

Disruption of the Rhythmic Activity of the Medullary Inspiratory Neurons and Phrenic Nerve by Fentanyl and Reversal with Nalbuphine

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The effects of intravenous administration of fentanyl (50 and 100 $\mu\text{g}/\text{kg}$) on the discharge activity of the medullary inspiratory neurons and of the phrenic nerve were studied following vagotomy in nine decerebrate, paralyzed mechanically ventilated cats. In six cats, the inspiratory neurons explored were in the dorsal respiratory group (DRG) associated with the nucleus of the tractus solitarius (NTS), while in the remaining three, they were in the ventral respiratory group (VRG). In the former group, the rhythmic discharge of the inspiratory neurons was disrupted by fentanyl and replaced by a continuous discharge superimposed with irregularly occurring bursts. These changes were also reflected by the phrenic nerve discharge. Inspiratory neuronal activity increased significantly ($P < 0.05$) at 1 and 5 min after completion of fentanyl injection. Disruption of the rhythmic activity of the inspiratory neurons and its replacement by a continuous and irregular discharge may lead to sustained contraction of inspiratory muscles and cessation of respiration. In the VRG, the activity of the inspiratory neurons was totally abolished by fentanyl. Thus, it appears that different groups of medullary inspiratory neurons have differential sensitivity to fentanyl. Nalbuphine, an opiate agonist-antagonist, restored the normal pattern and magnitude of the activity of the inspiratory neurons. (Key words: Anesthetics, intravenous: fentanyl. Antagonists, narcotic: nalbuphine. Brain: decerebration; inspiratory neuron; medulla oblongata.)

OPIATES DEPRESS RESPIRATION,¹⁻⁴ and decrease the ventilatory response to carbon dioxide inhalation.⁵⁻⁷ Since the brainstem respiration-related structures contain a high density of opiate receptors, and a high concentration of the endogenous opioid ligand enkephalin,⁸⁻¹³ it is reasonable to attribute opiate-induced respiratory depression to effects on the brainstem respiratory neurons. However, the direct effects of opiates on the respiratory neurons have not been adequately studied. Ngai showed that, in decerebrate cats, morphine and meperidine depress the responsiveness of the medullary respiratory centers to electrical stimulation without impairing the recruiting mechanisms.¹⁴ Denavit-Saubié *et al.* applied morphine and

methionine-enkephalin iontophoretically on the respiratory neurons of the medulla and pons.¹⁵ Morphine and enkephalin markedly reduced the spontaneous discharge and glutamate-enhanced firing of the majority of cells studied. Some cells, however, showed excitation following application of morphine, but not enkephalin.¹⁵

In the present investigation, the effects of intravenous (iv) administration of fentanyl (50 and 100 $\mu\text{g}/\text{kg}$) on the medullary inspiratory neurons and phrenic nerve of cats were studied. Fentanyl produced marked disruption of the rhythmic activity of the neurons and of the phrenic nerve. Nalbuphine hydrochloride, an opiate agonist-antagonist, restored normal activity of the neurons and of the phrenic nerve.

Material and Methods

Nine cats of either sex, weighing 2.5–3.5 kg, were anesthetized with halothane and nitrous oxide in oxygen. Following tracheostomy, femoral artery and vein cannulation, and bilateral cervical vagotomy, the cats were fixed in a stereotaxic instrument (David Kopf Instruments, Tujunga, CA). Decerebration was performed according to the previously described method.¹⁶ After decerebration, halothane and nitrous oxide were turned off, and the cats were paralyzed with intravenous gallamine triethiodide and ventilated with a Harvard ventilator using oxygen at 2 l/min. Posterior fossa craniotomy was done to expose the medulla oblongata. The phrenic nerve was exposed in the neck and kept in a pool of paraffin to prevent drying. Details of the surgical preparation have been given elsewhere.¹⁷ Bipolar silver wire electrodes were used to monitor the phrenic neurogram which was recorded on a polygraph (Grass Instrument Company, Quincy, MA) and a cathode ray oscilloscope (CRO) (Tektronix, Beaverton, OR). In six cats, a tungsten microelectrode (Fredrick Haer and Company, Brunswick, ME) with a tip diameter of 1 μm and an impedance of 10 megohm was inserted into the dorsal respiratory group (DRG) of the medulla in the region of the nucleus of the tractus solitarius (NTS) with the aid of a hydraulic microdrive (David Kopf Instruments). The microelectrode signal was amplified, passed through an amplitude discriminator (Quasitronics, Inc., Pittsburgh, PA), and monitored on the CRO. Further, the microelectrode signal was fed into a Grass audiomonitor. Also, the output from the ampli-

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TABLE 1. Location of Medullary Inspiratory Neurons Studied and Dose of Fentanyl Given in Nine Cats

Number of Cats	Location of Neurons	Dose of Fentanyl
3	DRG	50 $\mu\text{g}/\text{kg}$
3	DRG	100 $\mu\text{g}/\text{kg}$
3	VRG	50 $\mu\text{g}/\text{kg}$

DRG = dorsal respiratory group; VRG = ventral respiratory group.

tude discriminator was integrated and recorded on the Grass polygraph as spikes per second or impulses per second. Cells whose discharge activity was synchronous with that of the phrenic nerve were considered inspiratory neurons. Arterial blood pressure (ABP) and tracheal pressure were recorded on the Grass polygraph. Thus, continuous recording of the discharge activity of the inspiratory neurons (spikes/s), phrenic neurogram, ABP, and tracheal pressure was made on the polygraph, while the inspiratory neuronal activity and phrenic neurogram were also simultaneously displayed on the CRO. Rectal temperature was monitored by a thermistor and kept between 37 and 38° C using a servo-controlled water mattress and heat lamps. End-tidal CO₂ was monitored by an infra-red gas analyzer (Beckman Instruments, Schiller Park, IL) and maintained about 4%.

After a time lapse of at least 1½ h from termination of halothane and nitrous oxide, baseline values of the recorded variables were obtained, and fentanyl, 50 $\mu\text{g}/\text{kg}$ (three cats, group 1) or 100 $\mu\text{g}/\text{kg}$ (three cats, group 2) was given intravenously over a 2-min period (table 1).

In order to counteract the effects of fentanyl, nalbuphine hydrochloride, an opiate agonist antagonist, 0.1 mg/kg, was given intravenously; 6 min after fentanyl to one cat, and 10–20 min after fentanyl to the remaining five.

In three other cats, the microelectrode was inserted into the medulla, lateral to the NTS, and advanced ventrally such that the tip was 1500–2000 μm ventral to the

NTS and recorded the activity of the ventral respiratory group (VRG) neurons. After finding the inspiratory neurons at this depth, fentanyl, 50 $\mu\text{g}/\text{kg}$, was given intravenously. In this group, nalbuphine was given 45–50 min after fentanyl administration. Table 1 shows the location of the cells studied, and number of cats in each group.

Fentanyl was prepared in 0.9% NaCl solution such that each milliliter contained 50 μg . Prior to administration of fentanyl, an equal volume of 0.9% NaCl solution alone was given intravenously to serve as control. Student's *t* test was used to analyze data. *P* values less than 0.05 were considered statistically significant.

Results

Fentanyl changed both the pattern and the magnitude of the discharge activity of the inspiratory neurons of the NTS. These changes were also reflected by changes in phrenic nerve activity. The rhythmic activity of the inspiratory neurons was disrupted by fentanyl and replaced by an irregular type of discharge. The inspiratory neuronal activity is normally characterized by discharge during inspiration and silence during expiration, as is the case with the phrenic nerve activity (fig. 1). However, after fentanyl injection, the activity pattern was characterized by a continuous discharge superimposed with irregularly occurring bursts in five cats; the three cats of group 1 (fentanyl 50 $\mu\text{g}/\text{kg}$) and two of group 2 (fentanyl 100 $\mu\text{g}/\text{kg}$) (figs. 2, 3). In the remaining one cat of group 2 (fentanyl 100 $\mu\text{g}/\text{kg}$), the cell activity decreased, and remained so until nalbuphine was given 20 min after fentanyl. Analysis of the pooled data in these six cats revealed that the mean activity of the cells (spikes/s) was significantly greater ($P < 0.05$, paired *t* test) at 1 and 5 min after completion of fentanyl administration compared with the mean activity before fentanyl injection. The percent increase in the cells' activity at 1 and 5 min after fentanyl administration was 280 ± 15 and 130 ± 12 (mean \pm SEM), respectively. There was no statistically significant difference ($P > 0.05$, unpaired *t* test) between the mean activity of the cells of the two groups at 1 and 5 min after fentanyl administration. Ten minutes after fentanyl, analysis of the pooled data in five of the above six cats showed the cell's activity to be $85 \pm 20\%$ of the control (mean \pm SE, $P > 0.05$, paired *t* test). Since one of the cats of group 1 (*i.e.*, fentanyl 50 $\mu\text{g}/\text{kg}$) received nalbuphine 6 min after fentanyl administration, the pooled data at 10 min belonged to the other five cats.

In the three cats where inspiratory neurons were explored in the ventrolateral medulla (VRG), administration of fentanyl (50 $\mu\text{g}/\text{kg}$) totally abolished the activity of the inspiratory neurons. The activity reappeared after 25–30 min and reached control level (prefentanyl level) in 45–50 min (fig. 4).

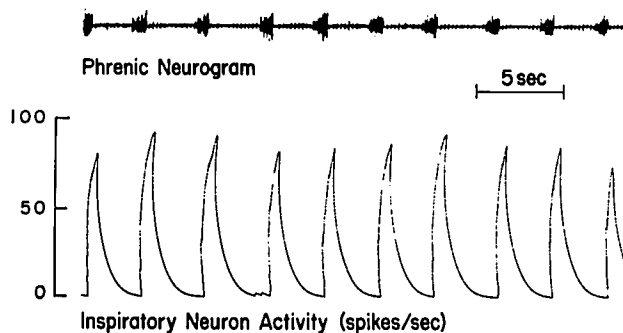
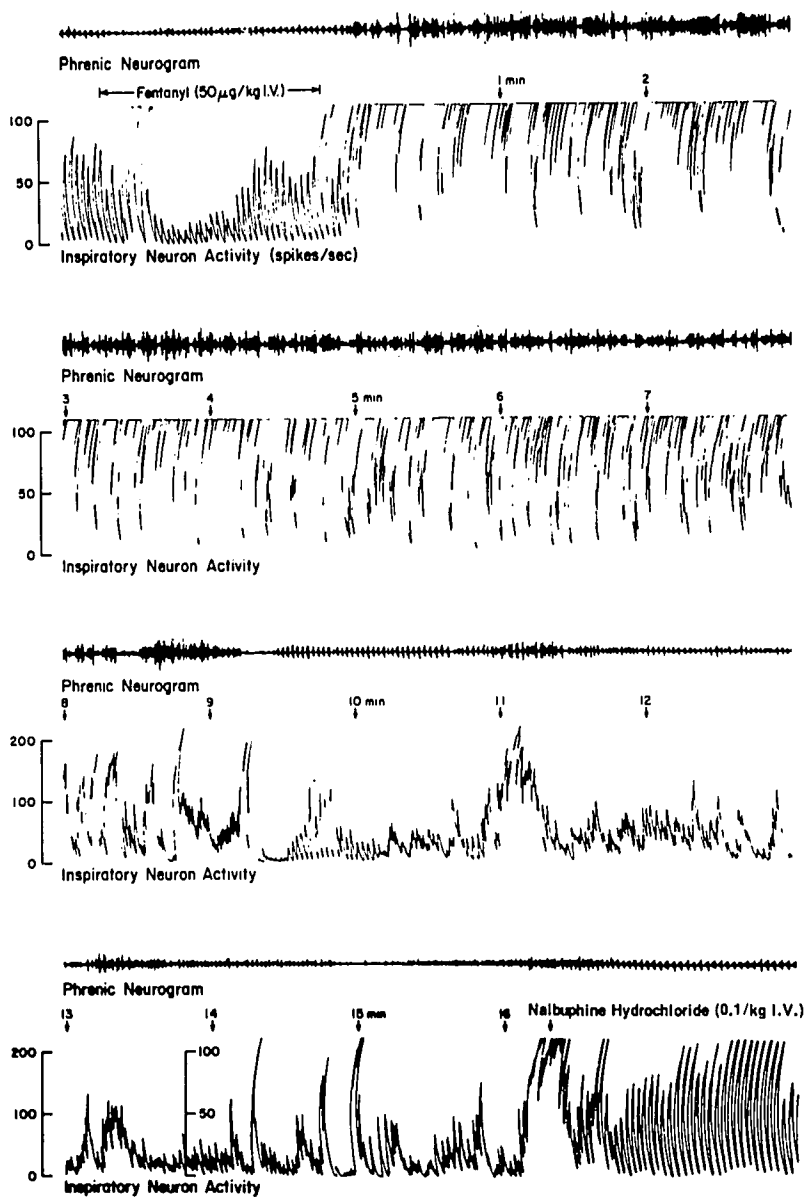


FIG. 1. Simultaneous polygraph recording of phrenic neurogram (upper trace) and integrated activity of an inspiratory unit (lower trace). Inspiratory neurons fire synchronously with phrenic nerve during inspiration, and are silent during expiration.

FIG. 2. Sequential polygraph recordings of phrenic neurogram and integrated activity of an inspiratory unit (spikes/s), showing the effects of intravenous administration of fentanyl (50 μ g/kg), and reversal with nalbuphine. The control period (before fentanyl) is characterized by rhythmic discharges of the phrenic nerve and the inspiratory neurons in synchrony. During the 2-min period of fentanyl injection, there is an initial short period of increased inspiratory neuronal activity followed by depression. After completion of fentanyl injection, the rhythmic activity of the phrenic nerve (upper trace of each pair) and of the inspiratory neurons (lower trace of each pair) was disrupted and replaced by irregular discharge. The inspiratory unit shows continuous activity (as reflected by the lack of return to zero activity or silence) superimposed with irregularly spaced bursts of discharge. About 9.5 min after fentanyl, the rhythmic activity of the phrenic nerve and inspiratory unit resumes transiently. About 16 min after fentanyl, administration of nalbuphine (0.1 mg/kg iv) restores the rhythmic activity of the inspiratory neurons and phrenic nerve. Note that the inspiratory neuron activity scale changes from 0–100 spikes/s to 0–200 spikes/s in some tracings, and from 0–200 spikes/s to 0–100 spikes/s in the middle of the last (bottom) tracing.



The ABP increased by 10–30% following administration of fentanyl, and returned to the prefentanyl control value within 3–10 min.

Administration of nalbuphine hydrochloride (0.1 mg/kg intravenously) restored the normal pattern and magnitude of the activity of the DRG cells and phrenic nerve (figs. 2, 3, 5). The latency of the response was 15–60 s. When nalbuphine was given, some cells were still irregularly hyperactive and some irregularly hypoactive. Nalbuphine reversed the irregular activity of the cells and restored the normal pattern of the activity. In two cats, a second dose of nalbuphine was necessary 10–12 min after the first dose to maintain the normal level of cells' activity.

When studying the effects of fentanyl on VRG neurons, we did not give nalbuphine so that spontaneous recovery of the cells' activity may occur. Once full recovery had occurred in 45–50 min, nalbuphine was given; 0.1 mg/kg iv, but added little to the cells' activity.

Discussion

The results indicate that fentanyl, in the doses administered, has profound effects on the pattern and magnitude of the activity of the medullary inspiratory neurons in cats. Because of prior vagotomy and decerebration, these effects are independent of possible actions on pulmonary receptors mediated vagally or higher brain struc-

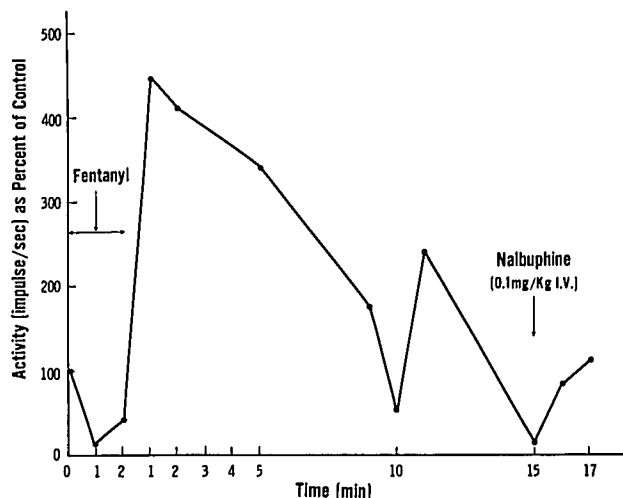


FIG. 3. Graphic presentation of the effect of fentanyl ($50 \mu\text{g}/\text{kg}$) on the discharge activity of an inspiratory unit. The ordinate shows the discharge activity (impulses/s or spikes/s) as percent of control, where 100 represents the control value. The activity decreases during the 2-min period of fentanyl injection, but increases tremendously to the first peak at 1 min after completion of fentanyl injection. A second peak appears at 11 min. The activity diminishes over the next 4 min to below the control value. Fifteen minutes after fentanyl, nalbuphine is given intravenously, which restores the unit activity to about normal.

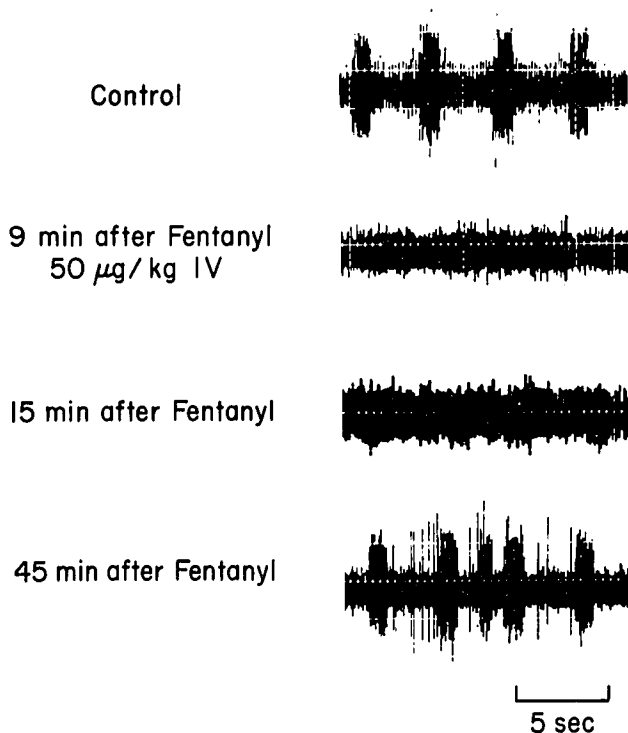


FIG. 4. Effect of fentanyl ($50 \mu\text{g}/\text{kg}$) on an inspiratory unit in the ventral respiratory group. The unit's activity is totally abolished by fentanyl. Full recovery occurred in 45 min. The effect of fentanyl on this unit is different from that on the units in the dorsal respiratory group.

tures. The effects seem to be due to direct action of fentanyl on brainstem respiratory neurons. The major concentrations of the brainstem respiratory neurons are the pontine respiratory group (PRG) in the rostral part of the pons, dorsal respiratory group (DRG) in the dorsomedial part of the medulla, and ventral respiratory group (VRG) in the ventrolateral part of the medulla.^{18,19} In the first six cats, the neurons explored and recorded from were in the DRG associated with the nucleus of the tractus solitarius.²⁰ In the last three cats, the neurons studied were in the VRG. VRG is composed of nucleus ambiguus,²¹ nucleus retroambiguus,²¹ and nucleus paraambiguus.²²

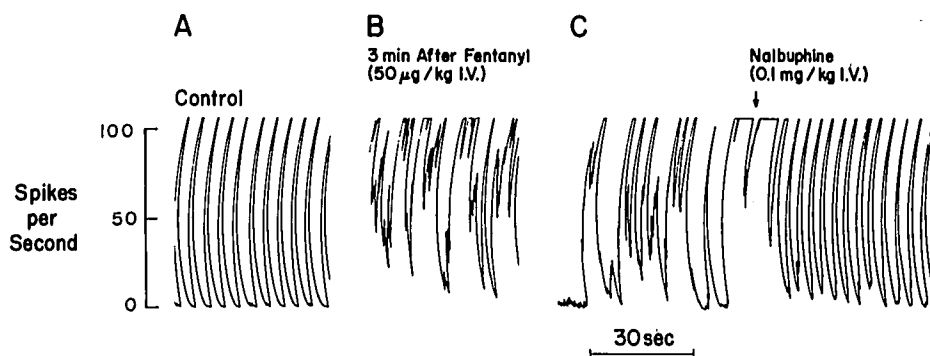
Our results indicate that there exists a differential sensitivity between cells of various respiratory groups to fentanyl, as indicated by transient but complete cessation of the discharge activity of the cells in the VRG *versus* excitation of the cells in the DRG.

In the DRG, on the basis of response to lung inflation, three types of inspiration-related cells have been identified; inspiratory-alpha (I-alpha),²³ inspiratory-beta (I-beta),²³ and pump cells (P-cells).²⁰ The P cells are silent in the absence of afferent input from the lungs, *e.g.*, after bilateral cervical vagotomy or in paralyzed animals without mechanical ventilation. Their activity closely follows lung inflation, and are assumed to be interneurons.²⁰ The DRG cells that we studied could not have been P cells, because vagotomy had been performed, and P cells in cats are silent following vagotomy. The I-alpha cells are affected by lung inflation such that the duration of their firing is shortened, although the slope of their firing frequency remains unchanged.²³ The axons of these cells project to the phrenic and external intercostal motoneurons of the spinal cord.¹⁹ The I-beta cells are stimulated by lung inflation such that the slope of their firing frequency is augmented by the afferent input from the inflated lung.²³ While some of the I-beta cells project into the spinal cord, the functional significance of these spinal projections is still unclear.¹⁹

The DRG neurons we studied could have been either I-alpha or I-beta cells. Our methodology does not allow to label them as one or the other.

The inspiratory neurons of the VRG in nucleus paraambiguus are called inspiratory-gamma (I-gamma) neurons to distinguish them from the I-alpha and I-beta neurons of the DRG.²³ The I-gamma neurons respond to lung inflation in a manner similar to the I-alpha neurons and their axons project to both phrenic and external intercostal motoneuron pools in the spinal cord.¹⁹ In the VRG, there are also a number of inspiratory neurons in the region of the nucleus ambiguus whose axons exit the brainstem along with other vagal efferent fibers and supply the laryngeal abductor (inspiratory) muscles *via* the recurrent laryngeal nerve.^{24,25}

FIG. 5. Disruption of the rhythmic activity of an inspiratory unit by fentanyl and reversal of fentanyl-induced changes by nalbuphine. Panel A shows the integrated activity of the inspiratory unit before fentanyl. Panel B depicts changes induced by fentanyl: the rhythmic activity has been replaced by an irregular and often continuous discharge. Panel C shows restoration of the normal pattern of activity by nalbuphine, administered 10 min after fentanyl injection.



In the medulla, there are also sympathetic neurons that show respiratory periodicity superimposed on their own tonic discharge activity.²⁶ Because the cells we studied were active during inspiration and silent during expiration, they could not have been sympathetic neurons.

The experiments were conducted on decerebrate cats in order to eliminate the need for background anesthesia, so that the effects of the test drug alone, *i.e.*, fentanyl, may be studied on respiratory neurons. Since the cats received muscle relaxant, decerebrate rigidity²⁷ was not an issue here. And because the mechanical ventilation before and after fentanyl administration was unchanged, the afferent impulses, resulting from the chest wall expansion, to the brainstem *via* the spinal cord ascending pathways should have remained unchanged before and after fentanyl. Decerebration, however, removes the conscious voluntary contribution to the act of breathing. It is possible that the DRG inspiratory neuronal activity and the phrenic nerve output would have been more intense if the cats were breathing spontaneously rather than being mechanically ventilated following fentanyl injection. With mechanical ventilation, P_{aCO_2} was normal while P_{aO_2} was increased above normal ($FI_{O_2} = 1$), whereas, with spontaneous breathing, one would expect hypercarbia and hypoxia owing to fentanyl-induced hypoventilation. Hypercarbia and hypoxia would stimulate inspiratory neurons, and, in the settings of our experiments, probably would have intensified inspiratory neuronal activity and phrenic output. As mentioned above, this is only a possibility and, because the cats were mechanically ventilated, our statement may be correct only inferentially.

The excitation of the inspiratory neurons by systemic administration of fentanyl was rather surprising, and may be related to the general excitation produced in cats by opiates. Our findings, however, are not without precedence. Denavit-Saubié *et al.* applied morphine and methionine enkephalin iontophoretically onto the brainstem respiratory neurons of cats while recording extracellularly.¹⁵ Morphine depressed 60% of the cells, excited 15%,

and had no effect on 25%. Methionine enkephalin depressed 65% of the cells, and had no effect on the remaining cells. The exact location of all the cells studied, *i.e.*, whether in the PRG, DRG, or VRG, was not specified by the authors.¹⁵

How can the observed effects of the intravenous injection of these doses of fentanyl on inspiratory neurons produce respiratory depression? The explanation is simple when fentanyl depresses the inspiratory neurons. Depression of the inspiratory neurons leads to reduction of the efferent impulses (efferent traffic) to the spinal cord inspiratory motoneurons, and, consequently, to the inspiratory muscles, resulting in respiratory depression. This explanation, however, does not seem valid when activity of inspiratory neurons is stimulated by fentanyl. Excitation of these neurons was characterized by continuous discharge superimposed with irregularly occurring bursts (fig. 2). This pattern of activity would cause continuous and amplified efferent traffic to the spinal cord inspiratory motoneurons, and, consequently, to the inspiratory muscles, resulting in sustained inspiration. Sustained inspiration would mimic apnea, and perceived clinically as "Tight Chest Syndrome." This explanation may be only part of the whole story, because we do not have information on the effects of fentanyl on the brainstem expiratory neurons, and, therefore, expiratory muscles. If fentanyl also causes excitation of the expiratory neurons, then expiratory muscles would contract and remain contracted, thus producing expiratory apnea and thoracoabdominal rigidity. In fact, Ngai showed that, in decerebrate vagotomized cats, breathing spontaneously, morphine, 2 mg/kg, produced a transient expiratory apnea followed by a slow rate of breathing with little change in tidal volume.¹⁴ In the present work, had the cats not been paralyzed and mechanically ventilated, they probably would have manifested apnea initially following fentanyl.

There are other examples of central nervous system response to fentanyl. Intravenous administration of fentanyl has been occasionally associated with convulsions in

humans (30–50 $\mu\text{g}/\text{kg}$)^{28,29} and with EEG seizure activity in cats (20–80 $\mu\text{g}/\text{kg}$) and rats (200 and 400 $\mu\text{g}/\text{kg}$).^{30–32} Convulsion^{28,29} and seizure activity^{30–32} are manifestations of central nervous system excitation or depression of inhibitory pathways.

Nalbuphine hydrochloride restored the normal pattern of the inspiratory neuronal and phrenic nerve activity after disruption by fentanyl. There are already several clinical reports indicating the efficacy of nalbuphine for the reversal of fentanyl-induced respiratory depression.^{33,34} §

Finally, the choice of the cat for these studies must be addressed. The brainstem respiratory neurons of cats have been extensively studied, and most of our present knowledge in relation to the anatomical organization and location of the respiratory neurons, their axonal projections, interconnecting networks, cell types, inputs, and regulation of respiration and breathing rhythmogenesis is based on studies conducted in cats.^{18,19,35} The brainstem respiratory neurons of other laboratory animals have not been nearly as extensively studied as those of cats. Thus, cats are generally used for physiopharmacologic studies on the brainstem respiratory neurons. And while fentanyl produces excitation and seizures in cats,³⁰ it causes similar reactions in other laboratory animals such as rats^{31,32} and mice,³⁶ although in larger doses compared with the dose for cats. For studies on medullary expiratory neurons, rats may offer a technical advantage because of the abundance of the expiratory neurons in the rat medulla.^{37,38}

In summary, intravenous administration of fentanyl (50 and 100 $\mu\text{g}/\text{kg}$) produced disruption of the normal rhythmic activity of the DRG inspiratory neurons of the medulla. The fentanyl-induced firing pattern was characterized by tonic activity superimposed with irregular bursts. These changes were also reflected by changes in the phrenic nerve activity. Nalbuphine, 0.1 mg/kg iv, injected 6–20 min after fentanyl, restored the normal rhythmic activity of the neurons and of the phrenic nerve. The activity of the VRG inspiratory neurons was suppressed by fentanyl.

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