Experimental Neurology 287 (2017) 243–253

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Review Article

The impact of inflammation on respiratory plasticity☆

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ARTICLE INFO

Article history:
Received 1 February 2016
Received in revised form 22 July 2016
Accepted 26 July 2016
Available online 27 July 2016

Keywords:
Respiratory plasticity
Inflammation
Neuroplasticity
Hypoxia
Acclimatization
Sensory plasticity
Motor plasticity

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 h of sustained hypoxia and inflammation induced by 8 h 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.

Contents

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 h of intermittent hypoxia followed by 16 h normoxia; HVR, hypoxic ventilatory response; AMS, acute mountain sickness; MAPK, mitogen-activated protein kinase.

☆ Supported by: NIH HL111598, Francis Family Foundation (AGH), University of Oregon (ADH, AGH), NIH RO1 HL081823 (FLP), NIH T32 5T32HL098062 (JAS).

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http://dx.doi.org/10.1016/j.expneurol.2016.07.022
0014-4886/

1. 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.

2. 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.

2.1. 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, 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