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Systemic inflammation impairs respiratory chemoreflexes and plasticity

A.G. Huxtable, **S. Vinit**, **J.A. Windelborn**, **S.M. Crader**, **C.H. Guenther**, **J.J. Watters**, and **G. S. Mitchell**
Department of Comparative Biosciences University of Wisconsin Madison, WI., 53706

Abstract

Many lung and central nervous system disorders require robust and appropriate physiological responses to assure adequate breathing. Factors undermining the efficacy of ventilatory control will diminish the ability to compensate for pathology, threatening life itself. Although most of these same disorders are associated with systemic and/or neuroinflammation, and inflammation affects neural function, we are only beginning to understand interactions between inflammation and any aspect of ventilatory control (e.g. sensory receptors, rhythm generation, chemoreflexes, plasticity). Here we review available evidence, and present limited new data suggesting that systemic (or neural) inflammation impairs two key elements of ventilatory control: chemoreflexes and respiratory motor (*vs*. sensory) plasticity. Achieving an understanding of mechanisms whereby inflammation undermines ventilatory control is fundamental since inflammation may diminish the capacity for natural, compensatory responses during pathological states, and the ability to harness respiratory plasticity as a therapeutic strategy in the treatment of devastating breathing disorders, such as during cervical spinal injury or motor neuron disease.

Keywords

long-term facilitation; intermittent hypoxia; LPS; plasticity; respiratory motor neuron

1. INTRODUCTION

Accurate and robust ventilatory control is critical to maintain adequate breathing when confronted with many disorders of the lung or central nervous system (CNS). Factors that undermine the efficacy of ventilatory control will diminish the ability to compensate for pathology, threatening life itself (Mitchell, 2007). Most lung and CNS disorders are associated with systemic and/or neural inflammation, including chronic lung diseases (Stockley, 2009), traumatic, ischemic and degenerative neural disorders (Teeling and Perry, 2009) and obstructive sleep apnea. Inflammation in sleep apnea presumably results, at least in part, from severe intermittent hypoxia experienced in this disorder (Wills-Karp, 1999, Decramer et al., 2008, Gozal, 2009, McDonald et al., 2011). Although inflammation has profound effects on important neural functions, such as synaptic transmission and plasticity

Correspondence: Gordon Mitchell, PhD Department of Comparative Biosciences School of Veterinary Medicine University of Wisconsin – Madison 2015 Linden Drive Madison, WI., 53706 TEL: 608-263-9826 mitchell@svm.vetmed.wisc.edu.

(Di Filippo et al., 2008), little is known concerning the impact of inflammation on the neural system controlling breathing.

Key elements in the ventilatory control system include rhythm generation, chemoreception (hypercapnic and hypoxic responses) and respiratory plasticity (reviewed in Feldman et al., 2003). Chemoreception and plasticity are critical elements of the ventilatory control system, enabling compensation for challenges to breathing capacity or stability presented by lung or neural disorders (Feldman et al., 2003, Mitchell and Johnson, 2003, Mitchell, 2007). Sporadic evidence has been accumulating in recent years, suggesting that systemic inflammation modulates several aspects of ventilatory control; such evidence is reviewed in the papers compiled in this special edition of *Respiration Physiology and Neurobiology*. In the present paper, our primary goal is to present evidence that inflammation impairs chemoreflexes and respiratory motor (vs. sensory) plasticity following acute intermittent hypoxia, which may leave an individual vulnerable to inadequate or unstable breathing during disease.

Systemic inflammation affects sensory receptors that modulate breathing, but can also trigger inflammatory responses in the central nervous system (CNS) through complex mechanisms. The primary CNS cells affected during systemic inflammation are microglia, the resident immune cells of the CNS, and astrocytes (Lehnardt, 2010). Since sensory processing and neuroplasticity are modulated by cell-cell interactions between neurons and microglia or neurons and astrocytes, factors that activate astrocyte and/or microglial inflammatory activities may alter respiratory chemoreflexes and/or plasticity.

In this review, we begin by discussing a common experimental model of systemic inflammation and its impact on the CNS. We then discuss major advances in our understanding of mechanisms whereby inflammation alters central neural processing of primary afferent neurons (particularly chronic pain), followed by consideration of how these advances relate to respiratory chemoreflexes (hypoxia/hypercapnia). Next, we discuss how inflammation affects hippocampal synaptic plasticity and spinal motor learning, followed by consideration of how these concepts relate to respiratory plasticity. We conclude by discussing the potential significance of interactions between inflammation and ventilatory control, and suggest areas where research is needed.

2. SYSTEMIC AND CNS INFLAMMATION

2.1 CNS inflammation: the role of microglia

Historically, the CNS was viewed as an immunologically privileged area that lacks traditional immune responses. Peripherally, the innate immune response activates signaling cascades that recruit immune cells (e.g. neutrophils and macrophages) to phagocytose foreign substances and release cytokines (Chen and Nunez, 2010). Cytokines trigger adaptive immune responses and activate lymphocytes. Collectively, these events eradicate foreign substances and promote tissue repair (Vivier et al., 2011). The CNS immune response differs in many respects since the blood-brain barrier, in most cases, prevents immune cell infiltration. Nevertheless, resident microglia trigger CNS inflammation (Carson et al., 2006, Graeber, 2010, Kaur et al., 2010).

Even when in their “resting state,” microglia are highly active, surveying their environment (Raivich, 2005, Parkhurst and Gan, 2010). When confronted with pathological conditions, such as neuronal injury/degeneration or bacterial/viral/fungal infection, they become “activated,” shifting from a stellate, ramified phenotype to an amoeboid shape (Kreutzberg, 1996). Activated microglia can be phagocytic, or they can release toxic and protective factors, including cytokines, prostaglandins, nitric oxide or neurotrophic factors (e.g. BDNF)

(Kreutzberg, 1996, Graeber, 2010). Despite the importance of microglia in immune function, they are diffuse in the CNS (~70-90% of CNS cells are glia; microglia are ~5-10% of those cells). At this point, we still have little knowledge on the complex role played by microglia in systemic and/or neural disorders, let alone what role they play in respiratory-related regions of the CNS.

2.2 CNS inflammation: other cell types

Although there is general agreement that microglia are major contributors to CNS inflammatory responses, debate exists concerning the relative ability of neurons and/or astrocytes to release pro-inflammatory molecules *in vivo*. Recent reviews describe astrocytic and neuronal contributions to CNS inflammation, and toll-like receptor (TLR, see below) expression in many cell types (Rivest, 2001, Escartin and Bonvento, 2008, Griffiths et al., 2009, Miller et al., 2009, Okun et al., 2009, Whitney et al., 2009). The specific TLRs expressed differ among cell types. Neurons do not express TLR-4 *in vivo* (Chakravarty and Herkenham, 2005, Mishra et al., 2006), with the exception of gigantocellular neurons of the reticular formation (Mishra et al., 2006). Other neuronally expressed TLRs do not induce cytokine production (Okun et al., 2009). Thus, neurons probably play a minimal direct role in CNS inflammation. Astrocytes, on the other hand, contribute to the overall inflammatory response since they release cytokines, triggering nuclear factor-kappa B (NFκB) signaling elsewhere in the CNS. Further, they express many TLRs, including TLR-4, capable of eliciting an inflammatory response (Li and Stark, 2002, Farina et al., 2007, Johann et al., 2008). Given their relative abundance, astrocytes may play a key role in CNS inflammatory responses.

2.3 Induced versus endogenous inflammation

Many studies focus on (exogenously) induced systemic inflammation as an experimental model. However, it is not understood how these results relate to endogenous neuroinflammation (for example, during autoimmune diseases, spinal injury, neurodegenerative diseases or ischemic injury) since few studies directly compare induced *versus* endogenous inflammation. Available information suggests that induced and endogenous inflammation share many common features, and studies of induced inflammation have many experimental advantages (e.g. inflammation without attendant issues such as mechanical injury or degenerative disease). Thus, induced inflammation is a reasonable model to begin investigations concerning the impact of inflammatory activities on ventilatory control.

2.4 Lipopolysaccharide (LPS)

The most frequently studied model of induced systemic inflammation is administration of the bacterial endotoxin, LPS. Although LPS is a component of Gram-negative bacterial cell walls, its most relevant feature is that it initiates inflammation primarily via activation of CD14/TLR-4 receptors (Poltorak et al., 1998). This is important since naturally occurring proteins, such as certain heat shock proteins, are endogenous ligands for TLR-4s (Ohashi et al., 2000, Lehnardt et al., 2008). Thus, LPS is a reasonable model to study inflammation, and is relevant beyond Gram-negative bacterial infections. LPS also activates beta 2 integrins (e.g. CD11c and CD18) and scavenger receptors (Fenton and Golenbock, 1998, Triantafilou and Triantafilou, 2002).

While LPS does not cross the blood-brain barrier (Singh and Jiang, 2004, Qin et al., 2007), systemic LPS administration elicits CNS inflammation through complex mechanisms, including indirect effects mediated by cytokines or other inflammatory molecules that do cross into the CNS. Candidate molecules triggering CNS inflammatory activities following systemic LPS include interleukins (IL-1β), tumor necrosis factor alpha (TNFα) and

prostaglandins produced by perivascular macrophages and/or endothelial cells that line the blood-brain barrier (Maier et al., 1998, Goehler et al., 1999, Laflamme et al., 1999, Blatteis and Li, 2000, Schnydrig et al., 2007, Rivest, 2009). Another means of transmission is via peripheral nerves (including the vagus nerves), which transmit inflammation into the CNS via unknown mechanisms (Ge et al., 2001, Roth and De Souza, 2001, Wieczorek et al., 2005, Blatteis, 2007).

2.5 Toll-Like Receptors (TLRs)

TLRs sense pathogens, quickly recognizing highly conserved pathogen-associated molecular patterns and triggering innate immune responses to eliminate the pathogen (e.g. bacteria, viruses, fungi, parasites) (Chen et al., 2007). TLRs (specifically TLR-2 and TLR-4) also recognize endogenously released damage-associated molecular patterns from necrotic or apoptotic cells (Chen et al., 2007). Thus, TLRs act as sensors for both exogenous (invading pathogens) and endogenous (cell death via apoptosis or necrosis) threats to tissue viability. While detailed signaling cascades triggered by endogenous *versus* exogenous inflammation are not fully understood, LPS is a viable model to begin studies of inflammation and ventilatory control since it is a TLR-4 ligand. Regardless, aspects of LPS-induced inflammation may not faithfully reflect inflammatory responses triggered by endogenous molecules.

TLR-4 receptors are cytokine family receptors that activate transcription factors, such as NFκB (Lu et al., 2008). NFκB regulates the expression of many inflammatory genes, including: IL-1β, -6 and -18, TNFα, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (Ricciardolo et al., 2004, Nam, 2006). Endogenous molecules known to activate TLR-4 receptors include (but are not limited to) heat shock proteins (specifically HSP60, Ohashi et al., 2000, Lehnardt et al., 2008), fibrinogen, surfactant protein-A, fibronectin extra domain A, heparin sulfate, soluble hyaluronan, *β*-defensin 2 and HMGB1 (Chen et al., 2007).

2.6 Inflammatory gene expression in tissue homogenates

Cytokine release is a key factor initiating general CNS inflammation, and traditionally has been assessed in tissue homogenates. However, it is important to bear in mind that CNS homogenates are >50% astrocytes. Thus, inflammatory gene assessment in tissue homogenates may be dominated by astrocytes, with less influence from more diffuse cell types, including microglia. More specific methods are necessary to assess gene expression in less abundant cell types, such as analyses of microglia freshly isolated from CNS tissues.

Chronic intermittent hypoxia (CIH) stimulates CNS inflammation, increasing inflammatory molecules in tissue homogenates from the hippocampus (e.g. COX-2 and iNOS) (Li et al., 2003, Row et al., 2003, Li et al., 2004, Xu et al., 2004, Gozal and Kheirandish-Gozal, 2008). No information is currently available concerning the specific cell types involved in this inflammatory response. Further, little is known regarding LPS effects on microglia *in vivo* in any region of the CNS since most studies evaluate homogenates only. Thus, cell-specific isolation from distinct regions of the CNS is an important step to advance our understanding of the relative roles played by microglia versus other cell types in regions of interest to ventilatory control. At this time, significant gaps in our understanding include: 1) lack of knowledge concerning inflammatory gene expression and protein levels in identified cell types; 2) specific effects of inflammation in CNS regions relevant to ventilatory control (e.g. brainstem and cervical spinal cord), where microglia have different properties than cortical microglia; 3) a time course of LPS effects on inflammatory gene expression in different cell types and regions of interest; and 4) comparative data between LPS and other inflammatory stimuli (such as chronic intermittent hypoxia).

3. INFLAMMATION AND SENSORY SYSTEMS

3.1 Nociception

The role of inflammation (and specifically microglia) in chronic pain has been studied extensively (reviewed in Woolf and Salter, 2000, Trang et al., 2006, Mika, 2008, Abbadie et al., 2009, Baumbauer et al., 2009). A remarkable story has emerged, demonstrating the interplay between neurons, microglia, inflammation and plasticity in this spinal sensory system. In short, inflammation induces both peripheral and central sensitization, leading to allodynia (hypersensitivity to otherwise non-painful stimuli) and hyperalgesia (exaggerated or prolonged responses to a noxious stimulus) (Mika, 2008).

Plasticity at peripheral nerve terminals increases synaptic inputs to the CNS from primary afferent neurons associated with nociception. Inflammation increases Aβ-mediated synaptic input to the dorsal horn and activates spinal microglia through increased afferent input or cytokines crossing the blood brain barrier, and thus increases neuropeptide expression and pro-inflammatory gene expression in the spinal dorsal horn (Baumbauer et al., 2009, Latremoliere and Woolf, 2009). Additionally, inflammation also increases microglial $P2X_4$ ATP receptor expression (Inoue, 2006), subsequently increasing expression of brain derived neurotrophic factor (BDNF; Coull et al., 2005). BDNF from these activated microglia down-regulates the chloride co-transporter KCC2 on second order nociceptive neurons (Coull et al., 2003), diminishing their chloride potential and, thus, the efficacy of inhibitory neurotransmission. Without the constraint of GABA/glycine inputs on nociceptive synaptic transmission, development of chronic pain results (Price et al., 2005).

Although scarcely explored, similar mechanisms may play major roles in ventilatory control, particularly in modulating sensory systems (e.g. chemoreflexes).

3.2 Chemoreflex control of breathing

An important aspect of ventilatory control susceptible to inflammatory modulation is the chemoreflex control of breathing. Chemoreflexes are critical for maintaining homeostasis of arterial blood gases *via* classical negative feedback (Mitchell et al., 2009), or acting as "teachers" that induce plasticity in the respiratory control system (Mitchell and Johnson, 2003). Major chemoreflexes include the hypoxic (Powell et al., 1998) and hypercapnic ventilatory responses (Nattie, 2001), arising predominantly from the peripheral arterial and central chemoreceptors (Lahiri and Forster, 2003).

3.2.1 Hypoxic ventilatory response—Systemic LPS decreases the hypoxic ventilatory response in cats, without change in ventilation during maximal chemoreceptor stimulation (Fernandez et al., 2008). Inflammation diminishes the hypoxic ventilatory response by a nitric oxide dependent mechanism in piglets (McDeigan et al., 2003). Further, TNFα diminishes carotid chemosensory discharge *in vitro* (Fernandez et al., 2008). Young rats treated with systemic LPS exhibit depressed hypoxic ventilatory responses (Ladino et al., 2007). Systemic LPS (3 mg/kg, i.p.) also reduces short-term hypoxic phrenic responses in anesthetized, vagotomized, paralyzed and ventilated adult rats (Vinit et al., 2011). Mechanisms whereby inflammation impairs the hypoxic response are not understood, and may involve multiple inflammatory molecules that influence peripheral and central chemoreceptors, or other respiratory neurons.

Another stimulus to plasticity in regions of interest to ventilatory control is chronic intermittent hypoxia (CIH). CIH increases carotid chemoreceptor responses to hypoxia, quite possibly due to peripheral chemoreceptor inflammation (Del Rio et al., 2010). In agreement, nocturnal CIH also augments the short-term hypoxic phrenic response in rats

(Ling et al., 2001). However, the extent of CIH-induced inflammation in the brainstem and spinal cord, and the potential contributions of CNS inflammation to this form of plasticity remain unclear.

3.2.2. Hypercapnic ventilatory response—To date, no studies have reported the impact of systemic inflammation on hypercapnic responses. However, increased CO_2 suppresses NFκB activation, possibly suppressing inflammatory gene expression (Taylor and Cummins, 2011). In fact, hypercapnia has been used to treat ischemia/reperfusion injury to decrease inflammation and reduce lung tissue damage (Laffey et al., 2000, O'Croinin et al., 2005, Curley et al., 2010, Li et al., 2010). In a rat model of Duchenne muscular dystrophy, where inflammation is a key component of disease progression, symptomatic mutant mice exhibit a diminished hypercapnic ventilatory response (Gosselin et al., 2003), consistent with the idea that inflammation may also impair hypercapnic ventilatory responses. Such impairment of ventilatory control may be due, at least in part, to impaired diaphragm mechanics resulting from increased TNFα expression. However, these studies do not rule out additional central neural effects of TNFα (Gosselin et al., 2003). Further work concerning the influence of systemic inflammation on hypercapnic ventilatory responses is warranted, particularly since impaired CO_2 chemoreflexes would allow greater hypercapnia and minimize the ongoing inflammation; in this sense, impaired hypercapnic ventilatory responses during inflammation may (in part) be adaptive.

3.2.3. Inflammation and chemoreflexes in rats—Here, we report new data concerning the impact of inflammation induced by systemic LPS on maximal chemoreflex stimulation of breathing in unanesthetized rats (Figure 1). Four treatment groups of adult, male Lewis rats were studied (each n=4): 1) vehicle controls (saline, 1ml/kg, i.p.), 2) LPS treated (5 mg/kg in saline, i.p.), 3) the non-steroidal anti-inflammatory, ketoprofen (12.5 mg/kg in 70% ethanol, s.c.), before and every 8 hours post-saline injection, and 4) ketoprofen before and every 8 hours post-LPS injection. 24 hours post-injection, ventilation was measured using whole-body plethysmography (Data Sciences International, St. Paul, MN, USA). Rectal temperature was measured before being placed in the chamber, and again at the end of protocols as rats were removed from the chamber. Due to a consistent equipment error in recording chamber temperature, we chose to express volumes in relative units (units/min/100g) rather than making a (small but) uncertain correction in absolute units (ml/min/100g). Regardless, chamber temperature measurement errors have no impact on recorded breathing frequencies, the main variable affected in these studies.

To determine ventilatory capacity in these rats, they were given maximal chemoreceptor stimulation by exposure to 10.5% inspired O_2 with 7% inspired CO_2 (balance N_2) for 15 min. LPS significantly affected breathing frequency, but not tidal volume (Figure 1). Specifically, LPS increased baseline breathing frequency (breaths/min) versus other treatment groups (LPS + vehicle = 133±11; Saline + vehicle = 81±0.2; Saline + Ketoprofen = 74±1.4; LPS + Ketoprofen = 90±8.5) (Figure 1A). Increased frequency during chemoreceptor stimulation was not evident in rats treated with LPS (LPS + vehicle baseline = 133±11 breaths/min; LPS + vehicle maximal stimulation = 117±14 breaths/min). However, the frequency response to chemoreceptor stimulation was restored when LPS-treated rats were also treated with the nonsteroidal anti-inflammatory agent, ketoprofen (LPS + Ketoprofen baseline = 90±9 breaths/min; LPS + Ketoprofen maximal stimulation= 121±11 breaths/min). LPS-induced inflammation may influence respiratory rhythm by direct actions on brainstem centers controlling frequency (e.g. the pre-Bötzinger Complex), or via indirect effects mediated by sensory receptors that project to these rhythm generating neurons.

In contrast to LPS effects on breathing frequency, neither LPS nor ketoprofen affected tidal volume in baseline conditions or during maximal chemoreceptor stimulation (Figure 1B). Overall, LPS reduced pulmonary ventilation during chemoreceptor stimulation (Figure 1C), reflecting its effects on breathing frequency. Specifically, LPS decreased chemoreceptor stimulated ventilation *versus* vehicle controls (control: 107±6 units/min/100g; LPS: 83±6 units/min/100g, Figure 1C; $p<0.05$). Ketoprofen failed to reverse these LPS effects on chemoreceptor stimulated ventilation (92±11 units/min/100g; $p>0.05$). The lack of reversibility of LPS effects on breathing with ketoprofen may reflect an inadequate dose or the timing of ketoprofen administration since inflammatory molecule expression changes over time with different inflammatory mediators peaking in expression level at different times during an inflammatory response (Lund et al., 2006, Natoli et al., 2011).

From the limited data presented here, we cannot determine conclusively if blunted chemoreflex frequency responses result from effects on peripheral chemoreceptors (Iturriaga et al., 2009), vagal pulmonary receptors (Lai et al., 2002) or central neural mechanisms (e.g. rhythm generating neurons). However, it is unlikely they resulted from known effects of inflammation on respiratory muscles (Hussain, 1998) or lung mechanics (e.g. pulmonary edema) since these effects would be expressed as changes in tidal volume *versus* frequency. Further, since LPS (3 hrs post-injection) diminishes amplitude responses in the short-term hypoxic phrenic response of anesthetized, paralyzed, vagotomized and ventilated rats (Vinit et al., 2011), contributions from vagal afferent neurons, respiratory muscles or lung mechanics can be ruled out in this reduced experimental preparation; these diminished hypoxic responses must arise from LPS effects on peripheral chemoreceptors and/or the CNS.

To confirm CNS inflammation 24 hours following systemic LPS, we examined changes in inflammatory gene expression in tissue homogenates from the brainstems of adult, male Sprague Dawley rats (iNOS, COX-2, and TNFα mRNA via quantitative RT-PCR). 24 hours post-LPS (10 mg/kg, i.p., n=3), iNOS ($p=0.03$) and TNFα ($p=0.009$) mRNA had increased; an apparent increase in COX-2 mRNA approached significance ($p=0.054$) (Fig 2). Thus, although LPS does not cross the blood-brain barrier, systemic LPS injection induces central neural inflammation in regions of interest to ventilatory control.

4. INFLAMMATION AND NEUROPLASTICITY

4.1 Non-respiratory systems

Inflammatory molecules induce/maintain synaptic plasticity in some neural systems (Woolf and Salter, 2000, Beattie et al., 2002), but inhibit plasticity in others (Di Filippo et al., 2008). Hippocampal synaptic plasticity and hippocampus-dependent learning are inhibited by inflammation (Vereker et al., 2000, Shaw et al., 2001), including COX-2 regulated prostaglandin synthesis (Shaw et al., 2005). Inflammation also impairs: 1) spinal instrumental learning (Vichaya et al., 2009); 2) contextual fear conditioning, and spatial learning in the Morris water maze (Shaw et al., 2001); 3) memory processing in day old chicks (Sell et al., 2001); and 4) memory consolidation (Thomson and Sutherland, 2005). When inflammation inhibits recognition memory and LTP in the dentate gyrus, plasticity-associated changes in growth factor expression are blocked (Hennigan et al., 2007), giving some clue as to potential sites of impairment in the cellular cascades leading to memory. On the other hand, cytokines are also reported to be necessary for learning, memory and hippocampal synaptic plasticity (Bohme et al., 1993, Zhuo et al., 1993, Malen and Chapman, 1997, Pollmacher et al., 2002, Avital et al., 2003, Brennan et al., 2003, Goshen et al., 2007).

4.2 Respiratory plasticity

Hippocampal synaptic plasticity and spinal somatic motor learning share many common cellular mechanisms with phrenic long-term facilitation (pLTF) following acute intermittent hypoxia, the most frequently studied model of spinal respiratory motor plasticity (Mahamed and Mitchell, 2007, Mateika and Sandhu, 2011). Indeed, systemic LPS impairs pLTF (Vinit et al., 2011), an effect similar to hippocampal synaptic plasticity and spinal motor learning, but unlike plasticity the spinal dorsal horn where sensitization prevails (Woolf and Salter, 2000). Given our emerging awareness that inflammation has considerable impact on neuroplasticity in other regions of the CNS (Woolf and Salter, 2000, Di Filippo et al., 2008), an understanding of mechanisms whereby inflammation impairs respiratory motor plasticity is of considerable interest.

We have made considerable progress towards an understanding of cellular/synaptic mechanisms giving rise to pLTF induced by acute-intermittent hypoxia (AIH, 3 × 5 min 10.5% separated by 5 min normoxia) *in vivo* (Mahamed and Mitchell, 2007, Baker-Herman and Mitchell, 2008, Mateika and Sandhu, 2011). We have recently come to realize that multiple, distinct mechanisms give rise to long-lasting phrenic motor facilitation (pMF), where pMF is used as a general term that includes pLTF induced by AIH (Dale-Nagle et al., 2010). These pathways interact in complex and interesting ways, providing a range of potential responses in the face of changing physiological conditions or the onset of disease. A detailed understanding of cellular/synaptic mechanism(s) giving rise to pMF may guide the development of novel therapeutic strategies for severe breathing disorders, including obstructive sleep apnea (Mitchell, 2007). Thus, an understanding of mechanisms whereby inflammation undermines respiratory plasticity is of fundamental importance, since inflammation may diminish the capacity for natural, compensatory plasticity during pathological states and undermine the ability to harness respiratory plasticity as a therapeutic tool in the treatment of respiratory insufficiency (Mitchell, 2007). By understanding mechanisms whereby inflammation impairs respiratory plasticity, we may speed development of new strategies to restore breathing capacity in devastating ventilatory disorders such as cervical spinal injury or motor neuron disease. Unfortunately, we have only begun to appreciate the impact of inflammation on any form of respiratory plasticity (Di Filippo et al., 2008, Iturriaga et al., 2009, Vinit et al., 2011).

4.3 Do microglia contribute to impaired pLTF following AIH

Here we report new data attempting to determine the role of microglia in LPS-induced impairment of AIH-induced pLTF using a “standard” approach to inhibiting microglial function. Specifically, we pretreated rats with minocycline, a semi-synthetic tetracycline known to inhibit microglial, with lesser effects on neuronal or astrocytic function (Kim and Suh, 2009). As we showed previously (Vinit et al., 2011), three hours post-LPS (3 mg/kg, i.p.), AIH-induced pLTF (3 × 5 min 10.5% O_2, separated by 5 min normoxia) is impaired (control: 74±14%, n=8; LPS: 22±5%, n=12) (Figure 3). Unexpectedly, minocycline alone also impaired pLTF (minocycline: 36±7%, n=8, 30 mg/kg, i.v., Figure 3), and had no impact on LPS-induced pLTF impairment (LPS + minocycline: 35±11%, n=8). Based on these experiments, it is not possible to make conclusions regarding the role of microglia in the impairment of pLTF following LPS administration. Rather, we suggest that minocycline independently impairs pLTF, possibly by inhibition of relevant protein kinase C isoforms (Nikodemova et al., 2006).

5. INFLAMMATION AND RESPIRATORY RHYTHM GENERATION

To date, little is known concerning the impact of inflammation on respiratory rhythm generation. Since astrocytes play an important role in brainstem rhythm generation

(Hulsmann et al., 2000, Grass et al., 2004, Haertel et al., 2009, Huxtable et al., 2010), and microglia are located in regions associated with rhythm generation, there is considerable potential for inflammation to alter cell-cell interactions and modulate this critical biological process. The increase in baseline breathing frequency in rats injected with LPS (5 mg/kg, i.p., Figure 2), and the failure to increase breathing frequency during chemoreceptor stimulation, suggest an influence of inflammation on brainstem centers controlling breathing frequency (see above). However, we do not yet know which inflammatory molecules may be responsible for these effects. It is essential to understand mechanisms whereby inflammation could disrupt respiratory rhythm generation, since infection and inflammation are implicated in apnea of prematurity and in devastating examples of respiratory arrest, such as sudden infant death syndrome (Blackwell et al., 2005, Blood-Siegfried, 2009, Marcus et al., 2009, Dale-Nagle et al., 2010).

6. SIGNIFICANCE, IMPLICATIONS AND FUTURE DIRECTIONS

A major implication of diminished chemoreflexes and respiratory plasticity with systemic inflammation is that, at a time when robust ventilatory control is needed the most (i.e. disease), the neural system controlling breathing may be compromised. A major goal should be to understand the extent and mechanisms compromising this critical homeostatic control system.

Although information is now becoming available concerning the impact of acute inflammation (<24 hrs) on ventilatory control, future investigations must explore longer time-domains. Longer time-domains are characteristic of chronic lung and neural diseases (Iturriaga et al., 2009, Del Rio et al., 2010). Further, inflammation is a dynamic process; specific combinations of inflammatory molecules expressed at any given time differ. Thus, it is not clear that acute and chronic inflammation will have the same impact on ventilatory control.

Here, we reviewed evidence that systemic inflammation activates brainstem and spinal inflammatory responses, impairing chemoreflexes and respiratory plasticity. However, most available evidence concerns exogenously induced models of inflammation, such as systemic LPS. Further research is necessary to confirm that this model reveals general principles applicable to endogenous inflammation characteristic of chronic lung disease (e.g. COPD), breathing disorders (e.g. sleep apnea) and neurological disorders, including traumatic, ischemic and neurodegenerative processes.

Sleep apnea and the attendant chronic intermittent hypoxia induce CNS inflammation and impair cognitive function (Gozal, 2009, McNicholas, 2009, Ryan et al., 2009, Inancli and Enoz, 2010, Kimoff et al., 2010). If chronic intermittent hypoxia-induced inflammation alters respiratory chemoreflexes and plasticity, then disease/ventilatory control interactions may contribute to the underlying pathophysiology. For example inflammation induced by sleep-disordered breathing may undermine spontaneous respiratory compensation, exacerbating the primary breathing disorder. Research concerning this possibility seems warranted.

In recent years, we have started to harness respiratory plasticity as a treatment for conditions associated with respiratory insufficiency, such as cervical spinal injury (Mitchell, 2007; Vinit et al., 2009). Inherent in these disorders is an element of (endogenous) inflammation, characterized by increased expression of pro- and anti-inflammatory molecules (Lehnardt, 2010). Patients with respiratory insufficiency are prone to greater rates of infection and generalized immune activation (Wills-Karp, 1999, Stockley, 2009, Oglesby et al., 2010). Because of the high incidence of inflammatory activity in respiratory disorders, a major obstacle in harnessing respiratory plasticity as a therapeutic tool may be overcoming the

limits imposed by inflammation. Thus, therapeutic induction of respiratory (or other motor) plasticity may be optimized if the patients are first given anti-inflammatory agents. Before such combinatorial therapies can/should be applied, we need more information regarding mechanisms whereby inflammation impairs the neural control of breathing.

Overall, the theme of this special edition is quite novel in the context of respiratory neurobiology. We are only now beginning to appreciate the impact of inflammation on neural function in other regions of the nervous system (Di Filippo et al., 2008, Abbadie et al., 2009, Iturriaga et al., 2009). Although many human clinical conditions that require rigorous ventilatory control to assure adequate breathing are associated with inflammation, we are only at the beginning of our understanding concerning how inflammation impacts neural mechanisms that underlie any aspect of ventilatory control (e.g. rhythm generation, chemoreflexes, plasticity). We should move quickly to understand the impact of this common biological event (i.e. inflammation) on respiratory control.

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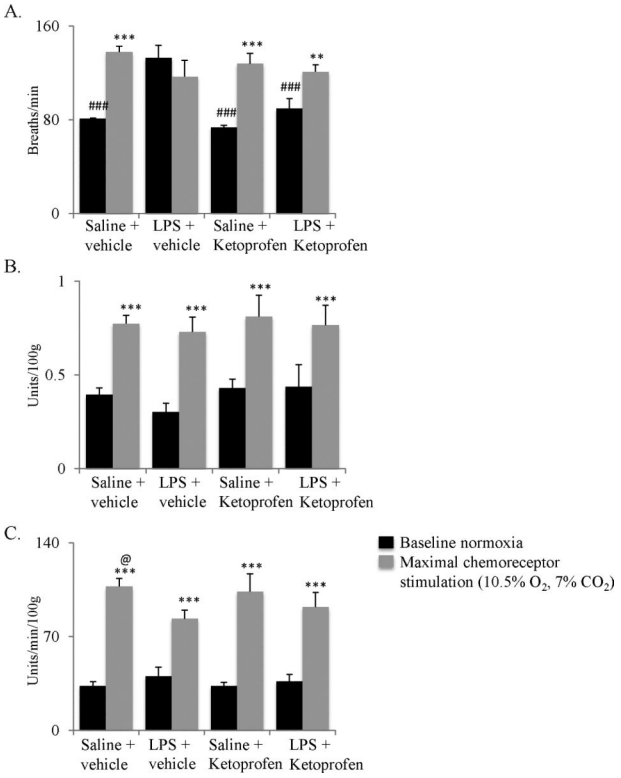

Figure 1.

Systemic LPS alters breathing frequency and minute ventilation in unanesthetized Lewis rats. A. Systemic LPS (5 mg/kg, i.p.) significantly increased baseline breathing frequency versus other baseline conditions; this effect was reversed by the non-steroidal anti-inflammatory drug, ketoprofen (12.5 mg/kg, s.c.). LPS also suppressed the frequency response to chemoreceptor stimulation (10.5% O_2, 7% CO_2, 15 min). B. Although chemoreceptor stimulation increased tidal volume in all groups, neither LPS nor ketoprofen had significant effects on this response. C. Although chemoreceptor stimulation increased minute ventilation in all treatment groups, LPS reduced this response versus saline + vehicle. Ketoprofen tended to restore maximal ventilation after LPS, but this change was not statistically significant. Ketoprofen controls had no significant effect on ventilation. ** $p<0.01$ *** $p<0.001$ indicates significant difference from baseline (black bars); ### $p<0.001$ indicates significant difference from LPS + vehicle baseline (black bar); @ $p<0.01$ indicates significant difference from LPS + vehicle (10.5% O_2, 7% CO_2, gray bar). Statistics: two-way, repeated measures ANOVA with Fisher's LSD *post hoc* test.

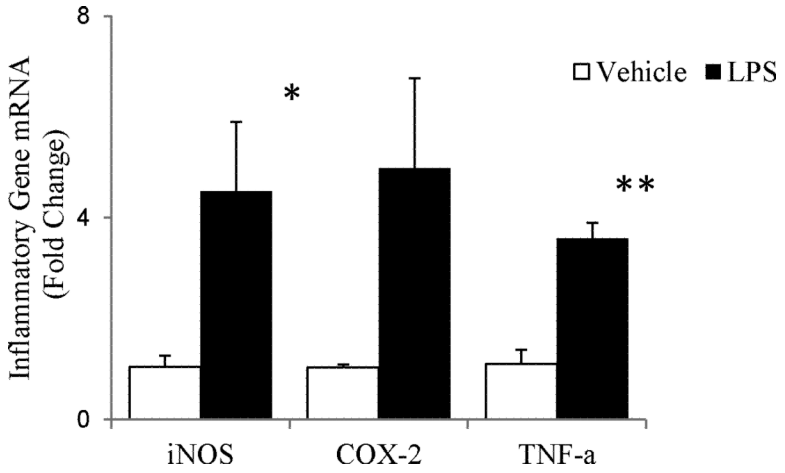

Figure 2.

Changes in inflammatory gene expression in brainstem homogenates from adult, male Sprague Dawley rats 24 hrs post-LPS (10 mg/kg, i.p.). iNOS and TNF-α increased significantly after LPS exposure (p=0.03 and p=0.009, respectively). An apparent increase in COX-2 was only marginally significant (p=0.054). Statistics: t-tests comparing vehicle vs. LPS for each gene.

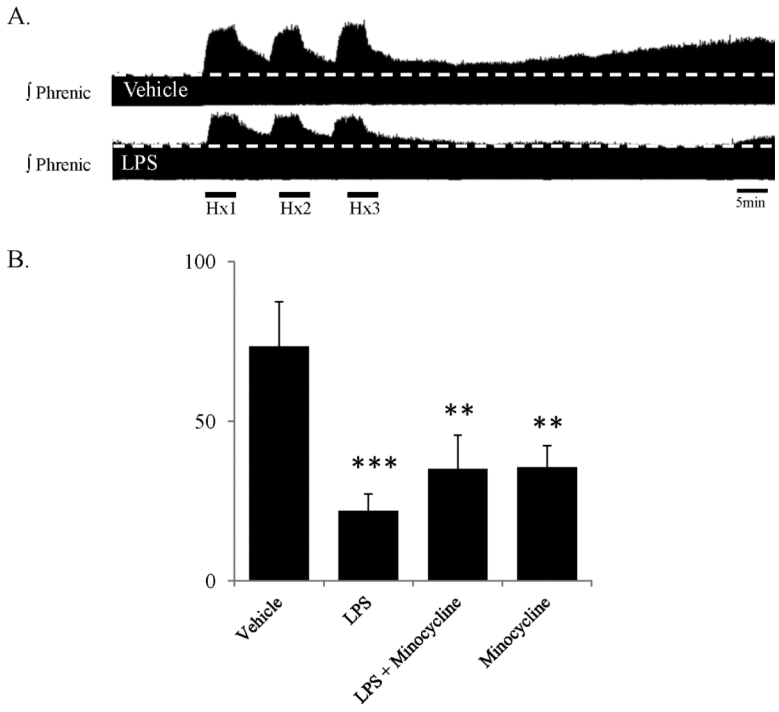

Figure 3.

The effects of systemic LPS on pLTF, with and without a known microglial inhibitor (minocycline). Both LPS and minocycline diminish AIH-induced pLTF. A) Compressed phrenic neurograms from in vivo anesthetized, vagotomized, paralyzed, ventilated rats demonstrating typical AIH-induced pLTF (upper trace), and reduced pLTF 3 hrs post-LPS (3 mg/kg, i.p.; lower trace). B) Group data demonstrating significant reduction in pLTF with LPS, LPS and minocycline (30 mg/kg, i.v.) and minocycline alone. (** $p<0.01$, *** $p<0.001$ indicates significant difference from vehicle response). Statistics: one-way ANOVA with Fisher's LSD *post hoc* test.