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OPIOIDERGIC AND DOPAMINERGIC MODULATION OF RESPIRATION

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Abstract

Opioids, dopamine and their receptors are present in many regions of the bulbar respiratory network. The physiological importance of endogenous opioids to respiratory control has not been explicitly demonstrated. Nonetheless, studies of opioidergic respiratory mechanisms are important because synthetic opiate drugs have respiratory side effects that in some situations pose health risks and limit their therapeutic usefulness. They can depress breathing depth and rate, blunt respiratory responsiveness to CO₂ and hypoxia, increase upper airway resistance and reduce pulmonary compliance. The opiate respiratory disturbances are mainly due to agonist activation of μ - and δ -subtypes of receptor and involve specific types of respiratory-related neurons in the ventrolateral medulla and the dorsolateral pons. Endogenous dopaminergic modulation in the CNS and carotid bodies enhances CO₂-dependent respiratory drive and depresses hypoxic drive. In the CNS, synthetic agonists with selectivity for D1- and D4- types of receptor slow respiratory rhythm, whereas D2-selective agonists modulate acute and chronic responses to hypoxia. D1-receptor agonists also act centrally to increase respiratory responsiveness to CO₂, and counteract opiate blunting of CO₂-dependent respiratory drive and depression of breathing. Cellular targets and intracellular mechanisms responsible for opioidergic and dopaminergic respiratory effects for the most part remain to be determined.

1. Introduction

The editors of this special issue of Respiratory Physiology & Neurobiology have presented me with a particular challenge: to review two seemingly disparate neuromodulatory systems, each playing important roles in the control of respiration. I ask pardon for not having the luxury to cite all of the many researchers who have made important contributions to the two areas of respiratory neuromodulation.

To begin this review, I provide a brief sketch of critical areas of respiratory control in the CNS where opioids, synthetic opiates and dopamine receptor ligands can produce their effects. For more comprehensive coverage of the chemical neuroanatomy of respiratory control, the reader is encouraged to consult the review of Alheid and McCrimmon in this special review. Next, I discuss opioidergic and dopaminergic respiratory modulation as separate issues, and then present evidence that manipulation of the latter can be used to offset respiratory depression by the former. For information about effects of dopamine in the carotid bodies, a topic not considered in depth here, see Hsiao C, et al., 1989, and Lopez-Barneo, et al., 2001.

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2. Areas of respiratory control in the CNS

Aggregates of respiratory neurons that discharge periodically during the three phases of breathing (inspiration, post-inspiration or otherwise known as early-expiration and late-expiration) are distributed bilaterally in the bulbar brainstem, from the rostral pons to the caudal border of the medulla. Synaptic interactions among respiratory neurons establish the network respiratory rhythm, and their connections with cranial and spinal motoneurons and interneurons set up the timing and pattern of contraction in the muscles of respiration [Richter, 1996]. Two regions of the medulla, within the ventrolateral respiratory group (VRG) in particular, have been studied for their roles in rhythmogenesis: the PreBötzinger Complex [Schwarzacher, et al., 1995; Smith, et al., 1991] and the Para-Facial region/Retrotrapezoid nucleus areas [Onimaru and Homma, 2003]. Their functional integrity is essential for a normal respiratory rhythm [Janczewski and Feldman, 2006; McCrimmon, et al., 2000; Onimaru, et al., 1987; Ramirez, et al., 1998; Wenninger, et al., 2004], and neurons with autorhythmic pacemaker properties within each region have been identified. It appears that the oscillating networks interact with each other to generate respiratory rhythm [Mellen et al., 2003; Onimaru and Homma, 2003].

Respiratory neurons of the brainstem receive modulatory synaptic input from non-respiratory regions such as the motor cortex, pontine and medullary reticular formations, cerebellum, hypothalamus, other limbic and cardiovascular regions of the brainstem as well as from extrapyramidal motor areas. These non-respiratory modulatory inputs adapt breathing rhythm and pattern for effective cardio-respiratory interactions and activities such as phonation, swallowing, coughing, physical exertion, defecation and postural change. [Feldman and McCrimmon, 2003]. Synthetic opiates, and perhaps endogenous opioids as well, have actions in most regions that affect respiration and analgesia, as well as cardiac, hemodynamic and immune responses [Molina, 2006].

3. Opioidergic respiratory modulation

3.1 Endogenous opioids and respiratory modulation

Anatomical and pharmacological evidence suggest that endogenous opioids play a role in modulating respiration, but their precise physiological functions are still largely a mystery. Immunoreactivity for μ , δ and κ -receptors is found in respiratory-related regions of the brain stem and spinal cord [Haji, et al., 2003a; Lonergan et al., 2003a, b; Wang, et al., 2002; Xia and Haddad, 2001]. In addition, five general types of endogenous opioids, each with different relative affinities for opioid receptor subtypes, are found in medullary and pontine respiratory-related regions: β -Endorphin ($\mu > \delta \gg \kappa$), Enkephalins ($\delta > \mu \gg \kappa$), Dynorphins ($\kappa > \mu > \delta$), and two endogenous peptides with extremely high selectivity for the μ -type receptor, Endomorphin-1 (EM-1) and Endomorphine-2 (EM-2) [Kiraly, et al., 2006; Martin-Schild, et al., 1999; Moss and Laferriere, 1999; Pierce and Wessendorf, 2000; Rutherford and Gundlach, 1993]. It has been proposed that endogenous opioids are tonically active and depressant to the respiratory network, because the opioid receptor blocker naloxone stimulates respiratory output in anesthetized, normoxic, normocapnic cats [Lawson, et al., 1979] and in unanesthetized animals exposed to hypoxia or hypercapnea [Schlenker and Inamder, 1995]. However, the presence of pain, hypercapnia, hypoxia or other stress factors that promote reactive increases of endogenous opioids might be necessary for respiratory stimulation by opioid receptor blockers [Shook, et al., 1990; Yeadon and Kitchen, 1989]. Endogenous opioids may be active during episodes of hypoxia or hypercapnea, suppress movement of respiratory muscles and lungs to reduce pain related to trauma or pleurisy and prevent premature respiratory effort in the fetus.

3.2 Synthetic opiates and respiratory disturbances in humans

Synthetic opiates with affinity for either the μ - or δ -type of receptor suppress all parameters of effective breathing. They depress rate and depth of respiration, induce chest and abdominal wall rigidity, reduce upper airway patency and blunt respiratory responsiveness to carbon dioxide and hypoxia [Jaffe and Martin, 1990; Lotsch, et al., 2005; O'Brien, 1995; Santiago and Edelman, 1985; Shook, et al., 1990; White and Irvine, 1999; Yeadon and Kitchen, 1989]. Therapeutic doses of opiates are much more depressant to respiration in patients suffering from chronic cardio-pulmonary and renal diseases because of desensitized CO₂-dependent respiratory drive. In chronic obstructive pulmonary disease (COPD) and sleep apnea syndrome, there is diminished responsiveness to hypoxic drive.

The occurrence of postoperative respiratory depression with opiates that act on μ or δ -receptors is significant. From an analysis of 20,000 patients documented in 165 reports, 3400 patients (17%) experienced opiate-induced respiratory depression when oxygen desaturation was used as the indicator [Lotsch, et al., 2005]. The elderly are at much greater risk because of physiological respiratory changes such as reduced lung elasticity, stiffening of the chest wall, decreased vital capacity and reduced forced expiratory flow rate [Smith, 1998]. In addition, altered pharmacokinetic responsiveness linked to reduced metabolism and plasma clearance, increase the respiratory depressant potential of opiates [Muravchick, 1998]. Females are more susceptible to opiate respiratory depression, for reasons that remain to be established [Romberg, et al., 2003]. The newborn are especially susceptible, possibly due to larger concentrations of opioid receptors on brain stem respiratory neurons, and an under-developed blood-brain barrier that permits greater entry of opiates into the CNS. [Moss and Inman, 1989; Moss, et al., 1993; Zhiang and Moss, 1995].

Highly selective μ -opioid receptor-binding opiates of the phenylpiperidine class (fentanyl, sufentanyl and remifentanyl, for example) are widely used as adjuncts to general anesthesia during surgery because of their potent, relatively short-lasting analgesic effects. They produce a greater variety of ventilatory problems than opium-derived, somewhat less selective (μ +++, κ +) phenanthrene derivatives such as morphine, codeine and oxycodone [O'Brien, 1995]. They not only reduce rate and depth of breathing, they increase the tendency for airway obstruction at glottic and supraglottic levels and produce rigidity of chest wall and abdominal musculature [Bennett, et al., 1997; Bowdle, 1998; Drummond, 1983; Marty and Desmond, 1981; Niedhart, et al., 1989; Seamman, 1983]. Like other classes of opiates, they also suppress the cough reflex, reducing the ability to expel airway mucous and salivary secretions during recovery from anesthesia. The effects occur unpredictably during and after operative procedures because phenylpiperidine opiates are highly lipid soluble and undergo recycling between brain, blood and other tissue. The reduction of chest wall and abdominal compliance are particularly hazardous in neonates [Bowdle, 1998; Marty and Desmond, 1981] who, even without opiates, have diminished ability to breathe against resistive loads, as well as chest wall instability and an increased tendency toward alveolar collapse. The newborn diaphragm also fatigues more easily [Lopes, et al., 1981; Staub, 1998]. Patients with chronic obstructive pulmonary disease are also particularly at risk [Taylor, et al., 2005].

3.3 In vitro studies of opioid actions on the bulbar respiratory network

Suzue and coworkers [Suzue, et al., 1983] pioneered the use of the unanaesthetized isolated brainstem-spinal cord preparation of the newborn rat, and with it showed that opioid peptides depress frequency and intensity of respiratory-rhythmic motor discharges recorded from cervical nerves [Murakoshi, et al., 1985]. Respiratory rhythm slowing and arrest evoked by μ - and δ receptor-selective opioid peptides also occurs in neonatal rat brainstem slices [Gray, et al., 1999; Mellen, et al., 2003] and in brainstem-spinal cord preparations of adult lampreys [Mutolo, et al., 2007]. Intracellular recording experiments with neonatal rat brainstem slice

[Grey, et al.1999] and brainstem-spinal cord [Takeda, et al., 2003] preparations showed that μ -opioid peptides hyperpolarize membrane potential (MP) of medullary Inspiratory neurons, with reversal potentials of around -80 mV [Takeda, et al., 2003] or -100 mV [Grey, et al. 1999], suggesting that they increase K-channel permeability. These effects may be related to suppression of the cAMP-PKA signal transduction pathway because in most CNS neurons so far tested, μ -opioids suppress cAMP-PKA signaling, which increases K-channel permeability. In the brainstem-spinal cord preparation of the newborn rat, bath application of cAMP-PKA stimulators reverses opioid-mediated MP hyperpolarization and depression of discharges in VRG respiratory neurons [Ballanyi, et al., 1997]. Not all medullary respiratory neurons are sensitive to opioids. Pre-Inspiratory Neurons of the Para-Facial Region that depolarize and discharge ahead of inspiratory motor nerve discharges are opioid-insensitive [Janczewski, et al., 2002; Mellen, et al., 2003; Takeda, et al., 2003], whereas in the PreBötzinger Complex there are opioid-sensitive and -insensitive Inspiratory neurons [Barnes, et al., 2007; Gray, et al., 1999]. At least some Inspiratory neurons in the Para-Facial region and PreBötzinger Complex have intrinsic burst generating properties [Arata, et al., 1993; Purvis, et al., 2007], but tests have not yet been made to determine whether they are opiate-sensitive.

3.4 Opioid microiontophoresis studies on respiratory neurons in vivo

Analysis of opioid effects confined to single respiratory neurons was first performed with multibarrel microelectrode assemblies for extracellular recording and microiontophoresis. The methodology allows controlled application of charge-carrying opioid molecules close to the cell body and neurites of a test neuron, ejected by polarizing current passed through the drug-containing pipette solution. Microiontophoresis of the highly selective μ -receptor agonists DAMGO or fentanyl, the moderately selective μ -agonists morphine ($\mu > \kappa \gg \delta$) or TRIMU -4 ($\mu > \delta$) or the moderately selective δ -agonist DSLET ($\delta \gg \mu$) suppresses both spontaneous and glutamate-evoked discharges of VRG Inspiratory neurons, indicating that the neurons are depressed postsynaptically [Lalley, 2003; Morin-Surun, et al., 1984; Ronduin, et al., 1981]. Haji and colleagues [Haji, et al., 2003a, b] used compound multibarrel assemblies for intracellular recording and extracellular microiontophoresis in their experiments, and also found that opiates postsynaptically depress excitability in VRG respiratory neurons. They showed that microiontophoresis of morphine hyperpolarizes MP and depresses discharges of VRG Inspiratory, Post-Inspiratory and Late-Expiratory neurons.

3.5 Respiratory network effects of opioids given systemically

The most frequently analyzed respiratory network response to opioids given systemically has been disturbance of rhythm [Haji, et al., 2003b; Janczewski and Feldman, 2006; Janczewski, et al., 2002; Kato, 1998; Lalley, 2003, 2006; Lonergan, et al., 2003b; Mellen, et al., 2003]. In the juvenile rat, fentanyl depresses an inspiratory rhythm generator in the PreBötzinger Complex, while an expiratory rhythm generator in the Retrotrapezoid Nucleus perseveres [Janczewski, et al., 2002; Janczewski and Feldman, 2006].

In adult midcollicular decerebrate cats, morphine has biphasic effects on rhythmic properties of VRG respiratory neurons [Haji, et al., 2003b]. Initial transient MP hyperpolarization, reduced discharge intensity and decreased cell membrane input resistance are followed by depression of depolarizing and hyperpolarizing MP fluctuations and increased input resistance. The initial responses are attributed to increased postsynaptic K-channel conductance, and the later effects to suppressed presynaptic transmitter release.

Lowest effective doses of the highly selective μ -opioid receptor agonist fentanyl given to adult anesthetized or decerebrate cats slows rhythm in VRG Inspiratory, Late-Inspiratory, Post-Inspiratory and Late-Expiratory neurons by prolonging waves of MP depolarization and lengthening the duration of respiratory related discharges [Lalley, 2005]. Increasing the

cumulative dose by small increments produces further slowing of rhythm by lengthening intervening waves of MP hyperpolarization. There is no effect on neuron input resistance, spike height or shape, nor on spike after-hyperpolarization. It seems, therefore, that the slowing of rhythm is linked to upstream effects. Potential primary targets for the rhythm slowing include the PreBötzinger Complex, and the rostral pons where opioid application produces a similar pattern of slowing [Eguchi, et al., 1987; Hurle, et al., 1983; Takeda, et al., 1987].

Opiates also disrupt rhythm and discharge properties in specific types of VRG neurons that regulate tidal volume, upper airway resistance and pulmonary compliance. Doses of fentanyl that abolish phrenic nerve activity hyperpolarize MP, arrest firing and decrease neuron input resistance in bulbospinal (figure 1) and propriobulbar Inspiratory neurons of anesthetized and decerebrate cats. The neurons provide excitatory drive to phrenic and inspiratory intercostal motoneurons, thus the cellular effects account for opiate depression of tidal volume [Lalley, 2003].

In propriobulbar Post-I neurons, laryngeal adductor motoneurons and bulbospinal Late-E neurons, arrest of phrenic nerve discharges by fentanyl is accompanied by abolition of periodic waves of hyperpolarizing synaptic potentials. [Lalley, 2003]. Robust, uninterrupted discharge activity develops, at a MP threshold that is more negative than under control conditions (figure 2). These effects occur without change of neuron input resistance or action potential properties. It seems that inhibitory synaptic transmission is selectively depressed by fentanyl in these neurons, allowing excitatory respiratory drive to go on without interruption.

Laryngeal abductor and pharyngeal constrictor motoneurons respond differently. When phrenic nerve activity is arrested by fentanyl, both depolarizing and hyperpolarizing waves are abolished and tonic firing of very weak intensity results. Input resistance is unchanged, evidently because excitatory and inhibitory synaptic inputs are equally depressed presynaptically [Lalley, 2003].

Discharge disturbances of the sort evoked by synthetic opiates in bulbospinal Expiratory neurons of the cat have also been documented in dogs and rabbits [Howard and Sears, 1990; Laubie et al., 1986]. The robust, tonic expiratory discharges explain how opiates promote rigidity of chest wall and abdominal musculature. They also increase discharge activity in the recurrent laryngeal nerve, which innervates all laryngeal muscles except for the cricothyroid, accounting for increased laryngeal resistance to airflow [Willette, et al., 1982]. Robust firing of laryngeal adductor motoneurons, in combination with severe depression of firing in laryngeal abductor and pharyngeal constrictor motoneurons, explain how opiates impair upper airway patency.

3.6 Opioid effects on CNS neurons: insights into potential mechanisms in the respiratory network

Opioids have diverse pre- and postsynaptic effects on many types of CNS neurons that are linked to a variety of cellular mechanisms. Some of the mechanisms might also apply to neurons of the respiratory network, although evidence for their existence is still for the most part lacking. In non-respiratory neurons opioids hyperpolarize MP, resulting in postsynaptic depression of excitability, but they also increase excitability by suppressing presynaptic release of γ -aminobutyric acid [Jiang and North, 1992; Madison and Nicoll, 1988; Travagli et al., 1996; Zhu and Pan, 2004]. Related to postsynaptic inhibition, they increase hyperpolarizing current through membrane potassium channels (voltage-dependent, inwardly rectifying K-channels; calcium-activated K-channels; and ATP-sensitive K-channels) and decrease current through depolarizing channels (voltage-gated L, N and P/Q-type calcium channels; persistent sodium channels; and nonspecific- I_h -cationic current channels) [Alreja and Aghajanian, 1993; Grudt and Williams, 1995; Schroeder, et al., 1991; Stefani, et al., 1994; Svoboda, et al., 1998]. Most

of the channel effects are linked to suppression of the cAMP-PKA signaling pathway [Grudt and Williams, 1995; Wimpey and Chavkin, 1992; Xie and Lewis, 1997]. Opioid receptor agonists, however, also increase glutamate-activated NMDA currents via the G(q/11)-PLA-PKC pathway [Martin, et al., 1997]. The latter mechanism has been invoked to explain fentanyl hyperalgesia [Rivat, et al., 2002] and tolerance to opiate analgesia [Celerier, et al., 1999].

3.7 Summary of opiodergic respiratory modulation

Endogenous opioids and their receptors are present in respiratory-related regions of the pons and medulla, but additional evidence is needed to establish their physiological roles in respiratory control. Administration of opioid peptides and synthetic opiates slows respiratory frequency in lowest effective doses; respiratory neurons of the PreBötzinger Complex and perhaps the dorsolateral pons seem likely immediate targets for the effect. In larger doses, they alter discharge properties of cranial motoneurons controlling the larynx and pharynx, and bulbospinal neurons controlling the diaphragm, chest wall and expiratory abdominal muscles. The discharge disturbances account for decreased tidal volume, increased upper airway resistance and reduced pulmonary compliance. An important goal of future research will be to identify the ion channel types and intracellular signaling pathways affected by opioids in various types of respiratory neurons.

4. Dopaminergic respiratory modulation

4.1 Endogenous dopaminergic modulation

Catecholamine detection procedures, pharmacological studies and experiments on mutant mice suggest that endogenous dopaminergic mechanisms in the CNS and in the carotid body modulate respiration.

Dopamine and the enzyme that synthesizes it, tyrosine hydroxylase, are present in nearly all regions of the bulbar respiratory network [Hsiao, et al., 1989; McNamara and Lawson, 1983; Milner, et al., 1986; Sun, et al., 1994].

Nurr1 mutant mice deficient in dopaminergic neurons have severe disturbances of respiration and diminished responsiveness to hypoxia [Nseghi, et al., 2004]. Nurr1, a transcription factor belonging to the family of nuclear receptors, is expressed in several respiratory-related regions including the NTS, nucleus ambiguus, and the dorsal motor nucleus of the vagus and in the carotid bodies. The mutant mice fail to develop midbrain dopaminergic neurons and do not survive beyond 24 hours after birth. They exhibit a severely disturbed breathing pattern characterized by hypoventilation, apneas and failure to increase breathing during hypoxia. Rhythm disruption and impaired hypoxic responsiveness are also evident from respiratory motor nerve recordings in isolated brainstem-spinal cord preparations lacking carotid body chemoreceptor input.

4.2 In vivo pharmacological studies

Lundberg and coworkers [Lundberg, et al., 1979] were the first to describe dopaminergic modulation of breathing. They reported that the non-selective dopamine receptor agonist apomorphine (APO) increases breathing frequency and minute ventilation in rats lightly anesthetized with halothane. They also showed that the ventilatory response to CO₂ was greatly increased by APO. Later, they showed that APO also increases tidal volume by actions in the carotid body and in the CNS [Lundberg, et al., 1982]. Direct modulation of respiratory neuron excitability was first demonstrated by Fallert et al. [Fallert, et al., 1979] who showed that microiontophoretic application of dopamine reduces action potential frequency of medullary inspiratory neurons in rabbits. Nielsen and Bisgard [Nielsen and Bisgard, 1983] demonstrated a role for central dopaminergic neurons in respiratory control in the anesthetized dog. They

showed that when carotid body influences are eliminated by denervation, CNS-impermeable dopamine has no effect on phrenic nerve activity whereas APO, which crosses the blood-brain barrier, prolongs phrenic nerve inspiratory discharges and shortens the expiratory silent period. They also showed that blockade of CNS dopamine receptors with haloperidol decreases baseline phrenic minute activity (the product of peak inspiratory discharge intensity times minute discharge frequency) and reverses APO-induced changes in phrenic nerve activity.

Overall, the pattern that emerges from those early studies is that dopamine receptor agonists given systemically act at one or more sites in the brainstem respiratory network to increase inspiratory motor nerve discharges and ventilation, even if direct effects of dopamine on inspiratory neurons are evidently depressant, as suggested by the microiontophoresis experiments. Systemically administered agonists evidently increase excitatory respiratory drive to a degree that it exceeds the capacity of dopamine to depress inspiratory neurons of the medulla postsynaptically, whether applied by microiontophoresis or endogenously released.

Other pioneer studies showed that dopamine injected into the 4th ventricle, as well as APO or L-DOPA given systemically, greatly increase CO₂/pH-dependent respiratory drive [Lundberg, et al., 1979; Nielsen and Bisgard, 1983; Olsen and Saunders, 1985]. Thus, chemoreceptor neurons could be direct targets for increased network excitatory drive, physiologically as well as pharmacologically. Reactivity of chemoreceptor neurons in the ventrolateral medulla to CO₂/H⁺ increases when the type-3 sodium-hydrogen exchanger (NHE-3) is down-regulated, causing increased intracellular [H⁺]. [Wiemann and Bingmann, 2001], and dopamine is a known down-regulator of NHE-3, at least in the kidney [Burckhardt, et al., 2002].

Dopamine also suppresses responsiveness to hypoxia, both in the carotid bodies and in the CNS [Hsiao, et al., 1989; Huey, et al., 2000; Olson and Saunders, 1985]. The physiological relevance is not established, but one possibility is that suppressed stimulatory responsiveness to hypoxia is a protective mechanism directed against excessive discharge activity in the CNS respiratory network, which can result in neuronal excitotoxicity [Richter, et al., 2000].

4.3 Dopamine receptor subtypes and respiratory effects

In early studies, it wasn't possible to relate dopaminergic effects to specific subtypes of dopamine receptor. The receptors had not been adequately characterized because cloning and other molecular techniques hadn't been developed, and selective agonists, antagonists and immunohistochemically reagents to identify them and define their actions weren't available. Later, after selective receptor ligands had been synthesized and characterized, D1 and D2 receptors were linked to respiratory drive and responsiveness to hypercapnea and hypoxia [Hsiao, et al., 1989; Huey, et al., 2000; Lalley, 2004a, b; Lalley, 2005; Srinivasan, et al., 1991], while D4 receptors were found to mediate slowing of rhythm *in vitro* [Fujii, et al., 2004].

4.4 D1-dopamine receptors (D1Rs) modulate Inspiratory neuron discharge frequency and intensity in the CNS

The D1R antagonist SCH-23390 given i.v. increases phrenic nerve discharge frequency in rabbits [Srinivasan, et al., 1991], whereas in cats it slows phrenic and recurrent laryngeal nerve discharge rates by prolonging inspiratory phase firing duration, and increases discharge intensity. [Lalley, 2004b]. Slowing of discharges by D1R antagonists as well as agonists suggests that endogenous dopamine acts not only on D1-receptors, but on other types of dopamine receptor as well, to slow respiratory rhythm.

D1R agonists increase discharge intensity in bulbospinal Inspiratory neurons of the cat and slow rhythm due to lengthening of discharge, paralleling the effects on phrenic and recurrent

laryngeal nerve activities. The effects on neuron and motor nerve discharge properties are antagonized by SCH-23390. A depolarizing shift of membrane potential throughout all phases of the respiratory cycle occurs in Inspiratory neurons after D1R agonist administration (figure 3), without a change of Input resistance. By contrast, microiontophoretic application of D1R agonist near to bulbospinal Inspiratory neurons has no effect on discharge properties [Lalley, 2004b], indicating that the neurons are not direct targets. The increases in discharge intensity and duration should result in deeper and more prolonged inspiratory effort. Perhaps dopamine and its receptors slow air inflow in order to increase the pressure-generating efficiency of the respiratory muscles [Corne, et al., 2000].

Since D1-agonist application by microiontophoresis has no effect on excitability of VRG inspiratory neurons, whereas application of dopamine is depressant [Fallert, et al., 1979], it can be reasonably suggested that dopamine has inhibitory neuromodulatory effects that are mediated by postsynaptic D2- or D4-subtypes of receptor [Rashid, et al., 2007].

4.5 D1-dopamine receptor agonists increase reactivity to CO₂ in the CNS respiratory network

D1R agonists given intravenously to anesthetized and unanaesthetized decerebrate cats lower the apnea threshold when end-tidal CO₂ (ETCO₂) is varied during hyperoxic ventilation, and they shift the minute phrenic nerve – CO₂ response curve to lower ETCO₂ levels [Lalley, 2004b]. Minute phrenic nerve activity at all levels of ETCO₂ is significantly greater than control, due to increased discharge intensity. The precise sites of action remain to be determined, but they are located somewhere in the brainstem caudal to the superior colliculus.

4.6 D1-dopamine receptors protect against opioid respiratory depression

Intravenous administration of D1R agonists to adult decerebrate or anesthetized cats reinstates respiratory related discharges in phrenic nerves (Figure 4A), recurrent laryngeal nerves and medullary respiratory neurons after arrest by fentanyl [Lalley, 2004b]. Reversal of respiratory depression involves mechanisms that counteract opiate blunting of CO₂-dependent respiratory drive (Figure 4B). Fentanyl shifts the CO₂-dependent apnea threshold to higher levels of ETCO₂, reduces the slope of the minute phrenic nerve-ETCO₂ relationship and reduces minute PNA activity at all levels of ETCO₂. D1R agonists produce a substantial but not total reversal of the fentanyl effects.

In cats breathing spontaneously, D1R agonists reverse severe respiratory depression by fentanyl. Depth and rate of respiration are increased, sufficient to return arterial hemoglobin oxygenation and ETCO₂ to control levels. Re-establishment of satisfactory breathing is affected without altering opiate antinociceptive effectiveness [Lalley, 2004a].

4.7 Endogenous activation of D1Rs acts against opioid depression of the respiratory network

When D1-dopamine receptors are blocked with SCH-23390, fentanyl slows and arrests respiratory rhythm in doses that have little or no effect on respiratory network rhythm and discharge intensity in the absence of D1R blockade [Lalley, 2005]. This finding indicates that endogenous dopamine antagonizes opioid respiratory depression. One of the many actions of opiates in the CNS is to trigger dopamine release [DiChiara and Imperato, 1988; Bagosi, et al., 2006]. Activation of D1Rs by endogenous dopamine can then act against opioid respiratory depression by increasing CO₂-responsiveness of chemoreceptor and respiratory neurons. By blocking this compensatory mechanism, D1R antagonists lower the threshold and increase the effectiveness of opiate respiratory network depression.

4.8 Summary of dopaminergic respiratory modulation

The presence of dopamine in many regions of the bulbar respiratory network and in the carotid bodies, the effects of dopamine receptor blockers on respiration and the marked disruption of breathing when dopaminergic neurons are missing in mutant animals indicate that there is significant endogenous dopaminergic modulation of breathing. Several types of dopamine receptor are implicated. D1R and D4R agonists slow respiratory rhythm, D2R agonists alter respiratory responsiveness to chronic hypoxia and D1R activation leads to increased respiratory responsiveness to CO₂ and acts against opioid depression in the bulbar respiratory network. The cellular mechanisms responsible for dopaminergic respiratory rhythm modulation are at present unknown. The ability of D1R agonists to avert opioidergic respiratory depression is evidently linked to increased CO₂-dependent respiratory drive, and likely but untested targets are CNS chemoreceptor neurons

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Figure 1.

Fentanyl hyperpolarizes membrane potential (MP), arrests discharge and reduces input resistance (Rn) of an *Inspiratory bulbospinal neuron (BSN)*. Effects of fentanyl are reversed by Naloxonazine (not shown). A, control rhythm is synchronized with phrenic nerve inspiratory discharge (PNA.). B, Collision testing identifies neuron as bulbospinal. Stars denote antidromically-evoked action potentials. Stimulus-evoked action potential is abolished by collision with spontaneous action potential in lower trace. C, Control recording shows uniformly spaced hyperpolarizing electrotonic potentials (downward deflections) evoked by constant current pulses, 60mS duration, that are proportional to cell membrane input resistance (Rn). D, intravenous injection of fentanyl hyperpolarizes MP, abolishes action potential discharge and decreases input resistance. E, hyperpolarizing electrotonic potentials identified by black bars under MP traces in panels C and D are enlarged. (Lalley, unpublished figure)

Figure 2.

Fentanyl i.v. evokes tonic discharge in propriobulbar Post-I (A.) and bulbospinal Late-E neurons (B.). Dashed lines in each panel denote threshold for action potential discharge under control conditions. Lengths of vertical arrows (A, lower and B, right) denote magnitudes of change in action potential threshold. (Lalley, unpublished figure.)

Figure 3. Increases in discharge intensity and duration evoked by i.v. administration of the D1-dopamine receptor agonist SKF-38393 in a bulbospinal Inspiratory neuron. [Figure from Lalley, 2004b]

Figure 4.

Reversal of respiratory network depression by selective D₁-dopamine receptor (D₁R) agonists in the anesthetized cat. Panel A, reversal of depression by the D₁R agonist 6-Chloro-APB (APB) in a single experiment. Records show the onset of network depression by fentanyl (2.), which then proceeds to arrest of phrenic nerve discharges (3. central apnea). APB given thereafter restores discharges to control intensity but at a slower frequency. Traces show the phrenic electroenceurogram (bottom trace) and the moving average of phrenic nerve activity (upper trace). Panel B, partial reversal of opiate-induced depression of respiratory responsiveness to CO₂ by the D₁R agonist Dihydroxidine (DHD) in 6 anesthetized cats. Ordinate, minute phrenic nerve activity as a percent of the maximal control value recorded during hypercapnia. Abscissa, percent end-tidal CO₂ (ETCO₂) normalized with respect to the control phrenic nerve apnea threshold (apnea threshold set to zero). [Figure modified from Lalley, 2004b]