D₁-dopamine receptor agonists prevent and reverse opiate depression of breathing but not antinociception in the cat

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Opioids depress respiration and decrease chest wall compliance. A previous study in this laboratory showed that dopamine-D₁ receptor (D₁R) agonists restored phrenic nerve activity after arrest by fentanyl in immobilized, mechanically ventilated cats. The reinstated phrenic nerve rhythm was slower than control, so it was not known whether D₁R agonists can restore spontaneous breathing to levels that provide favorable alveolar gas exchange and blood oxygenation. It was also not known whether the agonists counteract opioid analgesia. In the present study, anesthetized, spontaneously breathing cats were given intravenous doses of fentanyl (18.0 ± 3.4 µg/kg) that severely depressed depth and rate of respiration, lowered arterial hemoglobin oxygenation (HbO₂), elevated end-tidal carbon dioxide (ETCO₂), and abolished the nociceptive hind limb crossed-extensor reflex. Fentanyl (30 µg/kg) also evoked tonic discharges of caudal medullary expiratory neurons in paralyzed mechanically ventilated cats, which might explain decreased chest compliance. The selective D₁ agonists 6-chloro APB (3 mg/kg) or dihydrexidine (DHD, 1 mg/kg) increased depth and rate of spontaneous breathing after opioid depression and returned HbO₂ and ETCO₂ to control levels. Opioid arrest of the nociceptive reflex remained intact. Pretreatment with DHD prevented significant depression of spontaneous breathing by fentanyl (17.5 ± 4.3 µg/kg). Tonic firing evoked by fentanyl in expiratory neurons was converted to rhythmic respiratory discharges by DHD (1 mg/kg). The results suggest that D₁R agonists might be therapeutically useful for the treatment of opioid disturbances of breathing without impeding analgesia.

OPIATES ARE AMONG THE OLDEST and most frequently used drugs for the alleviation of pain, coughing, and smooth muscle spasticity. However, their therapeutic effects are produced at a cost to breathing. Tidal volume and gas exchange are depressed, and respiration is slowed or arrested after an opiate overdose. Therapeutic doses of opiates blunt respiratory responsiveness to carbon dioxide (32, 13, 28, 9), but normal breathing and ventilation are maintained in most individuals because carotid body and medullary chemoreceptors are further stimulated by elevated CO₂ and a consequent acid shift in pH of the arterial blood and extracellular fluid (27, 13). On the other hand, in some patients with renal, pulmonary and cardiac diseases, CO₂ desensitization predisposes them toward respiratory depression by normal doses of opiates (5, 6). In addition, fentanyl and its derivatives can impair ventilation during and after surgery by inducing chest wall rigidity (8a, 25).

Opiate receptor antagonists such as naloxone counteract respiratory effects of opioids, but they also block analgesia (5a). They can also produce hypertension, tachycardia, ventricular arrhythmias, and pulmonary edema (9). Thus novel pharmacological approaches are sought that will preserve the therapeutic usefulness of opiates, particularly analgesia, without depressing ventilation.

The underlying cause for opioid depression of the respiratory neural network seems to be downregulation of the cAMP-PKA signaling pathway leading to increased cell membrane permeability to potassium ions and decreased calcium ion permeability (1, 3), whereas nociception involves activation of cAMP-PKA (7). Therefore, one approach in laboratory studies has been to try reversing opioid depression of respiratory neurons selectively with neuromodulators that upregulate cAMP-PKA activity pre- or postsynaptically, or increase the activity of intracellular signaling pathways that have effects opposite to opiates on cell membrane K⁺ and Ca²⁺ permeability, without altering antinociception. In at least two previous investigations, this pharmacological approach has been successful. The 5-HT₁₃-serotonin receptor agonist BIMU-8 (21a), a cAMP-PKA activator, and thyrotropin-releasing hormone (11), a phospholipase C activator, reverse depression of breathing by opiates without impairing analgesia.

An earlier study in this laboratory demonstrated that selective D₁-dopamine receptor (D₁R) agonists, which are known to activate the cAMP-PKA signaling pathway in a variety of neurons (31), restored phrenic nerve activity after it had been abolished by the selective µ-opioid receptor agonist fentanyl in anesthetized and unanesthetized decerebrate cats that were immobilized and mechanically ventilated. This action was attributed to a demonstrated increase in reactivity of the respiratory neural network to carbon dioxide (17). The reinstated phrenic nerve discharges, the sole index of respiratory function, were more intense but slower in frequency than control activity. Therefore, it was not known whether they could drive spontaneous breathing sufficiently to restore satisfactory blood oxygenation and elimination of CO₂. It was also not known if the analgesic effect of fentanyl was preserved.

These questions were pursued in the present study. Two selective D₁R agonists were tested to determine whether they reverse and prevent depression of spontaneous breathing by fentanyl and restore blood oxygen and end-tidal CO₂ to satisfactory levels without impairing opioid analgesia.

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Another issue investigated was whether or not D₁R agonists alleviate opioid-evoked tonic discharges of caudal medullary expiratory neurons, an effect that was previously observed in pentobarbital-anesthetized and unanesthetized decerebrate cats (16), in chloralose-anesthetized dogs (18) and in motor nerve fibers that innervate the expiratory muscles of the chest wall in decerebrate rabbits (12). Because caudal medullary expiratory neurons provide excitatory synaptic drive to expiratory motoneurons (19), prevention of tonic discharges by D₁R agonists would suggest effectiveness against chest wall rigidity caused by opiates

METHODS

Animal preparation and surgical procedures. Results reported here were obtained in experiments performed on 17 pentobarbital-anesthetized adult male cats. Care and use of animals were in accordance with the Guide for the Care and Use of Laboratory Animals, as adopted and promulgated by the U.S. National Institutes of Health, and approved by the University of Wisconsin Medical School’s Institutional Animal Care and Use Committee. The animals were initially anesthetized with 5% halothane in 100% oxygen, administered while the animals were in an anesthesia chamber. During halothane anesthesia, the animals were removed from the chamber and given, in rapid succession, 40 mg/kg pentobarbital sodium intraperitoneally to maintain anesthesia and atropine methyl nitrate (0.2 mg/kg ip) to minimize airway fluid secretion. Ten to fifteen minutes were allowed for the pentobarbital anesthesia to become deep enough for surgical procedures. At least 2 h elapsed between the termination of halothane administration and the beginning of experimentation. Supplemental doses of pentobarbital (4–8 mg/kg iv) were administered if symptoms occurred that indicated significant lightening of anesthesia: 1) spontaneous increases of arterial blood pressure and heart rate, 2) irregular breathing or discharges of phrenic nerve activity that decreased in duration and increased in frequency, 3) shivering, and 4) movement and cardio-respiratory changes evoked by surgical procedures.

Surgical procedures involved placement of a catheter in the femoral artery to monitor blood pressure and obtain samples for measurement of blood oxygen and hemoglobin concentration, and catheters in both femoral veins to administer drugs and infuse Ringer lactate solution to maintain tissue hydration. A cannula was inserted into the trachea below the larynx. Animals were mounted in a stereotaxic head holder and suspended by thoracic and lumbar spinal clamps. Blood pressure, tracheal pressure, rate of breathing, body temperature, end-tidal CO₂ and inspired oxygen were monitored continuously and recorded on chart paper. Temperature was measured rectally and maintained at 36–38°C by external heating. In experiments where phrenic nerve activity and discharge properties of medullary expiratory neurons were recorded, animals were bilaterally vagotomized and paralyzed with gallamine triethiodide (4 mg/kg iv to start, 4–8 mg/h thereafter) and mechanically ventilated with oxygen-enriched (60% O₂) room air. Stroke volume of the ventilator was set at 10 ml/kg body wt, and end-tidal CO₂ was maintained within the range recorded during spontaneous breathing and adequate surgical anesthesia (4.6–5.3 vol%) by adjusting ventilation rate.

Breathing and ventilatory measurements. To assess the antidotal effectiveness of D₁R agonists against opiate depression of ventilation, breathing frequency, tracheal pressure, end-tidal CO₂ and femoral arterial blood oxygen saturation (HbO₂) were recorded in spontaneously breathing cats with intact phrenic nerves. Changes in tracheal pressure were measured by connecting the tracheal cannula to a T tube, with one side connected to a pressure transducer and the other open to room air through a variable resistor. The resistor clamp was adjusted by first calibrating a pressure transducer (Spectramed, Statham, Costa Mesa, CA) and transducer amplifier (Gould, Cleveland, OH) with a manometer and passing a calibration pulse equivalent to 10 mmHg from the amplifier to a data acquisition system (PowerLab S-8, AD Instruments, Castle Hill, Australia) and a thermal oscillograph recorder (Gould TA-2000). A 50-cc glass syringe was then connected to the system, and the resistor was adjusted so that injection of 40 cc of air, the average tidal volume of adult anesthetized cats (23), produced a signal equivalent to 5 mmHg. Measurements were made thereafter in cats with the same side arm outlet resistance and transducer amplifier gain. Control values of HbO₂ and ETCO₂ were unchanged when the cats breathed spontaneously into the pressure recording system.

Nociceptive reflex tests. The effects of D₁R agonists on opiate antinociception were tested in parallel with breathing measurements. Nociceptive reflexes were tested in two ways. In one test paradigm, the contralateral crossed-extensor reflex evoked by pressure applied to the left hind paw was recorded with two fine electromyographic (EMG) needles inserted in the right vastus lateralis (hind limb extensor) muscle. Anesthesia was allowed to lighten enough during the testing period so that under control conditions, a brief squeeze of the hind paw with a padded hemostat, just firm enough to cause ipsilateral hind limb withdrawal without altering blood pressure, heart rate or breathing, evoked a contralateral EMG discharge recorded with an AC preamplifier (2000 × amplification, 100–3000 Hz bandwidth). The reflex was again tested after opiate administration and after D₁R agonist administration. In the second paradigm, single electrical shocks were applied to evoke crossed-extensor reflex discharges and measure the discharge latencies. One stimulating needle, the cathode, was inserted under the Achilles tendon of the left hindlimb, and another needle, the anode, was inserted under the skin on the medial side of the left hind paw to stimulate the tibial nerve at the ankle and activate the reflex (30). Single shocks (70–90 V, 3-ms pulse duration) that evoked short- and long-latency contralateral reflex discharges of maximal intensity in the contralateral vastus lateralis muscle were delivered every 10 s. Ten EMG responses were averaged and recorded under control conditions, after opioid administration and after giving a D₁R agonist.

Intravenous administration of test solutions. Test solutions were injected slowly over durations of 30–60 s to minimize blood pressure changes. Drugs, dissolved in Ringer solution, were the selective µ-opioid receptor agonist fentanyl (0.4 mg/ml), the D₁R agonists 6-chloro-APB (6 mg/ml), and dihydrexidine (DHD, 3 mg/ml). Fentanyl, 6-chloro-APB and DHD were purchased from Sigma-Aldrich (St. Louis, MO), pentobarbital sodium (Nembutal) injectable from Abbott Laboratories (Abbott Park, IL).
Euthanasia. Experiments were terminated by intravenous injection of sodium pentobarbital in doses of 60 to 80 mg/kg that produced permanent cardiac arrest.

Statistics. Control and test values were evaluated for significance of difference by a paired Student’s t-test using SigmaPlot version 4.11 software (Jandel Scientific, San Rafael, CA). Differences were accepted as significant if $P < 0.05$. SigmaPlot was also used to derive means and standard errors.

RESULTS

$D_1R$ agonists reverse opiate depression of breathing. In tests performed on six cats that breathed normal room air (21% oxygen) spontaneously, the selective $D_1R$ agonists DHD (1 mg/kg, $n = 3$) 6-chloro-APB (3 mg/kg $n = 3$) reversed severe depression of respiration by fentanyl and restored blood oxygenation and end-tidal CO$_2$ to control levels. Results from one experiment are presented in Fig. 1.

The panels present arterial blood pressure, tracheal pressure during inspiration and expiration and values of end-tidal CO$_2$ (ETCO$_2$) and arterial hemoglobin oxygen saturation (HbO$_2$). Under control conditions, breathing frequency was 22 breaths/min, ETCO$_2$ 5.4%, and HbO$_2$ 95%. A dose of fentanyl (15 $\mu$g/kg) that severely depressed and slowed phrenic nerve activity in immobilized, mechanically ventilated cats (17) also depressed depth of breathing as reflected in reduced tracheal pressure, slowed frequency to 13 breaths per min, increased ETCO$_2$ to 6.3% and reduced HbO$_2$ to 63%. After giving APB, 3 mg/kg, depth of breathing exceeded the control level and despite a slower breathing frequency, preopiate levels of ETCO$_2$ and HbO$_2$ were restored. In another experiment not illustrated, fentanyl also elevated tracheal expiratory pressure. APB reversed this effect. Breathing frequency, ETCO$_2$, and HbO$_2$ were restored to control levels, whereas depth of breathing was greater.

In all experiments, $D_1R$ agonists increased depth and rate of spontaneous breathing after fentanyl depression of breathing and restored favorable blood oxygenation and alveolar gas exchange. Results from the six experiments are summarized as follows:

1) Under control conditions, the rate of spontaneous breathing was 22.8 ± 2.0 breaths/min (mean value ± SE); peak inspiratory tracheal pressure was 2.1 ± 0.9 mmHg; ETCO$_2$, 5.3 ± 0.1%; HbO$_2$, 93.8 ± 0.4%. Hemoglobin concentration (HbC) ranged from 14.8 to 15.1 g/dl.

2) After administering fentanyl, 18.0 ± 3.4 $\mu$g/kg, respiratory frequency was slowed to 10.0 ± 1.2 breaths per min ($P < 0.05$), peak inspiratory tracheal pressure was reduced to 0.5 ± 0.1 mmHg ($P < 0.05$), ETCO$_2$ increased to 6.3 ± 0.3% ($P < 0.05$), and HbO$_2$ was reduced to 74.0 ± 3.4% ($P < 0.05$). Blood pressure and heart rate were unchanged.

3) One to three minutes after $D_1R$ agonist administration, the rate of breathing was 17.1 ± 2.7 per min, inspiratory tracheal pressure was 2.5 ± 0.6 mmHg, ETCO$_2$ was 5.1 ± 0.2%, and HbO$_2$ was 94.2 ± 0.9%. These parameters remained steady over observation periods of 1 to 1.5 h. The $D_1R$ agonists had no effects on heart rate. APB elevated blood pressure, whereas DHD depressed it for 7–15 min after administration, as previously reported (17).

Fig. 1. The $D_1R$ agonist 6-chloro-APB reverses depression of breathing by fentanyl without suppressing antinociception. Records (A–C) illustrate femoral arterial pressure (BP), tracheal pressure (TP; expiration up, inspiration down) and the electromyogram (EMG) recorded from the vastus lateralis muscle. The bars under the EMG traces denote the stimulus (squeeze of the contralateral hind paw) that evoked the control EMG discharge. A: control recording; B: after intravenous administration of fentanyl; C: records taken after administering 6-chloro-APB (APB).
**Pretreatment with a D1R agonist prevents depression of breathing.** Pretreatment with DHD in five additional cats prevented significant depression of spontaneous breathing by fentanyl, as summarized in Fig. 2. In these experiments, fentanyl was given in a cumulative dose that significantly depressed breathing, and then time for complete recovery was allowed and DHD (1 mg/kg) was administered, followed by the dose of fentanyl that previously depressed breathing.

Fentanyl (mean cumulative dose, 17.5 ± 4.3 μg/kg) given before DHD depressed depth of breathing and reduced rate from 17.6 ± 1.0 per min to 10.0 ± 0.6 (P < 0.05), increased ETCO₂ from 5.0 ± 0.1% to 6.2 ± 0.2 (P < 0.05) and reduced HbO₂ from 93.9 ± 0.6% to 77.0 ± 2.4 (P < 0.05). Time to full recovery of breathing was 36.4 ± 3.2 min.

After recovery and DHD administration, rate of breathing was 17.4 ± 1.7 per min; ETCO₂, 5.1 ± 0.2 percent; HbO₂, 92.4 ± 1.0%. After D1R pretreatment, the second test dose of fentanyl did not significantly depress breathing. Rate of breathing after giving fentanyl was 14.7 ± 1.0 per min; ETCO₂, 5.6 ± 0.3%; HbO₂, 89.8 ± 1.0%.

**D1R agonist administration prevents fentanyl induction of tonic discharges in expiratory neurons of the caudal medulla.** Results to determine whether D1R agonists can prevent tonic firing in expiratory neurons of the caudal medulla were obtained in three experiments of the present study. In other pilot experiments, it was found that changes in blood pressure produced by D1R agonists made it impossible to maintain recording stability and test the effects of fentanyl before and after giving an agonist on the same cell. Instead, fentanyl disturbances of discharge properties were followed in a cell as long as recording conditions remained optimal and stable (48–52 min). After recovery from fentanyl was evident from the return of control phrenic nerve activity, DHD was administered. When blood pressure had returned to stable control levels, the effects of fentanyl were again tested on another cell. Results from one of three experiments are illustrated in Fig. 3.

Under control conditions (Fig. 3A1), caudal expiratory neurons exhibited periodic membrane hyperpolarization and absence of firing in parallel with an augmenting phrenic nerve discharge during the inspiratory phase, and then depolarized when phrenic nerve discharges declined during the postinspiratory phase and discharged action potentials that reached peak frequency during the expiratory phase at the end of the phrenic nerve silent period. Membrane potential properties of this type of neuron and their relationship to phrenic nerve activity were first described in detail by Ballantyne and Richter (2).

Fentanyl, in doses of 20–40 μg/kg, was previously shown to consistently abolish membrane potential hyperpolarization and respiratory rhythmic phrenic nerve discharges, so that caudal expiratory neurons fire tonically during phrenic nerve apnea (16). In all three experiments of the present study, 30 μg/kg doses of fentanyl produced tonic discharges in each of the three expiratory neurons subsequently recorded from discharged with a respiratory rhythm but earlier, that is, during the postinspiratory phase (Fig. 3B1). After the second 30 μg/kg test dose of fentanyl was administered, the neurons still exhibited respiratory-rhythmic discharges (3B2).

**Opioid analgesia is still present after reversing respiratory depression with D1R agonists.** In tests made on nine cats, doses of APB (3 mg/kg) or DHD (1 mg/kg) that reversed...
depression of spontaneous breathing by fentanyl had no effect on opioid depression of the nociceptive-crossed extensor reflex. The reflex discharges evoked by pressure applied to the hind paw were abolished by fentanyl \( (n = 6) \) experiments and were still absent after APB \( (n = 3) \) or DHD \( (n = 3) \) restored spontaneous breathing. Figure 1 illustrates the persistence of opioid antinociception after giving APB.

In three additional experiments, fentanyl arrest of shock-evoked nociceptive reflex discharges also persisted after DHD \( (1 \text{ mg/kg}) \) restored breathing. Results from one of the three experiments are illustrated in Fig. 4. Averaged control responses are shown on the left (Fig. 4, A and B). Single shocks \( (70–90 \text{ v}, 3\text{-ms pulse duration}) \) to stimulate the tibial nerve in the ankle evoked a maximal three-component reflex EMG discharge in the contralateral vastus lateralis muscle. The components labeled \( (1) \) to \( (3) \) had average onset latencies of 8 ms, 110 ms, and 310 ms. According to the analysis of Valero-Cabre and Navarro (30), the earliest discharge component is probably due to activation of A\( \beta \) fibers, whereas the two later ones are probably due to nociceptive A\( \delta \) and C fibers, respectively, in the tibial nerve. In all three experiments, fentanyl, 20 \( \mu \text{g/kg} \), abolished the 110 ms and 310 ms latency discharges (Fig. 4C) and depressed breathing (not shown), so that ETCO\(_2\) was elevated from 5.0 to 5.3% to 6.3 to 7.2%. Administration of DHD reinstated spontaneous breathing and brought ETCO\(_2\) to 5.2–5.4% but did not reinstate the opioid-depressed discharges (Fig. 4D).

**DISCUSSION**

Four principal results were derived from the present study. First, the selective full D1R agonists 6-chloro-APB and dihydrexidine restored satisfactory ventilation after depression of spontaneous breathing by the \( \mu \)-opioid receptor agonist fentanyl. Second, pretreatment with a D1R agonist prevented fentanyl depression of breathing. Third, the agonists did not suppress opioid analgesia. Fourth, they prevented induction of tonic discharges in caudal medullary expiratory neurons by fentanyl.

Antidotal effects of D1R agonists against opioid depression of breathing. The D1R agonists reversed opioid depression of breathing so that arterial oxygenation and carbon dioxide were satisfactorily restored. In all but one experiment, breathing was slower than control after giving D1R agonists. Therefore, it seems likely that the observed increase in depth of breathing played an important role in the full restoration of HbO\(_2\) and lowering of ETCO\(_2\). The technique used to measure tracheal pressure is crude; hence, precise estimates of changes in breathing effort were not obtained. Nonetheless, increased depth of breathing is also consistent with the finding that phrenic nerve discharges reinstated by D1R agonists after fentanyl depression are more intense and longer in duration (17). In addition, the peak of integrated action potential discharge frequency, an indicator of tidal volume (8), was increased by D1R agonists.

Two factors together might account for the slower reinstated breathing. First, D1R agonists alone prolong phrenic nerve and
bulbospinal inspiratory neuron discharges and slow their rate of occurrence (17). A second possibility is that phase-terminating types of bulbar respiratory neurons are relatively sensitive to opioid depression and more resistant to the actions of D1R agonists.

Another notable result in the present investigation was that D1R agonist pretreatment prevented fentanyl depression of breathing and induction of tonic expiratory neuron discharges. The lack of respiratory disturbances during the second test with fentanyl does not seem to be due to opioid tachyphylaxis, because it was previously found that dose-related alterations in phrenic nerve activity are the same after two or three consecutive tests with fentanyl (16). The effectiveness of pretreatment with D1R agonists against opioid respiratory disturbances suggests that they might be clinically effective when given before or with therapeutic doses of opiates.

**Opioid analgesia is maintained after D1R administration.**

The third important property of D1R agonists was that the effects on ventilation occurred without apparent impairment of opioid-mediated antinociception, since abolishment of the crossed extensor nociceptive reflex persisted after administration of the D1R agonists. It is important to point out that the average dose of fentanyl that depressed breathing in this study (18 µg/kg) is appreciably less than the dose range employed for analgesia in conscious cats (40–80 µg/kg) (10). It is assumed that general anesthesia lowered the dose required for respiratory depression in the present investigation. It remains to be determined whether and at what dose levels D1R agonists counteract opioid depression of spontaneous breathing in conscious subjects, and whether the required doses, if greater than those used in this study, compromise analgesia.

To date, there are no reports of how D1R agonists influence opioid analgesia in humans, and from rodent studies there is conflicting evidence. Some investigators found no effect (14), while others found that opiate analgesia is augmented (22) or impaired (4) by D1R agonists.

**Selective D1R agonists are thought to offset opioid respiratory depression at sites in the central nervous system.** Pharmacological studies point to participation of dopaminergic neurons in respiratory regulation. Parenteral administration of the nonselective dopamine receptor agonist apomorphine increases breathing frequency and tidal volume in lightly anesthetized rats, partly through effects on carotid body chemoreceptors and partly through actions within the central nervous system (20, 21). In cats, selective D1-dopamine receptor agonists reverse opioid depression of phrenic nerve activity in the central nervous system independent of effects on carotid body chemoreceptors (17).

How D1R agonists reverse opiate depression of the respiratory network has not yet been determined. An important component seems to be increased reactivity of respiratory neurons to CO2, as evidenced by a lower threshold for hypocapneic phrenic nerve apnea and a greater rate of change of phrenic nerve activity with varying end tidal CO2 (17). It is not known whether bulbar chemoreceptor cells are directly stimulated and if the excitatory synaptic drive on various types of respiratory neurons is otherwise augmented by D1R agonists. Fentanyl directly depressed bulbospinal inspiratory neurons (16), but the depression was not reversed postsynaptically by D1R agonists (17). A potential site of action could be on pre-Boßtinger respiratory neurons of the ventrolateral medulla, a site of respiratory rhythm generation where 5-HT4a receptor agonists appear to have a major respiratory restorative action against opioid depression (21a).

**Prevention of tonic discharges in caudal medullary expiratory neurons by fentanyl.** DHD prevented fentanyl-induced tonic firing of caudal medullary respiratory neurons in all tests, an opioid effect seen also in expiratory motor fibers of the chest.
wall, which allows “the bulbospinal output to express the prevailing balance of tonic inspiratory or expiratory drives to the motoneurons, with the expiratory drive dominant” (12). Furthermore, low clinical doses of opiates can indeed produce rigidity in rib cage and abdominal muscles of humans (25, 8a). However, the result of the present study does not establish a priori that D₁R agonists will be effective against opiate reduction of chest wall compliance. Opioids may also alter other neuronal mechanisms that promote chest wall rigidity, ones that have not yet been challenged with D₁R agonists and that could be resistant. For example, Tabatabai et al. (29) found that fentanyl induced tonic discharges of inspiratory neurons in the nucleus of the solitary tract in cats and suggested that the effect could be resistant. For example, Tabatabai et al. (29) found that fentanyl induced tonic discharges of inspiratory neurons in the nucleus of the solitary tract in cats and suggested that the effect might lead to sustained contraction of inspiratory muscles.

**Therapeutic potential.** D₁R agonists could turn out to be useful in preventing opioid respiratory depression or reversing it in patients with reduced respiratory sensitivity to CO₂, provided that they do not generate unfavorable side effects. Fenoldopam, a central nervous system-impermeable D₁R agonist, is used to lower blood pressure in severe hypertension (24). At present, however, there seem to be no centrally acting D₁R agonists used therapeutically.

D₁R agonists might also avert opioid reduction of chest wall compliance, as the results of the present report at least suggest. Future studies will hopefully determine whether D₁R agonists are useful for preventing and reversing opiate respiratory depression in other species, including humans, without compromising analgesia or introducing side effects and succeed in uncovering the underlying sites and mechanisms of action responsible for their respiratory effects.

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