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Review

Clinical and experimental aspects of breathing modulation by inflammation

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ABSTRACT

Neuroinflammation is produced by local or systemic alterations and mediated mainly by glia, affecting the activity of various neural circuits including those involved in breathing rhythm generation and control. Several pathological conditions, such as sudden infant death syndrome, obstructive sleep apnea and asthma exert an inflammatory influence on breathing-related circuits. Consequently breathing (both resting and ventilatory responses to physiological challenges), is affected; e.g., responses to hypoxia and hypercapnia are compromised. Moreover, inflammation can induce long-lasting changes in breathing and affect adaptive plasticity; e.g., hypoxic acclimatization or long-term facilitation. Mediators of the influences of inflammation on breathing are most likely proinflammatory molecules such as cytokines and prostaglandins. The focus of this review is to summarize the available information concerning the modulation of the breathing function by inflammation and the cellular and molecular aspects of this process. I will consider: 1) some clinical and experimental conditions in which inflammation influences breathing; 2) the variety of experimental approaches used to understand this inflammatory modulation; 3) the likely cellular and molecular mechanisms.

1. Introduction

Inflammation is a biological response which can be initiated by pathogens, toxins, trauma, hemodynamic changes, degeneration or damaged tissue, that aims to eliminate foreign substances and/or repair injured tissues (Kettenmann et al., 2011). It also produces secondary changes in functions of various organs including the brain (Del Rio et al., 2010, 2012; Xanthos and Sandkühler, 2014; Fig. 1). The exact mechanisms involved are still unknown, but immune system activation leads to the release of multiple inflammatory molecules combined with growth/trophic factors (Kettenmann et al., 2011; Kiernan et al., 2016; see Figs. 1 & 2) that are involved in both the inflammation and the associated modulation of tissue functions (Herlenius, 2011; Kettenmann et al., 2011). Neuroinflammation, mediated mainly by glial cells and to a lesser extent by neurons, allows the CNS to respond to similar challenges as those encountered by the immune system in the periphery (Xanthos and Sandkühler, 2014; Hamasaki et al., 2018; Fig. 1). More specifically, neuroinflammatory challenges include neuronal activity modifications (Xanthos and Sandkühler, 2014; Fig. 1), hypoxic conditions (Gozal et al., 2002) or local lesions (Gonzalez-Perez et al., 2002). Although the CNS was described as “immune-privileged”, there is now substantial evidence of systemic inflammatory signals altering CNS function (Kettenmann et al., 2011; Fig. 1). Breathing is one brain function that is highly influenced by inflammation (Herlenius, 2011; Fig. 1). This is possible because neural networks can be directly affected by inflammatory signals generated in the periphery (Del Rio et al., 2010, 2012; Fig. 1) and by the neuroinflammatory responses of glial cells (Elmore et al., 2014; Henry et al., 2009; Liu et al., 2012; Fig. 2). Glial cells continuously surveil and influence normal brain function (Kettenmann et al., 2011; Peña-Ortega, 2017; Xanthos and Sandkühler, 2014; Fig. 2) but also respond to peripheral or local inflammation (Elmore et al., 2014; Henry et al., 2009; Liu et al., 2012). Here I will review the clinical and cellular aspects of the inflammatory modulation of breathing generation and control, the experimental approaches used and the influence of inflammatory signals on glial cells and breathing (Peña-Ortega, 2012; Herlenius, 2011; see Fig. 2).

1.1. Generation and control of breathing

Breathing involves a motor program (one-, two- or three-phase rhythm: see Peña-Ortega, 2012, 2017; Ramirez and Baertsch, 2018; Del Negro et al., 2018) that leads to the pumping of air in and out of the

Abbreviations: DTP, diphtheria/tetanus/whole-cell pertussis; EP3, E-prostanoid receptor subtype 3; HIF-1α, hypoxia-inducible factor 1-alpha; iNOS, inducible NO synthase; IgG, immunoglobulin M; IgM, immunoglobulin M; IL-1β, interleukin-1 beta; IL-6, interleukin-6; ICV, intracerebroventricular; LPS, lipopolysaccharide; LTF, long-term facilitation; L-NAME, N(G)-nitro-L-arginine methyl ester; NADPH, nicotinamide adenine dinucleotide phosphate; NSAID, nonsteroidal anti-inflammatory drug; NF-kB, nuclear factor kappa B; nTS, nucleus of the solitary tract; OSA, obstructive sleep apnea; Pico, post-inspiratory complex; preBötC, preBötzinger complex; PGE2, prostaglandin E2; PGE-M, prostaglandin E metabolite; ROS, reactive oxygen species; RSV, respiratory syncytial virus; RTN/pFN, retrotrapezoid nucleus/parafacial nucleus; RVLM, rostral ventrolateral medulla; SIDS, sudden infant death syndrome; TRIF, TIR domain containing adaptor inducing interferon-beta protein; TLR, Toll-like receptor; TNFα, tumor necrosis factor alpha

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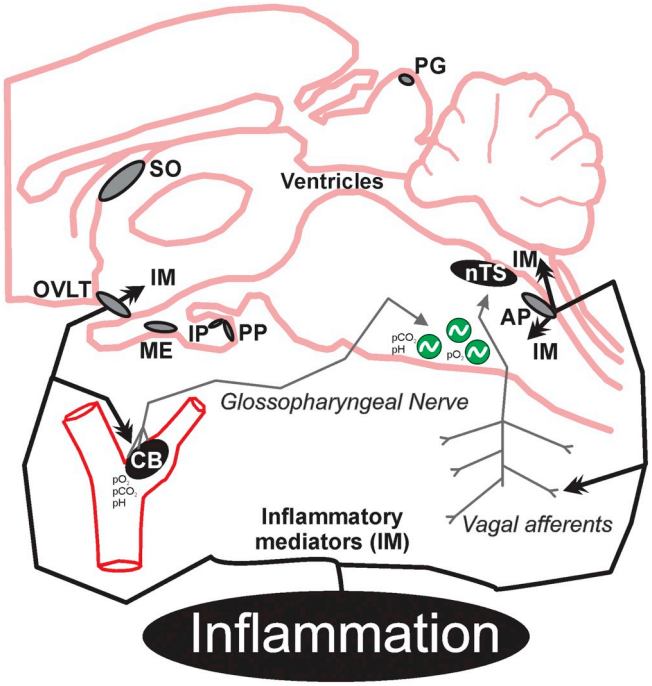

Fig. 1. Breathing central pattern generators and the possible modulation of respiratory rhythm generation/control by peripheral inflammation and chemosensory signals. Located in the ventrolateral portion of the medulla three central pattern generators (denoted with ~) have been identified to produce inspiration (the preBötzinger complex), post-inspiration (the post-inspiratory complex) and expiration (the retrotrapezoid nucleus/parafacial nucleus). All these networks, along with other respiratory circuits, are subject to modulation by other neural circuits (i.e., nucleus tractus solitarius, nTS), and directly by chemosensory signals, such as partial pressures of carbon dioxide (CO_2) or oxygen (O_2) and/or pH. The signal carried by inflammatory mediators (IM) released in the periphery can reach the brain, specifically the brainstem, via active transport or circumventricular regions (gray ovals) including the subfornical organ (SO), the organum vasculosum of the lamina terminalis (OVLT), the median eminence (ME), the intermediate pituitary (IP), the posterior pituitary (IP), the area postrema (AP) and the pineal gland (PG). Circulating IM can also activate the vagus nerve or the carotid body (CB), which translate this activation into the brainstem. CB is also involved in peripheral chemosensory transduction, which is then relied to brainstem circuits.

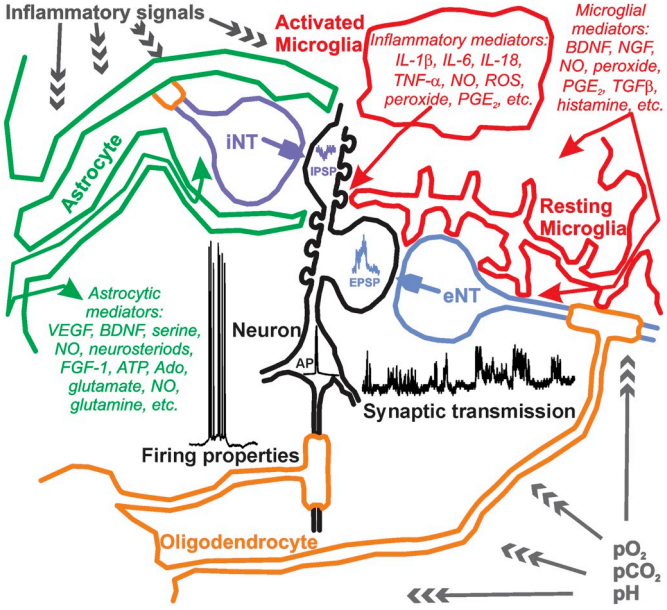

Fig. 2. Interactions among neurons a glia. Neural network activity is produced by the dynamic interactions between neurons' firing properties and their synaptic interactions. These synaptic interactions can be inhibitory (producing inhibitory postsynaptic potentials, IPSP) or excitatory (producing excitatory postsynaptic potentials, EPSP) in nature, which are dynamically integrated leading to, or avoiding, the production of action potentials (AP). Neural network activity is dynamically modulated by the interactions of neurons and a variety of glial types (astrocytes, oligodendrocytes and microglia). Most glial cells can change their phenotype by the process of glial activation. Glial cells establish physical interactions that modulate neuronal functions. In addition, all glial cell types release mediators that also modulate neural network activity by their actions on neurons and other glial cells. Regarding breathing generation and control, both neurons and glia located in respiratory circuits are sensitive to chemosensory signals. VEGF (vascular endothelial growth factor), BDNF (brain-derived neurotrophic factor), FGF-1 (fibroblast growth factor 1), Ado (adenosine), IL-1β (interleukin 1 beta), IL-6 (interleukin 6), IL-18 (interleukin 18), TNF-α (tumor necrosis factor alpha), ROS (reactive oxygen species), PGE_2 (prostaglandin E2), NGF (nerve growth factor), TGFβ (transforming growth factor beta).

lungs. The neural circuits involved in its generation and control reside in medullary and extramedullary CNS locations (Ramirez and Baertsch, 2018; Del Negro et al., 2018; Dutschmann et al., 2014; Fig. 2). Breathing consists of inspiration (when air is draw into the lungs), post-inspiration, and either passive or active expiration: active expiration is associated with specific behavioral and/or increased metabolic demands (Ramirez and Baertsch, 2018; Del Negro et al., 2018). The respiratory motor neuron pools involved receive various rhythmic commands generated by from premotor neurons: inspiration, the preBötzinger complex (preBötC); post-inspiration, the post-inspiratory complex (Pico); expiration, the retrotrapezoid nucleus/parafacial nucleus (RTN/pFN). These premotor neurons are involved in breathing pattern generation and are located in the medullary ventral respiratory column of the brainstem (Ramirez and Baertsch, 2018; Del Negro et al., 2018; Fig. 2). The rhythmicity of these pattern generators emerges through the dynamic interaction of excitatory and inhibitory transmission, and the intrinsic bursting properties of the network (Ramirez and Baertsch, 2018; Fig. 1). The intrinsic properties and interactions of cells within the breathing generating network are highly diverse and dynamic, changing in a state-dependent manner (Ramirez et al., 2004; Nieto-Posadas et al., 2014), and can be influenced by various nervous inputs (i.e., those arising from pontine nuclei or the nucleus tractus solitarius (nTS): Ramirez and Baertsch, 2018; Del Negro et al., 2018; Dutschmann et al., 2014; Fig. 2) and neuromodulators (Peña and García, 2006; Doi and Ramirez, 2008; Peña-Ortega, 2012), which can be released by glial cells, including astrocytes and microglia (Peña-Ortega, 2012; Beltrán-Castillo et al., 2017; Forsberg et al., 2016, 2017; Fig. 2). Neuromodulation may also involve inflammatory mediators (Forsberg et al., 2016, 2017; Fig. 2). This modulation is reflected in the findings that gliotoxins affecting astrocytes and microglia modify the frequency and/or amplitude of inspiratory activity both in vitro and in vivo (Hülsmann et al., 2000; Huxtable et al., 2010; Lorea-Hernández et al., 2016; Peña-Ortega et al., 2016; Sheikhbahaei et al., 2018; Camacho-Hernández et al., 2018). Astrocytes release mediators that modulate breathing (Gourine et al., 2010; Angelova et al., 2015; Beltrán-Castillo et al., 2017; Forsberg et al., 2016, 2017; Fig. 2) and are required for the actions of neuromodulators on respiratory rhythm generation (Huxtable et al., 2010). Astrocytes have been found also to function as transductors of chemosensory signals in respiratory networks (in vitro and in vivo studies: Gourine et al., 2010; Wenker et al., 2010; Angelova et al., 2015; Rajani et al., 2018; Beltrán-Castillo et al., 2017; Fig. 2). Breathing is regulated additionally by peripheral and central chemosensory feedback (Del Negro et al., 2018; Fig. 1) as well as mechanosensory feedback from the thoracic cage and the lungs (Del Negro et al., 2018). Carotid bodies, located at carotid artery bifurcation, monitor the partial pressure of O_2 and CO_2 as well as pH in arterial blood and signal to the brainstem via the glossopharyngeal nerve (Del Negro et al., 2018; Fig. 1). Several respiratory circuits and sensory organs are subject to modulation by inflammatory signals, as discussed throughout this review (Figs. 1 & 2).

2. Neuroinflammation induced by peripheral immune activation and its modulation of brainstem function

2.1. Peripheral and central inflammation

Despite the differential immune dynamics in the brain compared to the systemic immune responses, peripheral infection and inflammation can certainly induce central neuroinflammation (Elmore et al., 2014; Henry et al., 2009; Liu et al., 2012; Fig. 1), a phenomenon partially mediated by microglial recruitment (Elmore et al., 2014; Henry et al., 2009; Liu et al., 2012; Fig. 2). Peripheral inflammation can be signaled to the CNS through various pathways (Fig. 1). For instance, some circulating inflammatory molecules cross the blood–brain barrier into the CNS via active transport (Wilson et al., 2002; Banks et al., 1991, 1994) or via circumventricular regions that lack an effective blood–brain barrier (Wuchert et al., 2008, 2009; Fig. 1). Circulating cytokines also bind to brain endothelial cells and induce the production of proinflammatory molecules, such as nitric oxide (NO) or prostaglandins, that cross the blood–brain barrier or increase blood–brain barrier permeability (Ek et al., 2001; Engblom et al., 2002; Herlenius, 2011). Peripheral inflammation additionally can be signaled to the CNS through vagal afferents (Ek et al., 1998; Goehler et al., 2005; Balan et al., 2011; Fig. 1). Vagal nerve afferents express receptors for inflammatory mediators, including interleukin-1 beta (IL-1β) receptors (Ek et al., 1998; Goehler et al., 2005). In this way, peripheral IL-1β or lipopolysaccharide (LPS) can elicit brainstem inflammation mainly in the nTS (conscious and anesthetized animals: Jafri et al., 2013; Johnson et al., 2018). This inflammation can be abolished by subdiaphragmatic vagotomy (conscious animals: Layé et al., 1995; Bluthé et al., 1996; Romanovsky et al., 1997). Neuroinflammation can also be induced as a secondary response to neuronal activity, neuronal debris or to molecules released by neurons (Xanthos and Sandkühler, 2014). Injured or stressed neurons can release “damage-associated molecular patterns” that can induce further microglial activation and long-lasting neuroinflammation (Kettenmann et al., 2011; Pineau and Lacroix, 2009; Xanthos and Sandkühler, 2014). Neuroinflammation can transynaptically modulate neural networks beyond the site of the direct inflammatory influence by transmitting the change in activity at the original site to those networks directly connected to it (Daulatzai, 2012).

2.2. Microglia and neuroinflammation

Microglia are tissue resident macrophages of the CNS (Fig. 2). They are distributed ubiquitously and comprise ≈10–15% of cell population in the CNS (Lawson et al., 1990). Despite their ubiquity, microglia are distributed heterogeneously (Lawson et al., 1990; Savchenko et al., 2000; Mittelbronn et al., 2001; de Haas et al., 2008; Nikodemova et al., 2014; Smith et al., 2013; Tay et al., 2017). The differential distribution matches heterogeneous proliferation rates (Tay et al., 2017), heterogeneous chemical expression profiles and heterogeneous morphologies, which are hypothesized to be defined by their close environment (Lawson et al., 1990; de Haas et al., 2008; Mittelbronn et al., 2001; Nikodemova et al., 2014). Microglial heterogeneity is also revealed during development, since microglia undergo significant postnatal changes in their cell number, morphology and function (Crain et al., 2009; Crain and Watters, 2015; Nikodemova et al., 2015; Mosser et al., 2017). In newborns microglia are characterized by a round cell body (amoeboid shape) with no identifiable processes (Harry and Kraft, 2012; Crain et al., 2013; Fig. 2). During postnatal life their cell bodies display adult-like ramified morphology (Orłowski et al., 2003; Crain et al., 2013; Fig. 2). Such morphological changes are associated with changes in the biochemical phenotype of microglia (Crain et al., 2013). Microglial heterogeneity is also seen at the local level since various microglial phenotypes can co-exist within the same brain region (Perego et al., 2011; Crain et al., 2013; Kapoor et al., 2016; Tay et al., 2017; Fig. 2).

For a long time the function of microglia was considered solely to defend the integrity of the brain by detecting any internal or external threatening stimulus (Kettenmann et al., 2011) including hypoxia (Zhang et al., 2012; Tadmouri et al., 2014; Fig. 2). When subjected to activating stimuli microglia transform their phenotype from a highly ramified morphology with a small cell body to an amoeboid shape (Fig. 2) allowing them to proliferate, move easily, phagocytose debris and produce large quantities of neurotoxic and/or neuroprotective molecules (Kettenmann et al., 2011). However, increasing evidence suggests that microglia under basal conditions constantly surveil their close environment (Kettenmann et al., 2011; Tremblay et al., 2011; Miyamoto et al., 2013; Fig. 2) and play a physiological role in maintaining normal neuronal function (Kettenmann et al., 2011; Tremblay et al., 2011; Miyamoto et al., 2013); e.g., in their resting/surveilling state, microglia release neurotrophic factors (Tremblay et al., 2011; Ueno et al., 2013; Fig. 2) and/or perform synaptic pruning (Kettenmann et al., 2011; Tremblay et al., 2011; Miyamoto et al., 2013). Moreover, microglia constantly maintain neurons within their dynamic physiological working range by regulating their excitability and synaptic interactions (Kettenmann et al., 2011; Tremblay et al., 2011; Miyamoto et al., 2013; Fig. 2).

2.3. Neuroinflammation and brainstem function

As mentioned previously the brainstem constitutes an area highly related to the interface between peripheral and central inflammation (Ek et al., 1998; Goehler et al., 2005; Balan et al., 2011; Jafri et al., 2013). The number of microglia in the brainstem appears to be lower than in the rest of the brain (excluding the spinal cord; Lawson et al., 1990; Savchenko et al., 2000; Nikodemova et al., 2014; Smith et al., 2013). Despite the comparatively reduced levels of microglia in the brainstem this cell type is involved in regulating several brainstem functions (anesthetized and conscious animals: Bhandare et al., 2015, 2016, 2017; Lorea-Hernández et al., 2016; Kapoor et al., 2016); e.g., microglia are involved in trigeminal and facial nerve plasticity observed in animals after they have been exposed to ischemia or peripheral inflammation induced by dental injury when under anesthesia (Miremami et al., 2014; Fan et al., 2010). Similarly, brainstem microglia are involved in the reconfiguration of the ventral cochlear nucleus following sensory deafferentation under anesthesia (Janz and Illing, 2014). The evidence supports the contention that brainstem microglia contribute to the response of CNS networks to physiological and pathological conditions.

Changes in the respiratory responses to hypercapnia and hypoxia induced by omega-3 polyunsaturated fatty acid feeding and recorded in conscious animals involve modulation of brainstem microglia (Tenorio-Lopes et al., 2017). Furthermore, brainstem microglia are sensitive to various physiological and pathological conditions that directly modulate brainstem function. For instance in the ventrolateral medulla (excluding the nucleus ambiguus) upon induction of hypertension microglia increase their number and contacts with synapses (anesthetized animals: Kapoor et al., 2016). Similarly chronic intermittent hypoxia in conscious animals has been observed to activate microglia in the brainstem (Smith et al., 2013). Hypoxic modulation of brainstem microglia has also been observed upon sustained hypoxia in conscious animals, which changes a variety of brainstem functions and increases microglia cell numbers in the nTS and dorsal motor nucleus of the vagus (MacFarlane et al., 2016). The latter effects are inhibited by minocycline (MacFarlane et al., 2016), which is an antibiotic and anti-inflammatory drug that can inhibit microglial activation (Peña-Ortega, 2017). Similarly microinjection of minocycline in the ventrolateral medulla modulates sympathetic output and reduces the prolongation of QT interval during seizures in anesthetized animals (Bhandare et al., 2015, 2016, 2017). A powerful modulator of microglial function in the brainstem is hypoxia (Smith et al., 2013; Tadmouri et al., 2014;

Camacho-Hernández et al., 2018). Hypoxia and inflammation synergistically promote various breathing dysfunctions including those related to sudden infant death syndrome (SIDS) and sleep apneas (Scott et al., 1978; Williams et al., 1984a,b; Blackwell et al., 1992, 1999; Vege et al., 1999; Raza and Blackwell, 1999; Gilbert et al., 1992; Ryan et al., 2005; Rius et al., 2008; Liu et al., 2017). The evidence herein indicates that microglia contribute to the chemosensory responses of brainstem networks under physiological and pathological conditions (Fig. 2). In the next section I will review the relationship between hypoxia and inflammation.

3. Hypoxia-induced peripheral and central inflammation and its effect on breathing

3.1. Hypoxia and inflammation

Hypoxia is a powerful inducer of peripheral and central inflammation (Semenza and Prabhakar, 2007). Hypoxia-inducible factor 1-alpha (HIF-1α) and nuclear factor kappa B (NF-kB) are key mediators of hypoxia-induced inflammatory responses (Spranger et al., 1998; Guo and Bhat, 2006; Semenza and Prabhakar, 2007). NFκB contributes to HIF-1α protein accumulation in hypoxia (Rius et al., 2008). The activation of these transcription factors by hypoxia involves O_2-sensitive prolyl hydroxylases (Cummins et al., 2006; Rius et al., 2008). Hypoxia-induced activation of NFκB involves the IκB kinase activation by O_2-sensitive prolyl hydroxylases (Cummins et al., 2006; Rius et al., 2008). These transcription factors modulate the chronic respiratory changes induced by hypoxia, since HIF-1α increases in both the carotid bodies and the CNS respiratory centers upon chronic hypoxia (Powell and Fu, 2008). Chronic hypoxia regulates the activity of microglia throughout the brain (Huang et al., 2014; Merighi et al., 2015; Kumar et al., 2015) including breathing-related areas in the brainstem (Tadmouri et al., 2014). Intermittent hypoxia, the hallmark of obstructive sleep apnea (OSA), also produces the activation of proinflammatory transcription factors such as NF-kB (Ryan et al., 2005; Rius et al., 2008; Liu et al., 2017). Thus hypoxia induces the synthesis and secretion of proinflammatory cytokines by NF-kB and HIF-1α-dependent mechanisms (Semenza and Prabhakar, 2007; Spranger et al., 1998). Hypoxia also increases microglial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity (Spranger et al., 1998) and reactive oxygen species (ROS) production during hypoxia (Spranger et al., 1998; Pardo-Peña et al., 2018), so contributing to the induction of proinflammatory responses via hypoxia-induced calcium influx through voltage-gated calcium channels (Spranger et al., 1998).

Although acute hypoxia can induce inflammation (Guo and Bhat, 2006; Herlenius, 2011) a more powerful inducer of inflammation is intermittent hypoxia (Semenza and Prabhakar, 2007; de Lima et al., 2016). In animal models intermittent hypoxia activates NF-κB/P38 mitogen-activated protein kinases signaling (Liu et al., 2017), leading to the expression of proinflammatory enzymes including inducible NO synthase (iNOS) and NADPH oxidase and cyclooxygenase-2 (Zhan et al., 2005; Nair et al., 2011; Gao et al., 2012; Beaudin et al., 2014). Intermittent hypoxia also activates the inflammasome and contributes to production of IL-1β, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), prostaglandin E_2 (PGE_2) (Iturriaga et al., 2009; Smith et al., 2013; Liu et al., 2017) as well as Toll-like receptor (TLR) 4 (Yuan et al., 2014; Beaudin et al., 2014; Deng et al., 2015). It also increases endogenous TLR4 ligands such as heat shock protein 60 and α-synuclein (Gozal et al., 2002), increases ROS formation (Nair et al., 2011; Gao et al., 2012; Pardo-Peña et al., 2018) and promotes lipid peroxidation (Savransky et al., 2007). These experimental findings closely resemble those found in clinical observations in OSA patients that show increased serum levels of high mobility group box 1, interleukin-18, IL-1β, TNF-α and IL-6 (Teramoto et al., 2003; Alberti et al., 2003; Minoguchi et al., 2005; Lavie and Polotsky, 2009; Wu et al., 2010; Svensson et al., 2012) as well as upregulated TLR2 and TLR4 levels in circulating monocytes (Akinnusi et al., 2009). Moreover, the levels of the TLR4 ligand myeloid-related proteins 8 and 14 correlate with disease severity in children with OSA (Kim et al., 2010). Interestingly, TLR2, TLR4 and proinflammatory marker expression in OSA patients are normalized by continuous positive airway pressure (CPAP; Wu et al., 2010; Akinnusi et al., 2013). Sustained hypoxia in vitro also increases TLR4 expression and shifts TLR4 signaling from a myeloid differentiation primary response 88 to a TIR domain containing adaptor inducing interferon-beta protein (TRIF)-dominant pathway (Ock et al., 2007). It has been shown recently that in addition to the increased levels of IL-6 (Motamedi et al., 2018), OSA patients exhibit increased levels of the microtubule-associated protein tau (Motamedi et al., 2018), which we have shown can induce alterations in neural network function (Mondragón-Rodríguez et al., 2017, 2018; Cornejo-Montes-de-Oca et al., 2018). This evidence demonstrates that intermittent hypoxia is a powerful inducer of inflammatory responses that closely resemble those observed in OSA patients.

3.2. Hypoxia and microglial function

Hypoxia induces directly microglial activation (Suk, 2004; Wang and Wang, 2007; J.J. Li et al., 2008; Li et al., 2009; Pardo-Peña et al., 2018) and changes in microglial morphology (You and Kaur, 2000; Deng et al., 2008, 2009; Fig. 2), proliferation rate (Deng et al., 2009), phagocytic activity (Deng et al., 2008), production of proinflammatory enzymes (You and Kaur, 2000) and inflammatory mediators such as NO, IL-1β, IL-6, TNF-α, ROS and PGE_2 in an inflammasome-dependent manner (Suk, 2004; Deng et al., 2008, 2010, 2011; Smith et al., 2013; Liu et al., 2017; Pardo-Peña et al., 2018; Silva et al., 2018). Most of these effects on microglia are also observed in microglial cell lines (F. Li et al., 2008) and are inhibited by minocycline (Suk, 2004; Pardo-Peña et al., 2018; Silva et al., 2018). Moreover, acute hypoxia increases LPS effects on cultured microglia and potentiates iNOS, TNF-α and NF-κB expression (Guo and Bhat, 2006), clearly indicating that hypoxia induces a proinflammatory state through microglial activation. So far I have reviewed evidence supporting the view that CNS neuroinflammation, particular within the brainstem, can be induced via peripheral inflammatory signals modulating CNS microglial cell activity. Moreover, hypoxia also induces proinflammatory conditions in both the periphery and the CNS. Next, I will consider how hypoxia and inflammation influence breathing during normal and pathological conditions.

3.3. Hypoxia, inflammation and breathing

Hypoxia is a strong modulator of breathing (Peña, 2009; Peña-Ortega, 2012; Fig. 1) and, depending on the intensity and/or pattern, it induces various adaptive or pathological respiratory responses (Peña, 2009; Peña-Ortega, 2012) that are either transient or long-lasting in nature (Peña, 2009; Tadmouri et al., 2014; Hocker et al., 2017; Camacho-Hernández et al., 2018). Acute moderate hypoxia transiently increases ventilation (Popa et al., 2011; Silva et al., 2018), whereas profound hypoxia leads to gasping generation (Peña, 2009; Peña-Ortega, 2012) which contributes to autoresuscitation upon reoxygenation (Peña, 2009; Peña-Ortega, 2012; Rivera-Angulo and Peña-Ortega, 2014; Lorea-Hernández et al., 2016). Acute and moderate intermittent hypoxia induces a long-lasting increase in the frequency and/or amplitude of breathing referred to as long-term facilitation (LTF; Huxtable et al., 2015; Hocker et al., 2017). Chronic sustained hypoxia produces hypoxic acclimatization characterized by increased ventilation (Tadmouri et al., 2014) and increased hypoxic ventilatory response (Popa et al., 2011; Pamenter and Powell, 2016). These respiratory responses require a variety of oxygen-sensitive neural mechanisms (Peña, 2009; Peña-Ortega, 2012; Fig. 2) and also correlate with hypoxia-induced peripheral and central inflammation (Tadmouri et al., 2014; MacFarlane et al., 2016; Huxtable et al., 2015; Smith et al., 2013;

Darnall et al., 2017; Hocker et al., 2017; Silva et al., 2018; Fig. 1), which involve microglial and astrocytic activation (Tadmouri et al., 2014; MacFarlane et al., 2016; Turlejski et al., 2016; Silva et al., 2018; Fig. 2) and the production of pro-inflammatory mediators in the periphery and CNS (Popa et al., 2011; Huxtable et al., 2015; Smith et al., 2013; Pardo-Peña et al., 2018; Silva et al., 2018). For instance in conscious animals chronic sustained hypoxia induces the activation of microglia and astrocytes as well as the overproduction of IL-6 and TNF-α in the brainstem (Tadmouri et al., 2014; MacFarlane et al., 2016; Turlejski et al., 2016), so increasing ventilation and the hypoxic ventilatory response (Tadmouri et al., 2014; MacFarlane et al. 2015). In conscious animals these respiratory adaptations are reduced by the administration of minocycline (Tadmouri et al., 2014; MacFarlane et al., 2016; Stokes et al., 2017; Silva et al., 2018) and the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen (Popa et al., 2011). Ibuprofen prevents chronic sustained hypoxia-induced increases in inflammatory cytokines in the brainstem of rats (Popa et al., 2011). The attenuation of chronic sustained hypoxia-induced potentiation of the hypoxic ventilatory response by ibuprofen has also been observed in healthy volunteers after 48 h of acclimatization to high altitude (Basaran et al., 2016). In conscious animals minocycline also reduces the increase in ventilation induced by acute hypoxia, which is related to a reduction of proinflammatory mediators such as IL-1β and TNF-α (Silva et al., 2018). Other hypoxic respiratory response modulated by inflammation is the LTF induced by intermittent hypoxia (anesthetized and conscious animals: Ling et al., 2001; McGuire et al., 2003; Huxtable et al., 2015; Hocker et al., 2017). For instance, 8 h of intermittent hypoxia induces microglial activation and increases the expression of inflammatory cytokines and enzymes, which correlates with the blockade of LTF induction (anesthetized animals: Huxtable et al., 2015; Hocker et al., 2017): these effects are reversed by the NSAID ketoprofen (Huxtable et al., 2015; Hocker et al., 2017). The evidence herein indicates that hypoxia induces inflammation and modulates breathing in diverse time frames and in the short and long term. Moreover, it shows that hypoxia-induced modulation of breathing involves various inflammatory signals and, in some cases, triggers microglial actions on respiratory networks.

4. Pathological conditions linking inflammation and respiratory dysfunction

4.1. Sudden infant death syndrome (SIDS)

SIDS is a pathological condition that exhibits a clear relationship between hypoxia, inflammation and respiratory abnormalities (Vege et al., 1999; Scott et al., 1978; Williams et al., 1984a,b; Gilbert et al., 1992; Raza and Blackwell, 1999). SIDS has been associated with various signs of infection (Scott et al., 1978; Lundemose et al., 1990; Gilbert et al., 1992; Valdes-Dapena, 1988; Stoltenberg et al., 1992, 1995; Thrane et al., 1994) including: increased numbers of immunoglobulin M (IgM), immunoglobulin G (IgG) and immunoglobulin A immunocytes (Stoltenberg et al., 1995; Gleeson et al., 1993); increased eosinophils, T and B lymphocytes (Howat et al., 1994; Lorin de la Grandmaison et al., 1999); increased density of activated macrophages (Platt et al., 1989, 1994; Howat et al., 1994; Lorin de la Grandmaison et al., 1999); increased density of mast cells (Howat et al., 1994) associated with evidence of mast cell degranulation (Holgate et al., 1994; Baxendine and Moore, 1995). SIDS has also been related to respiratory tract inflammatory infiltrates (Howat et al., 1994; Baxendine and Moore, 1995) and higher immunoglobulins in the circulation (Valdes-Dapena, 1988) and in lung lavage fluids (Forsyth et al., 1989). In addition signs of immune stimulation in SIDS victims have been found in the salivary glands (Thrane et al., 1994), tonsils (Stoltenberg et al., 1995), tracheal wall (Stoltenberg et al., 1992), duodenal mucosa (Stoltenberg et al., 1992) and larynx (Vege et al., 1999). Increased levels of proinflammatory cytokines IL-1, IL-6, and TNF-α have also been found in body fluids and tissues of infants with SIDS (Vege and Rognum, 1999; Forsyth, 1999). For instance IL-6 is elevated in the cerebrospinal fluid (Vege et al., 1995, 1998, 1999) and laryngeal mucosa of SIDS infants (Vege et al., 1999). Furthermore the amount of IL-6 receptor in the arcuate nucleus is significantly higher in SIDS (Rognum et al., 2009). Accordingly there is an association between SIDS and high-producing IL-6 polymorphisms (Dashash et al., 2006; Moscovis et al., 2006; Opdal and Rognum, 2007). High-producing TNF-α polymorphism has also been reported in SIDS cases (Ferrante et al., 2008), whereas IL-1β polymorphism, which displays an increased response to the toxic shock syndrome toxin, was seen more often in the parents of infants who died from SIDS (Moscovis et al., 2004). In contrast there is an association between SIDS and low-producing interleukin-10 polymorphisms (Summers et al., 2000; Korachi et al., 2004; Opdal et al., 2003; Weese-Mayer et al., 2007). The association of SIDS and inflammation has also been supported by the identification of interferon alpha in neurons of the brainstem (Howatson, 1992) and the overexpression of IL-1β detected in the arcuate and dorsal vagal nuclei (Kadhim et al., 2003) of SIDS patients.

Specific infections with two or more bacteria or mixes of bacteria and viruses have been described in SIDS infants (Telford et al., 1989; Blackwell et al., 1992, 1999; Malam et al., 1992; McKendrick et al., 1992; Pattison and Marshall, 1997; Kerr et al., 2000). The two most commonly isolated bacteria from SIDS cases are *Staphylococcus aureus* and *Escherichia coli* (Telford et al., 1989; Bettelheim et al., 1990; Blackwell et al., 1992, 1999; Malam et al., 1992; McKendrick et al., 1992; Pattison and Marshall, 1997; Kerr et al., 2000). *Chlamydia* inclusions have also been reported in cases of SIDS (Lundemose et al., 1990). Furthermore there is an association between *Helicobacter pylori* urease subunit alpha gene and cytotoxin-associated gene A in the stomach, trachea and lung in cases of SIDS (Pattison and Marshall, 1997; Kerr et al., 2000). As a consequence of bacterial infection, there is a significant correlation between bacterial toxin levels and SIDS cases (Crawley et al., 1999; Goldwater, 2004), which is related to increased IgM to core endotoxin (Kilpatrick et al., 1998) and decreased IgG to bacterial toxins (Siarakas et al., 1999). Viruses are more commonly identified in cases of SIDS compared to controls with an average isolation rate of 22% in SIDS cases and 8% in controls (Samuels, 2003). SIDS has also been related to infections with adenoviruses (Bajanowski et al., 1996; Dettmeyer et al., 2004), respiratory syncytial viruses (Samuels 2003), enteroviruses, parvovirus B19 (Dettmeyer et al., 2004; Baasner et al., 2003), influenza viruses, rhinoviruses, cytomegalovirus, coxsackie B3 virus (Samuels, 2003; Cecchi et al., 1995; Dettmeyer et al., 2002) and Epstein-Barr viruses (Dettmeyer et al., 2004). These viral infections produce extended inflammation (Dettmeyer et al., 2004). Finally, cytomegalovirus brain inclusions associated with microglia have been reported in SlDS (Huff and Carpenter, 1987; Variend, 1990).

Changes in glial density and morphology have been documented in the brainstem of SIDS cases (Naeye et al., 1976; Takashima et al., 1978; Becker and Takashima, 1985; Oehmichen et al., 1989; Storm et al., 1994; Obonai et al., 1996; Sawaguchi et al., 2002; Biondo et al., 2004) with signs of glial activation in the dorsal nucleus of the vagus in the medulla oblongata correlating with the frequency of obstructive apneas (Sawaguchi et al., 2003). SIDS patients also exhibit microglial nodules in the brainstem (Variend, 1990; Variend et al., 1997) with microglia showing early signs of activation (Sparks and Hunsaker, 2002) and increased expression of human leukocyte antigen DR (Esiri et al., 1991).

4.2. Asthma

Another pathological condition linking inflammation and respiratory abnormalities is asthma. In fact respiratory failure is a common clinical symptom and a primary cause of mortality in asthmatic patients (Newcomb and Akhter, 1988; Molfino et al., 1991). It is generally recognized that patients with chronic bronchial asthma have a depressed hypoxic ventilatory response that may contribute to

respiratory failure (Hudgel and Weil, 1975; Chang et al., 1978; Hida, 1999; Hudgel and Weil, 1975; Hutchison and Olinsky, 1981; Kikuchi et al., 1994; Smith and Hudgel, 1980; Town and Allan, 1989) which has been associated with diminished hypoxic perception (Kikuchi et al., 1994).

4.3. Immunization

Immunization has also been related to respiratory dysfunctions, including an increased occurrence of cardiorespiratory events (Ben Jmaa et al., 2017) that are associated with single or recurrent apneas and are predominant in preterm infants (Clifford et al., 2011; Botham and Isaacs, 1994; Botham et al., 1997; Cooper et al., 2008; Faldella et al., 2007; Lee et al., 2006; Pfister et al., 2004; Sánchez et al., 1997; Slack and Schapira, 1999; Furck et al., 2010; Flatz-Jequier et al., 2008). Preterm infants experience either an increase in or a resurgence of apnea after vaccination (Botham and Isaacs, 1994; Botham et al., 1997; Pfister et al., 2004; Sánchez et al., 1997; Sen et al., 2001; Slack and Schapira, 1999; Slack et al., 2003), with major cardiorespiratory events after vaccination occurring more often in very low birth weight infants (Meinus et al., 2012) and in patients with preexisting cardiorespiratory events (Pfister et al., 2004; Faldella et al., 2007). Younger age, smaller size, and more severe illness at birth are important predictors of postimmunization apnea (Klein et al., 2008). The incidence of immunization-induced apnea increases between 10 and 20% in the first 24 h following preterm infant immunizations (Botham et al., 1997; Lee et al., 2006). Importantly most apneic events induced by immunization are self-resolving and do not have long-term adverse effects (Pfister et al., 2004).

Postimmunization apnea has been associated with the administration of vaccines such as the 10-valent pneumococcal conjugate vaccine (Omeñaca et al., 2011), the diphtheria/tetanus/whole-cell pertussis (DTP) vaccine (Botham and Isaacs, 1994; Pourcyrous et al., 1998; Pfister et al., 2004; Sen et al., 2001; Faldella et al., 2007), the DTP vaccine in combination with the *Haemophilus influenzae* type b (Hib) conjugate vaccine (Sánchez et al., 1997; Sen et al., 2001), the Hib vaccine (Pourcyrous et al., 1998), the pentavalent vaccine Diphtheria-Tetanus-Acellular-pertussis-Inactivated poliomyelitis-*Haemophilus influenzae* type b (Botham and Isaacs, 1994; Faldella et al., 2007; Pfister et al., 2004; Schulzke et al., 2005), the inactivated polio vaccine (Pourcyrous et al., 1998), the hepatitis B virus vaccine (Pourcyrous et al., 1998) and the pertussis vaccines (Botham and Isaacs, 1994; Sánchez et al., 1997; Sen et al., 2001; Slack et al., 2003). Postimmunization apnea could be the result of increases in IL-6 and C-reactive protein levels after vaccination (Pourcyrous et al., 1998).

4.4. Infection

A more direct link between inflammation and respiratory disturbances are the alterations in breathing induced by infection. There is a strong correlation between infection and apnea in newborn infants (Bruhn et al., 1977; Fanaroff et al., 1998). For instance, inflammation associated with pulmonary infection increases susceptibility to respiratory insufficiency including apnea of prematurity (Hofstetter et al., 2008; Kallapur et al., 2009; Pickens et al., 1989). Moreover a characteristic of sepsis is an increase in the respiratory rate (Montgomery et al., 1985; Bone et al., 1989; Magder, 2009), which in extreme conditions leads to respiratory failure (Amoateng-Adjepong et al., 1997) especially in the preterm infant (Fanaroff et al., 1998). Interestingly patients that recover from infection-induced respiratory failure show higher respiratory rate:tidal volume ratio than patients without sepsis (Amoateng-Adjepong et al., 1997).

The respiratory disturbances related to infection can be induced by either viruses or bacteria (Ralston and Hill, 2009; Schiller et al., 2011; Erez et al., 2014). Respiratory syncytial virus (RSV) infection is well known to be associated with breathing dysfunction and apnea in preterm infants (Ralston and Hill, 2009; Schiller et al., 2011; Erez et al., 2014), which has been reproduced by infecting weanling rats with RSV and recorded under anesthesia (Peng et al., 2007). Increased concentrations of IL-1β in pharyngeal secretions of infants infected with RSV have been associated with the increased severity of apneic events (Lindgren and Grögaard, 1996). Apneas have also been observed in infants infected with rhinovirus (Ricart et al., 2014) and other respiratory viruses (Jofré et al., 2007; Simon et al., 2007). Tachypnea is an early feature of meningococcal disease (Hameed and Riordan, 2002), whereas there is a correlation between *Clostridium botulinum* infection and respiratory failure (Arnon et al., 1981).

4.5. Experimental approaches to study inflammation-induced modulation of breathing

Most of the phenomena summarized in this review lack a detailed causal chain that explains their underlying cellular and molecular events, making it extremely important to identify experimental approaches employed to study the precise changes in respiratory function under inflammatory conditions, as well as the mechanisms involved. The number of animal models used to study the relationship between inflammation and breathing is vast, including those aiming to assess directly the inflammation-breathing relationship, as well as alternatives aiming to reproduce specific clinical conditions such as asthma. The most common antigen used to produce an animal model of asthma is ovalbumin, which is administered to anesthetized guinea pigs and rats, and reproduces most of the pathophysiological features observed in asthmatic patients (Cockcroft et al., 1977; Cartier et al., 1982; Hutson et al., 1988; Kuo and Lai, 2008), including pulmonary inflammation (Hutson et al., 1988). Analysis of breathing dynamics, in asthmatic conscious guinea pigs (Pazhoohan et al., 2017), shows a reduced "complexity" which is consistent with findings in asthmatic patients (Thamrin and Frey, 2009; Raoufy et al., 2016; Raoufy et al., 2016); i.e., decreased long-range correlations, lower entropy, increased regularity and memory length of respiratory pattern (Que et al., 2001; Shirazi et al., 2013; Raoufy et al., 2016). Importantly, an increased variability, decreased correlations of peak expiratory flow fluctuations (Frey et al., 2005), increased temporal self-similarity and variability of peak expiratory flow fluctuations observed in these patients have been related to poor asthma control (Kaminsky et al., 2017). Ovalbumin sensitization also induces an increased apneic response evoked by stimulating, in anesthetized rats and guinea pigs, bronchopulmonary C fibres (Kuo and Lai, 2008; Xu et al., 2005). When under anesthesia ovalbumin-sensitized guinea pigs show an attenuated ventilatory hypoxic response and a reduced response to carotid-chemoreceptor stimulation with sodium cyanide and doxapram (Xu et al., 2005) while retaining a normal ventilatory response to CO_2 (Xu et al., 2005).

RSV infection of weanling rats induces an increase in breathing frequency and in the apneic response to right atrial injection of capsaicin (under anesthesia: Peng et al., 2007). Similarly intravenous administration of any one of six common bacterial toxins induces bradycardia, hypotension and apneas, which often lead to sudden death (anesthetized rabbits: Siarakas et al., 1995). Subcutaneous injection of nasopharyngeal bacteria isolated from human SIDS infants was lethal in conscious weanling rats (Lee et al., 1987). In 12-day-old conscious rat pups exposure to the combination of influenza A virus and endotoxin was lethal, in contrast a single insult was not sufficient to cause death; i.e., when the viral challenge was given two days prior to the bacterial endotoxin injection, it caused mortality (Blood-Siegfried et al., 2002, 2004).

5. Modulation of breathing induced by lipopolysaccharide (LPS)

A popular pharmacological strategy to activate the immune system has been LPS (also known as lipoglycan or endotoxin), which is the major component of the outer membrane of Gram-negative bacteria. LPS binds different receptors including cluster of differentiation 14

(Wright et al., 1990; Pålsson-McDermott and O'Neill, 2004), scavenger receptor A (or cluster of differentiation 204, Haworth et al., 1997), TLR4 (Pålsson-McDermott et al., 2004) and complement receptor 3 (Flaherty et al., 1997). In all cases the activation of these receptors by LPS leads to immune cell activation (Wright et al., 1990; Flaherty et al., 1997; Haworth et al., 1997; Pålsson-McDermott et al., 2004). As endotoxemia has been observed in various pathological conditions associated with breathing disturbances, including SIDS (Platt et al., 1989, 1994), and as endotoxin administration in adult humans results in changes in the basal breathing pattern and dyspnea (Preas et al., 2001a,b), the administration of LPS has been a common tool to study the influence of inflammation on breathing generation and control, and plastic changes (anesthetized and conscious animals: Tang et al., 1998; Huxtable et al., 2011, 2015). In general systemic or local application of LPS increases breathing frequency (anesthetized and conscious rats: Gresham et al., 2011; Elorza-Ávila et al., 2017; anesthetized dogs: Hussain et al., 1985; anesthetized cats: Orr et al., 1993; conscious sheep: Esbenshade et al., 1982). LPS also increases sigh frequency (anesthetized rats: Davidson et al., 2002). The increase in breathing frequency induced by LPS often leads to apneas and respiratory failure in anesthetized and conscious animals (Esbenshade et al., 1982; Hussain et al., 1985; Orr et al., 1993; Davidson et al., 2002). In addition LPS administration shortens the time to apnea induced by lung inflation and weakens the Hering–Breuer reflex (anesthetized rats: Zila et al., 2012). The LPS-induced increase in breathing frequency is mostly due to peripheral influences since denervation of the peripheral chemoreceptor attenuated the LPS-induced hyperventilation and death, whereas vagotomy or vagus nerve blockade eliminated the tachypneic response to LPS injection in anesthetized animals (Tang et al., 1998). In contrast to the aforementioned effects of LPS, a significant decrease in breathing rate was observed after the peripheral administration of LPS to conscious rabbits (Riedel, 1983) and rats (Olsson et al., 2003). This decrease has also been observed after intracisternal application of LPS in conscious mice (Lorea-Hernández et al., 2016). In a subgroup of cats, LPS administration under anesthesia produced an abrupt apnea followed by transient rapid and shallow breathing (Orr et al., 1993). In addition peripheral LPS application reduced autoresuscitation and survival from anoxia in conscious rats (Olsson et al., 2003) and anesthetized piglets (Frøen et al., 2002), which was reproduced by intracisternal application of LPS in neonatal conscious mice (Lorea-Hernández et al., 2016). This effect was blocked by minocycline (Lorea-Hernández et al., 2016). Importantly it has been reported that peripheral application of LPS produces no change in basal breathing in newborn conscious piglets (McDeigan et al., 2003) and neonatal conscious rats (McDonald et al., 2016).

Regardless of its effect on basal breathing under normoxic conditions, systemic or local application of LPS blunts the breathing response to hypoxia (conscious rats: Ladino et al., 2007; Balan et al., 2011, 2012; Rourke et al., 2014, 2016; Master et al., 2015, 2016; Ribeiro et al., 2017; conscious piglets: McDeigan et al., 2003; anesthetized cats: Fernández et al., 2008; Zapata et al., 2011). In conscious rats, the breathing response to hypoxia is associated with a high incidence of mortality (Rourke et al., 2014, 2016) yet the breathing response to hypercapnia is not affected by systemic or local application of LPS (Ribeiro et al., 2017). The inhibitory effect of LPS on the breathing response to hypoxia is associated with an attenuated sensory response of the carotid body to hypoxia, which correlates with an increase in IL-1β and IL-6 gene expression (Ladino et al., 2007; Fernández et al., 2008; Gauda et al., 2013; Master et al., 2015, 2016). Intermittent hypoxia induces a long-lasting increase in breathing frequency and/or tidal volume (Vinit et al., 2011; Huxtable et al., 2011, 2013, 2015). This plastic change is absent after the systemic application of LPS (anesthetized rats: Vinit et al., 2011; Huxtable et al., 2011, 2013, 2015). We have recently shown that bath application of LPS reduce the increase in burst frequency of preBötC bursts induced by intermittent hypoxia (Camacho-Hernández et al., 2018).

There is evidence that the effect of LPS on breathing can involve changes in the CNS. For instance, intracisternal administration of LPS modulates not only basal breathing but also the autoresuscitation response to severe hypoxia (conscious mice: Lorea-Hernández et al., 2016). Furthermore the frequency of respiratory motor burst recorded from the phrenic rootlets in an isolated brainstem-spinal cord preparation is significantly reduced in LPS-injected animals (Johnson et al., 2018). In fact some preparations obtained from LPS-injected animals stopped producing rhythmic motor bursts in vitro (Johnson et al., 2018). Additionally in the brainstem slice preparation containing the preBötC, respiratory rhythm generation is depressed upon bath application of LPS (Lu et al., 2012; Lorea-Hernández et al., 2016; Camacho-Hernández et al., 2018), which is mimicked by other "microglial activators", such as fractalkine and fragmented DNA (Lorea-Hernández et al., 2016; Camacho-Hernández et al., 2018), and by the proinflammatory cytokine IL-1β in the brainstem-spinal cord preparation (Gresham et al., 2011). The effects of LPS on respiratory rhythm generation in vitro and on autoresuscitation in vivo, in conscious mice, are prevented by the microglial inhibitor minocycline (Lorea-Hernández et al., 2016). Similarly, minocycline also suppresses morphine-induced respiratory depression in conscious rats (Hutchinson et al., 2008), which may match the effects of LPS, considering that morphine can induce microglial activation (Zhang et al., 2011).

6. Inflammatory mediators that modulate breathing

6.1. Interleukin 1-beta (IL-1β)

Various pro-inflammatory mediators directly modulate breathing rhythm generation and control (Johnson et al., 2018). Among which IL-1β is a strong modulator of breathing (Johnson et al., 2018; Fig. 2) that has been suggested as a critical link between infection, apneas and SIDS (Lindgren and Grögaard, 1996; Vege et al., 1998; Guntheroth, 1989; Stoltenberg et al., 1994; Raza and Blackwell, 1999). IL-1β is key in the modulation of breathing rhythm generation and control because IL-1β receptors I and II are expressed in several brainstem circuits related to this function (Brady et al., 1994; Ericsson et al., 1995; Yabuuchi et al., 1994; Fig. 2), as well as in different peripheral respiratory-related structures such as the vagus nerve (Ek et al., 1998; Goehler et al., 2005; Fig. 2) and carotid bodies (Wang et al., 2002; Fig. 2). The presence of IL-1β receptors in respiratory-related circuits in the CNS corresponds to functional evidence of IL-1β responsive cells in those circuits (Brady et al., 1994; Ericsson et al., 1995).

There are various reports about the effect of systemic or local application of IL-1β. Some indicate that it increases breathing frequency (conscious rats: Graff and Gozal, 1999) and amplitude (anesthetized rats: Hocker and Huxtable, 2018), while others indicate that it reduces tidal volume and minute ventilation (conscious rats and mice: Olsson et al., 2003; Hofstetter and Herlenius, 2005; Hofstetter et al., 2007). The inhibitory effect of IL-1β on breathing is more potent than that induced by LPS (Olsson et al., 2003; Frøen et al., 2000, 2002). Accordingly, IL-1β prolongs apneas produced by laryngeal stimulation (anesthetized piglets: Stoltenberg et al., 1994; Frøen et al., 2000) and reduces gasping, autoresuscitation and survival from anoxic challenge (conscious neonatal rats: Olsson et al., 2003; anesthetized piglets: Frøen et al., 2000, 2002).

Aside from effects induced by peripheral application of IL-1β, its intracerebroventricular (ICV) application increases minute ventilation and tidal volume and inhibits the breathing response to hypercapnia and hypoxia (anesthetized rats: Aleksandrova and Danilova, 2010; Aleksandrova et al., 2015; Aleksandrova et al., 2017). There are differing reports concerning the effect of in vitro application of IL-1β to the brainstem-spinal cord preparation: some indicate that IL-1β application does not change rhythmic activity recorded from the phrenic rootlets (Olsson et al., 2003) and others indicate that IL-1β application decreases the breathing rhythm generated by this preparation (Gresham et al., 2011).

6.2. Tumor necrosis factor-α (TNF-α)

Another proinflammatory cytokine that modulates breathing is tumor necrosis factor-α (TNF-α; Ferrante et al., 2008; Moscovis et al., 2015). This cytokine has been related to pathological conditions exhibiting breathing disturbances such as SIDS and OSA (Ciftci et al., 2004; Minoguchi et al., 2004; Ryan et al., 2006; Ferrante et al., 2008; Moscovis et al., 2015). For instance a promoter polymorphism in the TNF-α gene has been related to the pathogenesis of SIDS (Ferrante et al., 2008; Moscovis et al., 2015). In addition OSA patients exhibit increased levels of TNF-α, which decrease upon CPAP treatment (Ciftci et al., 2004; Dorkova et al., 2008; Minoguchi et al., 2004; Ryan et al., 2006). Experimentally the application of TNF-α directly to the carotid body attenuates its sensitivity to hypoxia in vitro (Fernández et al., 2008) while its systemic administration increases the expression of cytokines in brainstem nuclei including the nTS (Nadeau and Rivest, 1999a,b; Anisman and Merali, 2002; Churchill et al., 2006). Interestingly the reduced ventilatory response to hypercapnia observed in conscious mice with muscular dystrophy is reverted by the genetic elimination of TNF-α (Gosselin et al., 2003). Finally when combined with IL-1β, TNF-α induces a small and transient decrease in respiratory rate that coincides with a sleep-like behavior in conscious rabbits (Tredget et al., 1988).

6.3. Prostaglandins

Prostaglandins are lipidic pro-inflammatory molecules with a strong influence on breathing (Moss and Inman, 1989; Alvaro et al., 2004). A clinical study shows a positive correlation between the number of spontaneous apneas and urinary PGE_2 and prostaglandin E metabolite (PGE-M) concentrations in preterm infants (Hoch and Bernhard, 2000; Hoch et al., 2000). A similar relationship has been found in infants with congenital cardiac anomalies who required treatment with prostaglandin E_1 (PGE_1; Heymann and Clyman, 1982). Accordingly PGE_1 produced respiratory depression in 12% of infants during their treatment for congenital heart disease (Lewis et al., 1981). PGE_2 and PGE-M increase during infection and are related to the respiratory disturbances associated with it (Siljehav et al., 2012, 2015).

The E-prostanoid receptor subtype 3 (EP3) which binds PGE_2 is located in respiration-related regions of the brainstem; e.g., the nTS, the rostral ventrolateral medulla (RVLM), the pre-BötC, the pFRG regions, nucleus ambiguus and nucleus parabrachialis (Tai et al., 1994; Ek et al., 2000; Nakamura et al., 2000; Hofstetter et al., 2007; Forsberg et al., 2016; Fig. 1). The activation of these receptors induces respiratory depression (in anesthetized and conscious lambs: Kitterman et al., 1983; Dawes, 1984; Murai et al., 1987; Jones et al., 1994; Hollingworth et al., 1996; Guerra et al., 1988; Tai and Adamson, 2000: anesthetized piglets: Long, 1988; conscious newborn mice: Hofstetter et al., 2007), which was observed to lead to apnea in anesthetized sheep (Kitterman et al., 1983; Wallen et al., 1986). Consequently prostaglandin synthetase inhibitors induce continuous fetal breathing movements (anesthetized and unanesthetized lambs: Dawes, 1984; Koos, 1985; Kitterman et al., 1983; Jansen et al., 1984; Koos, 1985; Patrick et al., 1987; Lee et al., 1989; Savich et al., 1995). Breathing inhibition induced by PGE_2 is maintained after peripheral chemoreceptor denervation, decortication, vagotomy, or transection at the level of the upper pons of anesthetized and conscious sheep (Dawes et al., 1983; Jansen et al., 1984; Koos, 1985; Murai et al., 1987; Hasan and Rigaux, 1992). Furthermore, PGE_2 blunted the hypercapnic response (conscious mice: Forsberg et al., 2016) probably by reducing central chemosensitivity to CO_2 (Kitterman et al., 1983; Tai and Adamson, 2000; Ballanyi et al., 1997).

In vitro, PGE_2 inhibits breathing rhythm generation and induces apnea in the brainstem-spinal cord preparation (Ballanyi et al., 1997; Ballanyi et al., 1999; Olsson et al., 2003). PGE_2 also reduces Ca^{2+} signaling frequency of respiratory neurons in the preBötC (Forsberg et al., 2017). This inhibitory effect of PGE_2 on the respiratory activity in the brainstem-spinal cord preparation is mimicked by PGE_1 (Ballanyi et al., 1997; Ballanyi et al., 1999). In contrast it has also been reported that PGE_2 augments fictive eupnea, sighs and gasping in the brainstem slice preparation by increasing the frequency and amplitude of bursting activity in neurons with pacemaker properties (Koch et al., 2015). The PGE_2-induced increase in sigh frequency was also observed upon ICV administration of this prostaglandin in conscious control mice but not observed in mice lacking the EP3 receptor (Forsberg et al., 2016). Prostaglandins are also involved in the increase in breathing rate induced by ICV administration of arachidonic acid in anesthetized rats (Erkan et al., 2017) as well as in the hypoventilation and inhibition of autoresuscitation induced by peripheral administration of IL-1β in conscious mice and rats (Olsson et al., 2003; Hofstetter et al., 2007).

7. Antioxidants and anti-inflammatory mediators that modulate breathing

7.1. Antioxidants

The influence of immune signals in the control of breathing has also been revealed by the changes in breathing induced by anti-inflammatory or antioxidant molecules (Kitterman et al., 1979, 1983; Koos, 1985; Lee et al., 1989; Del Rio et al., 2010; Peng et al., 2003). For instance, antioxidants such as vitamins E, A, and C or allopurinol and *N*-acetylcysteine increase the ventilatory response to hypercapnia in normal humans (Zakynthinos et al., 2007) and in patients with moderate chronic obstructive pulmonary disease (Hartmann et al., 2015). Mangiferin, an antioxidant polyphenolic compound, dampens the hypoxic ventilatory response in normal rats but prevents the reduction in the hypoxic ventilatory response in diabetic rats (conscious rats: Pokorski et al., 2012, 2018). This protective effect of mangiferin in diabetic rats is related to a reduction in the levels of TNF-α (Pokorski et al., 2018). Another antioxidant molecule, ascorbic acid, abolishes the hypoxic sensitization and sensory LTF induced by chronic intermittent hypoxia (anesthetized rats: Del Rio et al., 2010; Peng et al., 2003). N (G)-nitro-L-arginine methyl ester (L-NAME), a non-specific NO synthase inhibitor, attenuates the inhibition of the ventilatory response to hypoxia induced by LPS (conscious rats: Ladino et al., 2007) and the LPS-induced inhibition of respiratory rhythm generation in vitro (Lu et al., 2012). L-NAME also inhibits the increase in ventilation induced by intravenous administration of IL-1β (conscious rats: Graff and Gozal, 1999).

7.2. Anti-inflammatory mediators

Anti-inflammatory drugs, such as acetylsalicylic acid, indometacin and meclofenamate, induce continuous fetal breathing (anesthetized lambs: Kitterman et al., 1979, 1983; Koos, 1985; Lee et al., 1989) and stimulate both fetal and newborn ventilation (anesthetized lambs and piglets: Wolsink et al., 1994; Jansen et al., 1984; Long, 1988). Due to the potency and reliability of these effects, indomethacin has been used to treat apnea of prematurity (Hammerman and Zangen, 1993). Indomethacin blocked the inhibitory action of prostaglandins on breathing (anesthetized and unanesthetized lambs: Dawes, 1984; Koos, 1985; Alvaro et al., 2004) and the inhibition of breathing induced by IL-1β (conscious neonatal rats: Olsson et al., 2003), but it also induced an increase in breathing variability (anesthetized rats: Fan et al., 2010). Indomethacin and the thromboxane A2 receptor antagonist daltroban prevented the increase in respiratory rate, the reduction in tidal volume and the induction of apneas and shallow breathing produced by LPS administration (adult anesthetized cats: Orr et al., 1993). Indomethacin also inhibited the increase in ventilation induced by intravenous administration of IL-1β (conscious rats: Graff and Gozal, 1999). Another NSAID, diclofenac, eliminated the reduction in ventilatory response to CO_2 and to hypoxia induced by ICV administration of IL-1β (anesthetized rats: Aleksandrova et al., 2015; Aleksandrova et al., 2017).

Treatment with the NSAID ibuprofen significantly attenuated the increase in cardiorespiratory events induced by immunization in humans (Ben Jmaa et al., 2017). Ibuprofen also reduced the hyperventilation induced by arachidonic acid (anesthetized rats: Erkan et al., 2016) and abrogated the intermittent hypoxia-induced increase in the hypoxic ventilatory response (anesthetized rats: Del Rio et al., 2012). The latter correlates with the observation of a reduction in the levels of TNF-α and IL-1β in the carotid body and the number of c-Fos positive neurons in the nTS (Del Rio et al., 2010, 2012). Ibuprofen also blunted the ventilatory acclimatization to sustained hypoxia (humans: Basaran et al., 2016; conscious rats: Popa et al., 2011), which is related to a reduction of IL-1β and IL-6 in the brainstem (Popa et al., 2011). However, in conscious rats ibuprofen did not revert the ventilatory acclimatization to sustained hypoxia once it had been established (De La Zerda et al., 2018). Another NSAID, ketoprofen, blocked the reduction of LTF induced by LPS (anesthetized rats: Huxtable et al., 2013) and the respiratory depression induced by morphine (humans: Moren et al., 1997).

8. Conclusions

The literature considered in this review indicates that both peripheral and central inflammation affects the activity of neural circuits and peripheral components involved in breathing rhythm generation and control. One inducer of this modulation is hypoxia, which at the central level involves glial cells and their actions on respiratory circuits (Figs. 1 & 2). In general, the evidence supports the idea that the modulation of breathing by inflammation involves the actions of cytokines and other proinflammatory mediators. However, the precise causal chain has yet to be determined. Considering the close relationships between inflammation, hypoxia and respiratory disturbances and their possible involvement in pathological conditions, such as SIDS, OSA and asthma, it is important to unravel the cellular mechanisms and molecular events involved in these pathological interactions in order to identify the best therapeutic targets.

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