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Lamina-specific Suppression of Dorsal-horn Unit Activity by Morphine Sulfate

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The effects of morphine sulfate on single-unit activities of various dorsal-horn Rexed laminae were studied using an extracellular microelectrode recording technique in decerebrate spinal cats. Morphine sulfate, 0.5, 1, and 2 mg/kg, iv, suppressed in a dose-related manner spontaneous single-unit activities in Rexed laminae I and V, known to respond principally to noxious stimuli, but did not affect spontaneous activities in laminae IV and VI, known to respond to non-noxious stimuli. Morphine sulfate, 1 mg/kg, iv, also suppressed unit activities of laminae I and V evoked by noxious cutaneous stimuli by 35.5 ± 7.1 and 48.2 ± 4.0 ($\bar{x}$ ± 1 SE) per cent, respectively. The selective action of morphine on dorsal horn nociceptors may partially explain the analgesic action of morphine at the spinal level. (Key words: Analgesics, narcotic: morphine; Spinal cord: morphine.)

WHILE IT IS GENERALLY AGREED that morphine and its surrogates have no significant effect on peripheral nerves,[1,2] their mode and site of action centrally remain obscure.[3] They could act supraspinally, at the spinal level, or at both levels. Data on the effect of morphine supraspinally remain inconclusive.[4–14] There are, however, indications that morphine and related compounds have significant effects on the spinal cord. For instance, Wikler[15] demonstrated in spinal cats that morphine sulfate, 2–15 mg/kg, iv, selectively suppressed the responses to noxious stimuli, while the stretch reflexes (knee and ankle jerks) remained unchanged or were slightly enhanced. Koll *et al.*[16] also demonstrated in decerebrate and spinal cats that ipsilateral "nociceptive," "post-delta," and C-flexion reflexes were strongly depressed by "analgesic" doses of morphine sulfate (0.3–0.4 mg/kg). Despite these reports, however, there are no data on the effects of narcotics on activity and function of cellular elements within the spinal cord comparable to those available for barbiturates,[17] inhalational anesthetics,[18–21] and ketamine hydrochloride.[22,23]

We have shown that nitrous oxide[21] and ketamine hydrochloride[23] exert lamina-specific suppression of dorsal-horn unit activities. We conclude that a portion of the analgesic action of these agents is determined at the spinal level by differential suppression in dorsal horn laminae I and V of the activities of cells which respond primarily to noxious peripheral stimuli. The present study was undertaken to determine whether morphine sulfate acts at the spinal-cord level and whether such action is similarly directed specifically toward individual Rexed laminae. Single units whose spontaneous activity and evoked activity were studied were related to their various Rexed laminae by physiologic and anatomic criteria. Strict controls for physiologic status were adhered to throughout the experiment. A preliminary report has been published.[24]

Methods

Details of the experimental methods have been reported.[21,23] Procedures specific to the present investigation are as follows. Forty cats of either sex, weighing 3 to 4 kg, were used. Halothane, nitrous oxide, and oxygen anesthesia was used for tracheostomy, bilateral carotid-artery ligation, cannulation of the right femoral artery and vein, and laminec-

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TABLE 1. Effects of Morphine Sulfate (1 mg/kg iv) on Single-unit Activity (Percentage Changes (− Decrease, + Increase) Compared with Control Values

	Spontaneous Activity (Per Cent ± 1 SE)	Evoked Activity (Per Cent ± 1 SE)
Lamina I	−17.6 ± 7.3 $P < 0.05$	−35.5 ± 7.1 $P < 0.05$
Lamina IV	− 0.7 ± 4.5*	
Lamina V	−37.5 ± 5.9 $P < 0.01$	−48.2 ± 4.0 $P < 0.01$
Lamina VI	+ 2.1 ± 3.4*	

* Statistically not significant.

tomy. Each animal was rendered decerebrate and unconscious by bilateral electrolytic lesions in the midbrain reticular formation and the spinal cord was transected at L1–L2. Animals were then ventilated with 100 per cent oxygen using a volume-cycled ventilator connected to a nonrebreathing system. Femoral arterial pressure, endotracheal end-tidal P_{CO_2}, EKG, pulse rate, and rectal and spinal cord temperatures were recorded continuously and kept within physiologic limits. Direct arterial blood-gas analysis was performed from time to time; the ranges of P_{O_2}, P_{CO_2}, and *p*H were 300–500 torr, 32–36 torr, and 7.30–7.45, respectively. A glass rod platinum-sheathed Transidyne "Microtrode" microelectrode with a 1–2-micron exposed tip was then inserted by a hydraulic micromanipulator into the lumbar spinal cord near the L7 root entry zone. Neurons were characterized by their evoked responses and spontaneous firing patterns. Signals were recorded through a differential FET AC preamplifier on magnetic tape and were simultaneously monitored on a cathode-ray oscilloscope.

The pulsatile spontaneous activity of a single unit was counted electronically and the average frequency was displayed on a polygraph. Units were observed for 15 to 30 minutes after isolation to obtain a stable firing pattern and to control the effect of transient tissue distortion produced by insertion of the microelectrode. A 15-minute control period was then recorded, following which the effect of morphine upon spontaneous unit activity was studied by administration of 1.0 mg/kg morphine intravenously over a 30-second period. Unit activity was followed until spontaneous activity returned to control values. This took approximately 15–30 minutes.

The modality and receptive field characteristics of the cells recorded were studied prior to administration of morphine and at the time of recovery of cell activity from the effects of morphine. Electrolytic lesions placed through the recording microelectrode (DC current 20–50 microamperes for 10 to 20 seconds) produced histologic findings similar to those reported previously.[21,23] Such

TABLE 2. Salient Features of Physiologic Lamination of the Dorsal Horn of the Feline Lumbar Spinal Cord (Summary of Characteristics of Rexed Laminae)

	Spontaneous Activity	Receptive Field	"Modality"
Lamina I	Slow	Large	High-threshold cutaneous; thermal
Lamina II	None		
Lamina III	None (brief bursts)	Small	Low-threshold cutaneous
Lamina IV	Bursts and relative silence	Small–large	Low-threshold cutaneous; pressure; pinch; ethyl chloride
Lamina V	Bursts and steady firing	Large	High-threshold cutaneous; thermal; visceral
Lamina VI	Maintained bursts		Proprioceptive

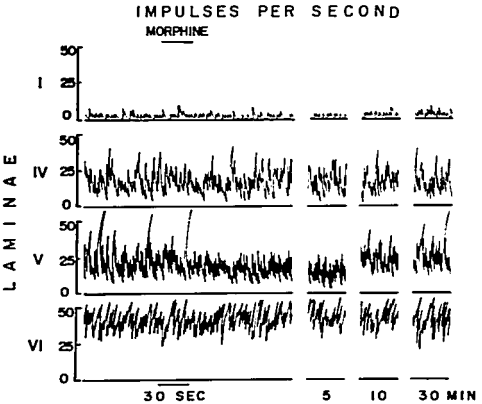

FIG. 1. Polygraph tracings of mean frequency (impulses/sec) of unit spike activity of laminae I, IV, V, and VI, before, during and after intravenous injection of morphine sulfate, 1 mg/kg.

lesions are destructive and reveal information about remaining cells only, but they localize anatomic locations of electrode tips within spinal cord layers.

Placing an alligator clamp in the center of the receptive field of nociceptors maintained the cellular firing frequencies of laminae I and V at a constant and elevated rate for 30–40 minutes. This technique was used to facilitate the study in some experiments.

To obtain dose–response information, an additional 14 animals were studied, three animals each with recordings from laminae I and IV, and four animals each with recordings from laminae V and VI. Following observation during the control period, morphine, 0.5 mg/kg, was administered iv, and the response followed for 30 minutes. A second dose of morphine, 1.0 mg/kg, was then administered, and the response again followed for 30 minutes. A third dose of morphine, 2.0 mg/kg, was then administered, and the response followed as before.

The statistical program used was STAP-12, DECUS 12–34, written by Urs R. Wyss of the University of Zurich. Spontaneous unit activity monitored on an external oscilloscope was presented to the program via an analog–digital converter input for 30 seconds during the control period, 5 minutes after injection of morphine, and during the recovery period. A subroutine (ICONIT) permitted computation of the time of occurrence of the maximal value of any spike potential above a given threshold. A second subroutine (SORTER) displayed an amplitude histogram of spike potentials from which spikes of specified size could be selected and trains composed of these spikes alone constructed. In this manner selection of single units could be performed. Spike intervals were stored in sequence on digital magnetic tape by a third subroutine (TRALIB) and ultimately retrieved from tape and used as data for a computation subroutine (STAPAR). Statistical parameters derived with the aid of STAPAR included the mean frequency. The significances of the mean values so obtained during the control period, following administration of morphine, and during the recovery period were assessed by Student's t test (table 1).

Spike interval histograms and burst interval histograms were compiled according to the method described previously.[31]

Results

The salient features of physiologic characterization of the lamination of the dorsal horn utilized in this study were previously reported[21,23] and are summarized in table 2.

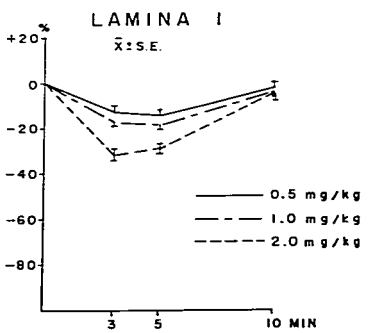

FIG. 2. Dose–response curves of the effects of morphine, 0.5, 1.0, and 2.0 mg/kg, on spontaneously firing single-unit activity of lamina I.

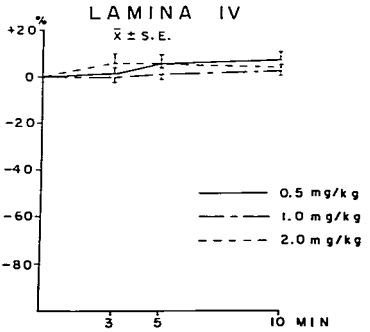

FIG. 3. Dose–response curves of the effects of morphine, 0.5, 1.0, and 2.0 mg/kg, on spontaneously firing single-unit activity of lamina IV.

The overall characteristics of the spontaneous and gross modality of responsiveness were correlated with the anatomic lamination of Rexed.[25]

LAMINA I (EIGHT CATS)

During the control study, while animals were ventilated with 100 per cent oxygen, the average rate of spontaneous activity was 9.8 ± 1.5 ($\bar{x} \pm 1$ SE) per second. Cells responded by increasing firing frequency only following high-intensity cutaneous stimulation, thermal stimulation, and extreme deformation of joints. As shown in figure 1 and table 1, morphine, 1 mg/kg, iv, depressed the spontaneous activity of lamina I cells by 17.6 ± 7.3 ($\bar{x} \pm 1$ SE) per cent of control values. Recovery of spontaneous activity began 10–15 minutes after administration of morphine and reached control values in another 15–30 minutes. Most of the units studied were mechano- and thermal receptors only.

LAMINAE II AND III

Cells in laminae II and III, having smaller cellular size, had no spontaneous unit activity whose potentials could be isolated from background noise with the technique used, except for brief bursts of single-unit activity evoked in lamina III by hair movement and light tactile stimuli.

LAMINA IV (NINE CATS)

The spontaneous activity of lamina IV cells was characterized by bursts in groups with interspike intervals of 2 to 5 msec with intervening relative silence. The average firing frequency of cells in lamina IV was 17.2 ± 1.3 ($\bar{x} \pm 1$ SE) per second. As shown in figure 1, morphine, 1 mg/kg, iv, did not suppress the spontaneous firing frequency of lamina IV cells. Statistical analysis of the unit activity showed that lamina IV spontaneous activity 5 minutes after iv administration of morphine, 1 mg/kg, was 99.3 ± 4.5 ($\bar{x} \pm 1$ SE) per cent of control values (table 1).

LAMINA V (NINE CATS)

Lamina V cells could be identified by a sudden loss in cell responsiveness to bending of hairs. The cells responded mainly to high-intensity stimuli applied to the receptive field. Their spontaneous activity was characterized by bursts followed by steady firing, with an average frequency of 26.1 ± 3.7 ($\bar{x} \pm 1$ SE) per second. As shown in figure 1,

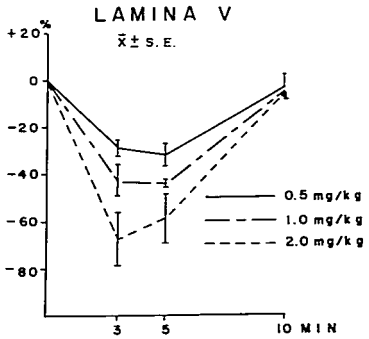

FIG. 4. Dose–response curves of the effects of morphine, 0.5, 1.0, and 2.0 mg/kg, on spontaneously firing single-unit activity of lamina V.

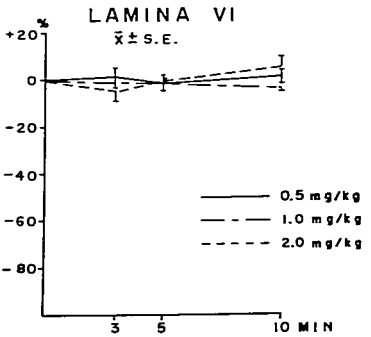

FIG. 5. Dose–response curves of the effects of morphine, 0.5, 1.0, and 2.0 mg/kg, on spontaneously firing single-unit activity of lamina VI.

morphine, 1 mg/kg, iv, markedly suppressed the spontaneous activity of lamina V cells. Statistical analysis of the unit activity of lamina V cells showed that spontaneous activity 5 minutes after administration of morphine, 1 mg/kg, iv, was suppressed by 37.5 ± 5.9 ($\bar{x}$ ± 1 SE) per cent (table 1) and returned to control values in 20–40 minutes.

LAMINA VI (EIGHT CATS)

Cells located in the most ventral portion of the dorsal horn were characterized by their greatly increased spontaneous activity in maintained bursts, having an average frequency of 42.5 ± 7.3 ($\bar{x}$ ± 1 SE) per second. The cells did not respond to cutaneous stimuli but responded solely to proprioceptive stimuli. As shown in figure 1, morphine, 1 mg/kg, iv, had no discernible effect on lamina VI cellular activity. Statistical analysis of unit activity of lamina VI cells showed that their spontaneous activity 5 minutes after administration of morphine, 1 mg/kg, iv, was 102.1 ± 3.4 ($\bar{x}$ ± 1 SE) per cent of control values (table 1).

DOSE–RESPONSE CURVES

As shown in figures 2, 3, 4, and 5, significant suppression of unit activities in a dose-related manner (0.5, 1.0, and 2.0 mg/kg) was demonstrated in laminae I and V cells but not in laminae IV and VI cells.

EFFECT OF MORPHINE ON EVOKED SINGLE-UNIT ACTIVITY

High-threshold central mechanoreceptors adapt slowly and could readily be maintained at a steady firing frequency during constant stimulation of their receptive fields. It was found that by placing an alligator clip over the center of the receptive field the activities of cells in laminae I and V could be maintained at a steady rate for 20–40 minutes.

Lamina I (Three Animals)

Morphine, 1 mg/kg, iv, suppressed the evoked unit firing frequency by 35.5 ± 7.1 ($\bar{x}$ ± 1 SE) per cent (table 1). Recovery occurred in 20–40 minutes.

Lamina V (Three Animals)

Morphine, 1 mg/kg, iv, suppressed the evoked unit firing frequency by 48.2 ± 4.0 ($\bar{x}$ ± 1 SE) per cent (table 1), and recovery occurred in 20–40 minutes.

Evoked single-unit activity in laminae IV and VI was not studied; lamina IV cells

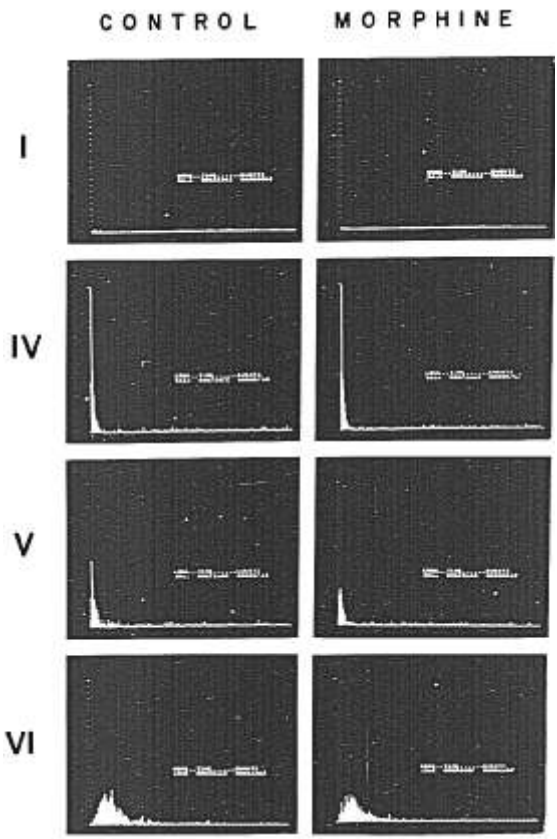

FIG. 6. Spike interval histogram of single-unit activity in laminae I, IV, V, and VI during a control period and 5 minutes after iv administration of morphine sulfate, 1.0 mg/kg. *Abscissa:* time base between successive spikes is 1 msec. *Ordinate:* the total number of spikes of that interval (one dot refers to five spikes).

rapidly adapt to low-threshold cutaneous stimuli; lamina VI cells have no cutaneous input.

The spike-interval histogram pattern (fig. 6) revealed lamina I to be firing infrequently in long intervals, lamina IV to be firing in short intervals, lamina V to be firing in short intervals more dispersed than those in lamina IV, and lamina VI to be firing in dispersed intervals with much more rapidity than lamina I. Administration of morphine produced marked changes in laminae I and V but little change in laminae IV and VI. The spike-interval histogram of lamina I showed a marked decrease in number of spikes, and that of lamina V showed a marked decrease in the number of shorter intervals.

The burst-interval histogram pattern (fig. 7) revealed lamina I cells firing without bursts, lamina IV cells firing in shorter intervals,

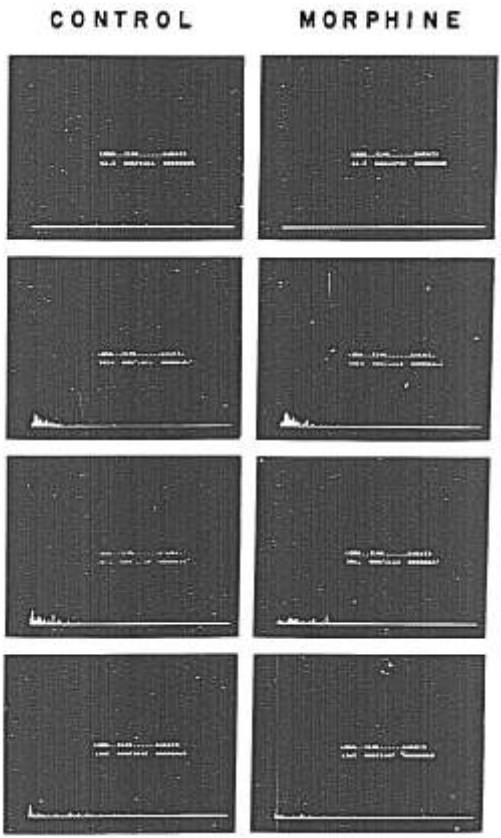

FIG. 7. Burst interval histogram of single-unit activity in laminae I, IV, V, and VI during a control period and 5 minutes after administration of morphine sulfate, 1 mg/kg. *Abscissa:* time base between successive bursts is 1 msec. *Ordinate:* the total number of bursts of that interval (one dot refers to five bursts).

lamina V cells firing in maintained bursts, and lamina VI cells firing regularly with very little burst activity. Morphine exerted a significant effect upon the burst-interval histogram of lamina V cells: a marked decrease in the number of shorter inter-burst intervals, without significant effect on the burst-interval histograms of the remaining laminae.

The effects of morphine on spike-interval histograms and burst-interval histograms of laminae IV, V, and VI are similar to those of nitrous oxide (Taub *et al.*[31]). The information on lamina I was not included in our previous report.

Discussion

The neurophysiologic basis of the analgesic action of morphine has been reviewed extensively,[4,28] yet there has been no defini-

tive evidence for the sites and mode of action of morphine and its surrogates, except perhaps in the studies of Wikler[15] and Koll *et al.*,[16] which suggest that spinal-cord function might be involved.

Theoretical considerations indicating that the locus of the depressant action of morphine may be on interneurons were advanced by Wikler,[15] who demonstrated that the responses to nociceptive stimuli (flexor and crossed extensor reflexes) were markedly depressed, while the responses to stretch (knee and ankle jerks) were either not affected or were slightly augmented by morphine sulfate, 2–15 mg/kg, administered intravenously in two cats. Koll *et al.*[16] demonstrated in decerebrated and spinal cats that ipsilateral "nociceptive," "post-delta," and C-flexion reflexes were strongly depressed by morphine sulfate, 0.3–0.4 mg/kg, iv. The results of the present study demonstrate specific depression of central nociceptors within the spinal cord. Anatomically, cells in Rexed laminae I and V are known to receive small myelinated and unmyelinated fibers of peripheral nerves.[27,28] Physiologically, they have also been shown to receive primarily high-intensity nociceptive input.[17,27,28,29]

The doses of morphine used in the present study are "analgesic." McKenzie and Beechey[5] studied the behavioral changes in cats after iv administration of morphine, 1–2 mg/kg, and found that analgesia was the most prominent action observed, with very few side effects. They noted that the effects of morphine on behavior changed over a fairly narrow dose range. At 4–6 mg/kg, iv, bizarre motor activity became dominant. The atypical response of cats to morphine, however, does not necessarily vitiate application of the data obtained in the present study to other mammals, as at smaller doses analgesia was the most prominent action observed.[5] Our demonstration of selective suppression of Rexed laminae I and V cellular activity by an analgesic dose of morphine strongly indicates that sites of the analgesic action of morphine may be at a spinal level, although the possibility still exists that cellular activity of further rostral relay stations may be more suppressed. The same dose of morphine did not depress spontaneous single-unit activity of cells in laminae IV and VI, which respond to light tactile cutaneous input and to proprioceptive input, respectively.

Since vital signs were kept within the range of physiologic normality, the specific suppressive effects of morphine demonstrated in the present study were not side effects of morphine. Supraspinal effects of morphine may be excluded in these studies, since the spinal cord was transected at the upper lumbar level, without interfering with the blood supply to the recording sites in the lower lumbar segments.

Results of studies of the effects of morphine on supraspinal levels are inconclusive. Chin and Domino[6] investigated the effects of morphine (0.2–2 mg/kg, iv) on certain midbrain responses to dental stimulation in dogs and observed enhancement of response amplitude in many of their recording sites, while McKenzie and Beechey[5] showed that in cats morphine, 2 mg/kg iv, selectively depressed somatic evoked responses in peripheral areas of the midbrain.

Although Fujita *et al.*[7,8] and Matsumura *et al.*[9] found that morphine inhibited cortical and intraspinal (T1–T2) potentials evoked by splanchnic afferent stimulation, the barbiturate their cats received as a basal anesthetic may have affected responsiveness to morphine; moreover, the doses of morphine used by these investigators (6–8 mg/kg) are well above those necessary for analgesia and may produce side-effects.

Other studies of the analgesic site of action of morphine include the report of Sinitsin,[10] who showed that morphine blocked impulses transmitted along the somatic ascending pathways to the association cortex and to the reticular formation, while leaving conduction of excitation along the classic ascending pathways of somatic sensitivity intact. Straw and Mitchell[11] also showed that evoked responses in periaqueductal gray matter are depressed by morphine, while primary somatosensory potentials are enhanced by morphine.[12] Satoh and Takagi[13] postulated that morphine facilitates the function of the lower brain stem, which in turn inhibits spinal sensory transmission, and that large doses of morphine are needed to exert a direct suppressive action at the spinal

level. Their method, however, differed from the present study in that Satoh and Takagi[13] did not utilize microelectrode recording technique to investigate unit cellular activity, and in that the parameters they observed were resistant to pentobarbital, whereas single-unit activities of dorsal horn neurons of the feline lumbar spinal cord are suppressed by pentobarbital.[17]

Studies of the effect of morphine on the electroencephalogram have also been inconclusive. Leimdorfer[14] showed decreases in frequency and voltage of the EEG, while Straw and Mitchell[11] showed no significant change in the EEG following morphine administration.

The present study demonstrates that an analgesic dose of morphine sulfate has a specific, statistically significant depressant effect upon the mean frequency of spontaneous and evoked single-unit activity of dorsal horn neurons of the feline lumbar spinal cord in cells of Rexed laminae I and V which respond primarily to nociceptive stimuli. The same dose of morphine does not suppress single-unit activity of cells in laminae IV and VI, which do not respond differentially to noxious stimuli. This selective suppressive action of morphine, demonstrated to occur at the spinal level may, in part, explain the analgesic action of morphine. This differential suppression of central nociceptors is similar to the effect of nitrous oxide on the lumbar spinal cord[21] and on the trigeminal nucleus caudalis,[30] as well as to the effect of ketamine hydrochloride on the lumbar spinal cord.[22,23]

Besson *et al.*[32] have recently studied the depressive effect of a morphinomimetic drug (phenoperidine) on a single dorsal horn lamina (lamina V). They did not determine whether this agent acts in a lamina-specific fashion,[21,23,24] and dose–response data were not presented.

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Neonatology

FETAL LUNG MATURITY Amniotic fluid total phospholipid phosphorus (TPP) levels are quicker and easier to measure than quantitative lecithin phosphorus (Lec. P) levels for assessing fetal maturity. Between 30 weeks gestation and term, there is a eightfold increase in TPP and a tenfold increase in Lec. P. At delivery a high correlation is found between simultaneous measurements of TPP and Lec. P. Low levels of either TPP or Lec. P are associated with an increased risk of associated RDS. TPP levels greater than 0.14 mg/100 ml are recommended as evidence of fetal pulmonary maturity. (*Nelson, G.H.: Determination of Amniotic Fluid Total Phospholipid Phosphorus as a Test for Fetal Lung Maturity. Am J Obstet Gynecol 115: 933–941, 1973.*)