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The impact of inflammation on respiratory plasticity

Austin D. Hocker[a], **Jennifer A. Stokes**[b], **Frank L. Powell**[b], and **Adrianne G. Huxtable**[a]

[a]Department of Human Physiology, University of Oregon, Eugene, Oregon, United States of America

[b]Division of Physiology, Department of Medicine, University of California San Diego, La Jolla, California, United States of America

Abstract

Breathing is a vital homeostatic behavior and must be precisely regulated throughout life. Clinical conditions commonly associated with inflammation, undermine respiratory function may involve plasticity in respiratory control circuits to compensate and maintain adequate ventilation. Alternatively, other clinical conditions may evoke maladaptive plasticity. Yet, we have only recently begun to understand the effects of inflammation on respiratory plasticity. Here we review some of common models used to investigate the effects of inflammation and discuss the impact of inflammation on nociception, chemosensory plasticity, medullary respiratory centers, motor plasticity in motor neurons and respiratory frequency, and adaptation to high altitude. We provide new data suggesting glial cells contribute to CNS inflammatory gene expression after 24 hours of sustained hypoxia and inflammation induced by 8 hours of intermittent hypoxia inhibits long-term facilitation of respiratory frequency. We also discuss how inflammation can have opposite effects on the capacity for plasticity, whereby it is necessary for increases in the hypoxic ventilatory response with sustained hypoxia but inhibits phrenic long term facilitation after intermittent hypoxia. This review highlights gaps in our knowledge about the effects of inflammation on respiratory control (development, age, and sex differences). In summary, data to date suggest plasticity can be either adaptive or maladaptive and understanding how inflammation alters the respiratory system is crucial for development of better therapeutic interventions to promote breathing and for utilization of plasticity as a clinical treatment.

Keywords

respiratory plasticity; inflammation; neuroplasticity; hypoxia; acclimatization; sensory plasticity; motor plasticity

Corresponding Author: Adrianne Huxtable, huxtable@uoregon.edu, 1240 University of Oregon, Eugene, OR 97403.

Introduction

Undermining the respiratory control system poses a critical threat to homeostasis. Many studies have examined how important molecules (like opiates) or diseases (like sleep apnea) cause dysfunction in the respiratory system, but only recently have we begun to recognize the interplay between the immune system and the respiratory system. A common attribute of almost all diseases and disorders, respiratory or other, is inflammation. Since we no longer recognize the central nervous system (CNS) as immune privileged, additional avenues whereby inflammation may undermine breathing are beginning to be understood. Increasing evidence supports a dynamic role for inflammation either by promoting or inhibiting different forms of neuroplasticity. Since respiratory plasticity (sensory or motor) has been proposed to be involved in disease development or treatment, many investigations into the role of inflammation in the respiratory system have focused on these areas. As will be discussed in this review, additional research into the interactions between inflammation and various forms of respiratory plasticity is still needed, in addition to increased focus on how inflammation might alter other aspects of respiratory control (rhythm generation, development, acclimatization). This review will highlight relevant models of inflammation and discuss the complex mechanisms by which inflammation can undermine or promote plasticity. The importance of inflammatory signals in the mechanism for neural plasticity in pain and nociception has been recognized for years (Di Filippo et al., 2008; Liu et al., 2011; Stemkowski and Smith, 2012; Watkins and Maier, 2002; Woolf and Salter, 2000). More recently, interest is growing into the effects of such signals for neural plasticity in other physiological control systems, such as the control of breathing and the heart (Powell and Kou, 2011). Despite the increased interest, many gaps in our knowledge of the effects of inflammation on the respiratory system remain and will be discussed. Understanding how inflammation alters the respiratory system is vital for development of better therapeutic interventions to promote breathing and utilization of plasticity as a clinical treatment.

Models of inflammation

Models of systemic inflammation are routinely used in research, in part, due to the increased appreciation for an underlying role for and the effects of inflammation in many pathologies. Here, we will briefly review some commonly used models of inflammation of particular relevance to research in respiratory control. Each model provides some similar, yet distinct, research advantages, but one common feature remains – all models activate some aspect of the innate immune system. Exogenous models like cytotoxins induce direct cell damage, causing release of cytokines and danger-associated molecular patterns (DAMPs) and inducing endogenous inflammation. Other exogenous models, like lipopolysaccharide (LPS), complete Freund's adjuvant (CFA), and Polyinosinic:polycytidylic acid (poly(I:C)), use components of pathogenic bacteria or viruses to activate receptors and stimulate endogenous immune responses. Relevant physiological perturbations, like hypoxia, can also induce inflammatory responses as discussed below.

There is now substantial evidence that systemic inflammation induces CNS inflammation. CNS inflammation is primarily associated with activation of microglia, the resident CNS immune cells, but other cell types (such as astrocytes) likely also play important roles.

Microglia, endothelial cells, neurons, and astrocytes all express functional levels of toll-like receptors (TLRs) which are activated by components of bacteria and viruses and lead to activation of NF-κB, stimulating release of cytokines, including IL-1β and TNFα, to cause inflammation. Furthermore, IL-1 and TNF receptors are found on microglia, neurons, astrocytes, and neurovascular endothelial cells (Lampron et al., 2013; Probert, 2015), suggesting inflammation can be sensed and further propagated by multiple cell-types in the CNS. For example, peripherally applied IL-1β induces prostaglandin synthesis in vascular endothelial cells of the blood brain barrier (BBB), which impairs respiration and is important for neonatal respiratory control during systemic infection (Hofstetter and Herlenius, 2005; Siljehav et al., 2015). Overall, the results of systemic inflammation are widespread in the CNS and multiple cell-types play important roles in mediating CNS inflammatory effects. Since systemic inflammation elicits many changes in the CNS, it is probable such CNS changes alter neural control of breathing.

Lipopolysaccharide and CNS inflammation

LPS, a component of gram-negative bacterial cell walls, activates the innate immune response via TLR4. TLR4 activation induces pro-inflammatory gene expression through activation of MAPKs JNK, ERK, p38, and the transcription factor NF-κB. Many endogenous ligands also activate TLR4 including proteins released from dead or dying cells, heat shock proteins, and modified low-density lipoproteins (Erridge, 2010; Lehnardt et al., 2008; Ohashi et al., 2000). Since LPS activates endogenous inflammatory pathways and much is known about its signaling cascade, it serves as a relevant ligand to induce systemic inflammation.

The magnitude of LPS effects are dependent on the organism from which LPS originates, and the species, sex, and age of the organism in which it is used (Nemzek et al., 2008). *E. coli*, *salmonella*, and other gram negative bacteria contain LPS, but the structure of the lipid component of LPS can differ between organisms, with some LPS molecules having more potent effects, likely due to changes in how they interact with TLRs (Jin et al., 2013; Li et al., 2013; Rietschel et al., 1994). High doses (>10 mg/kg in rats, >7 mg/kg in mice) of LPS cause sepsis and high mortality and even more moderate doses (5-6 mg/kg) of LPS can cause progressive neurodegeneration (Cardoso et al., 2015; Qin et al., 2007), long-term behavioral changes, and decreased neural markers of hippocampal plasticity (Anderson et al., 2015). Importantly, lower doses (typically 0.05-1 mg/kg) induce febrile responses in rodents similar to human responses to LPS (Nemzek et al., 2008; Redl et al., 1993). Furthermore, low doses of LPS increase cytokine expression similarly in humans and rodents, further supporting the relevance of LPS as a model to induce inflammation (Copeland et al., 2005). While some controversy exists about the use of LPS to mimic endotoxemia (Perlman et al., 2013; Seok et al., 2013), use of low-dose LPS as a TLR4 agonist is a reasonable model of low-level inflammation.

While the CNS was historically described as “immune-privileged”, there is now substantial evidence for systemic inflammatory signals altering CNS activity. Some pathogens, immune cells, and pro-inflammatory molecules can either cross the BBB under certain conditions or induce inflammatory signaling within the CNS via cross-talk between endothelial cells,

neurons, and glia (for further details refer to Lampron et al., 2013). Circumventricular organs also play a role in CNS responses to inflammation by allowing either LPS or cytokines to interact directly with neurons and glia. For example, the area postrema contains cells that are activated by LPS, TNFα, and IL-1β (Wuchert et al., 2008; Wuchert et al., 2009). Since the capacity for LPS penetration across the BBB is low (Banks and Robinson, 2010), recent research has highlighted multiple alternative transmission mechanisms. Even low-dose LPS (intraperitoneal or intratracheal) is sufficient to induce inflammatory gene and protein expression in the CNS without significant levels of LPS crossing the BBB (Balan et al., 2011; Banks and Robinson, 2010; Laye et al., 1995). Vagal afferents moderate communication of low-level systemic inflammation to the CNS, since vagotomy eliminates the febrile response associated with sickness and inflammation after very low doses of LPS (1ug/kg), but not higher doses. At higher doses, there are likely alternative routes for transmission and induction of CNS inflammation (Romanovsky et al., 1997). This is evident by subdiaphragmatic vagotomy inhibiting CNS gene expression of IL-1β after i.p. LPS (Laye et al., 1995), and cervical vagotomy inhibiting medullary IL-1β after intratracheal LPS (Balan et al., 2011). The mechanisms of this alternative transmission are still active areas of investigation.

Other models of induced inflammation

Viral infections are also common models of inflammation and induce similar inflammatory pathways to LPS-induced inflammation. RNA viruses induce inflammation through activation of TLR3, TLR7, and TLR8. The most common model of viral infections is the viral mimetic, poly(I:C), a synthetic dual-stranded RNA molecule activating TLR3. TLR3 activation elicits similar inflammatory profiles to other TLRs, including activation of NF-kB and MAPKs and increased proinflammatory gene expression. The inflammatory response induced by poly(I:C) is similar to LPS with respect to effects on systemic and CNS inflammatory cytokine expression, febrile response, and HPA axis activation (Arsenault et al., 2013; Cunningham et al., 2007; Gandhi et al., 2007). Furthermore, though poly(I:C) can compromise the BBB (Wang et al., 2004), other mechanisms of peripheral to central inflammatory transmission are likely similar between poly(I:C) and LPS. In summary, there are similar CNS inflammatory consequences of inflammation induced by LPS and poly(I:C), though LPS is a more widely used model. However, based on correlations between maternal viral influenza infection and the risk of offspring developing schizophrenia, poly(I:C) is increasingly being used to study perinatal CNS inflammation (Brown et al., 2004).

Generalized tissue damage and cell death induces systemic and CNS inflammation. Cell damage leads to release of DAMPs, which activate TLR4 to induce systemic inflammation. Bleomycin, a cytotoxin and anti-cancer chemotherapy drug, causes lipid peroxidation and DNA damage and has been used to model the effects of acute lung injury, induce cell damage, and cause inflammation (Tolle and Standiford, 2013). Intrapulmonary administration of bleomycin increased levels of inflammatory cytokines in lung tissue, area postrema and nucleus tractus solitarius (Jacono et al., 2011). Thus, generalized cell damage is another inflammatory model altering areas relevant to the neural control of breathing.

Hypoxia-induced inflammation

The mechanisms by which hypoxia activates inflammatory signals in the CNS are related to O_2-sensitive prolyl hydroxylases (PHD). Hypoxia activates NF-κB to promote transcription of proinflammatory cytokines when IκB kinase (IKK-β) is disinhibited by PHD (Cummins et al., 2006; Rius et all., 2008). This PHD mechanism of O_2-sensitivity is similar to that for hypoxia inducible factor-1α (HIF-1α), which is a master switch for gene expression in hypoxia (Prabhakar and Semenza, 2015). Perhaps it is not surprising that common molecular signals have evolved for two of the most evolutionarily ancient stress responses to tissue injury and hypoxia (Zinkernagel et al., 2007) and that they act synergistically. NF-κB is a critical transcriptional activator of HIF-1α and basal NF-κB activity is required for HIF-1α protein accumulation during hypoxia in the brain of hypoxic animals (Rius et al., 2008). Conversely, HIF-1α promotes the inflammatory response within a hypoxic environment, at least in peripheral immune cells (Cramer et al., 2003; Lipman et al., 2012; Peyssonnaux et al., 2005; Walmsley et al., 2005; Zinkernagel et al., 2007).

To summarize, multiple models are used to study inflammation and many share common mechanisms. LPS is the most commonly used model to study inflammation and acts as a TLR4 agonist at physiologically relevant levels, where it induces both systemic and CNS inflammation. Other models inducing inflammation such as poly(I:C), bleomycin, or CFA, though less commonly utilized, can induce inflammation via TLR activation and display similar increases in CNS inflammatory gene expression. CNS inflammation induced in all of these models is most likely a result of vagal afferent signaling and LPS/cytokine interactions with the BBB at low doses. In addition, hypoxia can stimulate inflammation in the CNS by directly activating similar mechanisms in neurons or glia, or via secondary effects of hypoxic activation of the sympathetic nervous system (*see High Altitude below*).

CNS inflammation and neuroplasticity

Inflammatory signals can cause or inhibit plasticity at every level of neural control systems, including afferent and efferent arms of a reflex, integration in the CNS, and during different stages of development.

Neuro-immune reprogramming and plasticity

Recent research revealed that perinatal inflammation has potent effects on future immune function. Like adults, neonates challenged with LPS develop a short-term tolerance to a subsequent LPS challenge (Biswas and Lopez-Collazo, 2009). However, there is a critical developmental window between P7 and P28 in which a low dose of LPS or poly(I:C) reprograms the immune system with effects lasting into adulthood (Ellis et al., 2005; Spencer et al., 2011; Spencer et al., 2006). After neonatal inflammation, adults exposed to subsequent inflammatory stimuli have reduced cytokine release, reduced febrile response, and elevated corticosterone levels as a result of long-lasting changes in neural regulation of anti-inflammatory pathways and altered HPA-axis regulation (Mouihate et al., 2010; Shanks et al., 2000). This developing field of research suggests a complex form of plasticity exists within the immune system, whereby activation of the immune system during a critical period induces long-lasting changes in immune function.

Similarly, perinatal inflammation has been implicated in impaired cognitive function and behavior into adulthood. For a detailed review of the many effects of early life information, we direct the readers to recent reviews (Bilbo and Klein, 2012; Bilbo and Schwarz, 2012; Yirmiya and Goshen, 2010). In brief, early-life infection causes lasting impairment of hippocampal plasticity and increases vulnerability for neuropsychiatric disorders (Bilbo et al., 2005; Hornig et al., 1999; Rantakallio et al., 1997). The magnitude and timing of perinatal inflammation, however, can have differential effects on adult behavior, memory, and learning (Bilbo and Schwarz, 2012). For example, high-doses of LPS cause significant long-term structural changes in the brain, including neuron loss and hypomyelination (Cardoso et al., 2015). In contrast, low-dose, neonatal LPS alters future immune responses and causes memory impairment in adults (Bilbo et al., 2005). Low-dose, neonatal LPS exposure also increases adult anxiety-like behaviors, suggesting even minor immune challenges during development can have lasting neural consequences (Walker et al., 2004). Similarly, the perinatal timing of inflammation causes differential effects on behavioral outcomes (Schwarz and Bilbo, 2011). Overall, perinatal inflammation appears to cause long-term detriments in a variety of neural functions, yet we know very little about the effects of perinatal inflammation on any aspect of respiratory control.

Nociception

The effects of inflammation on nociception have been extensively studied (reviewed in Ren and Dubner, 2015; Stemkowski and Smith, 2012; Woolf and Salter, 2000) and provide a framework to reference respiration related studies. Both systemic and local inflammation can induce peripheral and central neural sensitization leading to hyperalgesia and allodynia (Luo et al., 2014). Briefly, peripheral injury and inflammation sensitizes primary nociceptive neurons via inflammatory mediators including bradykinin and prostaglandins (reviewed in Pethő and Reeh, 2012). Peripheral sensitization and increased spontaneous activity of nociceptive neurons cause activity-dependent changes in the spinal dorsal horn second order neurons (Woolf and Salter, 2000), an effect mediated by multiple cell types including microglia, astrocytes, and neurons (Ren and Dubner, 2015). Microglia in the dorsal horn respond rapidly to increased primary afferent activity by increasing in number and changing morphology (McMahon and Malcangio, 2009). They are activated by purinergic signaling and can synthesize and release pro-inflammatory cytokines and mediate sensitization through release of BDNF (Fabbretti, 2013; Old et al., 2015).

More recently, fractalkine, a chemokine primarily released by neurons in the CNS, has been shown to play an important role in the pathogenesis of chronic pain. Fractalkine activates the CX3CR1 receptor, which is exclusively expressed on microglia in the CNS and induces release of inflammatory mediators (Clark and Malcangio, 2014). Intrathecal administration of fractalkine is sufficient to induce mechanical sensitization and, after peripheral nerve injury, a CX3R1 antagonist reduces mechanical pain sensitization, exemplifying the critical role of microglial activation in central sensitization (Milligan et al., 2004). Astrocytes contribute to central sensitization as well, most likely through regulating glutamate transport and releasing cytokines (Gao and Ji, 2010; Old et al., 2015). Together, these studies exemplify an interesting form of inflammation-induced neuroplasticity, which likely bear

mechanistic similarities to the role of inflammation in some forms of respiratory sensory plasticity.

Inducing peripheral inflammation with LPS can also cause nociceptive sensitization. In adults and neonates, i.p. doses of LPS cause acute sickness behavior and hyperalgesia (Watkins et al., 1994; Wiertelak et al., 1994) and neonates treated with intrathecal LPS also develop acute hyperalgesia (Moss et al., 2007; Zouikr et al., 2014), while adult male mice treated with intrathecal LPS develop a tactile allodynia lasting at least 7 days (Stokes et al., 2013). While immune responses to LPS are similar in neonates and adults, the long-term effects of LPS in the different age groups are substantially diverse. Adults develop a short-term tolerance to subsequent inflammatory stimuli (Biswas and Lopez-Collazo, 2009). In contrast, adults treated with LPS as neonates display nociceptive sensitivity (Boissé et al., 2005). However, in other models of nociceptive sensitization, neonates exhibit a short-term protection from inflammatory nociceptive plasticity. Spared nerve injury (SNI), a model of neuropathic pain which induces spinal inflammation and hyperalgesia, has no effect on nociceptive sensitivity in mice and rats until 4-5 weeks of age due to central production of anti-inflammatory IL-10 (McKelvey et al., 2015). These studies exemplify the importance of age and cause of inflammation (endogenous – like SNI, or exogenous – like LPS) in determining the long-term effects of inflammation on the nervous system (Schwaller and Fitzgerald, 2014).

Chemosensory Plasticity

Chronic intermittent hypoxia (CIH) induces sensory plasticity in the carotid sinus nerve. Ten days of CIH increases acute hypoxic ventilatory responses and sensitizes the carotid sinus nerve response to hypoxia. CIH also primes the carotid sinus nerve for augmented plasticity whereby acute intermittent hypoxia (IH; 10 × 15 sec 12% O_2, interspersed by 5 min of hyperoxia) causes greater sensory long-term facilitation (LTF) in the carotid sinus nerve compared to sensory LTF without CIH preconditioning (Peng et al., 2003). Additionally, CIH also leads to persistently elevated baseline carotid sinus nerve activity and augmented hypoxic ventilatory responses for 21 days, which may be an important step in the pathogenesis of hypertension (Del Rio et al., 2014). Sensory LTF appears independent of hypoxic severity and is reversible by a return to normoxia for 10 days (Peng et al., 2003).

Though the detailed molecular mechanisms of sensory LTF are still incomplete, significant progress has been made in determining the involvement of important molecular players, including inflammatory molecules. Intermittent application of both 5-HT and angiotensin II are sufficient to produce sensory LTF (Peng et al., 2003; Peng et al., 2011; Peng et al., 2006) and 5-HT is released from carotid bodies during acute IH after CIH. Similarly, CIH up-regulates components of the renin-angiotensin system including angiotensin type 1 receptors, which activate NOX2 and are required for sensory LTF (Lam et al., 2014; Peng et al., 2011). Reactive oxygen species (ROS) also have been suggested to contribute to sensory LTF in response to acute IH. ROS are increased by CIH through multiple mechanisms including transcriptional upregulation of NOX2, decreased SOD2 activity (Prabhakar et al., 2015) and induction of inflammation and immune cell infiltration in the carotid body (Lam et al., 2012). Furthermore, antioxidants given during CIH abolish hypoxic sensitization and

sensory LTF (Del Rio et al., 2010; Peng et al., 2003; Peng and Prabhakar, 2004; Prabhakar et al., 2015).

While antioxidants and ROS inhibitors abolish many of the effects of CIH (Iturriaga et al., 2015; Peng et al., 2003), anti-inflammatory drugs have no effect on chemosensitivity and sensory LTF (Del Rio et al., 2012; Iturriaga et al., 2015). Thus, though inflammatory cytokines are present in carotid bodies and may modulate carotid sinus nerve activity after CIH, inflammation per se does not significantly contribute to carotid body hypoxic sensitization (Del Rio et al., 2012). However, anti-inflammatory treatment during CIH mitigates CIH-induced hypertension and the elevated baseline carotid sinus nerve activity normally observed after CIH (Del Rio et al., 2012), suggesting a role for inflammatory molecules in modulating carotid body activity. In fact, direct application of IL-1β or LPS to carotid bodies increases carotid sinus nerve frequency (Fernández et al., 2008; Shu et al., 2007), but decreases carotid sinus nerve responses to excitatory stimuli (nicotine and hyperoxia) (Fernández et al., 2008). Thus, although LPS and CIH may both induce carotid body inflammation and modulate afferent activity, the hypoxic sensitization of carotid sinus nerve responses does not appear to depend on inflammation.

Sensory LTF of the carotid sinus nerve is an important form of respiratory plasticity related to inflammation and likely relevant to common pathologies like OSA and hypertension (Del Rio et al., 2014, Dempsey et al., 2010). When inflammation is induced by CIH, treatment with NSAID eliminates elevated carotid baseline activity and hypertension, but not hypersensitivity to hypoxia. However, details of the relationship between inflammation and sensory LTF have not been fully investigated so it is not known where NSAIDs exert an inhibitory effect. Regardless, inflammatory cytokines appear to modulate carotid sinus nerve activity and may alter neural activity in the CNS and contribute to CIH-induced hypertension (Iturriaga et al., 2015).

Chronic sustained hypoxia (CSH) also increases carotid body chemoreceptor O_2-sensitivity although this is not necessarily the same mechanism as sensory LTF with CIH. Liu and colleagues showed increased carotid body O_2-sensitivity with CSH (8-10 days) in rats was accompanied by an increased presence of immune cells (ED1+) in the carotid body (which are rare in control conditions), and increased cytokine (IL-1β, IL-6, TNFα) and chemokine (MCP-1) mRNA (Liu et al., 2009). Treating animals with dexamethasone or ibuprofen during CSH blunted or blocked these increases in carotid body O_2-sensitivity, immune cell invasion and cytokine increases. Cytokines showed differential expression time courses, which were not dependent just on immune cell migration because both type 1 and type 2 carotid body cells (neuronal and glial-like, respectively) produced cytokines (Liu et al., 2009). The significance of inflammatory signaling in different types of cells remains to be investigated, as does the potential consequence of different sources of immune cells migrating into the carotid body. For example, alveolar macrophages are the ‘first responders’ to environmental hypoxia in rats, and induce systemic inflammation by releasing chemokines (MCP-1) in the microvasculature after hypoxic activation in the lungs (Chao et al., 2011a; Chao et al., 2011b). Potential differences between such hypoxic alveolar macrophages and those from, for instance, an ischemic circulatory bed have not been studied. The possibility that such differences also contribute to the opposite effects of

inflammation induced by LPS versus inspired hypoxia on chemoreflexes (inhibiting vs. facilitating, respectively), remains to be tested. In a number of animal species, the hypoxic or hypercapnic ventilatory responses are actually attenuated by systemic inflammation (Fernández et al., 2008; Ladino et al., 2007; McDeigan et al., 2003).

While molecular signaling changes contribute to carotid body plasticity, hypoxia and inflammation can also induce morphological changes in the carotid body. For example, CSH induces hyperplasia and hypertrophy of glomus cells, increased expression of tryrosine hydroxylase, and neo-vascularization (Wang et al., 2002; McGregor et al., 1984), but it is not clear if this contributes to functional changes. The effects of anti-inflammatories on carotid body hypertrophy per se during CSH remain to be studied. CIH has no clear effects on glomus cell morphology (Prabhakar et al., 2015), but does induce macrophage infiltration, though no significant structural changes after CIH have been demonstrated in carotid bodies (Lam et al., 2012). Similarly, carotid body inflammation induced by intravenous or direct application of LPS causes immune cell infiltration and disorganizes glomus cell clusters, which may contribute to functional alterations (Fernández et al., 2008; Gauda et al., 2013). Neonatal LPS treatment also induces immune cell infiltration in the carotid body and a small reduction in carotid sinus nerve activity in response to hypoxia (Master et al., 2015). Further investigation is needed to determine whether or not inflammation leads to significant morphological changes in the carotid body.

Plasticity in medullary respiratory centers

Recent experiments indicate that inflammatory signals in respiratory centers of the central nervous system (CNS) contribute to plasticity during CSH. For example, ventilatory acclimatization to hypoxia involves a time-dependent increase in the hypoxic ventilatory response (HVR) during CSH (Pamenter and Powell, 2016) that is blocked by systemic application of the NSAID ibuprofen in rats (Popa et al., 2011). Ibuprofen during CSH also blocks increases in IL-1β and IL-6 expression in the nucleus tractus solitarii (NTS) of rats (Popa et al., 2011). The NTS is an important site for VAH the site of the primary synapse from carotid body chemoreceptors and exhibiting plasticity in glutamatergic neurotransmission that is necessary for VAH (reviewed by Pamenter and Powell, 2016). Together, these data suggest that inflammatory signals in the NTS are important for plasticity in VAH. Further, Popa and co-workers (2011) provide additional arguments that the results cannot be explained just by the known effect of ibuprofen to block increased carotid body O_2-sensitivty with CSH (Liu et al., 2009). CSH also increases the ‘CNS gain of the HVR’, which is an increase in ventilatory motor output (measured as integrated phrenic nerve activity or ventilation) for a given level of carotid body stimulation (Dwinell and Powell, 1999; Wilkinson et al., 2010) and this also must be decreased by ibuprofen during CSH to explain the results in rats (Popa et al., 2011). The importance of inflammatory signals for plasticity in VAH is also supported by significant decreases in the HVR of healthy human volunteers given ibuprofen during altitude acclimatization (Basaran et al., 2016), although the site of action cannot be determined in these studies. (see *High Altitude* below).

Similar to the discussion of the carotid body, the type of cells involved in generating inflammatory signals may be important for plasticity in CNS respiratory centers. Glial cells, specifically microglia and astrocytes, are present in respiratory centers of the brainstem surrounding neural synapses and neighboring blood vessels, and glial cells influence neuronal transmission and central respiratory control (Erlichman et al., 2010; Funk et al., 2015; Huxtable et al., 2010). For example, astrocytes residing in central chemoreceptor areas of the brainstem are chemosensitive and respond to physiological decreases in pH (Kasymov et al., 2013; Gourine et al., 2010). Recently, Tadmouri et al. (2014) used immunohistochemistry to show that microglia and astrocytes in the NTS were activated by 24 hours of CSH, with astrocyte activation peaking at 6 hours, followed by microglia at 24 hours of CSH. They also showed that systemic administration of minocycline, which inhibits microglia among other effects (Moller et al., 2016), blocked a time-dependent increase in ventilation observed following 24 hours of CSH, as well as immunohistochemical signals for microglia activation (Tadmouri et al., 2014). MacFarlane et al. (2015) also found that CSH (5 days) increased expression of microglia in the NTS and dorsal motor nucleus of the vagus, and this change was blocked by minocycline. Here, we present new data to show that minocycline blocks increases in inflammatory signals in the NTS in adult male rats with CSH. These experiments were carried out in accordance with the NIH guidelines for care and use of laboratory animals and approved by the UC San Diego Institutional Animal Care and Use Committee, using the same methods and primers described previously (Popa et al., 2011). Briefly, we used RT-PCR to measure changes in mRNA for cytokines in biopsies of the NTS after 24 hours of CSH with and without minocycline treatment (45 mg/kg i.p.). The results in Figure 1 show that CSH increased mRNA for IL-6 and TNFα in the NTS and these increases were blocked by systemic minocycline treatment. This data supports glial activation as a step leading to increased cytokines and inflammatory signals for ventilatory acclimatization to CSH. However, further experiments are necessary to determine the exact effects of minocycline (cf. Moller et al., 2016), the relative roles of microglia versus astrocytes and if the sequence of their activation is important as suggested by Tadmouri and co-workers (2014).

Similarly, more experiments are necessary to determine which inflammatory signals increase O_2-sensitivity in carotid bodies and ventilation. Hypoxia increases NF-κB as described above, and this can promote the transcription of IL-1β and other pro-inflammatory cytokines (Stanimirovic et al., 2001). IL-1β can directly affect CNS neurons (Aleksandrova et al., 2015) including those in the NTS (Jacono et al., 2011) and IL-1β is the major inducer of cyclooxygenase-2 (COX-2) in the CNS (Samad et al., 2001). COX-2 induction leads to increased production and release of prostaglandin E2 (PGE2) that can affect breathing via EP3 receptors in the NTS (Herlenius, 2011). PGE2 effects are of interest for plasticity in chemoreflexes because they are important for increased excitability in sensory nerve endings with hyperalgesia (Watkins and Maier, 2002). In fact, the first studies of inflammatory signals in carotid body sensitization from chronic hypoxia in Fidone's laboratory (Liu et al., 2009) were based on the hypothesis that the mechanisms of hyperalgesia increased carotid body O_2-sensitivity with chronic hypoxia. Further, the rate-limiting enzyme for PGE2 production (mPGES-1) is O_2-sensitive and induced by hypoxia (Herlenius, 2011). Hence, this pathway could be blocked by the COX-1 and COX-2 inhibitor ibuprofen that also blocks

the increase in carotid body and ventilatory O_2 sensitivity with CSH. Therapeutic levels of ibuprofen can block NF-κB induced transcription of cytokines independently of inhibiting COX in isolated cell experiments also (Scheuren et al., 1998; Stuhlmeier et al., 1999), although this effect is not observed in every case (Yamamoto et al., 1999).

Respiratory Motor Plasticity

As discussed above, peripheral injury and inflammation can *induce* plasticity in the spinal dorsal horn and sensory neurons, but CNS inflammation in the spinal ventral horn *inhibits* motor plasticity. One commonly studied form of respiratory motor plasticity, phrenic long-term facilitation (pLTF, induced by acute IH (AIH), 3 × 5 min episodes of hypoxia; (Devinney et al., 2013; Gonzalez-Rothi et al., 2015) is exquisitely sensitive to even low levels of systemic inflammation, since a low systemic dose of LPS induces CNS inflammation and abolishes pLTF for at least 24 hours (Huxtable et al., 2013). Increased inflammatory gene expression was observed immediately following LPS, but returned to baseline levels by 24 hours, despite the continued absence of pLTF. The effects of LPS were reversed by systemic application of an NSAID (ketoprofen), further supporting the hypothesis that LPS-induced inflammation abolishes pLTF.

We have also shown another, arguably more physiological, stimulus induces systemic inflammation and abolishes pLTF. Eight hours of intermittent hypoxia (2 min episodes, 10.5% O_2, followed by 16 hours of normoxia (IH-1) eliminated pLTF but was restored after systemic NSAID administration (Huxtable et al., 2015). Furthermore, IH-1 was shown to upregulate gene expression of IL-1β in microglia from the cervical spinal cord immediately after 8 hours of IH and for at least 16 hours post-IH. In CNS homogenates from the cervical spinal cord, only iNOS gene expression was elevated after IH-1 (despite a transient increase in IL-6 immediately after IH), indicating differential cellular contributions to the inflammatory response. To gain a greater understanding of the molecular pathway associated with pLTF inhibition, we targeted p38 MAPK, a common downstream signaling molecule activated by inflammation and which promotes further inflammation (Kumar et al., 2003). Like ketoprofen, spinal inhibition of p38 MAPK restored pLTF after IH-1, but suggested spinal inflammation is key to undermining pLTF (Huxtable et al., 2015). Since gene expression data suggests involvement of both microglia and other cell types, we used immunohistochemistry to begin to visualize changes in different cell types. Immunohistochemistry revealed activated (phosphorylated) p38 MAPK was predominantly localized to back-labeled phrenic motor neurons and nearby microglia in the ventral horn of the cervical spinal after IH-1-induced CNS inflammation. Thus, IH-1-induced inflammation activates p38 MAPK in phrenic motor neurons or nearby microglia to inhibit pLTF. While IH-1 elicits spinal inflammation and abolishes pLTF (Huxtable et al., 2015), seven days of IH (5 min hypoxia, 5 min normoxia, 12 hours) enhances pLTF and ventilatory LTF (Ling et al., 2001; McGuire et al., 2003). These differences may be due to the magnitude of inflammatory signaling or increased expression of trophic factors known to stimulate respiratory plasticity. For example, while one or three nights of IH induces inflammatory gene expression in spinal microglia (Huxtable et al., 2015; Smith et al., 2013), inflammatory gene expression in the spinal cord is not elevated after 14 consecutive nights of IH or after 4 weeks of thrice weekly IH (Peters et al., 2015; Smith et al., 2013).

Integrative examples

Inflammation may be relevant to respiratory control in a number of physiological and pathological conditions and here we consider two examples.

Respiratory Frequency Plasticity with Intermittent Hypoxia

While inflammation clearly has a profound effect on pLTF, it is less clear how inflammation effects frequency plasticity, defined as plasticity in phrenic burst frequency, which potentially translates to respiratory or breathing frequency and likely occurs in the central pattern generator in the medulla. (see Baker-Herman et al. 2008 for a review on frequency plasticity). Frequency plasticity is also evident after AIH, but is more variable than pLTF (Baker-Herman and Mitchell, 2008). Systemic inflammation, induced by a high or low-dose of systemic LPS, had no effect on frequency plasticity 3 hours post-LPS (Huxtable et al., 2013; Vinit et al., 2011). However, 24 hours after a low-dose of LPS, frequency plasticity was abolished and was not restored by the NSAID ketoprofen (Huxtable et al., 2013). The lack of restoration of frequency plasticity may be due to an independent or nonspecific effect of ketoprofen, which also reduced frequency plasticity in control animals (Huxtable et al., 2013). Importantly, frequency plasticity was only present in one of four saline-treated control groups reported in the studies cited above, suggesting the general variability of frequency plasticity following AIH likely masks the effects of inflammation on frequency plasticity (Baker-Herman & Mitchell, 2008).

To further explore the effects of inflammation on frequency plasticity, we analyzed frequency responses from our recent investigations about the effects IH-1 (Huxtable et al., 2015). Briefly, rats were exposed to IH-1 or normoxia and studied the next day. IH-1 decreased the frequency response during the short-term hypoxic ventilatory response (normoxia: 15 ± 1 bursts/min from baseline, n = 7; IH-1: 11 ± 1 bursts/min, n = 6; t-test, $p < .05$, data not shown). In a separate group, ketoprofen treatment after IH-1 restored the hypoxic frequency response (normoxia + ketoprofen: 16 ± 2 bursts/min from baseline, n = 7; IH-1 + ketoprofen: 19 ± 3 bursts/min, n = 6; t-test, $p = .38$, data not shown). Frequency plasticity was absent in normoxia and IH-1 treated animals; however, IH-1 caused a significant decrease in frequency relative to normoxia treated rats (normoxia: 3 ± 1 bursts/min from baseline, n = 7; IH-1: -3 ± 3 bursts/min, n = 6; time controls: -3 ± 2 bursts/min, n = 5; two-way repeated measures ANOVA, $p = .02$, data not shown). Furthermore, ketoprofen had no effect on normoxia and IH-1 groups (normoxia: 1 ± 2 bursts/min from baseline, n = 7; IH-1: 4 ± 2 bursts/min, n = 6; time controls: -6 ± 2 bursts/min, n = 6; two-way repeated measures ANOVA, $p = .24$, data not shown).

In a separate group, rats were treated with IH-1 or normoxia, with and without intrathecal application of a p38 MAPK inhibitor 15 minutes prior to AIH. The data presented in figure 2 have not previously been published, and were collected using IACUC approved methods as outlined in our recent publication (Huxtable et al., 2015). Figure 2A shows the short-term hypoxic frequency responses to acute hypoxia and figure 2B shows frequency changes 60 minutes after AIH. Neither IH-1 nor p38 inhibition significantly altered the short-term hypoxic frequency response. IH-1, however, blunted frequency plasticity, which was restored by intrathecal p38 MAPK inhibition (normoxia/vehicle: 9 ± 2 bursts/min from

baseline, n = 9; normoxia/p38: 10 ± 3 bursts/min, n = 7; IH-1/vehicle: 3 ± 4 bursts/min, n = 6; IH-1/p38: 11 ± 3 bursts/min, n = 7; time control/vehicle: 4 ± 3 bursts/min, n = 8; time control/p38: 3 ± 3 bursts per min, n = 5, two-way repeated measures ANOVA, $p < .05$). While frequency plasticity likely originates in rhythm generating neurons in the medulla, these data suggest that IH-1 activated p38 MAPK can alter expression of frequency plasticity. Interestingly, spinal application of serotonin also induces frequency plasticity, supporting a possible spinal mechanism to frequency plasticity (Baker-Herman & Mitchell, 2008). Taken together, the effects of systemic inflammation on respiratory frequency plasticity are variable and require further investigation. Other isolated preparations containing respiratory rhythm generating areas (i.e. rhythmic slices and brainstem spinal cord preparations) would be advantageous for studying the effects of inflammation on frequency plasticity (Blitz and Ramirez, 2002; Bocchiaro and Feldman, 2004)

High Altitude

Hypoxia exposure during ascent to high altitude fuels systemic responses that are necessary to maintain homeostasis in low a low-oxygen environment. With initial exposure to high altitude, cortisol is released from the adrenal cortex, mediated by the HPA axis (Humpeler et al., 1980; Sawhney et al., 1991). Cortisol, which is immunosuppressive, gradually returns to sea level values with acclimatization to hypoxia, as an individual's arterial oxygen content improves with acclimatization. In humans, IL-6 is elevated following both acute and chronic altitude exposure (Klausen et al., 1997; Mazzeo, 2005; Mazzeo et al., 2001). While classically thought of as a pro-inflammatory cytokine, IL-6 may have some anti-inflammatory properties as well (Scheller et al., 2011) including promotion of angiogenesis (Motro et al., 1990), and VEGF induction (Cohen et al., 1996). IL-6 may also influence the increase in red blood cell number through modulation of erythropoietin production (Faquin et al., 1992).

Several studies have shown increases in inflammatory cytokines in humans at high altitude (Klausen et al., 1997; Mazzeo et al., 2001) and these may contribute to respiratory plasticity. A recent double-blind, placebo controlled, cross-over trial found that the increase in isocapnic HVR observed with placebo in healthy volunteers over 48 hours at high altitude (3,800 m) was significantly less with ibuprofen treatment (Basaran et al., 2016). This is predictable from the animal studies showing decreased carotid body and ventilatory O_2-sensitivity with ibuprofen during CSH (Liu et al., 2009; Popa et al., 2011). However, despite these effects of ibuprofen on the isocapnic HVR, other mechanisms (e.g. CO_2 changes) apparently compensated to prevent decreases in total and alveolar ventilation or arterial oxygenation while breathing ambient air at this altitude. This agrees with studies on the effects of ibuprofen as a treatment for headache with acute mountain sickness (AMS). Gertsch and co-workers (Gertsch et al., 2010; Lipman et al., 2012) found no significant difference in SaO_2 with ibuprofen versus placebo. Hence, although NSAIDs may blunt plasticity in the isocapnic HVR during altitude acclimatization, this is not a contraindication for their use to treat AMS. Randomized controlled trials find significantly fewer sojourners have AMS when taking ibuprofen versus placebo (Lipman et al., 2012). However, the consequences of anti-inflammatory drugs on cardiopulmonary chemoreflexes in other pathological conditions, such as chronic hypoxemia with or without CO_2 retention in

chronic lung disease, remain to be investigated. Also, the effects of anti-inflammatory drugs administered after plasticity in chemoreflexes has been established versus the effects studied to date by administering them during chronic hypoxia, remain to be investigated.

Conclusion and Clinical Relevance

Here, we have reviewed some of the common models used to investigate the effects on inflammation and begun discussions about the impact inflammation has on nociception, chemosensory plasticity, medullary respiratory centers, motor plasticity, frequency plasticity, and adaptation to high altitude (summarized in Fig. 3). Additional research is necessary to understand the conditions in and mechanisms by which plasticity is adaptive or maladaptive in the respiratory system. As discussed, inflammation can have opposite effects on the capacity for plasticity, demonstrating the location of plasticity is an important determinant. It promotes plasticity in the spinal dorsal horn, but inhibits plasticity in the spinal ventral horn. The dose and duration of inflammation stimuli is also important in determining the effect on plasticity. For example, the dose of hypoxia, and thus subsequent inflammation, can alter plasticity expression. One night of intermittent hypoxia (IH-1) abolishes pLTF (Huxtable et al., 2015), but seven days of intermittent hypoxia enhances pLTF (Ling et al., 2001). Such differing results may be explained by changes in inflammatory and neurotrophic signaling during repetitive hypoxic episodes (Huxtable et al., 2015; Peters et al., 2015; Smith et al., 2013). Additionally, treatment with anti-inflammatories blunts ventilatory acclimatization to CSH in humans (Basaran et al., 2016), but during CIH does not inhibit hypoxic sensitization (Del Rio et al., 2012; Iturriaga et al., 2015), suggesting the role of inflammation in CSH and CIH are distinct. These results highlight the complexity of interactions between inflammatory stimuli and the respiratory system, but also the importance of further investigations to tease out the mechanistic intricacies.

There is no question inflammation (acute to chronic, minor to severe) occurs in almost every clinical disease and disorder, from the respiratory system and beyond. Yet before reducing maladaptive plasticity (like nociception) or promoting adaptive (like respiratory motor) plasticity can be exploited as a therapeutic intervention, we must first understand how it is caused or undermined, respectively.

Other areas of further investigation into the effect of inflammation during development, aging, and between sexes are also necessary before better therapeutic interventions can be developed. Neonatal infections cause a significant proportion of death in the first week of life (Chan et al., 2015) and account for approximately one third of all neonatal deaths (Black et al., 2010), while those neonates that survive neonatal infection are now recognized to have increased vulnerability to short- and long-term neurodevelopmental disability (Dammann et al., 2002; Ferreira et al., 2014; Stoll et al., 2002). At birth, the neonate must transition from the sterile environment of the mother to an environment filled with pathogens, microbes, and toxins, and must also begin robust, rhythmic breathing. Respiratory problems, such as apneas, represent a significant problem for neonatologists and characterizing this problem represents a significant clinical need (Martin et al., 2012). In fact, recurrent apneas are prevalent in 50% of premature infants (Poets et al., 1994; Poets and Southall, 1994), where infection is particularly common - up to 65% have at least one infection during

hospitalization (Stoll et al., 2002; Stoll et al., 2004). Despite this common clinical problem, we know virtually nothing about how early life infection alters functioning and plasticity of the respiratory system. Evidence is beginning to emerge that infants with high incidence of apneas are predisposed for obstructive sleep apnea (OSA) (McNamara and Sullivan, 2000), yet research lags significantly behind in understanding this link. Determining how neonatal inflammation impairs the respiratory system will ultimately lead to better treatments to promote breathing in all age groups and perhaps elucidate links between neonatal conditions and adult respiratory insufficiency.

There are also clear effects of sex and age on respiratory plasticity. pLTF is diminished with age in male rats (Zabka et al., 2001) and testosterone restores hypoglossal LTF (Nelson et al., 2011). In female rats, pLTF is enhanced with age (Zabka and Behan, 2001) and both male and female elderly rats display increased pLTF after CIH (McGuire et al., 2003; Zabka et al., 2003). Systemic inflammation is suggested to increase with age and is related to detrimental aging processes and incidence of chronic diseases (Chung et al., 2009). Furthermore, sex hormones (specifically estrogen which has anti-inflammatory effects) are suggested to be a cause of sexual dimorphism in neurological diseases and may account for some sex-differences in respiratory plasticity (Czlonkowska et al., 2005). Interestingly, in patients with inflammatory respiratory diseases, males are more susceptible to acute inflammation and women are more susceptible to chronic inflammation (Casimir et al., 2013), further suggesting sexual dimorphic characteristics of the effects of inflammation, and possibly plasticity. The potential for sex-differences in the effects of inflammation on respiratory plasticity have scarcely been investigated. To develop effective treatments for inflammatory diseases compromising breathing we need to further recognize the importance of sex and age differences in inflammatory responses.

Much remains to be learned about the role inflammation plays in altering various aspects of respiratory control. In this review, we have highlighted some of the recent studies and pointed out gaps in our knowledge. This research direction is ever changing and developing. The next few years will likely show exciting developments in these areas and many beyond.

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Abbreviations

CNS	central nervous system
DAMPs	danger-associated molecular patterns

LPS	lipopolysaccharide
CFA	complete Freund's adjuvant
Poly(I:C)	Polyinosinic:polycytidylic acid
TLR	Toll-like receptors
BBB	blood brain barrier
PHD	prolyl hydroxylases
IKK-β	IκB kinase
SNI	spared nerve injury
CIH	chronic intermittent hypoxia
LTF	long-term facilitation
CSH	chronic sustained hypoxia
IL	interleukin
TNF	tumor necrosis factor
COX	cyclyooxengenase
PGE	prostaglandin
pLTF	phrenic long-term facilitation
AIH	acute intermittent hypoxia
IH-1	8 hours of intermittent hypoxia followed by 16 hours normoxia
HVR	hypoxic ventilatory response
AMS	acute mountain sickness
MAPK	mitogen-activated protein kinase

Highlights

- Reviews the impact of inflammation on different forms of respiratory plasticity
- Inflammation contributes to chronic hypoxia induced oxygen sensitivity
- Inflammation abolishes phrenic long-term facilitation
- Highlights gaps in knowledge and relevance to clinical conditions and treatments

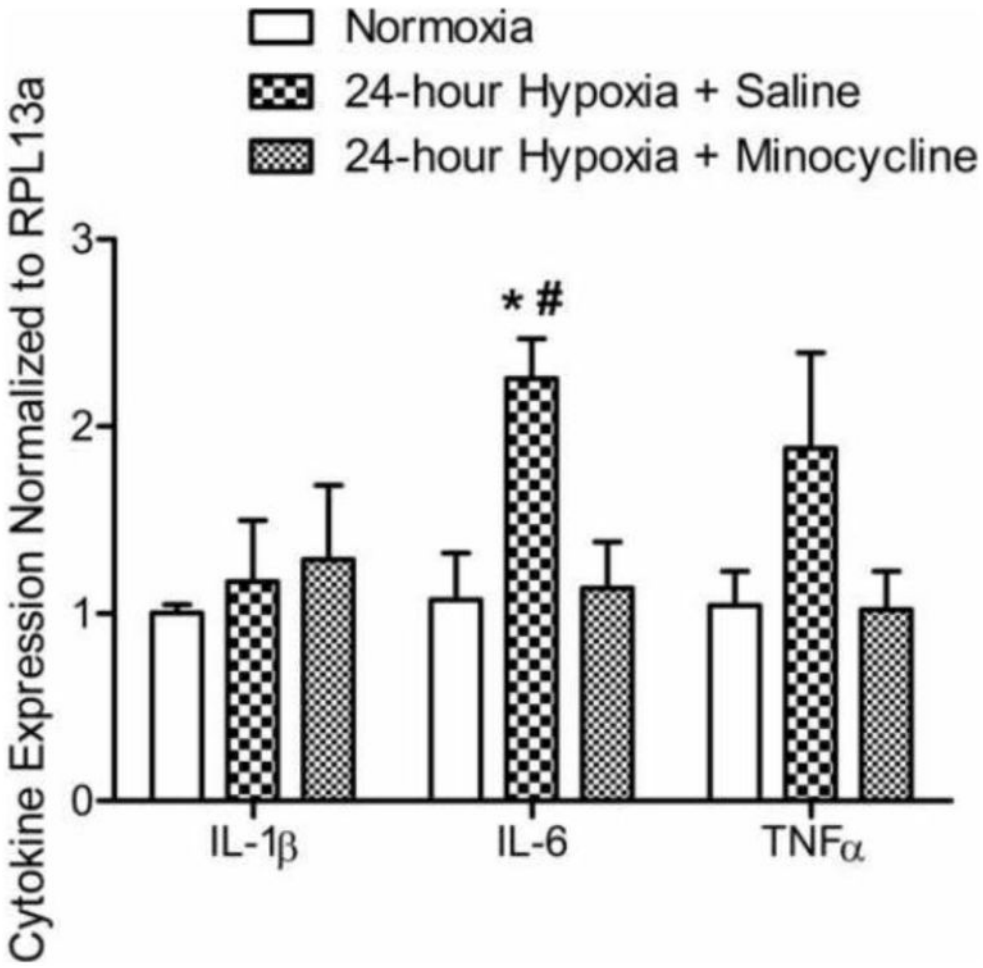

Figure 1.

Systemic minocycline administration inhibits cytokine gene expression in the NTS following 24 hours of CSH. Three groups of rats (n=5/group) were exposed to one of the following conditions: 1) Normoxic (controls); 2) 24-hour CSH (10% O_2) + i.p. saline; or, 3) 24-hour CSH (10% O_2) + i.p. minocycline (45mg/kg). RT-PCR was used to assess cytokine mRNA in the NTS region of the rat brainstem. Exposure to 24-hours of CSH increased both IL-6 and TNF-α mRNA compared to normoxic controls. Systemic minocycline administration blocked the IL-6 and TNF-α mRNA increase. All data presented as mean ± SEM. Two-way ANOVA, Bonferroni post-test; $p < 0.05$; * indicates difference between normoxia and 24-hour Hypoxia + Saline; # indicates difference between 24-hour Hypoxia + Saline and 24-hour Hypoxia + Minocycline.

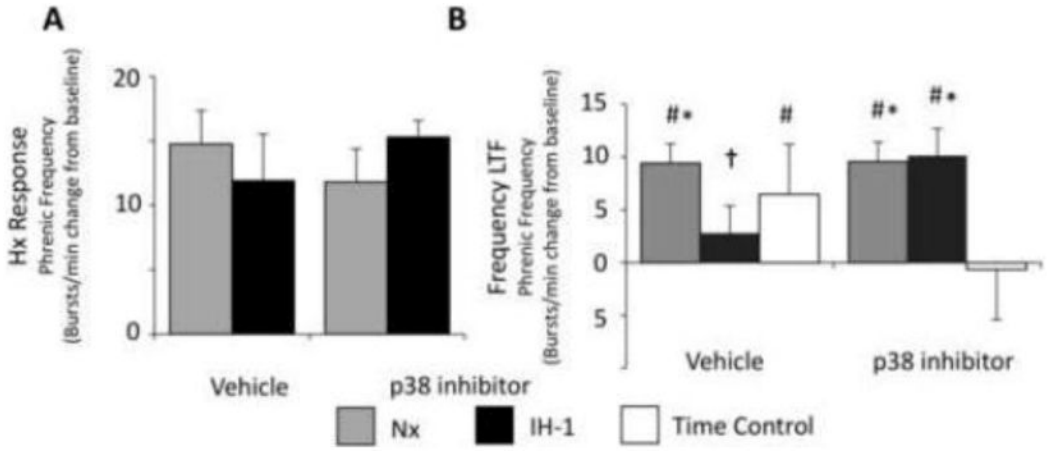

Figure 2.

Frequency plasticity is blunted by IH-1 and is restored after spinal treatment with a p38 MAPK inhibitor (SB202190, 1 mM, intrathecal). A) Phrenic nerve frequency responses during the short-term hypoxic response were not altered by IH-1 or intrathecal p38 inhibition. B) Frequency plasticity was evident in normoxia controls (n = 9) and was not altered by p38 inhibition (n = 7). Frequency plasticity was eliminated by IH-1 (n = 6), but was restored after p38 MAPK inhibition (n = 7). Time controls with intrathecal vehicle application (n = 7) did show increased phrenic frequency after 90 minutes relative to baseline, which was absent after the p38 inhibitor (n=5). (Two-way RM ANOVA, Fisher LSD post-test; # indicates difference from baseline, * indicates difference from p38 time controls, † indicates difference from normoxia vehicle controls.)

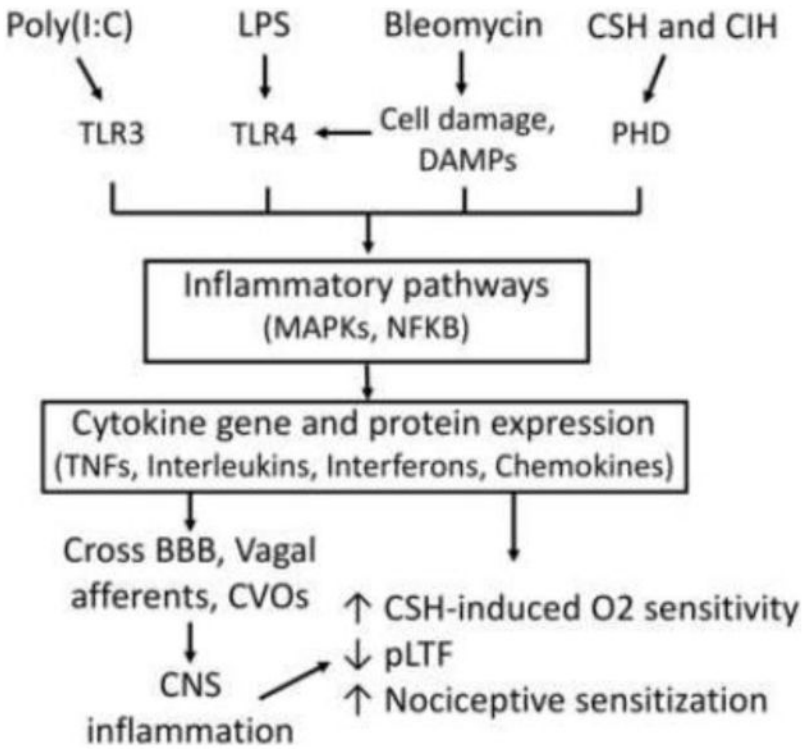

Figure 3.

Models of inflammation and effects on plasticity. Multiple models of inflammation converge on pro-inflammatory pathways that alter the expression of plasticity in respiratory and non-respiratory systems.