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Spinal Action of Narcotic Analgesics

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ONE OF THE PRIMARY AIMS of anesthesia is to render the patient analgesic, thereby permitting the performance of surgical procedures without discomfort. There have been major developments in the past decade with regard to the clarification of mechanisms of such analgesia produced by various anesthetic and analgesic agents. New developments in neurophysiologic techniques are providing insights into the effects of pharmacologically active agents upon specific areas of the central nervous system (CNS). In recent years, information has been accumulating about specific sites within the CNS that are likely to be involved with the modification of pain. With the demonstration of anesthetic and analgesic drug effects in the spinal cord isolated from rostral brain input by cord transection,[1,2] as well as the identification of opiate receptors in the spinal cord,[3–5] it became apparent that spinal sites were important in mediating analgesic effects. In addition, the discovery of profound analgesia in experimental animals following electrical stimulation of discrete brain areas[6–9] (stimulation-produced analgesia), or the placement of minute amounts of narcotic analgesics in similar specific loci within the brain[10–12] demonstrated that particular, well-defined areas of the CNS function to inhibit the perception of noxious stimuli. It has also been demonstrated that supraspinal sites can depress spinal cord neuronal activity via descending pathways.[8,13,14] Thus, as the body of knowledge about the mechanism of drug-induced analgesia increases, the effects at the spinal cord level assume even greater importance, not only for an understanding of analgesia, but also as a model site for the study of the interaction between neural systems conveying pain information and drugs that act to inhibit the transmission of that same information.

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In 1975, reviews of the effects of anesthetics and centrally acting analgesics upon neuronal activity in the spinal cord were presented in two separate papers.[15,16] Because of the important work done in that area since then, and the necessity of understanding the role of spinal cord sites in pain modulation, this review was undertaken.

In the last five years researchers have placed heavy emphasis on the interaction of narcotic analgesics with areas of the spinal cord thought to function in the transmission of information about painful events in the periphery. This review reflects that emphasis and deals only with studies that have considered narcotic analgesic effects in the spinal cord. Because of the large variation in techniques used, and therefore, in the interpretations of results, the review is divided into sections according to the methods of drug administration.

Systemic Administration

Investigators have approached the question of narcotic drug action in the spinal cord by using microelectrode recording techniques to monitor neural activity of single cells in the spinal cord before and after the systemic administration of opiates. Although many regions of the spinal cord have been studied, special emphasis has been placed upon differential drug effects upon specific cell types. In early studies, the cell types were referred to the Rexed laminae in which they were most often found. Thus, cells that responded only to low-threshold stimulation (*e.g.*, light touch) were usually found in lamina IV and thus were named lamina IV-type cells. Likewise, cells that responded over a wide dynamic range of stimulus intensities (*i.e.*, responded to increasing intensity of stimulation with increasing firing frequency, with maximum response elicited by noxious stimuli, see figure 1) were generally found in lamina V, and thus were referred to as lamina V-type cells. A third cell type was found to be responsive only to high-threshold stimuli (*i.e.*, within the noxious range) and was mainly

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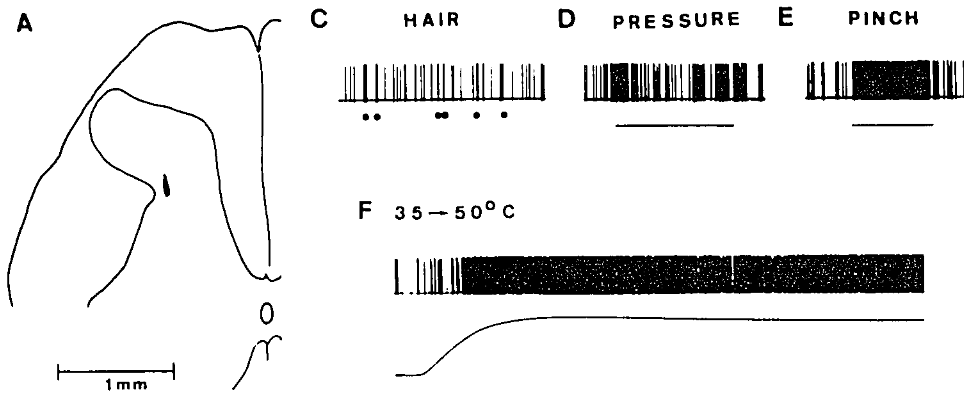

FIG. 1. Spinothalamic tract neuron with a wide-dynamic-range receptive field. The cell was located in the lateral portion of lamina V, as shown in *A*. The vertical lines in *C–F* are window discriminator pulses triggered by the action potentials of the cell and recorded on a pen writer. The cell was excited by hair movement (dots in *C* indicate times of stimulation), as well as by pressure and pinch, *D* and *E*, but the most effective of these was pinch. Temperature changes from 35 to 50°C also excited the cell. The lower trace in *F* is a record of temperature at the thermode–skin interface. The response profile of this cell is characteristic of WDR neurons found in the dorsal horn of the spinal cord. (Adapted, with permission, from Chung *et al.*, Excitation of primate spinothalamic neurons by cutaneous C-fiber volleys, J Neurophysiol 42:1354–1369, 1979.)

located in lamina I. These cells were referred to as lamina I-type cells. As researchers have gained more insight into the neurophysiology of the spinal cord, it has become apparent that the organization of the cell types is not strictly lamina-specific, and thus a new nomenclature has evolved which differentiates between the cell types based upon their neurophysiologic response properties rather than their anatomic locations. The lamina V-type cells are now referred to as WDR (wide-dynamic-range) neurons. The lamina IV-type cells are called LT (low-threshold) neurons. And the lamina I-type cells are now known as HT (high-threshold) neurons. Although most of the articles cited in this review still used the older system, we refer to the cell types by their newly adopted nomenclature when appropriate.

This interest in different cell types arises from the fact that LT cells respond maximally to low-threshold stimuli and do not increase their responses to high-intensity (noxious) stimuli. In contrast, the HT cells respond exclusively to noxious stimuli, and the WDR cells respond preferentially and with a much greater firing frequency to noxious stimuli (see fig. 1). As such, any differential drug effect on the nociceptive neurons in the dorsal horn (like the HT and WDR) could indicate a selective depression of neurons involved in the signalling of the occurrence of pain.

The anatomic organization of the substantia gelatinosa (SG) suggests that this area of the dorsal horn should be involved in the transmission of information about noxious stimuli. Unfortunately, the small size of SG neurons has so far hindered a neuropharmacologic study of the effects of drugs on that area of the spinal cord.

In agreement with earlier work from Kitahata's laboratories,[17,18] where intravenous administration of morphine sulfate was shown to selectively suppress spontaneous activity of cells that respond to noxious mechanical stimuli (HT and WDR) while not significantly altering the spontaneous activity of cells known to respond best to non-noxious stimuli (LT neurons and neurons found mainly in lamina VI that respond to proprioceptive input), Dohi, Toyooka and Kitahata,[19] utilizing noxious thermal stimuli, have recently reported that in decerebrate cats with transected spinal cords (L1), morphine, 1 and 2 mg/kg, iv, significantly suppressed both spontaneous and evoked activity of WDR neurons. The extent of suppression was related to the dose of morphine, and the suppression could be reversed by naloxone (.02–.04 mg/kg, iv). Yaksh[20] has reported similar findings in decerebrate, spinal cord-transected cats. The response profiles of the neurons activated by mechanical or electrical stimulation of their receptive fields would indicate that they were LT and WDR neurons. Yaksh reported that morphine (0.5 mg/kg) or etorphine (10 μg/kg) depressed the responses to high-threshold, noxious stimuli in all the cells studied, and also attenuated the responses to low-threshold stimuli in about 30 per cent of the cells. Neither dextrorphan (2 mg/kg), a non-analgesic isomer of levorphanol, nor naloxone (.05 mg/kg), by itself, had any significant effect on the activity of the cells.

Le Bars *et al.*[21–23] reported the effects of morphine on WDR cells of the cat. In two of their studies[21,22] all of the animals had their spinal cords transected (C1). The cells were activated by electrical stimulation of peripheral nerves or noxious pinching of the peripheral receptive field. In both studies, morphine (2 mg/kg) exerted a selective depression on spontaneous and evoked activity elicited by stimuli in the noxious range (A delta and C fiber activation). The effects were reversed by naloxone (0.2 mg/kg), but naloxone by itself had no significant effect on the neuronal firing.

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Activation of these cells by A-alpha fiber stimulation (A-alpha fibers are associated with non-noxious stimuli) was not significantly modified by morphine. In their third paper[23] the authors examined the effects of morphine on spinal activity of decerebrate cats with intact spinal cords and following reversible cold block of the spinal cord.

In decerebrate animals with intact spinal cords the activity of WDR neurons is significantly less than in the presence of a transected spinal cord. Under those conditions Le Bars *et al.* found that for some cells, the spontaneous activity and activity elicited by natural stimulation were not inhibited by morphine. They reported that five cells had their activity increased by morphine (four spontaneous, one natural stimulation). Following electrical stimulation, however, the morphine effect was similar to the spinal cord-transected state, except that two cells showed increased activity.

These authors also reported that morphine was much more effective in suppressing activity of WDR neurons during reversible cold block of the spinal cord than in the absence of the cold block. Unfortunately, they used bradykinin injections to activate the neurons instead of natural pinch or electrical stimulation, and provided only qualititative results. Their data do not permit a solid conclusion to be drawn about the possible differences in morphine effects in the presence or absence of reversible cold block of the spinal cord. The use of bradykinin eliminated the possibility of any valid comparison with the other portions of their reports.

Takagi *et al.*[24,25] reported that morphine did depress both spontaneous and bradykinin-induced activity in WDR cells of rabbits with sectioned spinal cords (L2), although there was a greater morphine effect when the spinal cord was left intact. The depression in the animals with transected spinal cords did, however, necessitate higher doses of morphine (5 mg/kg *vs.* 2 mg/kg). Nalorphine reversed that suppression in both intact and spinal cord-transected animals. In some cells the bradykinin-induced activity was inhibited by morphine, although the spontaneous activity of the same cell was not affected by the same amount of drug.

Calvillo *et al.*[26] recorded extracellularly from cells in laminae I, IV, V, and VI of the dorsal horn of cats that had their spinal cords transected. Some of the cells responded only to innocuous stimuli, some only to noxious stimuli, and some to both types of stimuli. Intravenously administered morphine (0.8 to 3 mg/kg), meperidine (10 to 25 mg/kg), and fentanyl (30 to 40 μg/kg) all depressed both the spontaneous and the noxiously evoked activity of nociceptive neurons. The depression was consistently reversed by naloxone (0.1 to 0.3 mg/kg, iv). At the same doses, the above-mentioned drugs had no effect or a slight depressive action on the response of the same cells to non-noxious stimuli.

Piercey and Hollister[27] reported that in spinal cord (C1)-transected cats, morphine (1.3 and 6 mg/kg, iv) reduced the activity in cells of laminae IV, V, and VI following noxious electrical stimulation of the peripheral receptive fields, as well as reducing the rate of spontaneous discharge. Morphine did not, however, reduce the responses of these cells to the arterial injection of bradykinin.

The lack of morphine effect on activation by bradykinin raises an important question about the adequate stimulus for experimental pain. Several of the reports included in this review stated that although the narcotics could suppress neuronal activity elicited by noxious mechanical, thermal, or electrical stimuli there was a relative resistance to suppression following intra-arterial bradykinin administration. Such differences point up the need for great care in the design and evaluation of experimental pain studies. Radiant heat, although not without disadvantages, provides an excellent means of applying a noxious stimulus to the peripheral receptive fields on the skin. It can be precisely controlled, accurately reproduced, and conveniently applied with minimal tissue damage and no accompanying confounding mechanical stimulation. In addition, the ability to present several precise intensities of stimulation increases the potential for data analysis and the determination of neuronal input–output relationships (*e.g.,* changes in the slope of the relationship between stimulus intensity and neuronal firing frequency).

Although some dorsal horn neurons (those of Rexed laminae I and V) have been carefully evaluated for nociceptive transmission and drug effects, some neurons in the ventral horn, especially lamina VII, are also an area of interest, because some cells in that lamina are considered to be cells of origin of the spinothalamic and spinoreticular tracts, which convey information from nociceptive afferents.[28–30] Toyooka *et al.*[31,32] reported that in spinal cord-transected cats, morphine depressed both the spontaneous and the noxiously evoked activity of cells of lamina VII (WDR neurons). In addition, the threshold intensity of heat needed to activate these cells was increased by morphine (1 mg/kg, iv), and the slope of the temperature *vs.* firing frequency regression line was significantly decreased. These effects were of long duration but were quickly reversed by naloxone (0.02 mg/kg, iv). The suppression of spontaneous activity in lamina VII was dose-dependent, and significantly greater than that seen in HT cells found in lamina I or WDR cells found in lamina V.

In contrast to research that has revealed that neuronal

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activity in the Rexed laminae can be depressed by opiates to a greater extent when the spinal cord is intact, Jurna and Grossman[33,34] and Grossman and Jurna[35] have reported that the opposite is seen in microelectrode recordings from ventrolateral tract axons, which have been shown to be activated by noxious stimuli. This work is important because it demonstrates a drug effect on ascending pathways. With the spinal cord (T10) transected, or reversibly cold-blocked (T7–T10), morphine (0.5 and 2 mg/kg) reduced the number of impulses discharged by ventrolateral tract axons following electrical stimulation of A delta and C fibers in the sural nerve. The depression amounted to as much as 50 per cent of the control activity. Naloxone and levallorphan reversed the depression by morphine. In decerebrate cats without the cold block (*i.e.*, with functional descending systems) the administration of morphine did not decrease the activity in selected ventrolateral tract axons in a predictable fashion, and in some instances caused increased activity.

The same laboratory[36] recently reported that C fiber-evoked activity in ascending axons of the spinal cords of decerebrate, spinal cord-transected rats was suppressed by morphine (0.5 mg/kg), pethidine (1.0 mg/kg), and levorphanol (0.5 mg/kg), and that the suppression was reversed by naloxone (0.2 mg/kg). Higher doses of the drugs produced depression of activity elicited by A delta stimulation, but only the morphine-induced depression was reversed by naloxone. Only pethidine inhibited activity resulting from A beta activation.

Spinal Administration

In addition to the large body of neurophysiologic evidence that narcotics can act directly in the spinal cord to modify nociceptive input, Yaksh *et al.*[37–39] have provided behavioral evidence that supports the idea that morphine and related drugs (*e.g.*, fentanyl, codeine, ethylmorphine, methionine–enkephalin, L-methadone) can act at the level of the spinal cord. In each of these papers, the authors report results from a technique in which small volumes of drugs (5 μl) are injected through a chronically implanted catheter into the lumbar subarachnoid space of the rat. The animals were tested for their responses to nociceptive stimuli in both hot plate and tail flick tests. In all instances, morphine and related drugs caused an elevation in the threshold temperature at which the animals withdrew from the noxious heat. Naloxone administered in a similar fashion, or intravenously, returned the threshold temperatures to control values. Yaksh[40] also demonstrated that intrathecally administered opiates can produce behaviorally defined analgesia in the cat (40 or 80 μg) and monkey (40 or 160 μg). The analgesia was of long duration (more than ten hours in the cat following 80 μg), and could be reversed by naloxone.

The authors provided several lines of evidence that the drugs administered intrathecally were acting in the spinal cord and not centrally through either intrathecal spread or vascular absorption and subsequent systemic effects. The lack of significant intrathecal spread was demonstrated by injecting either [^{3}H]-morphine or bromphenol blue dye into the subarachnoid space. Both techniques demonstrated a lack of significant spread beyond several centimeters from the injection site. The fact that intravenous administration of a dose equal to that injected into the rat's lumbar subarachnoid space (morphine, 15 μg, in 305–450-g rats) resulted in no change in the animals' responses to the tail flick or hot plate tests demonstrated that vascular absorption and subsequent systemic spread to other CNS sites was not the cause of the observed analgesia. These investigators also provided evidence that the spinal cord is not the only site of morphine action on the transmission of noxious stimuli. This was demonstrated by the fact that following intravenous administration of an analgesic dose of morphine the intrathecal administration of naloxone (1–40 μg) did not completely reverse the analgesic effect. This points to the fact that systemic morphine analgesia results in part from actions in the spinal cord, where the intrathecal naloxone is also effective, as well as from actions at other CNS sites not reached by an intrathecal injection.

Wang[41] confirmed these effects in rats and reported that gross and microscopic studies of the spinal cord, seven days after an injection of 25 μg in 50 μl, produced no adverse reaction. In the discussion section of that article, brief mention is made of a clinical trial of the technique in human subjects. This initial report of the clinical use of intrathecally applied morphine in man (by Wang and co-workers) was quickly followed by several reports of similar clinical work.

Wang *et al.*,[42] using a double-blind procedure and intrathecal administration of morphine (0.5 or 1.0 mg) at the L2–L3 interspace, found that in the eight patients studied there was significant pain relief. All of the patients had intractable pain in the back and hip secondary to malignancies. Two of the patients experienced a placebo effect following injection of saline solution, but the duration of pain relief was shorter than that following morphine. In all of the patients the intrathecally injected morphine produced long-lasting pain relief (mean duration 10–24 hours) without changing other neurologic functions. Behar

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et al.[43] studied the effects of epidural injections of 2 mg morphine in ten patients with severe acute (from surgery or trauma) or chronic pain. They also reported significant, long-lasting pain relief with no observable change in neuologic function. In this study the sites of injection ranged from T7 to L10, depending upon the location of the pain. The degrees of relief varied, but all patients reported at least 50 per cent reductions of pain. Epidural administration of bupivicaine was used in several patients, but was reported to be less acceptable by the patients because of the associated muscle weakness. Cousins *et al.*[44] studied the effects of preservative-free pethidine (30 or 100 mg) administered through an indwelling epidural catheter to patients with pain due to cancer ($n = 6$) or surgical operations for cancer ($n = 7$). The catheter tip was placed as close to the appropriate spinal segment as possible. Determinations of both CSF and blood pethidine concentrations, as well as naloxone reversal data, suggested that the major component of the high level of analgesia seen in all patients was due to a spinal action. Examinations before and after the epidural pethidine administration revealed normal neurologic function (sensory, motor, sympathetic). The 100-mg dose resulted in slight sedation of short duration (10–15 min). Naloxone (0.4 mg) was administered intravenously to two of the sedated patients. The naloxone immediately reversed the sedation without changing the level of analgesia.

These reports were followed in quick succession by several others, which supported their general findings. Samii *et al.*[45] used a high dose of intrathecally injected morphine (20 mg), and found the effects to be similar to those found in previous work using lower doses. Wolfe and Nicholas[46] studied epidurally administered fentanyl as a postoperative medication following cesarean section. They injected .01 mg of preservation-free fentanyl through an epidural catheter left in place following conventional local techniques employed during surgical procedures ($n = 20$). Satisfactory analgesia was reported for all 20 patients studied, with no noticeable side effect. Leslie *et al.*[47] reported that 0.5 mg of epidurally administered hydromorphone hydrochloride produced hypoalgesia to experimental pain (electrical stimulation and periosteal pressure). Bopat *et al.*[48] found that following epidural injection of morphine (2 mg, L3, L4), relief of chronic pain was of longer duration than that seen following acute pain.

In spite of the generally favorable reports of results of the use of this technique, there have been failures and complications associated with its use. Husemeyer *et al.*[49] found that 2 mg of preservative-free morphine injected into the lumbar epidural space in ten women in established labor failed to produce analgesia, although 8 ml of .375 per cent bupivacaine was effective. Scott and McClure[50] reported that 2 mg of epidurally injected morphine gave inadequate analgesia in the immediate postoperative period, but gave good results on the day after operation. They also reported two cases of severe respiratory depression following epidural administration of pethidine (50 and 100 mg). Intravenous injection of naloxone reversed the respiratory depression but, interestingly, had no effect on the analgesia. Glynn *et al.*,[51] Liolios,[52] and Davies *et al.*[53] have also reported cases of respiratory depression following the subarachnoid administration of morphine. In all three instances the depression was reversed by intravenous administration of naloxone. In the two cases observed by Glynn *et al.*,[51] they found that the naloxone did not decrease the level of analgesia in spite of the fact that respiratory depression was reversed. Ventrafridda *et al.*[54] reported that while cervical (C3–5 interspace) or lumbar (L3–4 interspace) intrathecal injections of morphine (1 mg in 1 ml) resulted in significant analgesia in cancer patients, drowsiness, orthostatic dizziness, itching, sweating, and nausea were observed in many of the 30 patients studied. Nausea was significantly less following lumbar administration, but in general, all other effects, including analgesia, were equal with the two routes of administration.

While these reports of the clinical effectiveness of narcotic spinal analgesia provide direct evidence of the importance of spinal sites in analgesia, many questions still need to be answered. Yaksh *et al.*[55] examined the problem of tolerance and withdrawal in rats following intrathecal morphine administration. They found tolerance to analgesia as tested by tail flick and hot plate following seven days of administration of morphine, 15 or 50 μg, intrathecally. In addition, there was cross-tolerance between intrathecally and systemically (20 mg/kg) administered morphine. Some signs of naloxone-elicited withdrawal were reported, but they were minimal. Ventrafridda *et al.*,[54] as shown in figure 2, found that the patients' evaluation of the analgesia following intrathecal administration of morphine decreased (*i.e.*, less analgesia) with each subsequent daily administration. This was most evident in the shortened duration of effect. The occurrence of tolerance and dependence in man following narcotic spinal analgesia is a question of great importance that requires further study.

Iontophoretic Administration

Following earlier iontophoretic morphine work by Calvillo *et al.*,[56] studies by Belcher and Ryall[57] (intact

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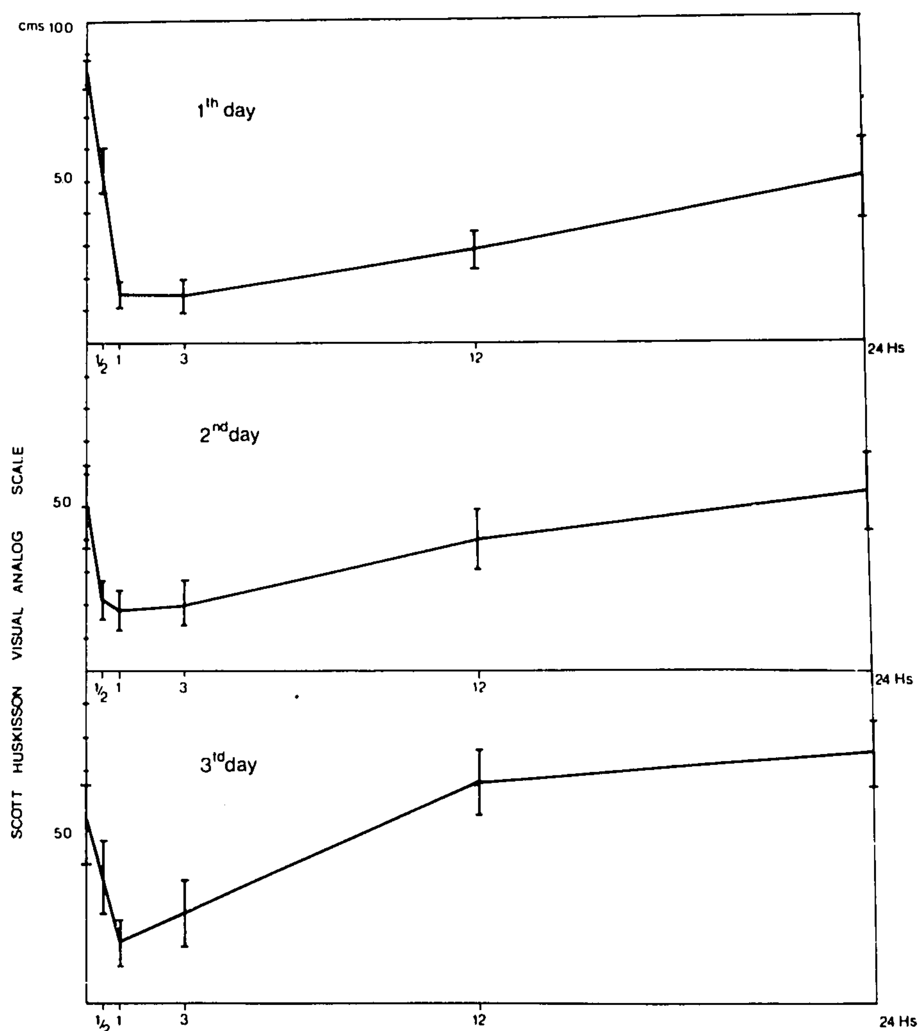

FIG. 2. Intensities of pain recorded for three days during daily intrathecal administration of 1 mg morphine to each of eight patients. [(From Ventrafridda *et al.*, Clinical observations on analgesia elicited by intrathecal morphine in cancer patients, Advances in Pain Research and Therapy, 3:559–565, 1979, with permission from Raven Press, New York). The patients used a visual analog scale (VAS) to rate their pain. A VAS is a straight line, the ends of which are defined as the extreme limits of the sensation to be measured (*i.e.*, no pain and the worst possible pain). Typically, when a subject/patient uses a VAS he or she simply places a mark on the line to record assessment of the pain at that time. Usually a new sheet is used for each rating so that preceding judgments do not exert an influence.]

cord) and Dostrovsky and Pomeranz[58] (transected cord) demonstrated variable results following the iontophoretic application of morphine (5–200 nA currents used for drug ejection). Although morphine did excite some cells, in general, inhibition was seen only in neurons that were responding to noxious stimuli. The depression, which amounted to 30 to 80 per cent, was usually much more pronounced for the evoked than for spontaneous activity. Recently, Calvillo *et al.*[59] reported that the iontophoretic application of opiates (morphine, meperidine, fentanyl, methadone, nalorphine) near cells in laminal I, IV, V, and VI selectively depressed the activity of neurons that were responsive to noxious cutaneous stimuli, and that 66 per cent of the cells were depressed. None of the cells that responded to low-threshold stimuli only were depressed. Intravenous administration of the opiates at anesthetic levels in the cat produced the same depression.

The question of what effect morphine has upon the resting membrane properties of spinal cord neurons was considered in a study by Zieglgänsberger and Bayerl[60] in which they examined the effects of opiates on cells in the spinal cords of cats that either had their spinal cords transected (Th9–10) or were anemically decerebrated and maintained anesthetized with pentobarbital (10 mg/kg, iv, *q.* 3 h). They made both extra- and intracellular recordings while administering various agents microelectrophoretically (30–150 nA currents used for drug ejection). Low- and high-intensity mechanical stimuli were used to activate the spinal neurons. Of 20 WDR neurons, 18 had their discharges depressed (20–100 per cent) by morphine or levorphanol. In eight of 12 cells tested, the depression was reversed by prior or subsequent administration of naloxone. They also reported that the responses of LT neurons were less sensitive to phoretically applied morphine than was activity evoked in

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WDR cells, and that these changes were also produced when the drugs were administered intravenously. Iontophoretically administered dextrorphan, the non-analgesic isomer of levorphanol, had no such depressant action. Intracellular recordings indicated that the levels of opiates used in the study did not alter the membrane potential or the steady-state membrane resistance, although the rate of rise of the excitatory postsynaptic potentials (EPSP) was slowed and the EPSP changes in LT neurons required higher doses of morphine than did similar changes in WDR neurons. This reduction in the rise time of the EPSPs was reversible by naloxone.

Such changes in the rate of rise of the EPSP without accompanying changes in resting membrane potential or resistance explain why the firing frequency of the individual neurons is decreased. In order for an action potential to occur, the depolarizing effects of several EPSPs must summate to the spike threshold level of the cell. If the rate of rise of the EPSP is slowed, then it is more difficult for the summed EPSPs to reach threshold, and therefore the likelihood of occurrence of an action potential is decreased.

The endogenous opiates are capable of modifying spinal cord activity in a fashion similar to the changes induced by the exogenous compounds. Randic and Miletic[61] found that microiontophoretic application of methionine enkephalin selectively depressed the activity of nociceptive dorsal horn neurons while it left unchanged, or weakly excited, units responding only to low-threshold stimuli in cats with transected spinal cords. Naloxone, administered either intravenously or iontophoretically, antagonized (to various extents) the depression of nociceptive neurons. Zieglgänsberger and Tulloch[62] reported that the iontophoretic application of methionine and leucine enkephalin reversibly depressed the neuronal activation by both non-noxious and noxious mechanical stimulation in most of the cells of laminae IV, V, and VI encountered in their study. Intracellular recordings revealed that the depression of neuronal activity occurred without a detectable change in resting membrane potential or resistance.

The distribution of spinal cord morphine receptors is greatest near the substantia gelatinosa (SG),[3,4,14] and thus, Duggan, Hall and Headley[63–65] studied the effects of iontophoretically applied opiates (30–250 nA currents used for drug ejection) in several parts of the dorsal horn. In these experiments the cats were anesthetized with α-chloralose and had their spinal cords transected at the T13–L1 level. Morphine, methionine enkephalin, or methionine enkephalin-amide, when ejected near cells in the SG, caused a selective suppression of neurons in laminae IV and V responding to noxious stimuli, while causing little or no change in the non-nociceptive responses of the cells. The depression was reversed by naloxone administered either intravenously or iontophoretically. When morphine was ejected near the cell bodies of lamina IV or V, rather than in the SG, there was little depression of neuronal activity. Davies and Dray[66] reported similar findings in their study of the effects of methionine and leucine enkephalin on cat spinal neurons. Although both drugs excited Renshaw cells, they were effective in suppressing WDR activity of some cells only when iontophoresed into the SG, but not when placed near the cell bodies. They did not suppress any LT neurons. The placement of the drugs in the SG, which anatomically is the area of the spinal cord with the highest concentration of opiate receptors, resulted in a much greater depression of neuronal activity evoked by noxious stimuli. Such an effect of opiates in SG is not at all surprising, considering the significant anatomic connectivity between small-diameter primary afferents, SG, and WDR neurons.

Naloxone Effects

In spinal cord-transected animals, where descending inhibitory influences have been removed, there have been consistent reports of a lack of any effect of naloxone other than the reversal of narcotic agonists. This would indicate that in the spinal cord itself there is no tonic system influencing activity of laminae IV and V that works locally via the opiate receptors in the spinal cord. These facts were dealt with directly by several investigators. Duggan *et al.*[67] studied the effect of intravenous naloxone on the activity of cells in lamina IV or V of cats anesthetized with α-chloralose, or in one case decerebrated, prior to the administration of opiates. Some of the cats had their spinal cords transected, while others were studied with a reversible cold block of the spinal cord. In three of four experiments, with the spinal cord transected, naloxone (0.6–1.6 mg/kg) had no effect on spontaneous as well as nociceptive and non-nociceptive responses (three cells in lamina IV, one in lamina V), while in the fourth experiment, naloxone (0.12 mg/kg) increased both nociceptive and non-nociceptive responses by approximately 30 per cent. In seven of eight experiments with and without cold block (intact spinal cord), naloxone (1.3–3.2 mg/kg) had no effect on the spontaneous firing and the nociceptive and non-nociceptive responses of the neurons studied. In the remaining experiment the naloxone effect was

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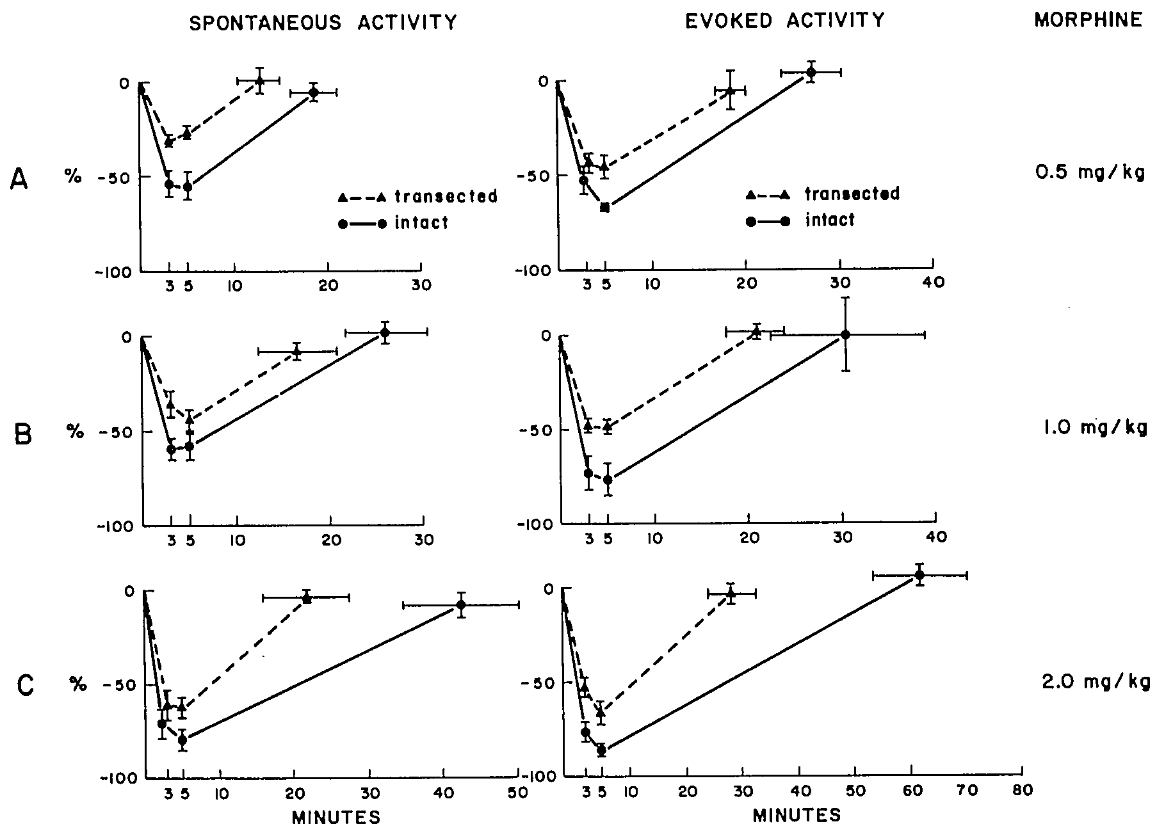

FIG. 3. Comparisons of effects of morphine sulfate, 0.5 mg/kg (*A*), 1.0 mg/kg (*B*), and 2.0 mg/kg (*C*), expressed as percentage decreases from the control values and their time courses. Notice the greater and longer depression in non-spinal cord-transected animals (——) as compared with spinal cord-transected animals (- - -). (Reproduced, with permission, from Hanaoka *et al.*, The relative contribution of direct and supraspinal descending effects upon spinal mechanisms of morphine analgesia, J Pharmacol Exp Ther 207:476–484, 1978.)

not great enough to indicate reversal of a tonic inhibitory system. Henry[68] recently reported just the opposite effect in cats prepared in a similar fashion in which all of HT and WDR neurons were excited by intravenously administered naloxone while LT neurons were unaffected. In addition, sectioning the dorsal roots did not eliminate the naloxone excitation. This indicates that since all of the animals had transected spinal cords, the effects were in the spinal cord. There is support for the idea that naloxone by itself can enhance spinal cord responses from three studies[69,70,71] that have shown that systemically administered naloxone can enhance the magnitude of the ventral root reflex. These results were interpreted as evidence for the presence of a tonic inhibitory system that contains a naloxone-reversible opiate component. The data suggested that the inhibitory effect was not on the motor system. At this time it is not possible to state with certainty how important such a tonic system may be in the modulation of afferent sensory information.

It is impossible, at this time, to determine whether a naloxone-reversible tonic inhibitory system is active in clamping afferent signals associated with nociception. Both human and animal studies have yielded ambiguous data concerning this question. We must await the results of future work before deciding on the importance of such tonic systems in the alleviation of pain.

Overview of Narcotic Effects

The work of Hanaoka *et al.*[72] illustrates the major implications of many studies of narcotic effects on the spinal cord. In that study the effects of morphine were examined in spinal cord-transected and non-spinal cord-transected cats. The data revealed that although the extent and duration of suppression by morphine were significantly greater in the animals with intact spinal cords, there was still a large morphine effect seen in animals with transected spinal cords (fig. 3). As Hanaoka *et al.*[72] pointed out, although there is an obvious supraspinal component to the analgesic effects of morphine, it is now evident that the opiates act in the spinal cord, independent of supraspinal control, to modify the transmission of information concerning noxious stimulation of pe-

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ripheral receptors. It is still not known how important this spinal action is to the total analgesic effect in the intact animal, but it is obvious that the potential exists for a direct involvement of spinal sites. In addition, the possibility exists that some of the action seen at the level of the spinal cord may reflect drug effects on primary afferents.

We have emphasized the fact that narcotics can work at the level of the spinal cord. However, we have not addressed the question of whether the drug effect seen at that level results in part from an effect of the drug acting on the primary afferents. It is generally held that anesthetics and analgesics do not significantly affect primary afferents until concentrations become high enough to produce a local anesthetic effect. There have been, however, several recent reports in the literature suggesting that narcotics may have a presynaptic effect on the primary afferents. Jurna and Grossmann[73] reported that in both *in-vivo* and *in-vitro* studies morphine exerted different effects on nerve fibers with different functions. No effect was seen in motor fibers, while small-diameter fibers were influenced by the presence of morphine. Sastry[74,75] has reported that morphine and met-enkephalin can enhance the excitability of presynaptic terminals of A delta and C primary afferents. These results can be interpreted as reflecting an increase in presynaptic inhibition on primary afferents, which is induced by narcotics. These studies are certainly suggestive of the possibility that narcotic analgesia may result, in part, from either direct or indirect effects on primary afferents.

Concluding Remarks

In spite of the differences in techniques and drugs and the non-uniformity of some results, the papers reviewed here all point to a common fact. In contrast to earlier views that anesthetics and analgesics exert their pharmacologic action by depressing supraspinal sites, it is now obvious that these drugs can have potentially important influences on the transmission of sensory information in the spinal cord. This knowledge is important not only because it provides evidence for specific sites of drug action and enhances our understanding of how information about noxious stimuli is transmitted from the periphery, but most importantly because it provides us with a greater understanding of the mechanism of action of analgesics. However, the overall role of spinal cord depression in analgesia can be determined only when it is possible to record from spinal neurons in a drug-free, physiologically intact preparation prior to and following the administration of analgesic and anesthetic agents. In addition, further knowledge must be gained about the ability of such drugs to influence neuronal activity at the level of the primary afferents.

Note. As a result of very active current interest in spinal narcotic analgesia, a series of studies dealing with the general topic of this review, which are not referenced in this work, have been published since the submission of this manuscript.

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