led to certain fundamental advances in the clinical management of pain. The likelihood of

comparable advances having clinical relevance in other aspects of spinal autonomic and motor dysfunction make this an exciting area of investigation.

In summary, examination of the pharmacology of the effects produced by intrathecally administered opioids in the unanesthetized and intact animal has revealed the relevance of diverse spinal opioid–receptor systems. The combination of this in vivo methodology with single-unit recording and ligand-binding techniques has begun to provide insights into the subtle actions of exogenous opioids on spinal sensory, autonomic, and somatomotor function. This information clearly yields insight into the natural role played by the endogenous opioid systems and potential advances in the management of clinical problems dependent on spinal processing.

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