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Spinal Plasticity following Intermittent Hypoxia: Implications for Spinal Injury

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Abstract

Plasticity is a fundamental property of the neural system controlling breathing. One frequently studied model of respiratory plasticity is long-term facilitation of phrenic motor output (pLTF) following acute intermittent hypoxia (AIH). pLTF arises from spinal plasticity, increasing respiratory motor output through a mechanism that requires new synthesis of brain derived neurotrophic factor (BDNF), activation of its high affinity receptor, tropomyosin-related kinase B (TrkB) and extracellular-related kinase (ERK) mitogen-activated protein (MAP) kinase signaling in or near phrenic motor neurons. Since intermittent hypoxia induces spinal plasticity, we are exploring the potential to harness repetitive AIH as a means of inducing functional recovery in conditions causing respiratory insufficiency, such as cervical spinal injury. Since repetitive AIH induces phenotypic plasticity in respiratory and motor neurons, it may restore respiratory motor function in patients with incomplete spinal injury.

Introduction

Since breathing is a critical homeostatic control system essential for life, the neural system controlling breathing is often inappropriately thought of as autonomic. To the contrary, breathing shares features with somatic motor behaviors, such as lifting, locomotion or visual saccades (i.e. it exhibits volitional control, and is mediated by spinal alpha motor neurons acting on striated skeletal muscle). As with other motor control systems, respiratory motor control exhibits considerable plasticity, meaning a change in future system performance based on experience,[1] and *meta*plasticity, or plastic plasticity.[2-4] In recent years, considerable progress has been made towards an understanding of cellular mechanisms giving rise to **spinal** respiratory plasticity.[1] One frequently studied model of spinal respiratory plasticity is phrenic long-term facilitation (pLTF), a prolonged increase in phrenic nerve activity following exposure to acute intermittent hypoxia (AIH).[5-8]

Spinal cord injury (SCI) disrupts motor output and causes paralysis below the site of injury. Thus, ventilatory failure is the most frequent cause of death following cervical spinal injury. [9] An important goal of SCI research is to harness plasticity, restoring respiratory (and somatic) motor function *via* enhancement of spared synaptic pathways to motor neurons below the site of injury.[10] Using a similar approach, it may be possible to restore breathing capacity in cases of ventilatory compromise arising from diverse etiologies including spinal injury, motor neuron disease and obstructive sleep apnea.[11] Despite

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differences in the pathogenesis of these disorders, each shares a common therapeutic goal: increased synaptic strength onto respiratory motor neurons *via* spontaneous and/or induced neuroplasticity.[11]

Considerable effort in our laboratory is focused on strengthening synaptic pathways to respiratory motor neurons *via* physiological or pharmacological approaches. We have recently come to realize that multiple, distinct signaling pathways give rise to long-lasting phrenic motor facilitation (PMF) *via* spinal mechanisms.[12-15] The most frequently studied model of PMF has been AIH-induced pLTF.[7-8,16] In brief, pLTF requires spinal serotonin type 2 receptor activation, new synthesis of BDNF, activation of the high affinity BDNF receptor, TrkB, and then ERK MAP kinase signaling.[12,17] We refer to this signaling cascade as the "Q pathway" to phrenic motor facilitation since serotonin type 2 receptors are metabotropic receptors coupled to Gq proteins, and other Gq protein coupled metabotropic receptors elicit similar PMF.[15]

In contrast, activation of Gs protein coupled metabotropic receptors, such as adenosine 2A or serotonin type 7 receptors, elicits long-lasting PMF *via* a unique mechanism independent of BDNF synthesis. This mechanism requires new synthesis of an immature TrkB isoform, and phosphoinositide 3 (PI3) kinase/protein kinase B signaling.[13,17] We refer to this signaling cascade as the "S pathway" since multiple metabotropic receptors coupled to Gs proteins elicit the same effect.[15] The S pathway does not contribute to AIH-induced pLTF under normal circumstances [14] . In fact, the S pathway appears to inhibit to the Q pathway following AIH, attenuating AIH-induced pLTF via cross talk inhibition.[14]

Both the S and Q pathways to PMF have potential to induce functional recovery following SCI via pharmacological interventions.[11] However, in this review, we focus on the capacity for intermittent hypoxia (and therefore the Q pathway) to enhance ventilatory capacity following chronic cervical spinal injury since it has been investigated more thoroughly.

Phrenic Long-Term Facilitation (pLTF)

Phrenic LTF was originally described as a persistent increase in phrenic motor output following repeated stimulation of the carotid sinus nerve.[18-19] Similar pLTF is also observed following repeated hypoxic episodes (see Figure 1).[7,16] pLTF requires spinal serotonin type 2 receptor activation for its induction, but not maintenance.[12,20] Conversely, intra-spinal injections of serotonin or 5-HT2 receptor agonists are sufficient to elicit PMF without hypoxia.[21] Downstream from (type 2) serotonin receptor activation, pLTF requires new BDNF synthesis,[22] activation of its high affinity receptor (TrkB),[22] and the activation of ERK MAP kinases.[17,23] Events downstream from TrkB/ERK activation are unclear, but may involve phosphorylation and insertion of glutamate receptors at the synapse between pre-motor and respiratory motor neurons,[7,24-26] changes in motor neuron excitability,[1] or effects on spinal interneurons.[27] Aspects of our working cellular model of pLTF are shown in Figure 2.

pLTF is pattern-sensitive since intermittent, but not sustained, hypoxia elicits its underlying mechanism.[28] Details of the intermittent hypoxia protocol seem relatively unimportant since the magnitude of pLTF is similar with hypoxic episodes ranging from 15 seconds to 5 minutes in duration,[29-30] and from 28 to nearly 70 mmHg arterial PO_2.[8,24,30] Thus the intermittent pattern is more important than the duration or severity of hypoxia. Serotonin receptor activation is both necessary and sufficient to elicit PMF,[12,21] and serotonin-induced PMF exhibits pattern sensitivity similar to hypoxia.[21] Thus, pLTF pattern-sensitivity may arise "downstream" from serotonin receptor activation versus hypoxia *per se*. Similar pattern sensitivity is characteristic of other models of serotonin-dependent

neuroplasticity, including serotonin-induced facilitation of *Aplysia* sensory-motor synapses[31-32] and *in vitro* LTF in neonatal XII motor neurons.[26]

Although we do not yet have a complete understanding of mechanisms giving rise to pattern-sensitivity in AIH-induced pLTF or serotonin-induced PMF, considerable progress has been made in recent years.[33-37] Our working model is that repetitive serotonin release in the phrenic motor nucleus activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, thereby increasing reactive oxygen species (ROS) formation. ROS, in turn, inhibit the activity of okadaic acid-sensitive serine/threonine protein phosphatases that normally constrain pLTF expression.[21,34-35] NADPH oxidase and protein phosphatase 2A appear to constitute a "regulatory cassette" that regulates pLTF expression and confers its pattern sensitivity because: 1) okadaic acid-sensitive phosphatases constrain pLTF during sustained, but not intermittent hypoxia;[36] 2) ROS [34-35] and NADPH oxidase activity [37] are necessary for pLTF; and 3) pLTF can be rescued in rats with suppressed ROS levels by spinal okadaic acid administration.[36] The relevant ROS production arises from repeated serotonin receptor activation, since serotonin-induced PMF requires NADPH oxidase activity.[21]

Collectively, these data demonstrate that intermittent (versus sustained) hypoxia and/or spinal serotonin receptor activation have the requisite properties to initiate spinal plasticity of potential relevance in the treatment of SCI. However, unique properties become apparent following repeated exposure to intermittent hypoxia.

Repetitive Intermittent Hypoxia

Considerable research has focused on extreme protocols of intermittent hypoxia (frequent episodes for ~8-12 hours per day over many days to weeks) due to interest in the pathophysiological consequences of sleep disordered breathing.[38] Although such chronic intermittent hypoxia (CIH) protocols elicit robust spinal plasticity,[39] pathophysiological effects (see below) make CIH unsuitable as a therapeutic tool in cases of spinal injury. More modest protocols of intermittent hypoxia (Figure 3) may trigger spinal plasticity without adverse side effects.

Acute intermittent hypoxia (AIH; 3 to 10 hypoxic episodes in < two hours) elicits spinal plasticity of relatively short duration (see discussion of pLTF above). To prolong and enhance AIH effects, we utilize repetitive AIH, including daily exposure for one week (dAIH)[23] or three times per week for 4 to 10 weeks (3xwAIH).[40,41] Although the optimal protocols are not yet known, dAIH and 3xwAIH both elicit spinal plasticity without obvious adverse consequences and, thus, may be useful in the treatment of chronic SCI. [42]

Chronic intermittent hypoxia (CIH)

CIH elicits plasticity at multiple sites of the respiratory control system, including increased: 1) carotid body chemosensitivity,[29,43] 2) synaptic strength in the nucleus tractus solitarius,[44] and 3) synaptic strength in spinal pathways to phrenic motor neurons.[39] Pretreatment with CIH also elicits metaplasticity, or plastic plasticity. [2-4] Examples of respiratory metaplasticity include: 1) enhanced AIH-induced pLTF [45-46] and 2) revelation of a unique form of sensory long-term facilitation in carotid chemo-afferent neurons, an effect not expressed in naïve rats.[29,47] Although each of these forms of plasticity/metaplasticity may enhance respiratory function, only spinal plasticity has the potential to elicit functional recovery below the site of injury since "upstream" regions (eg. medulla) are effectively blocked from communication due to the injury itself.

Offsetting the potential benefits of CIH-induced spinal plasticity, deleterious side effects may result from such severe protocols including hypertension,[48] impaired baroreflex control of heart rate,[49] neuro-cognitive deficits [50] and metabolic syndrome.[51]

Repetitive acute intermittent hypoxia

dAIH consists of 10, 5-minute hypoxic episodes with 5-minute intervals per day for seven days.[23,52-53] dAIH increases ventral cervical BDNF protein levels, particularly within phrenic motor neurons, and increases ERK phosphorylation following AIH,[23] an effect associated with spinal plasticity. These effects were observed without evidence of hypertension.[23] 3xwAIH consists of 10 episodes per day, three days per week for 10 weeks. 3xwAIH also up-regulates proteins critical for plasticity in phrenic motor neurons, including BDNF, TrkB, phospho-ERK1/2 and phospho-Akt.[54] 3xwAIH increases serotonin terminal density within the phrenic motor nucleus and serotonin 2A receptor expression on presumptive phrenic motor neurons.[54] In association, 3xwAIH enhances AIH-induced pLTF, similar to CIH (3 fold increase) [41] demonstrating that repetitive AIH elicits spinal plasticity *and* metaplasticity.

Collectively, these observations in normal rats are consistent with the possibility that repetitive AIH may be an effective treatment to improve respiratory function following cervical spinal injury. However, of considerable interest, we observed similar changes in non-respiratory motor neurons from regions of the spinal cord not associated with respiratory motor control.[40] Thus, intermittent hypoxia may also enable plasticity in non-respiratory motor neurons and, potentially, improve non-respiratory motor function following chronic SCI.

Intermittent Hypoxia and SCI

Upper cervical SCI affects both respiratory and somatic motor systems. Because SCI is generally not complete, there is considerable potential to strengthen spared spinal synaptic pathways as a therapeutic approach.[10] One frequently studied experimental model of SCI is C2 cervical hemisection (C2HS), which enables study of normally “silent” crossed-spinal synaptic pathways to phrenic motor neurons.[55] Following C2HS, some spontaneous recovery of phrenic (and diaphragm) activity below the injury is observed over weeks or months, an effect known as the “crossed phrenic phenomenon”.[55] However, spontaneous recovery is limited, and therapeutic strategies that further strengthen these pathways would be of considerable benefit.[11,42] Thus intermittent hypoxia has considerable potential as a therapeutic approach in persons with high cervical SCI.

Acute intermittent hypoxia

Two weeks following C2HS, rats exposed to AIH do not express pLTF on the side of injury. [56] However, by 8 weeks post-injury, robust AIH-induced pLTF is observed.[56] Since serotonergic innervation of the phrenic motor nucleus decreases dramatically two weeks post-C2HS, but substantially recovers by eight weeks, the capacity to express pLTF may be limited by serotonergic innervation in the phrenic motor nucleus. On the side opposite C2HS, limited capacity for pLTF is observed, even eight weeks post-C2HS,[57] suggesting that compensatory responses to unilateral cervical SCI prevent pLTF expression in contralateral phrenic motoneurons. However, the capacity to express contralateral pLTF is restored by pretreatment with dAIH.[58] One important point from these studies is that the capacity to induce spinal plasticity *via* intermittent hypoxia is limited shortly after SCI, but recovers progressively with serotonergic innervation below the site of injury. Thus, intermittent hypoxia may be most effective therapeutically in cases of chronic (*versus* acute)

SCI. On the other hand, spontaneous compensation may limit the capacity for induced plasticity in fully intact motor pools (e.g. side opposite C2HS).

CIH

Even two weeks post-C2HS, CIH strengthens crossed-spinal synaptic pathways to phrenic motor neurons.[39] Thus, more robust protocols of intermittent hypoxia may overcome limitations caused by reduced serotonergic innervation within the phrenic motor nucleus. CIH may induce spinal plasticity through “brute force” due to the greater number of hypoxic episodes, but this ability may also relate to an up-regulation of relevant serotonin receptors (5-HT2A) within the phrenic motor nucleus.[59]

Repetitive AIH

We have treated rats with dAIH beginning one week post-C2HS and demonstrated considerable potential for induced functional recovery of breathing capacity.[52-53] Specifically, dAIH nearly restored the capacity to increase tidal volume during hypercapnia, [52] increased spontaneous phrenic motor output at graded levels of hypercapnia, and increased spinally evoked potentials ipsilateral and contralateral to injury.[53] Similarly, in rats treated with dAIH one week post-C2HS, AIH-induced pLTF was observed contralateral to injury, suggesting that repetitive AIH has the capacity to restore ventilatory capacity (i.e. plasticity) and to enhance the capacity for additional plasticity (i.e. metaplasticity). We have not yet performed 3xwAIH on rats with cervical spinal injury; such experiments are currently under way.

In addition to respiratory plasticity, preliminary observations suggest that intermittent hypoxia also induces plasticity in non-respiratory motor behaviors in persons with incomplete, chronic, cervical spinal injuries.[60] Collectively, the demonstrated capacity of intermittent hypoxia to induce functional recovery of breathing capacity (and possibly limb movements) following cervical spinal injury is exciting, and suggests that further exploration of this area is warranted.

The S Pathway and SCI

Although our best evidence to date indicates that the S pathway inhibits the Q pathway to PMF following AIH,[14] these interactions may change during chronic disturbances, such as repetitive AIH or SCI. It remains to be explored if the S pathway contributes to plasticity induced by repetitive AIH in normal rats, or if it plays a greater role following SCI. From another perspective, knowledge that both the Q and S pathways are capable of inducing PMF suggests additional therapeutic strategies for patients with SCI. For example, drugs known to activate the S pathway may be of benefit, restoring respiratory and/or non-respiratory motor function following acute or chronic SCI.[13]

Conclusion

Because plasticity is an important feature of the respiratory control system, we are interested in understanding and harnessing these intrinsic mechanisms to strengthen synaptic connections and induce functional recovery following spinal injury. We have only recently come to realize that intermittent hypoxia increases phrenic motor output via spinal plasticity, and that this plasticity may restore breathing capacity in rodents with impaired breathing function.[11] This exciting line of research has considerable potential to develop novel therapeutic approaches to devastating ventilatory control disorders with few effective treatments and no known cures (e.g.. spinal injury, ALS or obstructive sleep apnea).

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List of abbreviations

AIH	acute intermittent hypoxia
3xwAIH	thrice weekly acute intermittent hypoxia
ALS	amyotrophic lateral sclerosis
BDNF	brain-derived neurotrophic factor
C2HS	C2 hemisection
CIH	chronic intermittent hypoxia
dAIH	daily acute intermittent hypoxia
ERK	extracellular-regulated kinase
MAP	mitogen-activated protein
NADPH oxidase	nicotinamide adenine dinucleotide phosphate oxidase
PI3-Kinase	phosphoinositide 3-kinase
(p)LTF	(phrenic) long-term facilitation
PMF	phrenic motor facilitation
ROS	reactive oxygen species
SCI	spinal cord injury
TrkB	tropomyosin-related kinase B

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Figure 1.
Compressed phrenic neurogram showing phrenic long-term facilitation (pLTF; bracket) following acute intermittent hypoxia. Compressed 1.5 hr time scale shows the short-term hypoxic responses (dramatic increase in phrenic amplitude) during 3 hypoxic episodes (arrows). pLTF results from these intermittent hypoxic episodes and is an example of the Q pathway to PMF.
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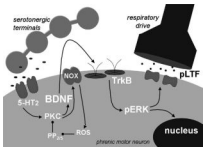

Figure 2.

Working model of cellular mechanisms giving rise to pLTF. Intermittent activation of serotonergic 5-HT2 receptors during hypoxic episodes activates protein kinase C (PKC). This, in turn, initiates new BDNF protein synthesis and increases NADPH oxidase (NOX) activity. After BDNF binds its high affinity receptor, TrkB, downstream signaling molecules include ERK MAP kinases. Although less clear, we suggest that ERK activity increases synaptic strength between descending respiratory pre-motor neurons and phrenic motor neurons, thereby expressing pLTF. Protein phosphatases (PP2A/5) normally constrain pLTF. However, ROS formation via NADPH oxidase activity inhibits these phosphatases and relieves their inhibitory constraint to pLTF. When this pathway is activated chronically, we propose that increased gene transcription occurs (i.e. in the cell nucleus), enhancing the expression of elements critical in this form of plasticity. For further detail, see ztext.
340×241mm (600 × 600 DPI)

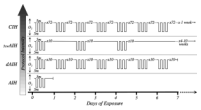

Figure 3.

Experimental protocols of intermittent hypoxia vary in their duration and intensity. The most limited protocol, acute intermittent hypoxia (AIH), elicits pLTF in short time domains. Daily AIH (dAIH) involves 10 hypoxic episodes per day for seven days. Thrice weekly AIH (3xwAIH) involves 10 episodes per day, three days per week for 4-10 weeks. These intermediate protocols of repetitive AIH upregulate key “plasticity proteins” involved in pLTF and confer metaplasticity to phrenic motor output. Whereas chronic intermittent hypoxia (CIH) also elicits spinal plasticity and metaplasticity, its intensity (72 episodes of hypoxia per day for 7-14 days) causes deleterious side effects such as hypertension and learning disabilities. 327×182mm (600 × 600 DPI)