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Spinally Administered Epinephrine Suppresses Noxiously Evoked Activity of WDR Neurons in the Dorsal Horn of the Spinal Cord

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This study was designed to determine if spinally administered epinephrine is capable of suppressing noxiously evoked activity of wide dynamic range (WDR) neurons in the dorsal horn of the spinal cord. Extracellular activity was recorded from single WDR neurons in the dorsal horn of decerebrate, spinal cord-transected (T-12) cats. Activity was evoked by the presentation of a noxious radiant heat stimulus (51°C) to the cells' receptive fields on the hind paws. Evoked activity was monitored both before and after the spinal administration of either 50 μg (n = 6) or 100 μg (n = 6) epinephrine. Both doses of epinephrine produced a significant suppression of noxiously evoked activity, which was dose-dependent. In addition, the 100-μg dose produced a suppression that was of longer duration than that seen following the 50-μg dose. Recovery from suppression was recorded following both the 50- and 100-μg dose. These results indicate that spinally administered epinephrine is capable of suppressing noxiously evoked activity of WDR neurons in the dorsal horn of the spinal cord. Since WDR neurons have been identified as cells of origin for the spinothalamic tract, such an action may block the central transmission of afferent pain information. This may be a mechanism by which spinally administered epinephrine enhances the duration or intensity of spinal anesthesia produced by local anesthetics and may also explain spinal analgesia resulting from the spinal administration of adrenergic agonists.

Interactions between spinally administered epinephrine and spinally administered opioids also were studied. Following spinal fentanyl administration, 10 μg of spinally administered epinephrine produced significant suppression of noxiously evoked activity within 6 to 9 min (n = 3). In contrast, 10 μg of spinally administered epinephrine by itself produced no significant suppression of noxiously evoked activity (n = 4). Interpretation of these results suggests that adrenergic agonists may act in a multiplicative fashion with spinally administered opiates to produce a profound suppression of noxiously evoked activity. (Key words: Analgesia. Anesthetic techniques: spinal epinephrine, spinal fentanyl. Pain: noxious heat. Spinal cord: WDR neurons.)

THE INCLUSION OF EPINEPHRINE with a local anesthetic for the enhancement of spinal anesthesia has been a clinically accepted practice for many years. The classic explanation of any epinephrine-induced enhancement of spinal block has been that epinephrine causes a local vasoconstriction, which reduces the vascular uptake of the local anesthetic, thus maintaining a higher concentration of the local anesthetic near the neural tissue for a longer period of time.[1] Although this mechanism of action is widely accepted, recent work has questioned its importance to the enhancement of spinal anesthesia.[2]

Research into pain modulation and, in particular, endogenous systems that control afferent pain signals, indicates that there are descending supraspinal pathways that are noradrenergic in nature and which, when activated, are capable of suppressing noxiously evoked activity at the level of the dorsal horn of the spinal cord.[3] In addition, it has been demonstrated that the spinal administration of alpha-adrenergic agonists is capable of producing behavioral analgesia in experimental animals.[4] It thus seemed possible that an alternate explanation may exist for epinephrine enhancement of spinal blockade (*i.e.*, that epinephrine itself interacts with spinal adrenergic receptors to block pain transmission pathways).

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The present study was carried out to determine if spinally administered epinephrine, in doses comparable to those used in human surgical patients, was capable of suppressing noxiously evoked activity of wide dynamic range (WDR) neurons in the dorsal horn of the spinal cord of cats. (WDR neurons have been associated with central transmission of information about pain.) This was done not only to examine an alternative explanation for epinephrine enhancement of spinal anesthesia, but also to emphasize the importance of the spinal cord as a site of action for many pharmacologic interactions that may block ascending pain signals.

We also examined the interaction of low-dose spinal epinephrine with spinal opioid analgesia. It recently has been established in animals that the combination of a low-dose opioid and a low-dose, alpha-adrenergic agonist is capable of producing significant behavioral analgesia, in spite of the fact that the dose of either drug by itself would produce minimal analgesia.[4] If multi-drug combinations can be found that reduce the total drug requirement, it may be possible to produce spinal analgesia with fewer attendant side effects and less likelihood of tolerance development. We were particularly interested in determining if, by administering epinephrine well after the opiate had an effect on the neurons under study (*i.e.*, after significant opiate distribution had occurred), we could detect any effects that would be caused by actions other than changes in vascular uptake.

Methods

Extracellular, single-unit recordings were obtained from the lumbar dorsal horn in decerebrate, spinal-cord transected cats (n = 23). Surgical preparation was carried out with halothane/nitrous oxide/oxygen anesthesia until the point at which animals were rendered decerebrate. Following decerebration, anesthesia was discontinued and the animals were ventilated with room air. This sequence allowed us to insure that the animals were pain-free during both the surgical preparation and neurophysiologic recordings, and yet permitted us to study the epinephrine effects in a preparation that was drug-free (except for the neuromuscular-blocking agent).

The first phase of the surgical preparation involved animal instrumentation in order to monitor and maintain physiologic variables within normal limits. Jugular vein and carotid artery catheterizations were performed and provided routes for intravenous fluid and drug administration and for monitoring of arterial blood pressure. The urinary bladder was catheterized, and rectal temperature was monitored and maintained within normal limits. The trachea then was intubated and the animals were paralyzed with gallamine triethiodide (0.1%, 4–8 $ml \cdot kg^{-1} \cdot h^{-1}$) and mechanically ventilated.

Following animal instrumentation, the cats were rendered decerebrate by electrolytic lesions in the midbrain reticular formation and the spinal cord was transected at T-12 (spinal cord transection allowed us to monitor epinephrine effects on the dorsal horn of the spinal cord in the absence of descending supraspinal influences). A laminectomy then was performed which provided access to the lumbar enlargement. The dura was cut and reflected, and the spinal cord was bathed with 37° C physiologic saline. (The cut bone and dura formed a natural trough that held the saline in place and allowed us to selectively bathe the spinal cord with the drug solution.) Tungsten microelectrodes were advanced into the lumbar enlargement of the dorsal horn of the spinal cord while receptive fields on the ipsilateral hind paw were stimulated. When activity of a single cell was encountered, amplitude discrimination was used to insure that only single-unit activity was recorded. Quantitative analysis was carried out only on activity that was recorded from neurons that had characteristic WDR profiles. Upon isolation of a suspected WDR neuron, stimuli of increasing intensity from light brushing through 51° C radiant heat were applied to its receptive field on the hindpaw. If the response profile indicated a WDR neuron, control studies then were performed in which both spontaneous and noxiously evoked activity were recorded. (Noxiously evoked activity was activated by the presentation of a 51° C radiant heat stimulus for eight seconds on the receptive field on the hind paw.) The stimulator was always placed in an attempt to maximize receptive field stimulation (*i.e.*, the center of the radiant heat stimulus was focused on the center of the most excitable area of the receptive field). Only one neuron was studied in each animal.

Following control studies (n = 12), the saline, which had been bathing the spinal cord, was removed (gentle suctioning) and replaced by 0.5 ml of 37° C physiologic saline that contained either 50 μg (n = 6) or 100 μg (n = 6) epinephrine. (The epinephrine was obtained from the same source as that used clinically for inclusion with local anesthetics.) Following spinal application of the drug, which was accomplished by gently dropping the solution onto the spinal cord in the area immediately surrounding the electrode, noxiously evoked activity of the individual neuron was monitored every three minutes for periods of up to 30 min. In some instances, neuronal activity was recorded for longer periods of time in an attempt to monitor recovery following spinal epinephrine administration.

Qualitative studies of the effects of spinally administered epinephrine were carried out on two low threshold neurons that were activated by light brushing of their receptive fields, and also on the spontaneous activity of two proprioceptive (lamina VI-type) neurons.

The studies of epinephrine effects on spinal opiates

differed in the following ways. In the cells in which epinephrine alone was evaluated (n = 4), 10 μg of epinephrine in 0.5 ml of saline were placed on the spinal cord, and noxiously evoked activity was recorded every three minutes. In those cells in which the effects of spinally administered epinephrine were studied following spinal opioid administration (n = 3), the epinephrine (10 μg) in 0.5 ml of saline was placed on the spinal cord at least 30 min after the spinal application of the opiate (15 μg fentanyl). Again, following spinal epinephrine administration, noxiously evoked neuronal activity was recorded every three minutes.

The occurrence of each action potential as it was recorded extracellularly, as well as the time of stimulus on and off, and the analog temperature recorded at the skin surface were converted to a digital signal stored on a computer disk (PDP 11/40). In addition, the ratemeter output of neuronal events and the analog skin temperature were recorded on a polygraph. Data evaluation and analysis were carried out off-line (PDP 11/40). For the epinephrine mean data, differences from control were evaluated by Student's *t* test for paired data. Student's *t* test for unpaired data was used to assess statistical significance of differences between the two doses. Because of the small sample size, no statistical analysis was performed on the data dealing with the interaction of epinephrine and fentanyl.

Results

Epinephrine Effects on WDR Neurons

Data were obtained from 23 cats. All neurons from which noxiously evoked activity was recorded were classified as WDR neurons (n = 19).

Both the 50- and 100-μg doses of spinally administered epinephrine affected the noxiously evoked activity of WDR neurons in this study. Figure 1 shows the effects of 50 μg of spinally administered epinephrine on a single WDR neuron, and subsequent recovery from that effect. Following the 50-μg dose, the cell shown in figure 1 began to recover rapidly from the effect, and by 60 min after spinal administration, the evoked activity of this individual neuron had returned to control values. The effects following 100 μg of spinally administered epinephrine differed slightly. Figure 2 demonstrates the effect of 100 μg of spinally administered epinephrine on an individual cell. In this case, even with drug washout at 30 min, the evoked activity still was suppressed significantly 90 min after spinal administration. The effects of 50- and 100-μg doses of spinally administered epinephrine on the mean evoked activity of all the neurons studied are seen in figure 3. It is clear that in both cases, each dose produced significant suppression of the mean noxiously evoked activity. A comparison of the effects of each of the doses, however, reveals that the amount of suppression following the 100-μg dose was greater than that following the 50-μg dose. At all time points past 18 min, there was a statistically significant difference between the mean suppression ($P < 0.01$) produced by the two doses. In addition, there appears to be a plateau effect following the 50-μg dose, such that a maximum level of suppression has been reached within 30 min. However, this does not appear to be the case following the 100-μg dose.

Control studies indicated that neither the placement of saline on the spinal cord, nor the sequence of noxious stimulus presentation, caused significant changes in the evoked activity of the neurons studied. At no time did either dose of spinally administered epinephrine cause a detectable change in any animal's blood pressure, in spite

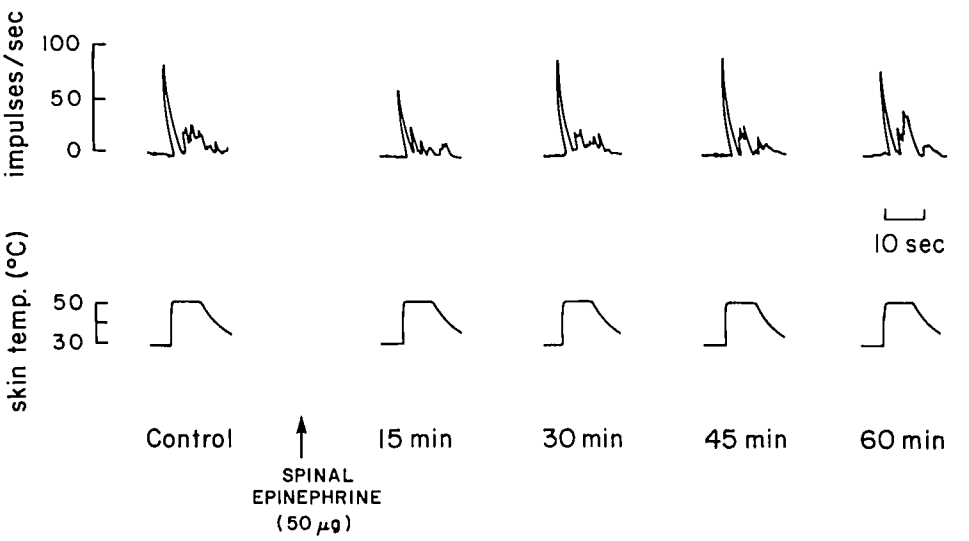

FIG. 1. Effects of 50 μg of spinal epinephrine on a single WDR neuron and subsequent recovery. In this and subsequent figures, the bottom traces represent the skin temperature recorded at the center of the receptive field of the neuron. The top traces represent the evoked activity expressed as impulses per second following the application of a 51° C radiant heat stimulus for eight seconds to this neuron's receptive field on the foot pad. Fifty micrograms of spinally administered epinephrine caused suppression of this neuron (*e.g.*, activity was reduced to 55% of control at 15 min). By 60 min after epinephrine administration, the noxiously evoked activity of this neuron had returned to control values.

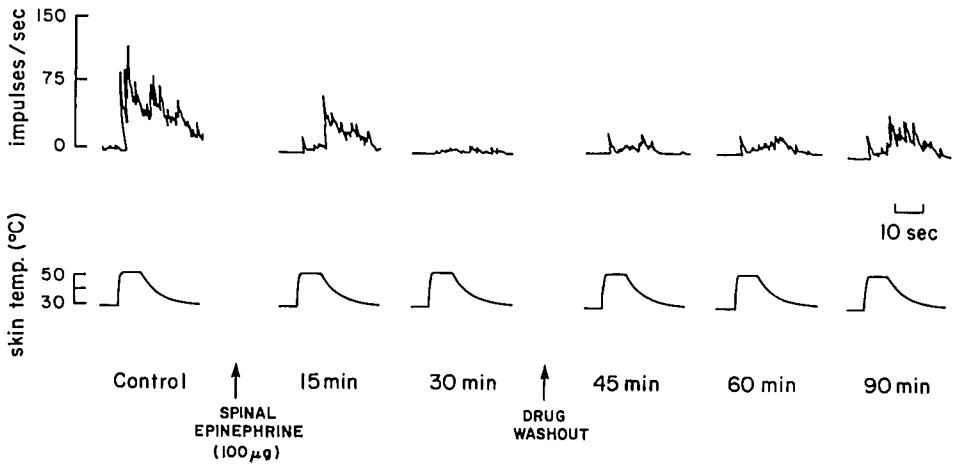

FIG. 2. Effects of 100 μg of spinally administered epinephrine on a single WDR neuron. Note that 100 μg epinephrine produced significant suppression of this neuron to within 8% of control 30 min after its application. In spite of removal of all the epinephrine-containing saline at 30 min, there was still significant suppression of the noxiously evoked activity of this neuron at 90 min (42% of control).

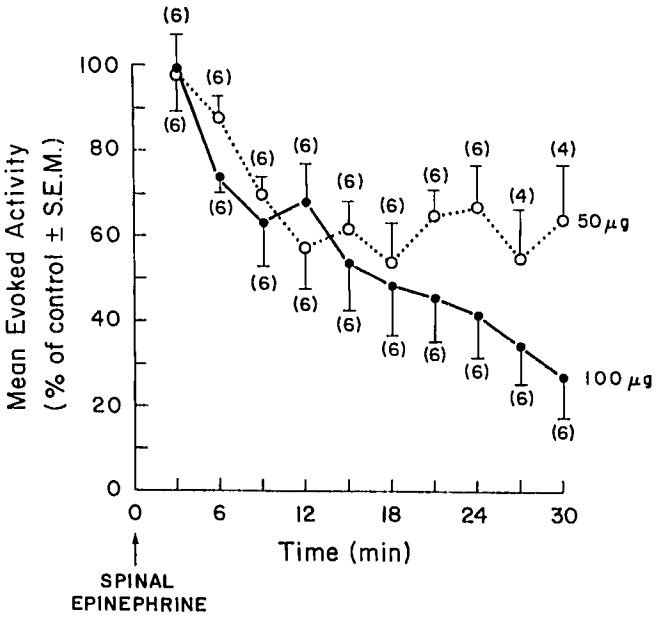

FIG. 3. Effects of 50 μg and 100 μg of spinally administered epinephrine on the mean evoked activity of all the neurons included in this study. Abscissa: time in minutes after spinal epinephrine administration. Ordinate: mean evoked activity expressed as a percent of control. The numbers in parentheses indicate the number of cells studied at each point. The flags represent ±1 SEM. Within nine minutes after the spinal administration of 50 μg epinephrine, there was a significant reduction in the mean noxiously evoked activity of all the neurons studied. This effect appeared to reach a plateau level within 12 min after spinal epinephrine administration. Within six minutes after the spinal administration of 100 μg epinephrine, the mean noxiously evoked activity was suppressed significantly. In contrast to the effects of 50 μg of spinal epinephrine, the suppression of the noxiously evoked activity by 100 μg continues to increase with time up to the 30 min time point. A comparison of the amount of suppression produced by the 100-μg dose of spinally administered epinephrine with the 50-μg dose indicates that at all time points after 18 min, the 100-μg dose produced a statistically significantly greater suppression of the noxiously evoked activity.

of the fact that comparable doses of intravenously administered epinephrine produced increases in blood pressure.

Microscopic observation of the spinal cord prior to and immediately after epinephrine administration, revealed no tissue blanching. In addition, the electrophysiologic characteristics of the neurons under study gave no indication of damage comparable to that observed following known anoxic insults to the spinal cord.

The selectivity of the epinephrine effect appears to be greater for noxiously evoked activity than for activity evoked by non-noxious stimuli. In the four cells in which qualitative studies of non-noxious stimuli were conducted, there was no significant suppression of the recorded activity following the spinal administration of epinephrine, suggesting that the suppression of activity may be relatively selective for noxiously evoked activity. Because of the placement of the thermal stimulator, it was impossible to evaluate the effect of spinal epinephrine on the non-noxiously evoked activity of the individual WDR neurons that were studied.

EPINEPHRINE FOLLOWING SPINAL FENTANYL

Figure 4 demonstrates the lack of an effect of 10 μg of spinally administered epinephrine on the noxiously evoked activity of a single WDR neuron. In contrast to the ineffectiveness of 10 μg of spinally administered epinephrine alone, figure 5 demonstrates a large suppression of noxiously evoked activity of a single WDR neuron that was produced by 10 μg of spinally administered epinephrine when given subsequent to spinal opioid administration (15 μg fentanyl). Table 1 summarizes the results of these studies. Data are presented for only the first 12 min after drug administration because that was the time required for the maximum epinephrine effect to occur

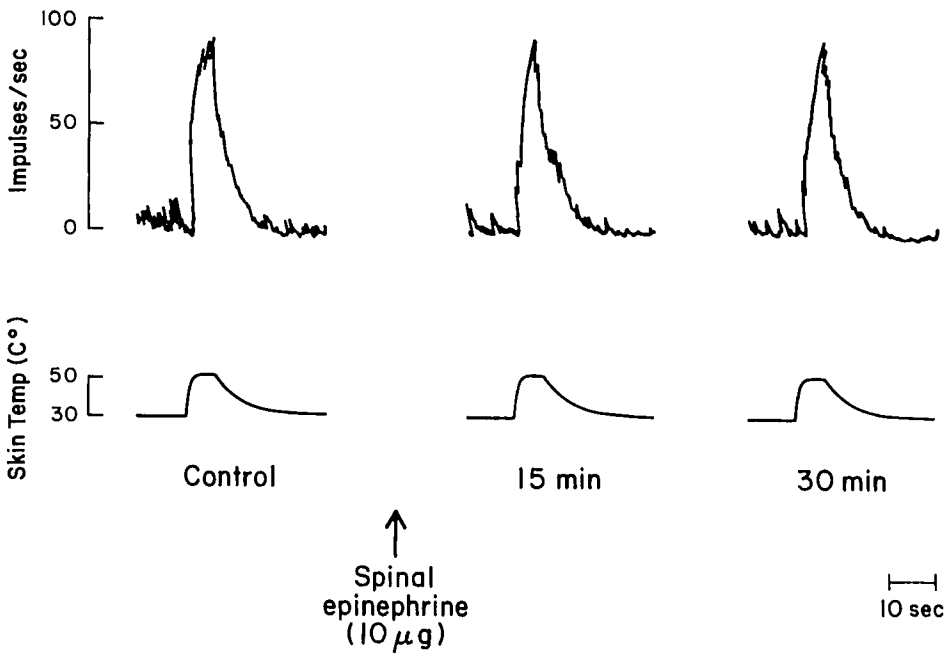

FIG. 4. Effects of 10 μg of spinally administered epinephrine on noxiously evoked activity of a single WDR neuron. In the control situation, the presentation of a 51° C radiant heat stimulus for eight seconds to the neuron's receptive field on the glabrous skin of the hindpaw caused significant activation of this neuron. Subsequent spinal administration of 10 μg of epinephrine produced no significant suppression of activity for a period of up to 30 min.

following spinal opioid administration. Although not analyzed statistically because of the small sample size, it seems clear that epinephrine has a much more profound effect on noxiously evoked activity when it is administered subsequent to spinal fentanyl. This is especially true in light of the fact that the suppression was in addition to that produced by the spinally administered fentanyl. In all three instances, the suppression caused by epinephrine lasted for the entire 30 min of neuronal recording.

Discussion

EPINEPHRINE EFFECTS ON WDR NEURONS

The clinical efficacy of including epinephrine with local anesthetics in order to enhance spinal anesthesia is widely accepted among practicing anesthesiologists. It has been assumed that the major way in which epinephrine enhances spinal anesthesia is through local vasoconstriction,

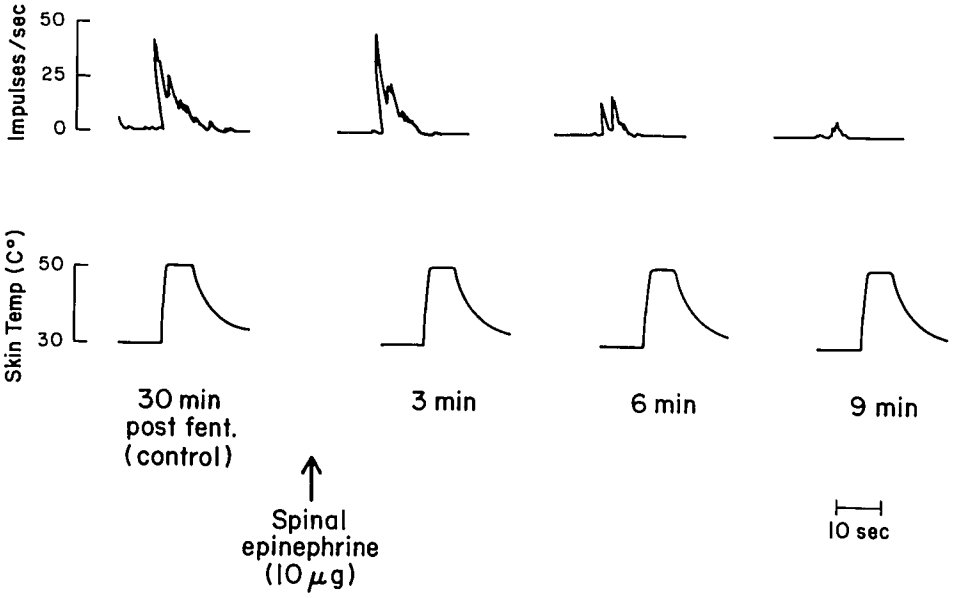

FIG. 5. Effect of 10 μg of spinally administered epinephrine following spinal fentanyl. In the control situation (*i.e.*, 30 min after the spinal application of 15 μg fentanyl), this neuron is still activated by the presentation of the noxious stimulus. The response, however, is less than that seen prior to fentanyl administration. [This cell was suppressed to a maximum of 27% of control by spinal fentanyl at 16 min after its administration. The control value shown in this figure was 65% of pre-drug (fentanyl) control, *i.e.*, recovery from the fentanyl effect was occurring.] Subsequent spinal administration of 10 μg epinephrine produced a rapid and significant suppression of the noxiously evoked activity, such that within nine minutes the evoked activity was reduced to 9% of the post-fentanyl control value.

TABLE 1. Effects of 10 μg of Spinally Administered Epinephrine on Noxiously Evoked Activity of WDR Neurons

Time after Epinephrine Administration	Epinephrine Alone*	Epinephrine Following Spinal Opiates*
3 min	99 ± 5% (4)	40 ± 20.2% (3)
6 min	90 ± 3% (4)	25 ± 12.7% (3)
9 min	80 ± 5% (4)	16 ± 10.4% (3)
12 min	85 ± 1% (3)	13 ± 2.9% (3)

* Values represent mean per cent of the control ± SEM; numbers in parentheses indicate the number of cells averaged at each point.

resulting in decreased vascular uptake of the local anesthetic and thus a higher concentration of the local anesthetic near the neural tissue for a longer period of time. Although this mechanism may be important, it has been challenged by recent research.[2] In light of neurophysiologic and pharmacologic studies indicating the presence and importance of adrenergic modulation of spinal cord activity,[3,4] it was apparent to us that another possible mechanism of action may exist.

The results from the present study demonstrate that the spinal administration of epinephrine in the spinal cord-transected, decerebrate animal is capable of significantly reducing (in a dose-dependent manner) noxiously evoked activity in a group of neurons that have been demonstrated to be cells of origin of the spinothalamic tract in the cervical cord of cats[5] and in the lumbar cord in monkeys,[6] and which are felt to be importantly involved in the central transmission of information about pain.[7,8] These data suggest that a possible mechanism by which spinally administered epinephrine may enhance spinal anesthesia may be due to a direct action of epinephrine upon the noradrenergic systems at the level of the dorsal horn of the spinal cord. Such adrenergic activation, in turn, is capable of blocking, or decreasing, the supraspinal transmission of information about pain by decreasing the response of pain-signalling cells at the level of the spinal cord. A recent report that epidural epinephrine alone (50 μg in 10 ml of saline) produced "objective signs of limited segmental hypoalgesia" in a human volunteer[9] to ice and pinprick further supports this explanation.

The recovery of normal responses over time and the normalcy of neuronal response patterns suggest that the effects observed in this study are due to a specific drug effect on neuronal activity rather than to a non-specific effect that may result from vascular effects of epinephrine. The lack of effect of the spinally administered epinephrine on blood pressure supports the concept that the effect is caused by local spinal action rather than by significant systemic uptake of the drug or by a change in neuronal firing due to changes in blood pressure.

The pharmacology of this spinal adrenergic system requires further study. Epinephrine is not the drug of choice for such studies, but rather more selective adrenergic agonists need to be employed. In addition, *p*H must be controlled, blood flow studies must be conducted, and specific adrenergic blockers must be employed. Such studies are presently underway in this laboratory.

EPINEPHRINE EFFECTS ON SPINAL FENTANYL

The presence of the spinally administered opiate "set the stage" for a significant suppression of noxiously evoked activity that was not seen when a small dose of epinephrine was administered by itself. The timing of the effect, *i.e.*, 30 min after fentanyl administration, makes it unlikely that the observed effect resulted from vascular changes (*i.e.*, a redistribution of fentanyl caused by adrenergic-induced vasoconstriction), although the data do not rule out that mechanism of action. Yaksh and Reddy[4] have reported that adequate analgesia can be produced in monkeys by administering low doses of an opioid and an alpha-adrenergic agonist. Although, in that study, neither dose by itself was capable of producing a high degree of analgesia, the combination resulted in a high degree of long-lasting analgesia that was less likely to produce tolerance. The present study provides neurophysiologic evidence that there is an important interaction at the spinal level between opiate and adrenergic receptors or agonists. In light of the known descending adrenergic pathways that modulate spinal pain transmission (see references 3, 10, and 11), this finding is not surprising.

Many questions remain to be answered in a more precise fashion. Epinephrine is probably not the ideal alpha-adrenergic agonist to be used. It is likely that both alpha-1 and alpha-2 receptors are involved in the spinal modulation of pain (Yaksh: personal communication). In addition, careful dose-response studies must be carried out in order to determine exactly how this effect is produced and whether or not it is multiplicative. In spite of the obvious problems, however, the results indicate the presence of an important interaction between an alpha-adrenergic agonist (in this case, epinephrine) and spinally administered opiates. The results of this study suggest the possibility of employing low doses of an alpha-adrenergic agonist in combination with low doses of an opiate in order to produce significant suppression of noxiously evoked activity at the level of the dorsal horn of the spinal cord. Such suppression of noxiously evoked activity can be assumed to be associated with a decrease in the ability of pain messages to be sent centrally, and thus to be associated with the production of spinal analgesia.

The clinical implication of this study and of studies like those done by Yaksh and Reddy[4] may be far reaching.

The spinal or epidural administration of opioids for the relief of specific types of acute or chronic pain is a powerful tool that is, at present, limited by attendant side effects. Respiratory depression and tolerance are the most important factors that limit the use of this technique for acute and chronic pain, respectively. Just as the use of nitrous oxide reduces the dose requirements for other inhalation agents and thus reduces the likelihood of attendant side effects, it may be possible to achieve a reduction in side effects of spinal opioid analgesia by employing a multi-drug approach. A careful evaluation of interactions among known spinal neurotransmitters may help to identify appropriate multi-drug combinations.

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