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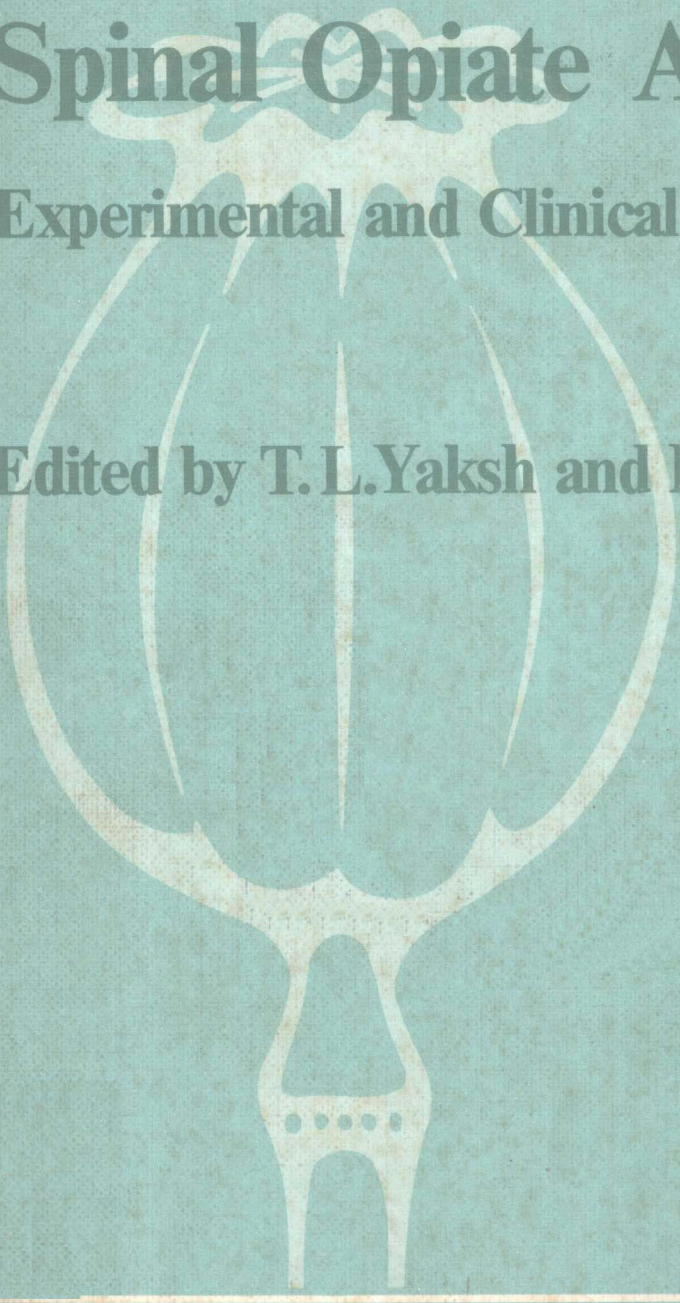
Spinal Opiate Analgesia

Experimental and Clinical Studies

Edited by T. L. Yaksh and H. Müller



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With 55 Figures and 54 Tables

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Preface

The recent development of the use of spinal opiates as a rational therapy for pain rests on clear and certain experimental data. We have long known the spinal cord to be a highly complex structure. Anatomical studies of the substantia gelatinosa have repeatedly demonstrated signs of massive synaptic interaction between primary afferents, descending pathways and intrinsic neurons. Yet, to date that knowledge, insofar as clinical therapy is concerned, has permitted us only to destroy certain connections within the spinal cord in the hopes that the substrate mediating pain could be anatomically differentiated from those which mediate other function. Though cordotomies are clearly effective under certain circumstances, they suffer from the fact the spinal cord is not organized in such an anatomically discrete fashion as is often times drawn in basic medical text. Rather, functions intertwine exquisitely and specific physical interventions are no more likely to produce a specific effect than smashing of the fingertip with a hammer will produce just a loss of the fingernail. The development of specific therapies of the spinal cord has come about by our growing awareness of the intricate organization of the pharmacological substrates associated with specific neural function. Thus, ten years ago had someone suggested the possibility of controlling pain transmission by specifically blocking a pain transmitter, the suggestion would have been foresightful, but groundless, as we had no concept of the fact that there might be different primary afferent transmitters for the different sensations. Though we are still not aware of such specific separations, the observation that primary afferents may contain one of several peptides including substance P, vasoactive intestinal peptide and cholecystokinin, leads us to suspect that these afferents may subserve different functions.

Similarly, we have become increasingly aware of the practical significance of the early literature which indicated that the spinal cord was under massive control by intrinsic and extrinsic modulatory systems. We are now aware, that such modulatory systems are likely associated with the release of a number of specific neurotransmitters, including monoamines, certain amino acids, and most definitely, intrinsic opioid-like materials. It is classical knowledge

There have been reported in this volume and in the literature, cases of life threatening respiratory depression. It is quite likely that what is reported may be the tip of an ice berg. The use of spinal opiates, while recommended under many conditions, must not be treated lightly. It cannot be assumed the drugs which have the ability to alter spinal function in so profound a fashion can be thought of as trivial. The benefits, however, which accrue from such a powerful addition to the therapeutic regimen, makes it worthwhile to consider this procedure.

In sum, we, the editors, would point out that the use of spinal opiates that has developed so explosively, with what appears to be great promise, is only the beginning of what will likely be a revolution in somatic pain therapy. As indicated above, opiates are not the only system within the spinal cord which modulate sensory transmission. Other systems, no doubt many yet undefined, may offer even more specific pharmacological manipulations. *The rational advances in pain therapy, must be preceded not by random injection of drugs of every sort into the spinal space, but by concerted efforts to understand – at the most basic level – spinal function.* Investigations into the pharmacology and physiology of spinal transmission is an imperative which we must all obey. The advantages and potential advances are without question potentially staggering in their implications for the control of pain.

January 1982

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Animal Studies on the Spinal Action of Opiates in Analgesia

T. L. Yaksh

Summary. Animal studies demonstrated that the local action of opiates in the spinal cord would produce a highly significant elevation in the nociceptive threshold in a variety of species including the rat, cat and primate. Two important aspects of this observation were that first the effects were related to a change in the pain threshold, with little effects being observed on motor function, or autonomic activity. The second major observation, was that this effect of spinal opiates was mediated through its effects on a specific receptor system. Evidence for this derives from the fact that these effects of spinal opiates are 1. dose dependent, 2. stereospecific, 3. characterized by a precise structure activity relationship and 4. antagonized in a dose dependent fashion by opioid antagonists. The physiological correlate of this behaviorally defined analgesia appears to be reflected in the fact that systemic opiates will antagonize the discharge of nociceptive neurons in the spinal cord evoked by small, but not large fiber stimulation. The fact that opiates will antagonize the release of substance P, an 11 amino acid peptide thought to mediate small afferent synaptic transmission, may underlie some of the analgetic effects of spinal opiates. Future directions in analgetic therapy may derive from the fact that other intrinsic modulatory systems exist within the spinal gray.

It is my pleasure and privilege to stand before you today to open this first international session on epidural and intrathecal opiates. In this paper, I will review for you the animal literature which first indicated the properties and mechanisms for the analgesia observed following the spinal administration of opiates in clinical patients.

First, it is no surprise to us now that opiates administered intrathecally elevate the nociceptive threshold, but in the mid 70's we were not so certain. It was clear that opiates could inhibit the discharge of nociceptive neurons [1, 2, 3] and spinal reflexes [4] in the spinal animal, but we did not know if this had any relationship to "pain". Early animal studies carried out by Dr. Thomas Rudy and myself employed the intrathecal catheterization procedure [5, 6] to examine the effects of intrathecally administered opiates in unanaesthetized, freely behaving rats, rabbits and cats (Fig. 1).

Our earliest observations revealed that an action of opiates limited to the spinal cord would produce a significant elevation in the nociceptive threshold of a variety of species including the rat, rabbit, cat and primate [7, 8, 9]. Importantly, this intrathecal effect was observed on a variety of nociceptive tests including tasks mediated by spinal reflexes such as the tail flick or skin twitch, simple pain threshold tests such as the hot plate and the flinch jump test, pain of a visceral origin as in the writhing test, and in complex operant threshold tasks such as the shock titration task (Fig. 2). Thus, pain behavior evoked by a wide spectra of physical stimuli including thermal, mechanical, chemical and electrical could be selectively attenuated by a local action of opiates in the spinal cord. This analgesia was largely limited to the caudal regions of the body, suggesting that the effects were upon the segments affected by the opiate and not by redistribution to supraspinal sites.

Of particular significance was the fact that a single dose of spinal opiate was able to produce a prolonged elevation in the pain threshold. As shown in a representative series of

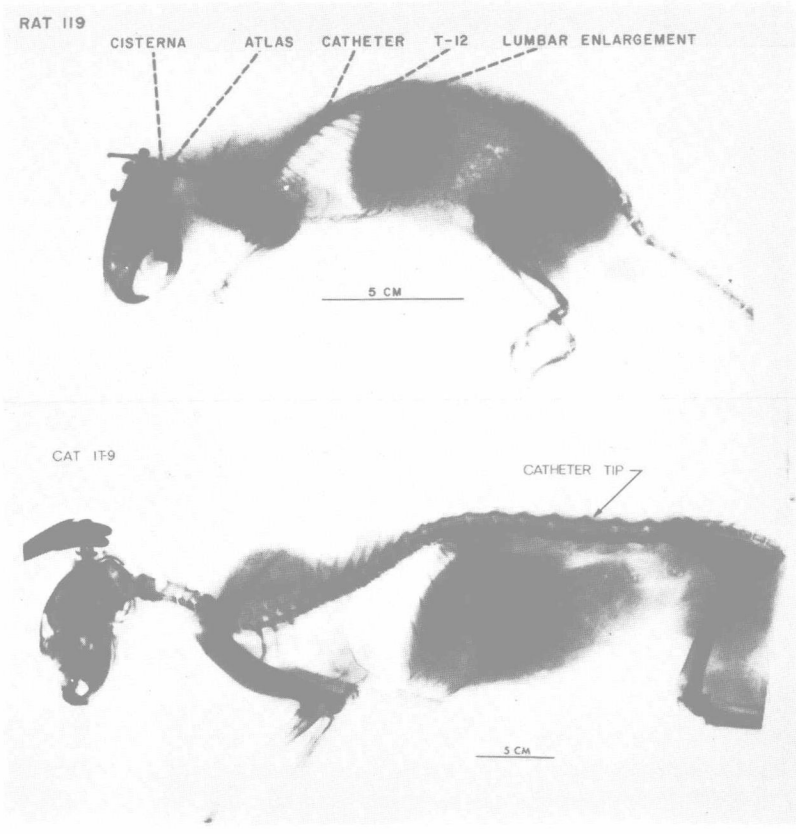
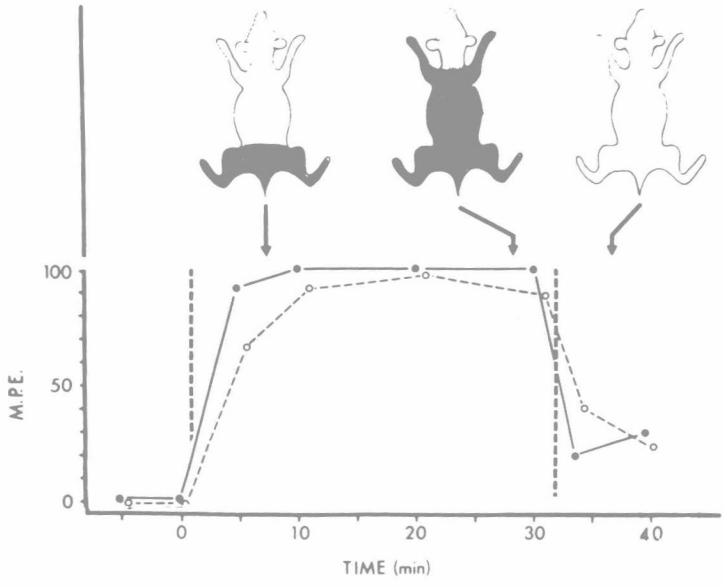
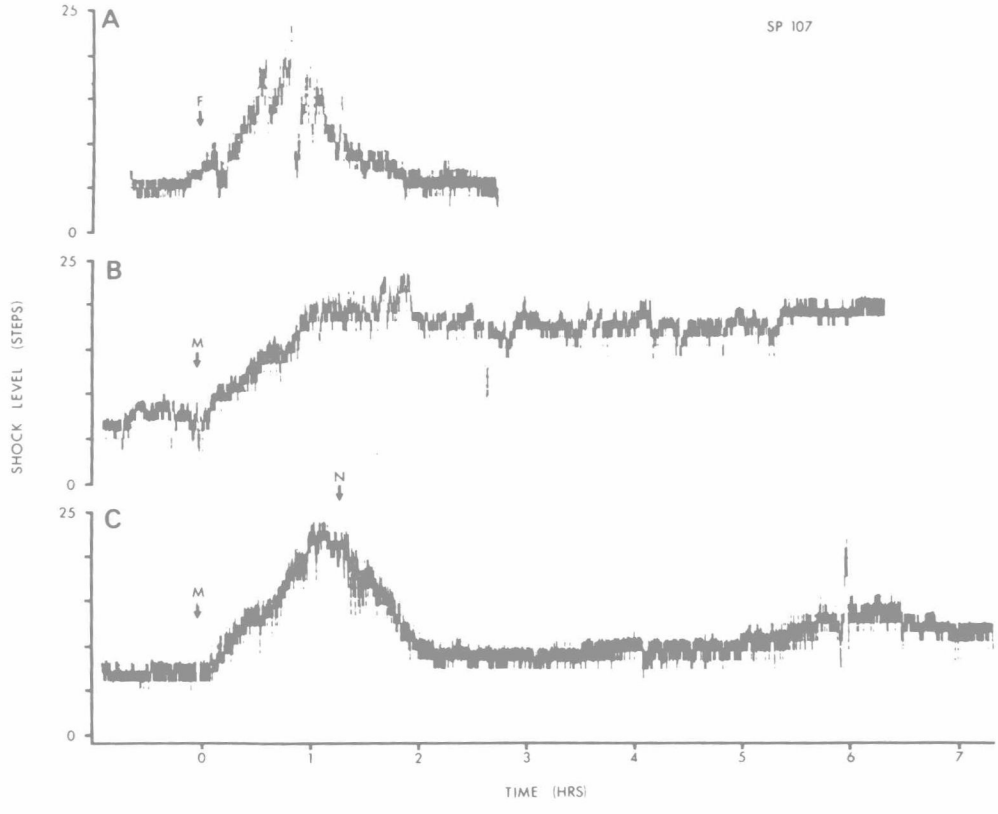


Fig. 1. Radiogram showing the placement of the spinal catheter (polyethylene-10: $\sim$ 0.5 mm o.d.) in the rat *(top)* and cat *(bottom)*. These distances of insertion are $\sim$ 7.5 cm in the rat and 30 cm in cat, respectively

Fig. 2. *(Top)* The effects of morphine administered either into the spinal subarachnoid space (*top*, 15 μg) on the tail flick (●———●) and hot plate (○———○) responses. The effect of these morphine injections on the pinch withdrawal response to forceps pinch is shown in the rat silhouettes with the shaded regions being nonresponsive to such pinch. At the second vertical dashed line, naloxone was administered systemically (1 mg/kg). The ordinate is the maximal percent response *(M.P.E.)* whereas the abscissa is time in minutes after the administration of morphine.
(Bottom) Shock titration records taken from a series of three experiments carried out in the same rat (107) at intervals of 7 and 9 days, respectively. The ordinate for each graph is the shock level in steps, with each step equal to 0.16 mA, while the abscissa is time in hours after the injection of the narcotic. In these experiments, fentanyl (F; *A* 9 μg) and morphine (M; *B* and *C*, 45 μg) were administered intrathecally at the first arrow. In *C*, the antagonism of the narcotic effect is demonstrated by the administration of naloxone (N; 2 mg/kg i.p.) at the second arrow. Data are taken from [7]





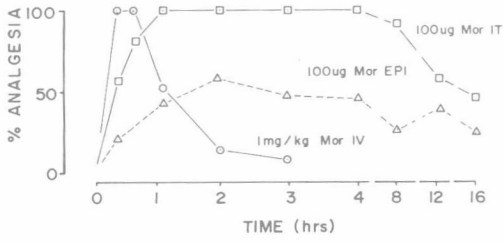


Fig. 3. The figure displays the antinociceptive effects in the cat, as measured by the skin twitch response following the intrathecal administration of 100 μg morphine sulfate, 100 μg morphine epidurally, or 1 mg/kg morphine intravenously. The *ordinate* gives the analgesia in terms of the percent of the maximum permissible escape latency and the *abscissa* is the time in hours after the opiate administration. Each time response curve, represents the mean of the responses of four animals. The standard deviation is < 15% of the mean

cat experiments in Fig. 3, comparable effects could *not* be achieved with single subtoxic doses given systemically.

Equally important was the failure of these animal experiments to observe any significant effects on other aspects of the animal's behavior. Of particular significance was the failure to see any effects on voluntary motor function, i.e. ambulation, righting reflexes, response to light innocuous tactile stimulation. Non-nociceptive reflexes such as stepping or placing reflexes or tendon reflexes were unaltered by spinal doses of opiates which blocked polysynaptic nociceptive reflexes. Similarly, in the early investigations, we failed to see any significant effect of intrathecal opiates on autonomic measures, such as blood pressure or heart rate. Also, opiates with an action limited to the spinal cord would produce the significant analgesic effects without significantly altering respiration [5, 7, 9, 26].

Of equal significance to the behavioral specificity was the fact that this effect was mediated by an action limited to the spinal cord. In initial studies, we examined the distribution of radiolabeled opiates in the body and brain following intrathecal administration. These animal studies repeatedly revealed that while small amounts of opiates might gain access after some delay to brain, the concentrations achieved were 10–100 times less than that required to produce a significant elevation in the nociceptive threshold if the drug had been administered systemically. Perhaps the most direct proof that functionally significant quantities of opiates were not exerting their effect by movement to periventricular sites was the fact that intrathecally administered naloxone would antagonize spinal opiates, but naloxone administered intraventricularly would not [7].

The slow clearance of polar molecules from the spinal fluid, and the relatively large concentration of opiates applied within the proximity of the spinal cord, accounts for their significant effect and prolonged duration of action. Significantly, in this regard, compounds which are more polar and cross the blood-brain barrier more rapidly [21] tend to have shorter durations of action.

Thus, in Fig. 4 we can see the effects of approximately equally active doses of morphine, methadone and fentanyl on the block of the skin twitch response in the cat. As can be seen, the more polar the molecule the longer the duration of action. Diffusability of the molecule also plays a role in the onset of the analgesic response. As will be noted below, the site of action of opiates lies within the spinal gray, a locus which is covered by the myelinated

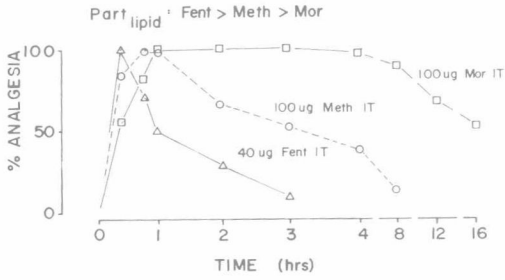


Fig. 4. The figure presents the effects in cat of injecting intrathecally 100 μg of morphine, or 100 μg of methadone, or 40 μg of fentanyl intrathecally. The compounds show an increasing lipid partition coefficient in the order of fentanyl > methadone > morphine. Other details of this figure are as in Fig. 2. Each time response curve represents the mean of four cats; the standard error is always < 15% of the mean

funiculi. Spinal drugs must penetrate this barrier to reach the deeper gray matter. It is not therefore surprising that the effect after intravenous administration may be more rapid than when given superficially to the cord. This also provides insight into the relative effects of epidural vs. intrathecal administration. Epidural morphine must penetrate the dural sheath and then diffuse to the spinal gray. As illustrated in Fig. 3, morphine, a polar compound shows a retarded time of onset in contrast to the intrathecal route.

A third consideration revolved around the systems on which this intrathecal opiate was acting. Our predisposition as pharmacologists, required that we examine the receptor characteristics of this intrathecal effect. These investigations revealed that the intrathecal administration of morphine was producing analgesia by a mechanism: that was dose-dependent; that revealed a highly regular structure activity relationship; that required an L versus the D isomer for activity and that was antagonized in a dose-dependent fashion by naloxone [10, 11]. Importantly, the analgesic effect is produced not only by the classical alkaloids such as morphine and methadone [7, 9] but by a variety of opioid peptides including met-enkephalin [24] D-ala-enkephalin-amide [11] and β-endorphin [22]. Moreover the spinal effect of all of these agents are antagonized in a systematic fashion by naloxone. A fifth and less desirable observation was that repeated intrathecal administration of opiates did in fact result in the development of spinal tolerance [9, 12].

The precise pharmacology which appeared to be associated with this behavioral effect, revealed two things: First, that the effect was not due to a general membrane effect as might be expected from a local anaesthetic, but was associated with an action on a specific receptor system. Secondly, the functional/behavioral specificity of the effect indicated that the receptor systems must be associated largely with certain aspects of spinal systems, mainly those associated with the transmission of nociceptive information.

It was observed that opiate binding was extremely high in the substantia gelatinosa of the spinal cord [13], a region where primary afferents are known to terminate and make connection with the second order neurons [25]. A corollary to this observation was that a significant proportion of the opiate binding in the dorsal horn disappeared following dorsal rhizotomy [14]. These data suggest that opiates with an action limited to the spinal cord are acting on the receptors co-existent with the primary afferent terminals. Advances in the field of peptide histochemistry have led to the discovery that substance P, an 11 amino

acid peptide, is located within the substantia gelatinosa and in the small population of dorsal root ganglion cells [15]. These observations are consistent with the disposition of this peptide in small primary afferent terminals. Substance P is a candidate transmitter for primary afferents associated with the transmission of nociceptive stimuli [16]. Recently, we have demonstrated that the intrathecal administration of opiates will inhibit the release of substance P from the spinal cord [17] (see Fig. 5). Thus, intrathecal opiates *may* produce their specific analgesic effects because the receptors upon which they act are associated with small diameter primary afferents which transmit nociceptive stimuli to the second order neuron by the release of substance P and may therefore in part antagonize the rostrad transmission of nociceptive information. This paradigm accounts in part for the apparent specificity of the antinociceptive effects of intrathecal opiates.

These results are corroborated by electrophysiological investigations where it has been shown that the discharge of cells in the spinal cord evoked by noxious nerve stimulation are reduced by opiates. Importantly, C fiber input appears more readily blocked than Aδ input, suggesting that second or dull pain will be more readily affected than first or "sharp" pain.

It should be noted, however, that the question of spinal specificity is also subject to dose. As shown in Fig. 6, low doses of opiates administered systemically in the decerebrate-spinal animal will preferentially inhibit the late discharge evoked by high intensity sciatic nerve stimulation input in a lamina V neuron. Higher doses will begin to inhibit the early discharges as well, presumably reflecting the general depression observed during high dose opiate anaesthesia [9]. This would suggest that at nominal spinal doses, a functionally selec-

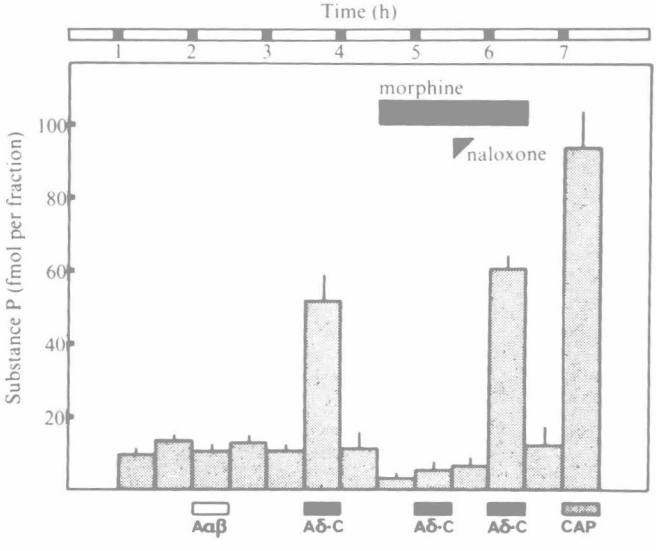


Fig. 5. Release of *substance P* from superfused cat spinal cord in response to sciatic nerve stimulation and capsaicin. Cats were anaesthetized with chloralose-urethane and prepared with a tracheal tube and jugular and carotid catheters. Stimulation of the nerve was performed with rectangular pulses (3–4 V, 0.05 ms, 50 Hz for activation of Aα and Aβ fibres and 40–50 V, 0.05 ms, 50 Hz for recruitment of Aδ and C fibres). Each value is the mean ± S.E.M. from four separate experiments [17]

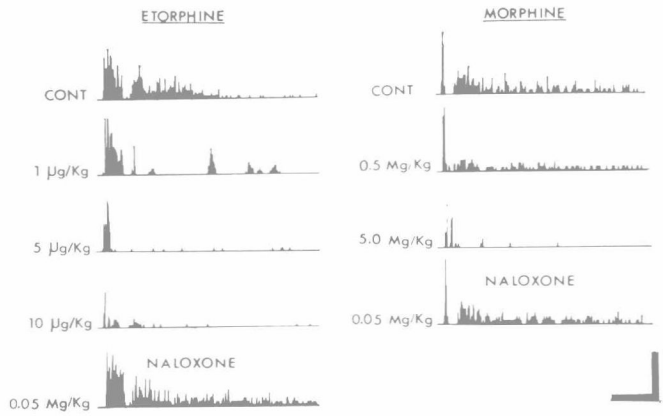


Fig. 6. The figure presents the post-stimulus time histogram observed in two cells in the dorsal horn of the spinal cord of the decerebrate spinal cat as a result of increasing doses of the etorphine *(left)* or morphine sulfate *(right)* on the response evoked by electrical stimulation applied to their peripheral receptive fields. After the effects of each dose have that stabilized, the next higher dose was administered. Following the highest dose, naloxone-HCl (0.05 mg/kg) was administered intravenously. The *vertical* and *horizontal* axis at the *lower right* of the figure indicate the number of spikes (100) and the time scale (100 ms), respectively. (Data from [19])

tive inhibition might occur on fibers mediating dull, throbbing pain, but be less effective on sharp or acute pain. Thus, we would *not* expect opiates at analgesic doses to block the pain of an incision. Similarly, while we have shown that spinal opiates will not alter parturition in rats and rabbits [27], this does not mean that spinal opiates will block the pain of all stages of delivery. Indeed, we suspect that the latter stages, characterized by sharp, acute stimuli, might be unaffected because of the reduced ability of opiates to block early spinal nociceptive discharges.

In sum, the animal studies reveal that the spinal action of opiates are likely on a receptor system lying in the dorsal horn of the spinal cord. The behavioral characteristics of the effect is due to the fact that the receptors acted upon by spinal opiates are associated with systems mediating the processing of Aδ/C fiber input while the duration of action is related to the reservoir effect produced when polar drugs are introduced into the subdural space. Future directions of research will no doubt take advantage of the fact that opiate receptors are not the only receptor systems in the spinal cord associated with nociceptive sensory processing [18, 20, 28].

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Theoretical Aspects and Practical Considerations Concerning Selective Opiate-Analgesia

H. Müller, U. Börner, M. Stoyanov and G. Hempelmann

Summary. The observation of opiate binding in the substantia gelatinosa of the spinal cord, a region known to function in the modulation of sensory processing, and the observation that locally applied opiates would inhibit the discharge of nociceptive neurons, represents the substrate whereby animal and subsequent human investigations observed a powerful antinociceptive effect of spinally administered opiates.

The clinical use of spinal opiate action must be made on the basis of several considerations:

1. The superficially administered drugs must penetrate to the receptor sites lying within the spinal cord. Drugs which penetrate readily through lipid layers, will produce a more rapid onset and consequently will be more rapidly cleared. Drugs with low lipid-solubility will be characterized by a slow onset and a long duration of action. Polar agents will be less effective than lipid permeable agents following epidural administration.
2. The knowledge of how opiates exert their spinal effect give rise to certain partial considerations:

a) It is known that the actions of opiates on the spinal cord are more potent against those inputs which arise from C-fibers, and will be less effective against acute pain, i.e. that of cutting, or perhaps acute distension and as observed in final stages of delivery.

b) The specific analgetic effects of spinal opiates are made less specific by diffusion to supraspinal sites mediating respiratory and cardiovascular activity. The ability of lipid soluble drugs to diffuse into the vasculature makes it likely that such agents will produce higher blood levels.

c) As the effects of opiates are mediated by an action on specific membrane receptors, the properties of the spinal effects will be defined by this receptor interaction. Thus, the effect should be dose dependent and subject to a similar structure activity relationship as that seen following peripherial administration and antagonized by naloxone.

Introduction

In 1885 the neurologist J.L. Corning, blocking the neural conduction to the hind extremities by injecting cocaine-solution into the lumbar vertebral interspace of a dog, was the first to perform epidural anaesthesia. His aim was the application of drugs in proximity to the spinal cord to treat or even heal painful nervous diseases [14]. The general effect of local anaesthetics on all excitable membranes, however, makes it difficult to achieve a mere analgesic action with epidural anaesthetics. An additional impairment of touch and motor function as well as unwanted hemodynamic reactions by sympathetic blockade are common consequences of this therapy [46].

The discovery of receptors for opiate alkaloids and endorphins in the spinal cord [1, 27, 48, 58] has brought about the possibility to effect, by intrathecal or epidural opiate-injection, a reduction of pain alone. Thus, after nearly 100 years we are now turning full circle back to Corning's original idea of "local medication of the cord".