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Optimal interaction of respiratory and thermal regulation at rest and during exercise: role of a serotonin-gated spinoparabrachial thermoafferent pathway

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Abstract

Recent evidence indicates that the lateral parabrachial nucleus (LPBN) in dorsolateral pons is pivotal in mediating the feedback control of inspiratory drive by central chemoreceptor input and feedforward control of body temperature by cutaneous thermoreceptor input. The latter is subject to descending serotonergic inhibition which gates the transmission of ascending thermoafferent information from spinal dorsal horn to the LPBN. Here, a model is proposed which suggests that the LPBN may be important in balancing respiratory and thermal homeostasis, two conflicting goals that are heightened by environmental heat/cold stress or exercise where the effects of respiratory thermolysis become prominent. This optimization model of respiratory-thermoregulatory interaction is supported by a host of recent studies which demonstrate that animals with serotonin (5-HT) dysfunction at the spinal dorsal horn—due to 5-HT antagonism, genetic 5-HT defects or spinal cord injury—all display similar respiratory abnormalities that are consistent with hyperactivity of the spinoparabrachial thermoafferent (and pain) pathway.

Keywords

Lateral parabrachial nucleus; serotonin; respiratory control; thermoregulation

1. Introduction

Monoamines such as serotonin (5-HT) are thought to modulate many state-dependent changes in cardiorespiratory, thermoregulatory and pain/nociception physiology (Lydic 1987; Audero et al. 2008; Gargaglioni et al. 2008). Recently, the effects of 5-HT on control of breathing and thermoregulation have received much attention (Hodges et al. 2008a; Hodges et al. 2008b; Hodges et al. 2008c; Li et al. 2008; Mitchell et al. 2008). Less well appreciated, however, is the interplay between these regulatory processes in balancing respiratory and thermal homeostasis through ventilatory CO₂ elimination and respiratory thermolysis, two conflicting goals that are heightened by environmental heat/cold stress or muscular exercise particularly

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in panting animals. Such unaccounted-for confounding factors have led to many ambiguities in the interpretation of these previous data.

At the same time, other recent studies (Morrison et al. 2008; Nakamura et al. 2008; Song et al. 2009a; Song et al. 2009b) have identified a critical area in the dorsolateral pons – the lateral parabrachial nucleus (LPBN) – as a pivotal relay for both central and peripheral chemoreceptor afferents and cutaneous thermoreceptor afferent. These findings indicate that the LPBN may be important in coordinating respiratory and thermal regulation. Here, I show that this hypothesis is consistent with a host of recent studies demonstrating the effects of 5-HT on control of breathing at rest and during exercise or following spinal cord injury (SCI). Of particular significance is the emergent respiratory-modulating effect of a serotonin-gated thermoafferent (and pain) pathway from spinal dorsal horn to the LPBN, which proves to be a possible missing link that may resolve many of the ambiguities in recent studies of 5-HT modulation of breathing (Hodges et al. 2008a; Hodges et al. 2008b; Hodges et al. 2008c; Li et al. 2008; Mitchell et al. 2008). The resultant model suggests a neural mechanism whereby respiratory and thermoregulatory pathways may interact to reconcile conflicting demands for respiratory homeostasis and thermal homeostasis during increased metabolic and/or thermal challenges.

2. Graded potentiation of exercise hyperpnea by increased dead space and hypercapnia: a hallmark of ventilatory optimization

2.1. Characteristics of ventilatory optimization during exercise

In humans, ventilatory output ($\dot{V}_E$) is tightly geared to metabolic CO_2 production ($\dot{V}_{\text{CO}_2}$) from rest to moderate exercise and this exercise ventilatory response is potentiated (with a steeper linear $\dot{V}_E$ - $\dot{V}_{\text{CO}_2}$ relationship) when the normal isocapnic state is made hypercapnic at a constant elevated arterial P_{CO_2} (Pa_{CO_2}) level by breathing varying CO_2 -enriched mixtures (Poon et al. 1985). The potentiation effect is even more pronounced when the hypercapnia is caused by breathing through an *external* dead space instead (Poon 1992b). The greatest potentiation effect is found in congestive heart failure patients who suffer significant increases in *physiological* dead space, but remarkably are able to maintain near eucapnia with augmented ventilatory output at rest and during exercise to compensate for the dead space (Wasserman et al. 1997; Johnson 2001; Poon 2001). Thus, the interaction of hypercapnia and exercise inputs has both additive and multiplicative ventilatory response components. The additive component is smaller and the multiplicative component greater when the hypercapnia is induced by increased external dead space instead of by CO_2 inhalation. The additive component is smallest and the multiplicative component greatest in congestive heart failure patients in the face of increased physiological dead space, so much so that eucapnia is almost completely restored.

Remarkably, these wide-ranging ventilatory interaction effects for exercise and hypercapnic or dead space inputs all prove to be well predicted by an optimization model of ventilatory control first proposed some 25 years ago (Poon 1983; Poon 1987; Poon 1992a; Poon et al. 2000; Poon et al. 2007)—which posits that ventilatory output is not simply driven by chemical and exercise reflexes per se but may be controlled centrally to balance certain chemical and mechanical costs of breathing through optimal integration of chemoafferent and mechanoafferent inputs and efferent outputs, without the need for an explicit feedforward “exercise stimulus” (Appendix I). Additionally, the model accurately predicts the effects of ventilatory mechanical loading on the ventilatory pattern response to exercise, hypercapnia or dead space and their interactions [reviewed in (Poon et al. 2007)].

More generally, it has been suggested that the apparent optimality of respiratory homeostasis at rest and during exercise is not absolute and its maintenance may be subject to many

counteracting physiological, behavioral and defensive factors besides the normal chemical and mechanical costs of breathing that are all part of the overall optimality equation (Poon 2007; Poon et al. 2007). In particular, the optimization of respiratory homeostasis may be counterbalanced by concurrent optimization of thermal homeostasis (Mortola et al. 2000; Poon 2007) (Appendix II). In what follows, I present a systematic review of recent studies regarding the effects of 5-HT on control of breathing and thermoregulation and show that they all point to a hitherto unsuspected mechanism of respiratory-thermoregulatory interaction and optimization involving the LPBN and other pontomedullary and suprapontine nuclei.

2.2. Short-term modulation and ventilatory optimization

Recently, Mitchell et al. (2008) reported a similar potentiation of exercise ventilatory response by increased external dead space in goats and an abolition of such potentiation effect after spinal administration of methysergide, a nonselective antagonist for 5-HT₁, 5-HT₂ and 5-HT₇ receptor subtypes. Calling the potentiation effect under increased external dead space “short-term modulation” (STM), these authors propose that “[the observed] diminished V_T/T_I [mean inspiratory flow, an approximate measure of inspiratory motor outflow] responses following spinal methysergide... are consistent with the hypothesis that serotonin receptors modulate respiratory motoneuron excitability, thereby causing STM.” Using a conventional additive chemoreflex and feedforward “exercise stimulus” model to fit the data, they further suggest that “intraspinal methysergide completely blocked STM elicited by increased dead space.” Finally, noting that P_{aCO_2} regulation during exercise with increased external dead space was impaired after spinal administration of methysergide or the specific 5HT_{2A}-receptor antagonist ketanserin, they conclude that “spinal 5-HT₂ receptors modulate the exercise ventilatory response with increased [dead space] in goats.”

However, close examination of the reported data suggests an alternative, and more likely, explanation. For one, the authors propose that “diminished V_T/T_I responses following spinal methysergide are consistent with the hypothesis that serotonin receptors modulate respiratory motoneuron excitability, thereby causing STM”. This hypothesis neglects the nonconformance of this restrictive model to a wealth of critical experimental observations that are well predicted by the ventilatory optimization model – such as graded potentiation of the exercise ventilatory response by increased physiological dead space and hypercapnia, and the modulation of such graded interaction by ventilatory mechanical loading or unloading (Poon et al. 2007; Poon 2008). All these effects involve changes in both V_T/T_I and respiratory frequency (f) instead of V_T/T_I alone (Poon 1992b; Wasserman et al. 1997). Thus, “STM” of respiratory motoneuron excitability modulating V_T/T_I as described by Mitchell et al. (2008) in goats may represent a special case of an overarching respiratory optimization framework (Appendix I and Appendix II) that underlies the control of the overall ventilatory pattern (ventilatory output and respiratory rhythm) subject to varying interactions between the respiratory controller and the pulmonary gas exchange process, the respiratory mechanical process and myriad other physiological, behavioral and defensive processes (Poon 2007; Poon et al. 2007; Poon 2008).

Furthermore, it has been suggested that the optimization of ventilatory pattern for minimal chemical-mechanical cost of breathing during exercise may be mediated by self-tuning adaptation of respiratory afferent and/or efferent neurotransmission efficacy (Poon 1993; Poon et al. 2000; Zuperku et al. 2002), a control scheme that may provide an ‘internal model’ estimate of the changing metabolic demands in lieu of an explicit feedforward “exercise stimulus” (Young et al. 1998; Young et al. 2001; Poon et al. 2005; Tin et al. 2005; Poon et al. 2007). Thus, “STM” of V_T/T_I may be part of such self-tuning adaptation of the internal model for ventilatory optimization.

3. Modulation of ventilatory pattern by spinal 5-HT antagonism during exercise with increased external dead space

3.1. Limitations of the short-term modulation model

Another limitation of the “STM” model is the assumption that changes in V_T/T_I necessarily reflect similar changes in spinal respiratory motoneuron excitability. It is important to recognize that a decreased V_T/T_I response to exercise following spinal (intrathecal) methysergide¹ may also result from decreased descending respiratory (inspiratory and/or expiratory) drive². How could spinal methysergide possibly affect respiratory drive emanating from supraspinal respiratory neurons? The telltale signs for such a possibility are indeed evident from the reported data (Mitchell et al. 2008), which show that spinal methysergide not only led to diminished V_T/T_I but also decreased f responses during exercise with increased external dead space (Table 1). Since V_T was reportedly unchanged, it follows that the decreases in V_T/T_I and in f were due to corresponding increases in T_I .

To explain such diminished exercise f responses, Mitchell et al. (2008) hypothesize that “methysergide had unanticipated effects on spinomedullary transmission of sensory afferent inputs to the thoracic and/or cervical spinal cord. For example, antagonism of 5-HT receptors that inhibit sensory inputs to the spinal dorsal horn may indirectly influence rhythm generation (*via* subsequent projections to brainstem respiratory neurons)”. This hypothesis can be parsed into the following critical questions for systematic experimental and modeling explorations: (Q1) Which types of somato-viscerosensory afferent input are involved in such spinal serotonergic modulation of exercise f and T_I responses? (Q2) Why do they affect control of breathing only during exercise with increased external dead space? (Q3) Where are the central targets of these ascending somato-viscerosensory signals? (Q4) What specific roles do these central targets play in the control of respiratory rhythm and/or respiratory drive?

3.2. Gating of thermal and other somato-viscerosensory afferents by spinal 5-HT

Neurons of the superficial spinal dorsal horn (laminae I and II) are the target of descending serotonergic pathways which exert inhibitory influence on afferent transmission, either directly or indirectly (Yoshimura et al. 2006; Lu et al. 2007). These neurons receive primary afferent inputs from cutaneous and visceral receptors involved in nociception, pain and temperature sensing, and from a variety of muscle afferents. It is difficult to envisage how pain and nociceptive afferents from the skin and viscera might be activated by increased external dead space in modulating exercise f , V_T/T_I and T_I responses. On the other hand, it has been variously proposed that group III and IV thin-fiber afferents from working muscles or their vasculature may mediate the augmented exercise ventilatory response in congestive heart failure patients with increased physiological dead space (Scott et al. 2000) and may contribute to the putative feedforward “exercise stimulus” in healthy human subjects (Haouzi et al. 2008) [but see (Wells et al. 2008)] and in sheep (Haouzi et al. 2005) [but see (Yu et al. 2006)], or entrain the respiratory rhythm via the LPBN in rats (Potts et al. 2005). Similarly, group III and IV phrenic nerve afferents from the diaphragm *per se* reportedly may also stimulate breathing (Road 1990; Frazier et al. 1991; Teitelbaum et al. 1993; Yu et al. 1999). One would expect that the effects of these muscle afferents (if any) should be augmented upon disinhibition by antagonism of 5-HT receptors in spinal dorsal horn. However, the data of Mitchell et al. (2008) show that

¹In contrast to methysergide, spinal ketanserin reportedly had no consistent effects on f , V_T or V_T/T_I responses and had insignificant effect on the exercise ventilatory response (in the face of paradoxical significant increase in exercise PaCO_2 response) caused by the addition of dead space (Mitchell et al. 2008). The data for ketanserin were therefore inconclusive and will not be addressed herein.

²The model of Mitchell et al. (2008) identified the descending inspiratory drive during exercise as a “feedforward exercise stimulus” (see legend to Fig. 7 in the said paper). This is at variance with the classical definition of the putative “feedforward exercise stimulus” as a distinct stimulus in the afferent instead of efferent pathway. See: Grodins, F.S., 1950. Analysis of factors concerned in regulation of breathing in exercise. *Physiol Rev* 30, 220–239.

spinal methysergide in goats had no effects on the normal PaCO_2 regulation at rest and during exercise. If anything, spinal methysergide resulted in a higher PaCO_2 during exercise with increased external dead space. These observations argue against a significant role of serotonergic control of muscle afferents in mediating exercise hyperpnea with or without increased external dead space.

By the process of elimination, this then leaves thermoafferent signals from cutaneous and spinal warm/cold receptors as the remaining type of sensory input that is most likely involved in spinal serotonergic modulation of exercise f and T_I responses and perhaps, V_T/T_I response to boot (Q1). But why do they affect control of breathing only during exercise with increased external dead space (Q2)?

4. Balancing respiratory and thermal homeostasis during exercise in panting animals

4.1. Interplay of ventilatory CO_2 elimination and thermolysis during panting

To address this dilemma (Q2), it is paramount to point out that exercise hyperpnea in many furry mammalian species (but not humans (Whipp et al. 1970)) is important not only for respiratory regulation through pulmonary gas exchange, but also thermoregulation through respiratory evaporative heat loss as well (Gautier 2000; Robertshaw 2006; White 2006). The latter has been extensively documented in many animal models (including goats, sheep, and dogs) that are traditionally used in studies of exercise hyperpnea, all of which rely on panting for thermolysis during exercise particularly under high ambient temperatures (Schmidt-Nielsen et al. 1970; Goldberg et al. 1981; Baker 1982; Schroter et al. 1987; Nijland et al. 1992; Entin et al. 2005; Robertshaw 2006). Even in the horse, which is one of few non-human mammalian species that dissipate heat during exercise principally by evaporation of sweat, marked panting-like increases in f during exercise are said to account for some estimated 30–40% of the evaporative heat loss in compensation for their high mass-specific rate of heat production and low mass-specific surface area for heat dissipation compared to humans (McConaghy et al. 1995; McConaghy et al. 1998; Lindinger 1999). Although the increases in ventilatory output associated with the characteristic rapid and shallow breathing pattern during panting are confined largely to the *anatomic* dead space (where water vaporization takes place) to maximize evaporative heat loss without excessive CO_2 elimination and dehydration, alveolar hyperventilation inevitably ensues as core body temperature rises and panting intensifies (Hales et al. 1968; Robertshaw 2006). The increased work of breathing is minimized by panting at the resonant frequency of respiratory mechanics (Crawford 1962). It has been suggested that the panting response may represent an optimal tradeoff between increased respiratory thermolysis and increased work of breathing to maintain PaCO_2 /pH homeostasis and thermal homeostasis, whereas the concomitant decrease in PaCO_2 and increase in core temperature during severe exercise or severe thermal load in those animals may represent an ultimate tradeoff between inevitable departures from respiratory homeostasis and thermal homeostasis as both physiologic demands are “negotiated” by the respiratory controller to maximize the chance for survival (Poon 2007; Poon et al. 2007).

4.2. Disruption of thermal hyperpnea by spinal 5-HT antagonism

In panting animals like the goat, an increase in external dead space presents a significant challenge not only to pulmonary gas exchange but also to respiratory evaporative heat loss during exercise (due to increased distances for both CO_2 and temperature gradients from the airways to ambient), thus heightening the conflict between respiratory homeostasis and thermal homeostasis particularly during exercise (Q2). Spinal methysergide may tip the balance of respiratory and thermal homeostatic regulation by disinhibiting (hence exaggerating) the feedforward thermoafferent inputs from cutaneous cold receptors [which are active at room

temperatures (Tominaga 2007; Morrison et al. 2008)] – thereby disrupting the normal feedback control of thermal hyperpnea via central thermosensitive neurons in the preoptic area (POA) of the anterior hypothalamus (Romanovsky 2007; Morrison et al. 2008). Such an exaggeration of spinal cold receptor afferent activity following 5-HT antagonism may account (in whole or in part) for the decreases in f and V_T/T_I responses in those panting animals reported by Mitchell et al. (2008) during exercise with increased external dead space. A conceptual model delineating the postulated optimal interaction of respiratory and thermal regulation under metabolic thermal stress during exercise in panting animals is presented in Appendix II.

5. Effects of genetic 5-HT defects on respiratory-thermoregulatory interaction

5.1. Abnormal ventilatory pattern in mice with genetic 5-HT deficiency or excess

The above-postulated effect of 5-HT on respiratory-thermoregulatory interaction is supported by several lines of evidence. Recently, Hodges and Richerson (2008b) reported that mutant mice with near-complete absence of central 5-HT neurons due to conditional knockout of the transcription factor *Lmx1b* displayed decreased core temperature (at an ambient temperature of 25°C) and blunted hypercapnic ventilatory response compared with wild-type mice, whereas the hypoxic ventilatory response was not affected (Table 1). In previous work, these authors (Hodges et al. 2008c) have shown that such blunting of hypercapnic ventilatory response persists even when core temperature is kept normal at a thermoneutral temperature (30°C), and that the blunting effect is reversed by intracerebroventricular infusion of 5-HT. Similar blunting of the hypercapnic ventilatory response and not hypoxic ventilatory response has also been reported in serotonin transporter (5-HTT) knockout mice (Table 1) which exhibit chronic excess 5-HT in cerebrospinal fluid, a condition that is believed to result in over-adaptation and ultimate reduction of 5-HT function in adulthood (Li et al. 2008).

Equally of note, the *Lmx1b* knockout mice also displayed abnormal resting ventilatory pattern characterized by decreases in f and V_T/T_I (with no appreciable changes in V_T) compared with wild-type mice under thermoneutral conditions (Hodges et al. 2008c) (Table 1). In contrast, baseline f (but not baseline V_T) in the 5-HTT knockout mice was reportedly increased, although this could be due in part to increased basal metabolic rate (in terms of oxygen consumption) in these mutant animals (Li et al. 2008).

The blunted hypercapnic ventilatory response with intact hypoxic ventilatory response in the *Lmx1b* knockout mice may at first seem to support the notion that some 5-HT neurons are respiratory CO₂ chemoreceptors (Hodges et al. 2008c; Li et al. 2008). However, the demonstration of similar effects in the 5-HTT knockout mice and the complete rescue of the hypercapnic ventilatory response by intracerebroventricular infusion of 5-HT in the *Lmx1b* knockout mice indicate that the mechanism of 5-HT modulation of the hypercapnic ventilatory response is postsynaptic rather than intrinsic to 5-HT neurons. One possibility is that 5-HT may enhance the activity of nonserotonergic chemoreceptors [such as retrotrapezoid nucleus neurons (Mulkey et al. 2007)] or the gain of respiratory neuronal response to input from chemoreceptors (Hodges et al. 2008c; Li et al. 2008). However, it is not clear why such postsynaptic mechanisms would affect only the resting f and V_T/T_I but not V_T . Conversely, 5-HT may conceivably influence the resting f and V_T/T_I via putative neuromodulation, neuroplasticity and/or neurotrophic effects on respiratory rhythm or pattern generation or on respiratory motoneuron excitability [reviewed by Hodges et al. (2008a)]. However, such factors would likely affect both hypercapnic and hypoxic ventilatory responses instead of the hypercapnic ventilatory response alone. As per Hodges et al. (2008c), the dilemma is that “any explanation of the mechanisms involved must take into account the selective effect of 5-HT on respiratory frequency, ventilatory drive and the [hypercapnic ventilatory response], without effects on tidal volume or the hypoxic response.”

5.2. Similarities of respiratory abnormalities induced by 5-HT deficiency/excess and spinal 5-HT antagonism

To address this dilemma, it is again worthwhile to point out that the reported decreases in V_T/T_I but not in V_T imply that T_I was increased in the *Lmx1b* knockout mice.³ Thus, a decrease in V_T/T_I coupled with corresponding increase in T_I would leave V_T unchanged. The decreases in f and V_T/T_I and increases in T_I with no change in V_T in the *Lmx1b* knockout mice are reminiscent of similar effects resulting from spinal methysergide in goats during exercise with increased external dead space mentioned above (Table 1). Equally important, the decreases of the hypercapnic ventilatory response in the *Lmx1b* knockout mice and 5-HTT knockout mice are once again consistent with the impaired PaCO_2 regulation observed after spinal methysergide (Table 1). The striking similarities of the results with such disparate experimental preparations are not surprising, since 5-HT deficiency/excess or intracerebroventricular 5-HT infusion may affect not only supraspinal neurons but also spinal neurons that are serotonin-dependent (Hodges et al. 2008c).⁴ Indeed, 5-HTT is highly expressed in the rat spinal cord and its distribution parallels the descending serotonergic innervation (Sur et al. 1996); hence its elimination could lead to over-adaptation and reduction of 5-HT function at the spinal level.

The totality of the aforementioned observations boils down to this key question: Could serotonergic inhibition/disinhibition of second-order warm/cold sensory neurons in spinal dorsal horn be the common missing link that contributed (in whole or in part) to the serotonin-dependent respiratory effects reported by Hodges et al. (2008b; 2008c), Li et al. (2008) and Mitchell et al. (2008) (Table 1)? Or, in terms of the two remaining questions: (Q3) Where are the central targets of these serotonin-modulated ascending thermosensory signals? (Q4) What specific roles do these central targets play in the control of respiratory rhythm and/or respiratory drive?

These intriguing questions are now illuminated by several exciting new developments regarding the organization of the respiratory and thermoregulatory afferent pathways.

6. A serotonin-gated spinoparabrachial thermoafferent pathway for respiratory-thermoregulatory interaction

6.1. Possible role of LPBN in respiratory-thermoregulatory interaction

Sensation of ambient temperature is traditionally thought to be mediated primarily by a spinothalamocortical pathway in which afferent signals from cutaneous and spinal warm/cold receptors are projected from the spinal and trigeminal dorsal horns to the thalamus and then relayed to the primary somatosensory cortex (Craig et al. 1994). The spinothalamic projections also have extensive collaterals to the LPBN (Hylden et al. 1989) before going to the thalamus (Romanovsky 2007). Recently, systematic investigations of this spinoparabrachial pathway using multiple electrophysiological and pharmacological techniques and anterograde/retrograde neural tracing techniques in rats have unequivocally established that neurons in the LPBN (mainly the external-lateral subnucleus with an extension into the central subnucleus) also play a pivotal role in relaying cutaneous cool signals to the POA (Morrison et al. 2008; Nakamura et al. 2008), where they are integrated with feedback signals from POA thermosensitive neurons (Romanovsky 2007). Preliminary evidence indicates that the spinoparabrachial-POA excitatory pathway probably also mediates the transmission of cutaneous warm signals to the POA as well (Morrison et al. 2008).

³An increase in the resting T_I of the *Lmx1b* knockout mice has been documented at room temperature (Hodges and Richerson 2008b) but not at thermoneutral temperature.

⁴Intracerebroventricular 5-HT did not reverse the cold-induced hypothermia in the *Lmx1b* knockout mice, perhaps because of its inability to reach the thermogenic effector neurons in the periphery (Hodges et al. 2008c).

If the LPBN is the central target of spinal thermoafferent signals involved in thermoregulation (Q3), then what specific roles does it play in the control of respiratory rhythm and/or respiratory drive (Q4)? The answer to this final and most crucial question may lie in two latest studies (Song et al. 2009a; Song et al. 2009b), which suggest that the central and peripheral chemoreceptor afferents in rats are organized centrally in parallel and segregated pathways that separately modulate inspiratory drive, T_I and T_E . Specifically, these studies showed that LPBN lesions in anesthetized and vagotomized rats selectively attenuated the response in inspiratory drive to hypercapnic input without affecting the response in inspiratory drive to hypoxic input, indicating that inspiratory drive is modulated by central and peripheral chemoreceptor inputs via distinct LPBN and extra-LPBN pathways. The lesioned areas (mainly in the external-lateral and central subnuclei of the LPBN) are known to receive thermal, pain and nociceptive afferents from spinal dorsal horn (Gauriau et al. 2002; Nakamura et al. 2008).

These revelations immediately suggest a model of respiratory-thermoregulatory interaction (Fig. 1) that may explain the multi-experimental data shown in Table 1. Presumably, spinal thermoafferents that project to the LPBN may depress the gain of the central chemoreceptor input to LPBN neurons that mediate the modulation of inspiratory drive, thereby diminishing V_T/T_I and the hypercapnic ventilatory response without affecting the hypoxic ventilatory response. These spinoparabrachial thermoafferent signals may be normally suppressed by descending serotonergic inhibition at the spinal dorsal horn but could be unleashed by 5-HT deficiency, antagonism or over-adaptation, such as reported previously (Hodges et al. 2008b; Hodges et al. 2008c; Li et al. 2008; Mitchell et al. 2008). Additionally, the studies of Song et al. (2009a,b) show that a subset of LPBN neurons also mediate the shortening of T_E by either hypercapnic or hypoxic inputs, although these neurons are clearly distinct from those that mediate the control of inspiratory drive by hypercapnic (but not hypoxic) input. Absent any data concerning the effects of 5-HT dysfunction on the control of T_E from previous studies (Hodges et al. 2008b; Hodges et al. 2008c; Li et al. 2008; Mitchell et al. 2008), however, it is presently not clear whether these T_E -shortening LPBN neurons are also modulated by spinal thermoafferent inputs.

6.2. Other candidate loci for respiratory-thermoregulatory interaction

On the other hand, the data of Song et al. (2009a,b) show that lesions of the LPBN have little effects on the shortening of T_I evoked by hypercapnia and hypoxia. Thus, T_I -shortening by central and peripheral chemoreceptor inputs is probably mediated by extra-LPBN pathways in these anesthetized and vagotomized animals. Possible loci that may mediate such T_I -shortening responses include the Kölliker-Fuse nucleus (KF) and the medial parabrachial nucleus, which constitute the classical ‘pneumotaxic center’ that lies adjacent to the LPBN (Song et al. 2004; Song et al. 2006). These dorsolateral pontine nuclei are thought to be critical for the control of T_I and “inspiratory off-switch” (Cohen et al. 2004), in that lesions or NMDA receptor blockade in these areas may provoke apneusis in vagotomized animals [reviewed in (Song et al. 2004)]. It has been shown that in awake rats with vagi intact, the hypercapnic responses in V_T and f are depressed by prior lesions at KF or LPBN indicating that both these pontine nuclei participate in modulating the central chemoreceptor feedback control of ventilatory pattern (Mizusawa et al. 1995). Like the LPBN, KF also receives dense projections from neurons in the superficial spinal dorsal horn (Cechetto et al. 1985; Feil et al. 1995). Collectively, these functional and anatomical data suggest that the KF is a possible site for integration of chemo- and thermoafferents that contribute to the control of T_I (Fig. 1). The emergent significance of the LPBN (and probably KF) in integration of chemical control of breathing and thermoregulation is reminiscent of their demonstrated role in mediating the interaction of nociception and breathing (Jiang et al. 2004). This revelation provides a possible missing link that may account for the paradoxical serotonin-dependent modulations (or lack thereof) of f ,

V_T , T_I , V_T/T_I responses at rest and during hypercapnia, hypoxia and exercise reported previously (Hodges et al. 2008b; Hodges et al. 2008c; Li et al. 2008; Mitchell et al. 2008).

Alternatively, thermoafferent modulation of ventilatory pattern may also be mediated by medullary respiratory-related neurons (Fig. 1). Previous retrograde/anterograde neural tracing studies have identified a spinomedullary pathway that relays somato-viscerosensory signals from superficial spinal dorsal horn neurons to various medullary respiratory-related areas including the nucleus tractus solitarius and caudal and rostral ventrolateral medulla (Brodal et al. 1956; Menetrey et al. 1987; Gamboa-Esteves et al. 2001; Potts et al. 2002). However, it is not clear whether these ascending signals are related to thermoregulation or have influence on the hypercapnic ventilatory response.

Finally, respiratory-thermoregulatory interaction may also occur at anterior or posterior hypothalamic structures (Hinrichsen et al. 1998) where respiratory-related neurons have been identified (Kastella et al. 1974). Recent data show that electrical stimulation of the hypothalamic defense area elicits a tachypneic response (due to a shortening of expiration) that is abolished after inhibition of LPBN neuronal activity with muscimol (Diaz-Casares et al. 2009), an effect that is consistent with the demonstrated critical role of the LPBN in the chemoreflex regulation of T_E (Song et al. 2009a; Song et al. 2009b). Further studies are needed to elucidate the functional roles of these hypothalamic and LPBN respiratory-related neurons in respiratory-thermoregulatory interaction.

7. Gating of pain and thermoafferent transmission by dorsal horn 5-HT_{1A} receptor activity

7.1. Dorsal horn 5-HT_{1A} receptor activation restores respiratory drive after spinal cord injury

Another instance of spinal 5-HT dysfunction where the proposed model of respiratory-thermoregulatory interaction (Fig. 1) may prove instructive is SCI. In a series of recent studies, conscious rats recovering from incomplete contusion SCI at the T8 or C5 level were found to display a rapid and shallow breathing pattern at rest as well as depressed ventilatory response to hypercapnia (Teng et al. 1999; Teng et al. 2003; Choi et al. 2005), abnormalities that can be attributed in part to postinjury dysfunction of the motoneurons in spinal ventral horn that innervate related respiratory muscles (Teng et al. 1999). Paradoxically, these abnormalities were reversed after intraperitoneal injection of 5-HT_{1A} receptor specific agonist 8-OH DPAT or buspirone (Teng et al. 2003; Choi et al. 2005). Although these agents may potentially act at multiple spinal and supraspinal respiratory-related sites that express 5-HT_{1A} receptors [see (Choi et al. 2005)], subsequent study confirmed that increases in phrenic discharge amplitude (in anesthetized, vagotomized, pancuronium-paralyzed and ventilated rats) could be evoked by direct application of 8-OH DPAT to the dorsal aspect of the cervical spinal cord (Zimmer et al. 2006). The effect was greater in rats recovering from C2 hemisection compared with controls (with enhanced activity in the intact nerve and facilitation of crossed phrenic activity in the nerve ipsilateral to the hemisection), and was blocked by prior application of the specific 5-HT_{1A} antagonist WAY-100635. Presumably, the inhibitory effect of 8-OH DPAT on dorsal horn neurons may be mediated postsynaptically via hyperpolarizing 5-HT_{1A} receptors and presynaptically via putative “5-HT_{1A}-like” receptors, a 5-HT receptor subtype that is activated by 8-OH DPAT but not blocked by WAY-100635 (Yoshimura and Furue, 2006). Because reduction of spinal 5-HT_{1A} activity after SCI may lead to hyperexcitability and spontaneous firing of dorsal horn sensory neurons (Hains et al. 2003) that are normally inhibited by activation of 5-HT_{1A} receptors (Zemlan et al. 1994; Ito et al. 2000; Yoshimura et al. 2006), these data were taken to imply that dorsal horn inputs from certain respiratory muscle afferents may inhibit respiratory motor output via some local spinal reflex especially after SCI (Zimmer et

al. 2006) or via projection to supraspinal respiratory centers (Teng et al. 2003; Choi et al. 2005).

7.2. Gating of spinoparabrachial pathway for pain and thermoafferent transmission by dorsal horn 5-HT_{1A} receptor

An alternate hypothesis for interpreting these data is suggested by the above-proposed model of serotonin-gated respiratory-thermoregulatory interaction (Fig. 1). To put in perspective, it should be noted that SCI may impair 5-HT function not only at the injury site but potentially throughout the lower section of the spinal cord caudal and ipsilateral to the wound as well (Hains et al. 2002). Therefore, SCI at the C2, C5 or T8 levels may disrupt not only corresponding respiratory muscle afferents at these levels but also many other afferents innervating the lower body. For example, thoracic or lumbar SCI in rats has been shown to produce bilateral mechanical allodynia and warm/cold hyperalgesia in the limbs and torso during postinjury recovery (Hains et al. 2002; Hains et al. 2003; Wu et al. 2003; Colpaert et al. 2004), behavioral consequences that are consistent with the development of primary and secondary sensitization in pain and thermoafferent transmission (Poon et al. 2006). Administration of 5-HT_{1A} agonists alleviates these sensitization symptoms (Wu et al. 2003; Colpaert et al. 2004) and attenuates the corresponding hypersensitivity of dorsal horn sensory neurons (Hains et al. 2003). These allodynia-hyperalgesia effects are analogous to the chronic central pain experienced by many SCI patients, a neuropathic sensation that often develops across the upper and lower body irrespective of the SCI level (Ullrich et al. 2008). Indeed, possible treatment of such SCI-induced chronic pain with new high-efficacy, selective 5-HT_{1A} agonists has been proposed (Colpaert 2006).

The SCI-induced sensitization to thermal and pain stimuli and the reported effects of 5-HT_{1A} agonists in ameliorating these symptoms and attenuating dorsal horn sensory neuron hyperexcitability (Hains et al. 2002; Hains et al. 2003; Wu et al. 2003; Colpaert et al. 2004; Ullrich et al. 2008), when taken together, suggest that decreased 5-HT_{1A} receptor activity after SCI may result in chronic hyperactivity in the spinothalamic pathways that mediate pain and temperature sensations (Gauriau et al. 2002; Romanovsky 2007; Morrison et al. 2008). Since the spinothalamic projections have extensive collaterals to the LPBN (Hylden et al. 1989), it is reasonable to expect similar chronic hyperactivity in the spinoparabrachial branch of pain and thermoafferent pathways after SCI (Fig. 1). It is likely that such 5-HT_{1A} receptor-gated tonic spinoparabrachial activity (and corresponding postinjury hyperactivity) may exert negative influences on LPBN neurons that mediate the central chemoreceptor modulation of inspiratory drive (Song et al. 2009a), thus potentially explaining in part the enhancement of phrenic (or crossed-phrenic) amplitude by 5-HT_{1A} activation in anesthetized, vagotomized, paralyzed and ventilated rats especially after high-cervical SCI as reported previously by Zimmer et al (2006).

Similar 5-HT_{1A} receptor-gated spinoparabrachial hyperactivity may also contribute to the reported decreases in V_T following mid-cervical or thoracic SCI and the enhancement of V_T by 5-HT_{1A} agonists in conscious rats (Teng et al. 1999; Teng et al. 2003; Choi et al. 2005). However, in this case V_T is likely also encumbered by dysfunction of the motoneurons innervating intercostal/abdominal respiratory muscles (for thoracic SCI) and the diaphragm (for mid-cervical SCI). The resultant severe reduction in V_T (and increase in V_D/V_T) is accompanied by a corresponding increase in f to partially restore alveolar ventilation, a pattern which is characteristic of patients with lower thoracic SCI or other forms of respiratory muscle failure (Rochester et al. 1983; Prakash 1989). Such a rapid and shallow breathing pattern represents an optimal control strategy, in that it allows Pa_{CO_2} homeostasis to be maintained with reduced work of breathing (subject to a corresponding increase in V_D/V_T , see Appendix

I), hence sparing the respiratory muscles in the face of debilitating neuromechanical limitation (Poon 1983; Poon 1987; Poon 1992a; Poon et al. 2000; Poon et al. 2007).

8. Conclusion

The foregoing systematic review provides strong evidence that the LPBN plays a critical role in mediating respiratory-thermoregulatory interaction at rest and during exercise via a spinoparabrachial thermoafferent feedforward pathway. The latter is normally gated at the spinal dorsal horn by descending serotonergic inhibition presumably via the 5-HT_{1A} receptor subtype. Disruption of the serotonergic inhibition by spinal 5-HT antagonism, genetic 5-HT defects or SCI unleashes the thermoafferent feedforward signal thereby resulting in exaggerated cold-induced bradypnea and decrease of the hypercapnic ventilatory response, whereas activation of spinal dorsal horn 5-HT_{1A} receptors by specific agonists produces the opposite effects. The potential respiratory-thermoregulatory interaction via the proposed spinoparabrachial pathway argues against the classic set-point models for exercise hyperpnea (Oren et al. 1981) and for thermoregulation (Boulant 2006), and suggests that ventilatory pattern at rest and during exercise may be optimally “negotiated” by the respiratory controller to balance the conflicting demands for respiratory homeostasis and thermal homeostasis through coordinated ventilatory CO₂ elimination and respiratory heat loss.

Appendix I. Optimization model of respiratory control [excerpted from (Poon et al., 2007)]

The optimization model of ventilatory control (Poon 1983; Poon 1987) posits that ventilatory output is judiciously “chosen” by the controller to minimize the following respiratory cost function:

$$J = J_c + J_m = \left[\alpha \left(P_{a_{CO_2}} - \beta \right) \right]^2 + \ln \dot{W} \quad (1)$$

where J_c , J_m represent the chemical and mechanical costs of breathing (α , β are parameters). The dependence of $P_{a_{CO_2}}$ on $\dot{V}_E$ in the steady state is given by the pulmonary gas exchange relationship:

$$P_{a_{CO_2}} = P_{i_{CO_2}} + \frac{863 \cdot \dot{V}_{CO_2}}{\dot{V}_E \cdot (1 - V_D/V_T)} \quad (2)$$

where $P_{i_{CO_2}}$ is the inspired P_{CO_2} . The term $\dot{W}$ in Eq. (1) is a measure of the work rate of breathing defined (to a first approximation with a fudge factor) as:

$$\dot{W} = \dot{V}_E^2 / (1 - \dot{V}_E / \dot{V}_{max})^2 \quad (3)$$

where $\dot{V}_{max}$ is the maximal ventilation that could be sustained by the respiratory pump and the factor $(1 - \dot{V}_E / \dot{V}_{max})^2$ represents the pump’s neuromechanical efficiency, which is ~1 at low ventilatory levels and approaches 0 as $\dot{V}_E \rightarrow \dot{V}_{max}$.

The optimal $\dot{V}_E$ that minimizes J (Eq. 1) subject to the chemical constraint (Eq. 2) and mechanical constraint (Eq. 3) is given by:

$$\dot{V}_{E0} = 863\alpha^2 P_{a_{CO_2}} - \beta \frac{\dot{V}_{CO_2}}{(1 - V_D/V_T)} \quad (4)$$

$$\dot{V}_E = \frac{\dot{V}_{E0}}{1 + \dot{V}_{E0}/\dot{V}_{max}} \quad (5)$$

where $\dot{V}_{E0}$ is the optimal $\dot{V}_E$ when the latter is $\ll \dot{V}_{max}$. Thus, the controller gain is not constant but may be adjusted to track the metabolic $\dot{V}_{CO_2}$.

Equation 1 has been extended (Poon et al. 1992) to model the integrative control of $\dot{V}_E$ and respiratory pattern, by expressing $\dot{W}$ in terms of the isometric respiratory driving pressure $P(t)$ (instead of $\dot{V}_E$). The respiratory mechanical system in this case is defined by the following equation of motion:

$$P(t) = \dot{V}(t)R_{rs} + V(t)E_{rs} \quad (6)$$

whereby all ventilatory variables can be derived successively from the $P(t)$ waveform as follows:

$$P(t) \rightarrow \dot{V}(t), V(t) \rightarrow V_T, T_I, T_E \rightarrow \dot{V}_E \quad (7)$$

where R_{rs} , E_{rs} are respectively the total (extrinsic and intrinsic) respiratory resistance and elastance; $\dot{V}(t)$, $V(t)$ are instantaneous respiratory airflow and volume; T_I and T_E are inspiratory and expiratory durations. This integrative model captures both the optimal ventilatory response characteristics of Eqs. 4 and 5 and the corresponding optimal ventilatory pattern.

In particular, in SCI the resultant respiratory muscles dysfunction causes a decrease in the maximal $P(t)$ and $\dot{V}_{max}$. In this case a rapid and shallow breathing pattern is favorable for the mechanical constraint (Eq. 3) but this optimization strategy is restrained by a corresponding increase in V_D/V_T which is unfavorable for the chemical constraint (Eq. 2). The resultant optimal breathing pattern is determined by the balance of these two counteracting factors.

Appendix II. Model of optimal interaction of respiratory and thermal regulation

The optimization model of ventilatory control presented in Appendix I may be extended to include the interaction with thermoregulation under heat or cold stress. In this event the respiratory cost function (Eq. 1) may be rewritten as:

$$J = J_c + J_m + J_\theta \quad (8)$$

where J_θ represents the 'thermal cost' for departure from thermal homeostasis. The precise functional dependence of J_θ on $\dot{V}_E$ or $P(t)$ is presently unclear and is likely to vary with different animal species and thermal conditions. Nevertheless, it may be surmised that during metabolic or environmental heat stress J_θ is decreased with increases in $\dot{V}_E$ (characterized by a rapid

shallow breathing pattern) and resultant respiratory thermolysis, a strategy that may account for the observed thermal hyperpnea in many species (Robertshaw 2006; White 2006). In contrast, during environmental cold stress J_0 is decreased with decreases in $\dot{V}_E$ (characterized by a slow deep breathing pattern) to minimize respiratory heat loss, a strategy that may account for the reported cold-induced hypoventilation (Diesel et al. 1990; Mortola et al. 2000; Deveci et al. 2007). In both cases, disruption of serotonin-dependent inhibition of spinal dorsal horn relay neurons may exaggerate the transmission of feedforward thermoafferent inputs from cutaneous warm/cold receptors to the LPBN (Fig. 1), resulting in possible over-expression of cold afferents-induced hypoventilation with decreases in f and in hypercapnic ventilatory response as indicated in Table 1.

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Fig. 1.

Spinoparabrachial pathway for respiratory-thermoregulatory interaction. Cutaneous warm/cold receptor afferents are gated at the spinal dorsal horn by descending serotonergic inhibition. The resultant ascending feedforward thermoafferent input is relayed via parallel pathways to the thalamus and to the pre-optic area of anterior hypothalamus via the lateral parabrachial nucleus (LPBN), the proposed site of respiratory-thermoregulatory interaction. Other potential sites for respiratory-thermoregulatory interaction include the Kölliker-Fuse nucleus (KF), nucleus tractus solitarius (NTS), caudal and rostral ventrolateral medulla, and the hypothalamus. Amb, nucleus ambiguus.

Table 1

Effects of 5-HT dysfunction on ventilatory pattern in three animal models.

	f	V _T	V _T /T _I	T _I [*]	CO ₂ response ^{**}	Hypoxic response
Spinal methysergide (Mitchell et al. 2008)	↓	—	↓	↑	↓	?
<i>Lmx1b</i> knockout (Hodges et al. 2008b, c)	↓	—	↓	↑	↓	—
5-HTT knockout (Li et al. 2008)	?	—	?	?	↓	—

All effects are relative to corresponding controls. ↓decrease; ↑increase; —no change; ?uncertain.

* Changes in T_I are inferred from reported changes in V_T and V_T/T_I.

** The effect of spinal methysergide on the CO₂ response in the study of Mitchell et al. (2008) is inferred from a corresponding increase in PaCO₂ at constant exercise level.