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Effects of morphine on visceral nociception evoked by colorectal distension in rats: comparative examinations of electrophysiological and behavioral responses

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Abstract: The purpose of this study was to compare the effects of intravenously administered morphine on electrophysiological and behavioral responses to colorectal distension (CRD) and to examine the influence of noxious stimuli applied to another part of the body (a laminectomy) on the visceromotor response to CRD. The effects of morphine (0.1–6.4 mg·kg^{-1}) were examined in rate anesthetized with pentobarbital. Electrophysiological (n = 16) and behavioral experiments (n = 47) were done. Electrophysiological experiments were conducted to examine the effects of morphine on the responses of visceral dorsal horn neurons to CRD; behavioral studies were conducted to compare the effects of morphine with and without a laminectomy (intact group: n = 24; laminectomy group: n = 23). Morphine suppressed the evoked activities of the visceral dorsal horn neurons in a dose-dependent manner. Similar suppression of the behavioral visceromotor response was observed. Visceromotor thresholds were significantly lower in the intact group than in the laminectomy group during the control study. When morphine was administered, the visceromotor thresholds in both groups increased to a similar level. Behavioral and neurophysiological responses to CRD were suppressed in a similar fashion by morphine. Although laminectomy affected the threshold values of CRD for visceromotor responses, the laminectomy per se plays an insignificant role when adequate morphine is administered.

Key words: Visceral dorsal horn neuron, Visceromotor response, Colorectal distension, Nociception, Morphine, DNIC, Nocigenic inhibition

Introduction

Spinal analgesia utilizing analgesic agents has been a part of clinical practice over the past two decades. Our laboratory has an ongoing interest in spinal sensory processing of information about visceral pain. We are particularly interested in examining spinal neuronal responses to noxious visceral stimuli and the ability of analgesic drugs to modify those responses, and in comparing the effects of drugs on neuronal responses with that on behavioral responses.

There are reports about the effects of morphine on sensory responses of dorsal horn convergent neurons activated by thermal, mechanical or chemical stimuli [1–4], and some reports about the effects of morphine on visceromotor responses [5] and on visceral responses of dorsal horn neurons to colorectal distension (CRD) [6–8]. There are, however, no reports comparing the effects of morphine sulfate on visceral responses of visceral dorsal horn neurons as defined by Ness and Gebhart [6,8] and visceromotor responses [5] elicited by visceral stimuli such as CRD in similar conditions.

There has been evidence that noxious stimuli associated with surgical preparation for an acute neurophysiological study of the spinal cord could alter both the neuronal responses to a noxious visceral stimulus as well as the impact of analgesics on those neuronal responses [9,10]. Noxious stimuli in distant parts of the body have been shown to suppress noxiously evoked activity in the spinal dorsal horn [9–11]. This phenomenon has been termed "nocigenic inhibition" [9,10] or "diffuse noxious inhibitory controls (DNIC)" [11]. On the other hand, increasing levels of surgical trauma have been reported to enhance reflex responses to mechanical pinch stimulus [12].

The purpose of this study was to compare the effects of intravenously administered morphine sulfate on electrophysiological and behavioral responses to CRD and to examine the influence of noxious stimuli applied to another part of the body (a laminectomy) on a visceromotor response elicited by the same noxious CRD.

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Materials and methods

This study protocol was approved by the Yale Animal Care and Use Committee, and institutional, state and federal guidelines for humane care and use of laboratory animals were observed during all aspects of this study. The experiments were performed on 63 adult male Sprague-Dawley rats (CAMM) weighing 240–480 g at the start of the experiments. Two kinds of experiments were done: behavioral experiments (n = 47) and electrophysiological experiments (n = 16). The conditions were very similar in all of the experiments. The one important difference was the presence or absence of a laminectomy. The behavioral group was divided into two groups, one without laminectomy and one with laminectomy. Animals were anesthetized with intraperitoneal pentobarbital 40 mg·kg^{-1}. After 10 min of observation, if animals responded to initial surgical incision, an additional 20 mg·kg^{-1} pentobarbital was administered intraperitoneally. Among the three groups (behavioral study with laminectomy, behavioral study without laminectomy, and electrophysiological study with laminectomy), the average doses of intraperitoneal pentobarbital were 46.9 mg, 46.7 mg, and 47.5 mg, respectively. An intravenous pentobarbital infusion was started approximately 30 min after intraperitoneal injection at a rate of 4–6 mg·kg^{-1}·h^{-1}. The level of anesthesia described by Sandkühler and Gebhart [13] was monitored for 10 min to assure the absence of spontaneous movement and the presence of corneal, auricular, pinnal, and limb flexion reflexes. If spontaneous movement was present, the dose of intravenous pentobarbital was increased by 0.35 mg·kg^{-1}·h^{-1} and that rate was continued. If reflexes were absent, the intravenous pentobarbital dose was decreased by 0.35 mg·kg^{-1}·h^{-1}. This level of anesthesia was monitored and maintained throughout the experiments. In the behavioral experiments with or without laminectomy, the animals were breathing spontaneously. This level of anesthesia was sufficient to maintain the animals without spontaneous movement. In the electrophysiological study, the same level of anesthesia was monitored throughout except for a 1-h period when actual neuronal recording was made. During this period, pancuronium was administered intravenously to record stable single neuron activity, and the animals were mechanically ventilated. We therefore assumed that a similar proper level of anesthesia was present during the single neuron recording.

Behavioral studies

Behavioral studies were done with and without a laminectomy (laminectomy group and intact group, respectively). The purpose of the laminectomy in the behavioral experiment was to make comparable animal preparations between the behavioral study and the electrophysiological study which necessitated laminectomy. Following tracheostomy, an external jugular vein and an internal carotid artery were cannulated for fluid and drug administration and for monitoring of arterial blood pressure. In the laminectomy group, a laminectomy from T12 to L1 was performed. No muscle relaxant was used for the behavioral study. Intravenous pentobarbital was started approximately 30 min after intrapertoneal injection. The behavioral study was begun within 1 h after completion of laminectomy. At this point and throughout the behavioral study, the animals presented no spontaneous movement with this level of anesthesia. A light level of anesthesia described by Sandkühler and Gebhart [13] with corneal, auricular, pinnal, and limb flexion reflexes present in the absence of spontaneous movement was maintained throughout the duration of the experiment by continuous intravenous infusion of pentobarbital (4–6 mg·kg^{-1}·h^{-1}). End-tidal CO_2 was maintained around 40 mmHg for the duration of the experiment (Capnometer Model 2200 Traverse Medical Monitors, CA, USA). Body temperature was monitored with an esophageal probe and maintained within normal limits.

CRD was used as a noxious visceral stimulus. The method of CRD we used is similar to that described by Ness and Gebhart [5]. Distension of the descending colon and rectum was achieved by a pressure-controlled, air inflation of a 7-cm-long distension balloon inserted intra-anally [5–8]. The distension balloon was connected to a pressure-controlled balloon inflator [14] through a ballon catheter, and was inflated at a rate of 4 mmHg·s^{-1} beginning at 0 mmHg until a maximum of 80 mmHg was reached. A small detection balloon (1–1.5 cm long, flexible, made of latex) was attached distal to the tip of the distension balloon catheter to monitor changes in intraluminal pressure [15]. It was filled with 0.6 ml of air to monitor intraluminal pressure which was found to be stable at this level of anesthesia. This intraluminal pressure was set at zero pressure on the recording chart. Abdominal muscle contraction in response to CRD (viscerosomatic response), which were defined as visceromotor responses by Ness and Gebhart [5] is signaled by the detection balloon with a sudden rise in pressure. The pressures within the detection and distension balloon were recorded on a chard recorder simultaneously. A sudden rise in pressure of 1 mm or greater followed by continual rise can be detected easily on the recording chart. At the same time, muscular contraction was observed which verified the rise in the intraluminal pressure seen on the recording chart. Our decision to determine positive visceromotor response was based on the long lasting rise in pressure following an initial 1-mm rise and observation of abdominal

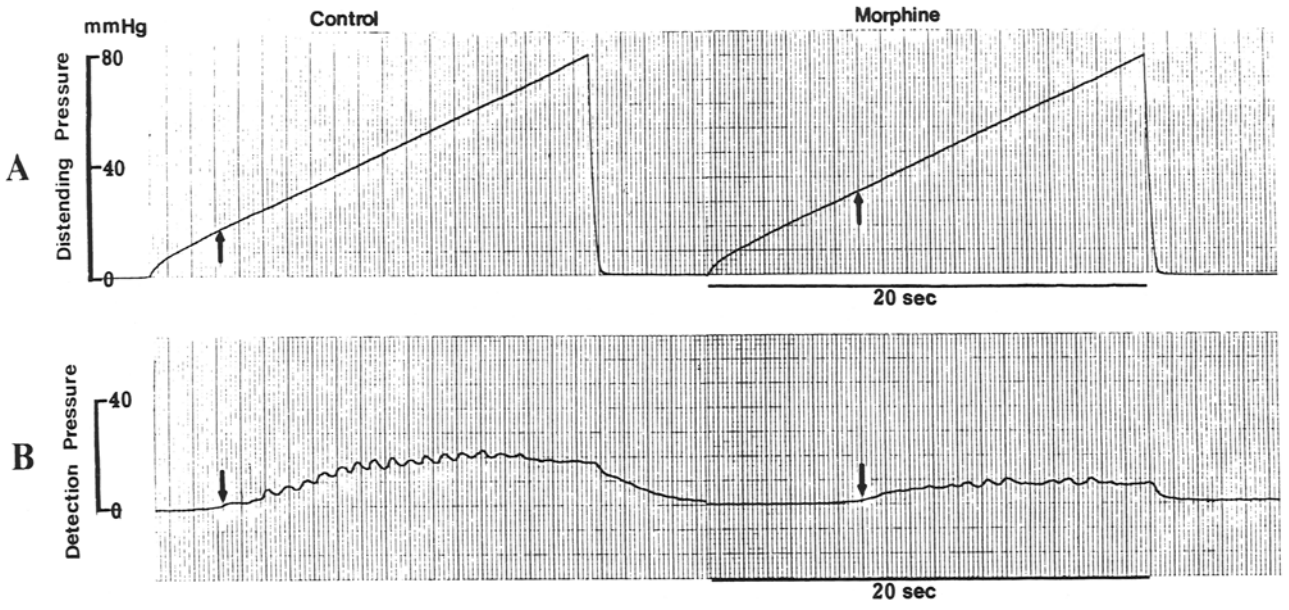

Fig. 1A,B. This is an example of a pressure tracing from the distension balloon (**A**) and the detection balloon (**B**) in the behavioral study. Abdominal muscle contraction is shown by the detection balloon with a sudden rise in pressure shown by *downward arrows*. The long lasting rise in pressure following the initial 1-mm rise can be detected on the recording chart above the baseline which was set at zero. The *upward arrows* in **A** indicate corresponding visceromotor threshold and latency in the control study and after the administration of morphine

muscle contraction. We then went back to the recording chart and marked the 1-mm rise as the initiation of the visceromotor response (Fig. 1). The baseline contraction of abdominal and hindlimb musculature in response to three CRD separated by 4 min interstimulus intervals was measured and averaged. Ten search stimuli were given to ascertain visceromotor response in both the laminectomy group and the intact group. After the baseline observation, the effects of each dose of morphine were studied 7 min after administration. Cumulative doses of morphine sulfate (0.1, 0.4, 1.6, and 6.4 $mg \cdot kg^{-1}$) were subsequently administered intravenously at 8-min intervals. This mode of morphine administration is similar to that described by Ness and Gebhart [7]. Naloxone hydrochloride (1 $mg \cdot kg^{-1}$ i.v.) was administered at the end of the experiments to examine the reversal of drug effects.

Behavioral data for the dose–response curves were converted to percent maximal possible effect (%MPE) using the following equation [16]:

$$\%MPE = \frac{\text{Postdrug response–Predrug control}}{\text{Cut-off time–Predrug control}} \times 100$$

For this calculation, time latency expressed in seconds. The latency to response with cut-off time (set at 20 s) was measured rather than distension pressure. Postdrug response means the latency to response after administration of morphine. Predrug control means the latency to response before the administration of morphine.

Electrophysiological studies

The electrophysiological studies were performed on 16 animals prepared the same way as in the behavioral study except that the rats were immobilized with pancuronium bromide (initial dose: 0.3 $mg \cdot kg^{-1}$, maintenance dose: 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$). Immobilization was necessary during the single-neuron recording which took 1 h, as the visceromotor response prevented stable single-neuron recording. After the completion of laminectomy, before immobilizing the animals for single-neuron recording, the level of anesthesia used for the behavioral study was confirmed by observing the absence of spontaneous movement and the presence of corneal, auricular, pinnal, and limb flexion reflexes as described by Sandkühler and Gebhart [13]. During this period, animals were mechanically ventillated with a 2.5- to 3.0-ml stroke volume, 60–70 strokes·min^{-1} with oxygen mixed with room air throughout the experiment to maintain Pao_2 above 100 mmHg, $Paco_2$ around 40 mmHg and *heart rates around 300/min*. (Rodent ventilator model 683, Harvard Apparatus, MA, USA). Internal carotid arterial pressure was continuously monitored and data obtained from animals with arterial pressure below 80 mmHg at any time were excluded from the study. With adequate oxygenation and normocapnia, there was no visual evidence of spinal cord swelling. After laminectomy, the dura mater was carefully cut and the spinal cord was bathed with 37°C physiologic saline. The physiological parameters of the

animals were maintained within normal limits. Colorectal distension was used as a noxious visceral stimulus (inflation rate of 4 mmHg·s^{-1} from 0 mmHg to 80 mmHg) in the same way as in the behavioral study.

A tungsten microelectrode (4–10 MΩ, FHC, Brunswick, ME, USA) was advanced into the spinal cord in the T12-L1 spinal segments by a hydraulic microdrive (0.3–1.0 mm lateral from the midline and 0.2–1.0 mm deep from the spinal cord dorsum) to record extracellular activity from visceral dorsal horn neurons. Electrophysiological data were collected and analyzed by an IBM AT Personal Computer utilizing Spike 2, data acquisition and analysis program (Cambridge Electronic Design, Cambridge, UK). Ten colorectal distensions were used as search stimuli. This was a comparable amount of search stimuli as used in behavioral and neurophysiological studies. During the baseline study, both spontaneous and nexiously evoked visceral dorsal horn neuronal activities were recorded. The baseline study was completed within 1 h after the completion of the laminectomy. Doses of morphine, as given in the behavioral study, were subsequently administered intravenously at 8-min intervals.

The spontaneous neuronal activities were counted for 20 s and the count was repeated 3 times at 4-min intervals. Stable spontaneous neuronal activity was observed throughout the baseline study. Evoked activity was counted for 20 s from the beginning of the stimulus, and the evoked response to CRD was defined as the total number of action potentials minus spontaneous activity. Evoked activities were recorded 3 times at 4-min intervals. The average evoked activities during the control period were compared with activities after morphine administration in terms of percent suppression. Only one cell was studied in each animal so that the animals were subjected to a series of pharmacological interventions only once.

Data analysis

The *t*-test for independent (unpaired) samples was used to compare control values between the laminectomy and intact groups. Two-factor repeated measures analysis of variance (ANOVA) was used to compare the laminectomy group to the intact group over the four levels of morphine. Within the three groups, naloxone values were compared to control values using a paired *t*-test. A least-squares regression analysis was used to calculate the 50% effective dose (ED_{50}) values and correlation coefficients of the dose-response curve. Regression analysis with dummy variables was used to test the hypothesis that pairs of regression lines for any two of the three groups were parallel and coincident. $P < 0.05$ was taken as the level of significance.

Results

Effect of morphine on behavioral response to CRD in pentobarbital-anesthetized animals with or without a laminectomy

Figure 2 shows the %MPE and dose of morphine regression lines in the intact and laminectomy groups. In both groups, the systemic administration of morphine sulfate attenuated significantly the visceromotor responses to CRD in a dose-dependent manner. The ED_{50} values were 0.64 mg·kg^{-1} in the intact group and 0.78 mg·kg^{-1} in the laminectomy group. Naloxone 1 mg·kg^{-1} reversed the effects of morphine sulfate on visceromotor responses to CRD in the intact group ($P = 0.092$) and in the laminectomy group ($P = 0.17$).

Effect of morphine on electrophysiological response to CRD in pentobarbital-anesthetized animals

All neurons ($n = 16$) were located in the T12-L1 spinal segments (0.3–1.0 mm lateral from the midline and 0.2–1.0 mm deep from the spinal cord dorsum). All neurons responded to CRD and were similar to the short-latency abrupt neurons as defined by Ness and Gebhart [6,8].

Activities from 16 neurons were recorded in this part of the study. Baseline spontaneous neuron activity was 7.7 ± 1.9 (mean ± SE) impulses per second (i.p.s.). Spontaneous activity at the highest dose of morphine was 1.6 ± 0.8 i.p.s. Following the administration of naloxone, it returned to 7.0 ± 2.0 i.p.s. Figure 3 demonstrates the dose–response regression line for morphine in the electrophysiological experiments. The systemic administration of morphine sulfate suppressed the

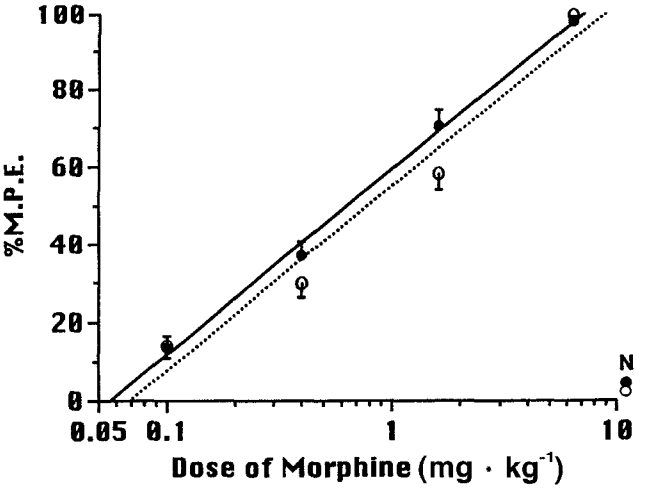

Fig. 2. The log dose-response regression lines in the intact group (*closed circles*: $r = 0.83$, $P < 0.01$) and the laminectomy group (*open circles*: $r = 0.89$, $P < 0.01$) in the morphine behavioral study. Each point represents the mean ± S.E. *N*, reversal by naloxone; *MPE*, maximal possible effect

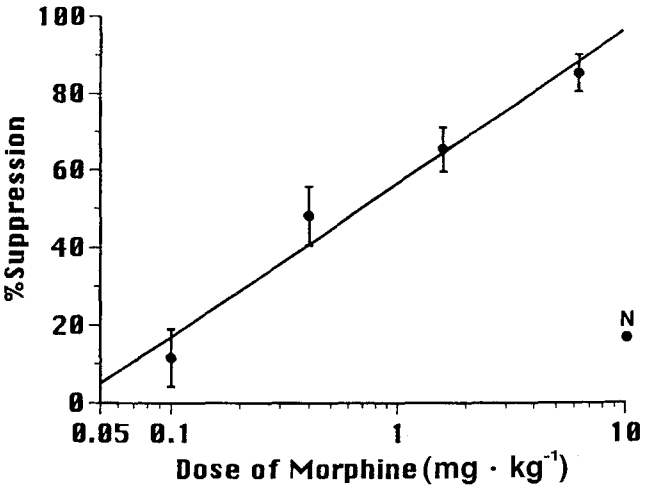

Fig. 3. The log dose – percent suppression of the visceral dorsal horn neurons relation in the electrophysiological experiments ($r = 0.72$, $P < 0.01$). Each point represents the mean ± S.E

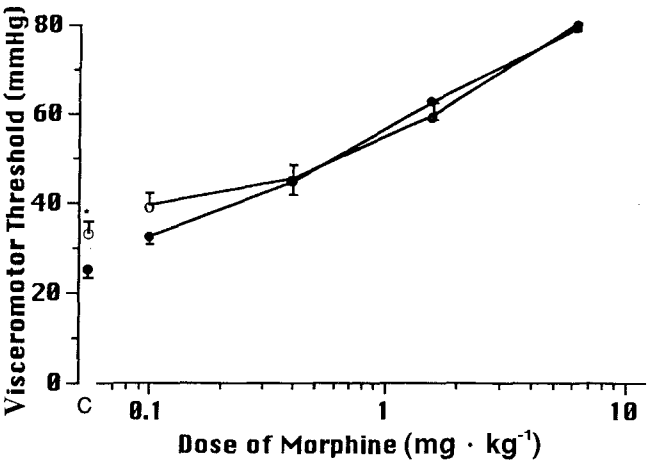

Fig. 4. Comparison of visceromotor thresholds versus log dose of morphine between the intact group (*closed circles*) and the laminectomy group (*open circles*) in the morphine behavioral study. *C*, control value; * $P < 0.01$

evoked activity of the visceral dorsal horn neurons in a dose-dependent manner. The ED_{50} was 0.69 mg·kg^{-1}. Naloxone 1 mg·kg^{-1} reversed the effects of morphine sulfate on CRD ($P = 0.0653$).

Comparison of the regression lines among groups

Comparing the regression line for %MPE in the intact (non-laminectomy) group to that for suppression of neuronal activity, it was found that the hypothesis of parallelism could not be rejected ($P = 0.15$) and that the hypothesis of coincidence of the regression lines could not be rejected ($P = 0.56$). Similar results were obtained comparing the suppression of neuronal activity regression line to that for %MPE in the laminectomy group ($P = 0.12$ for parallelism, $P = 0.55$ for coincidence) as well as for %MPE in the laminectomy group compared to %MPE in the intact (non-laminectomy) group ($P = 0.95$ for parallelism, $P = 0.13$ for coincidence). The regression line for each group reflects the effects of morphine on the measured response in each group. Since the regression lines were not proven to be significantly different, this is suggestive of a similar morphine effect in the three groups.

Effect of laminectomy on behavioral response to CRD in pentobarbital-anesthetized animals with or without morphine

We wanted to compare the effect of laminectomy in morphine-free animals. Since the measurement of %MPE requires the administration of morphine, we measured the threshold pressure of CRD to elicit visceromotor response (Fig. 4). In Fig. 4, using the *t*-test for independent (unpaired) samples, there was a significant difference ($P = 0.0068$) in the control values between the intact group (25.7 ± 1.2 mmHg) and the laminectomy group (32.7 ± 2.1 mmHg). However, morphine administration was associated with the loss of any significant difference between the two groups. Using repeated-measures ANOVA, there was no significant relation between the morphine dose and surgical procedure groups ($F[3,135] = 2.162$, $P = 0.095$), and no significant difference between the laminectomy and intact groups ($F[1,135] = 0.304$, $P = 0.584$). As shown in Fig. 4, the visceromotor threshold was significantly lower in the intact group than in the laminectomy group during the control study. When morphine was administered, the visceromotor thresholds in both groups increased to a similar level, confirming the results obtained with %MPE measurement.

Discussion

CRD has been widely used to elicit visceral nociception. Using this experimental model, the systemic administration of morphine has been shown to have a depressant effect on dorsal horn neurons [6–8] and aversive behavior [5]. However, because of the different conditions of animals, it has been difficult to directly compare the effect of drugs on the electrophysiological and behavioral responses. The present investigation has addressed this problem by utilizing the same level of anesthesia.

In the present investigation, as shown in the dose-response regression line of the morphine electrophysiological experiments, the systemic administration of morphine sulfate suppressed the evoked activity of the

visceral dorsal horn neurons in a dose-dependent manner (Fig. 3) with an ED_{50} of $0.69\,mg \cdot kg^{-1}$. This is in accordance with the results by Ness and Gebhart [7] who reported that morphine produced a dose-dependent, naloxone-reversible inhibition of both spontaneous activity and/or neuronal responses during CRD. Since the regression lines were not proven to be significantly different, we assumed that there was no difference in the ED_{50} for the electrophysiological and behavioral experiments. Another important finding is that a behavioral response to CRD and a neurophysiological response to the same stimulus are suppressed in a similar fashion by morphine.

Considering the effect of nocigenic inhibition [9,10] or DNIC [11], it is possible that noxious stimuli applied to another part of the body may increase pain thresholds at stimulus-applied sites [17–19]. The present study showed that the threshold at which a visceromotor response is elicited by CRD was lower in the intact group than in the group of animals that had undergone a laminectomy under a same level of pentobarbital anesthesia. It was likely that the activation of an endogenous pain control system was responsible for this difference in baseline thresholds although this was not verified in the present study.

The results of the present investigation are in accordance with the hypothesis that a laminectomy increases the threshold for visceromotor response to CRD. However, when the doses of morphine sulfate were administered, the visceromotor thresholds in both groups increased to a similar level. Thus, the systemic administration of morphine eliminated this difference in thresholds between the laminectomy group and the intact group observed in the baseline study. The elevation in the threshold for CRD observed after morphine administration is in accordance with the results shown by Ness and Gebhart [5] who noted that morphine produced a dose-dependent inhibition of visceromotor responses to CRD. However, the results are in contrast with those of Hartell and Headley [12] who demonstrated that when the degree of surgical intervention was increased, the reflex response to a uniform mechanical pinch stimulus was facilitated. It is difficult to explain the differences in the results. However, the difference in experimental methodology such as mode of stimulation and involvement of somatic nociception rather than visceral nociception may be the cause of the differences.

Ness and Gebhart [6] demonstrated that the neurons responsive to CRD could be separated into four groups based upon their response to an 80-mmHg, 20-s CRD: (1) short latency-abrupt (SL-A) neurons, (2) short latency-sustained (SL-S) neurons, (3) long latency neurons, and (4) inhibited (INHIB) neurons. All the neurons studied in this experiment abruptly terminated responses following the termination of the stimulus. Therefore, they were similar to the short-latency abrupt neurons as defined by Ness and Gebhart [6,8], although the latency was not short because of the graded increase of pressure used for the stimulus in this study.

In the past, it has been unclear to what extent the suppression of spinal neuronal activity demonstrated in the electrophysiological study contributes to the overall antinociceptive action as determined in the behavioral experiment. The importance of the present study is the fact that this is a comparison of behavioral and electrophysiological studies utilizing the same stimulus parameter under a similar level of anesthesia.

Thus, having conducted both behavioral and electrophysiological experiments under the same level of anesthesia utilizing the same method of stimulation, the results of the present investigation have demonstrated that the results obtained by the two different methods of investigation are comparable. This finding has a significant bearing on the importance of these two basic science experiments, both of which are needed as preclinical studies for the advancement of spinal analgesia. It points out the importance of both methods of investigation, one dealing with the single-neuronal activity concerned with sensory processing, and the other examining the responses of intact animals which involve motor function. We have also succeeded in demonstrating the effects of surgical intervention on the processing of visceral nociception. Although surgical intervention such as laminectomy affects the threshold values or CRD for visceromotor responses, the laminectomy plays an insignificant role when an adequate amount of morphine is administered.

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