Chorioamnionitis, Inflammation and Neonatal Apnea

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Preterm birth is considered when childbirth occurs <37 weeks of gestation and represents an important risk factor for neonatal morbidity and mortality worldwide, with an average of 15 million preterm births annually and 1.1 millions infants who die from various complications.

Keywords: inflammation ; chorioamnionitis ; brainstem ; cytokines storm

1. Introduction

Preterm birth is considered when childbirth occurs <37 weeks of gestation and represents an important risk factor for neonatal morbidity and mortality worldwide [1], with an average of 15 million preterm births annually and 1.1 millions infants who die from various complications [2].

Causes of preterm birth are multifactorial, including fetal/maternal abnormalities [3] and environmental factors [3].

Interestingly, more than 60% of preterm infants with a gestational age (GA) <28 weeks are exposed to chorioamnionitis [4], with the disease the being considered the most important antecedent of prematurity [5][6][7].

In the transition from intra- to extrauterine life, processes of complex adaptation to environmental factors that assure an effective shift from maternal dependence to neonatal autonomy occur [5][6][7].

A primary physiological event to succeed in this extrauterine transition is lung aeration [8], and this is possible by a proper clearance of lung liquid, normal surfactant production, and variations in cardiovascular resistances with increasing blood flow, which occur upon birth [8]. At this time, the autonomous nervous system and the brainstem should be fully functional, with its vital respiratory centers responsible for rhythm generation and breathing biomechanics coordination [9].

Preterm neonates frequently develop a respiratory distress syndrome (RDS) upon delivery [10], which is attributed to insufficient lung liquid clearance, immature development of their lungs, and surfactant deficiency, with subsequent failure in respiration, inadequate gas exchanges, and apneic episodes [11].

When a preterm infant presents with RDS, an emergent respiratory support at delivery is mandatory, with subsequent ventilation during the transfer to the neonatal intensive care unit (NICU) [12].

Further, preterm babies who are exposed to inflammation and/or infection causing chorioamnionitis usually need greater requirement for respiratory support, with a greater risk to develop severe neurological damage with respect to those neonates who are not exposed to chorioamnionitis [13][14][15][16][17].

Chorioamnionitis is defined as a perinatal condition presenting with inflammation of the fetal membrane, including the chorion and the amnion [13][14][15][16][17]. The clinical presentation of this disease can vary based on microbiologic, histologic, and clinical features, which interact among one another to varying degrees [13][14][15][16][17].

Acute chorioamnionitis is an expression of maternal host response. Intraamniotic infection generally has been found to be the main cause of acute chorioamnionitis; however, recent studies indicate that “sterile” intraamniotic inflammation, without demonstrable microorganisms inducing infection, is frequently associated with acute chorioamnionit. In the context of intraamniotic infection, pro-inflammatory cytokines and chemokines establish a gradient that allows the migration of neutrophils and other immune cells from the maternal or fetal circulation into the chorioamniotic membranes [17].

Literature data have widely demonstrated the link between inflammation and periventricular leukomalacia (PVL), cerebral hemorrhage, and post-hemorrhagic hydrocephalus (PHH); nevertheless, the effects of inflammation on the development

of the autonomous nervous system and the brainstem centers responsible for breathing regulation remain largely unknown [5].

2. The Link between Chorioamnionitis and Brainstem Function

Literature data showed that lipopolysaccharide-LPS (cell wall constituent of Gram-negative bacteria) is used to model chorioamnionitis in animal studies [16][18][19]. This bacterial endotoxin is responsible for important and reproducible inflammatory responses. It is frequently used to reproduce chorioamnionitis in vitro.

LPS is a ligand for Toll-like receptors (TLR), which stimulate downstream signaling pathways, thus inducing inflammatory cytokines production [20][21]. LPS especially binds to TLR4, activating a pathway that results in interferon (IFN)-related cytokines production, and potentiating the gene transcription of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) [22]. This transcription is responsible for the secretion of interleukins including: IL-1b, IL-6, and IL-8; Tumor Necrosis Factors: TNF-a, TNF-b; inducible cyclooxygenase (COX-2 favor prostaglandin synthesis); and inducible nitric oxide synthase (iNOS) [23][24][25].

TLRs are also expressed in microglia and astrocytes within the brain, playing an important role in cytokine production [26].

3. Proinflammatory Cytokines and the Brainstem

Literature data have recently demonstrated that inflammation and consequent “cytokine storm” are responsible for alterations of the brainstem, with consequent abnormal function of the respiratory center, which finally results in episodes of apnea. This system is reproducible also for neonatal apnea of the premature when exposed to chorioamnionitis.

In rats brainstem, LPS exposure upregulates IL-1b and IL-6 mRNA expression [27] with consequent alteration of neuronal function within the pre-Botzinger Complex (pBTOC), whose neurons are included in the respiratory group of the ventral area of the medulla oblongata [27].

Electrophysiological traces of pre-Botzinger neurons in the pBOTC from neonatal mice after intrauterine LPS injection caused changes in the functions of pacemaker neurons, showing large amplitude bursts, at irregular and slow frequency [28].

Studies showed that IL-1b and IL-6 depress inhibitory synaptic signaling and contemporarily increase excitatory signaling within the pBOTC, thus explaining the onset of longer inspiratory drive and absent respiratory activity. These processes are then responsible for apnea in the neonate [28].

Neuronal activity can be rapidly modified by cytokines, with changes that persist long-term [29]. IL-1b, IL-6, and TNF-a can modulate neuronal functions of the central nervous system (CNS) by enhancing signaling of excitatory pathways and depressing inhibitory ones [30]. These pro-inflammatory cytokines alter neuronal excitability causing post-translational modification of the receptor of GABAergic, glutaminergic, and glycinergic nature, and affecting synaptic plasticity and neurotransmission [29][30].

In vitro and animal studies showed that IL-1b alters neuronal function according to its blood concentrations; at low concentration, IL-1 inhibits voltage-gated calcium currents and decreases calcium intracellular concentrations by inhibition of neurotransmitters release. At high concentrations, IL-1b increases inotropic glutamate (NMDA) receptor expression, and in rat cerebellar and hippocampal slices, reduces transmission at GABAergic and glycinergic receptors [29][30][31][32].

TNF-a alters neuronal excitability through the upregulation of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA receptors; in rat hippocampus and cerebellum cultures, TNF-a induces gamma-aminobutirric acid (GABA) receptor endocytosis [30][33][34]. This causes an increase in excitatory output, with consequent excitotoxicity, as well as a decrease in inhibitory pathways. IL-6 seems to also have both destructive and protective functions within the CNS. Literature data showed that IL-6 induces a decrease in the expression of metabotropic glutamate receptor, and thus also induces excitotoxicity by excessively activating NMDA receptors [32][35][36][37]. Moreover, IL-6 has also shown the ability to reduce GABAergic and glycinergic neurotransmission in neurons of the dorsal horn of spinal cord in rat models [38].

It is now established that systemic inflammation/infection induced by LPS injection can alter chemosensory responses and breathing frequency, however, the pathways responsible for these modifications in respiratory functions are still not completely understood [39].

An imbalance between excitatory and inhibitory neurotransmission signaling has been previously shown in the brainstem of rats and piglets under hypoxic conditions [40][41][42][43], but little is known about the effects of inflammation and inflammatory molecules on neurotransmission within the brainstem. As brainstem neurons of the respiratory nuclei utilize GABA, glutamate, and glycine, cytokines involved in inflammation could affect the balance between excitatory and inhibitory neurotransmitters, and thus, cause consequent changes of neuronal function and respiratory responses [5].

Systemic injection of IL-1b, IL-6, and TNF-a induces the expression of their own mRNA within rat nucleus tractus solitarius (NTS) [44]. IL-1b injection into the rat NTS increases inspiratory time about 20 min after, and delays respiratory activity (usually after 80 min) [45]. Furthermore, IL-1b injection causes a reduction in respiratory frequency and induces apneustic episodes [45].

To date, it is unclear whether IL-1b causes modifications in neurotransmission within the NTS respiratory centers with consequent modulation of the respiratory rhythm, or whether it does so involving other downstream pathways. Robust IL-1b-immunoreactivity has been described in animal NTS and area postrema after LPS injection [27]. Previous studies showed that vagotomy can abrogate the NTS increase of IL-1b mRNA expression [27].

Administration of IL-1b to animal lungs and peritonea attenuates hypoxic and hypercapnic responses [27][46], suggesting that chemosensory reflexes are impaired in response to inflammatory stimuli. Literature data have still to clear whether altered chemosensory responses are secondary only to compromised central chemoreceptor functions, or whether modifications to vagal afferent signaling to the NTS are also responsible for these abnormalities, with consequent impaired diffusion of peripheral chemosensory information to brainstem respiratory centers by NTS neurons of second-order. It seems that inflammation/infection would induce robust changes to both peripheral and central chemoreflexes.

In addition to IL-1b expression in the NTS, literature data showed that LPS administration can cause robust immunoreactivity in the area postrema [27]. Studies have also described that the loss of blood brain barrier integrity plays a key-role in brain inflammation and injury as a consequence of systemic inflammatory cytokines and endotoxin exposure [47]. However, the NTS has connections with the area postrema, this last area representing a circumventricular region of the brainstem that could function as an entrance for inflammation.

In rat models, LPS injection also induces c-Fos immunoreactivity in neurons of the rostral ventrolateral medulla, NTS, and the respiratory nuclei [48], suggesting that neurons from these respiratory nuclei are reactive to inflammation/infection. Nevertheless, the exact mechanism for how (and which) inflammatory mediators modify the functions of neurons related to breathing has not been described [5].

Table 1 shows a resume of the activity of proinflammatory cytokines on the brainstem and how they modulate the respiratory centers to cause apnea. As shown in **Table 1**, studies have been performed in animal models, and clinical literature data are missing. Therefore, further studies on human models have to confirm these results.

Table 1. Resume of proinflammatory cytokines' actions on the brainstem respiratory centers and modification of the respiratory activity. Abbreviations as used in the text.

Author (Reference No.)	Year of Publication	Population Studied	Cytokines Studied	Effect on the Brainstem
Balan et al. [27]; Ramirez et al. [28];	**2012 2016**	**Animal models**	**IL-1b IL-6**	• Depresses inhibitory synaptic transmission • Elevates excitatory signaling in the pBOTC • Causes prolonged inspiratory drive and absent respiratory activity that leads to apnea

Author (Reference No.)	Year of Publication	Population Studied	Cytokines Studied	Effect on the Brainstem
Galic et al. [30]; Vezzani et al. [29];	**2012 2015**	**Animal models**	**IL-1b IL-6 TNF-a**	• Potentiates excitatory signaling in the CNS. • Depresses inhibitory transmission in the CNS. • Alters neuronal excitability through post-translational modification of GABAergic, glutaminergic, and glycinergic receptors, ultimately affecting synaptic plasticity and neurotransmission.
Wang et al. [31]; Wang et al. [32]; Galic et al. [30]; Vezzani et al. [29];	**2000 2007 2012 2015**	**In vitro Animal models**	**IL-1b**	• Alters neuronal function in a concentration-dependent manner: • *at low concentration* inhibits voltage-gated calcium currents, and lowers intracellular calcium concentrations (thus decreasing neurotransmitter release); • *at high concentrations* increases inotropic NMDA receptors expression, and reduces transmission at GABAergic and glycinergic receptors in rat cerebellar and hippocampal cultures.
Beattie et al. [33]; Fourgeaud L et al. [34]; Galic et al. [30];	**2002 2010 2012**	**Animal models**	**TNF-a**	• Alters neuronal excitability through the upregulation of AMPA and NMDA receptors, and induces GABA receptor endocytosis, as observed in rat hippocampus and cerebellum. This causes an increase in excitatory output (and possibly excitotoxicity), as well as a decrease in inhibitory signaling.
D'Arcangelo et al. [36]; Conroy et al. [35]; Wang et al. [31]; Vereyken et al. [37];	**2000 2004 2007 2007**	**Animal models**	**IL-6**	• Reduces metabotropic glutamate receptor expression. • Induces excitotoxicity by excessively activating NMDA receptors. • Decreases GABAergic and glycinergic neurotransmission in dorsal horn neurons of rat spinal cord.
Gresham et al. [45]; Siljehav et al. [46].	**2011 2014**	**Animal models**	**IL-1b**	• IL-1b injection into the rat NTS increases inspiratory time as early as 20 min post-application, with associated delayed respiratory activity (usually observed after 80 min). • The systemic administration of IL-1b causes a decrease in respiratory frequency and induces apneustic episodes. • Intrapulmonary and intraperitoneal injection of IL-1b to animal models attenuates hypoxic and hypercapnic responses, suggesting that chemosensory reflexes are impaired in response to inflammatory stimuli.

4. Prostaglandin Effects on the Brainstem

It is well-established that mitogen-activated protein kinases (MAPK) and NF-kB signaling can induce COX isozyme expression. This event causes elevated PGs synthesis [49].

COX-1 and COX-2 are the two main COX isoforms. The first is constitutively expressed; the second is induced by tissue inflammation and injury. COX isozymes convert arachidonic acid prostaglandin H2 (PGH2) (precursor of the arachidonic acid) [50]. PGH2 is involved in the synthesis of PGE2, PGD2, PGF2a, and prostacyclin [49]. In detail, microsomal prostaglandin E2 synthase-1 (mPGES-1) catalyzes the synthesis of PGE2 from PGH2 [51]. Literature data have shown that COX2-mediated PGE2 production is involved in the inflammation of neonatal brain, especially in preterm babies, causing abnormalities of neurons involved in respiratory functions [52][53][54][55].

Similarly to what was described for cytokines, PGE2 can alter neuronal excitability and neurotransmission. This PG seems to be able to both enhance and inhibit glutaminergic transmission, modulate GABAergic receptor expression, and depress glynergic signaling pathways, although the exact mechanisms has not still clearly been identified; neuromodulation seems to be dependent on the type of PGE2 eicosanoid receptors (EPRs) enhanced [56][57][58][59][60][61].

In animal slices, PGE2 seems to be responsible for irregular breathing in vivo, and for inhibitory effects on respiratory centers in the brainstem modifying the respiratory rhythm and producing chemosensory responses [46][62][63]. Moreover, in fetal sheep, PGE2 seems to decrease respiratory frequency and induce hypoventilation, thus being responsible for the onset of apnea [64][65]. If directly injected at low concentrations (<200 nM) into the mouse pBOTC, PGE2 causes an increase of sigh frequency without any effect on eupneic breathing. High concentration of PGE2, however, seems to enhance eupneic breathing [66]. These opposing results on breathing functions may be context dependent.

Indomethacin injection in fetal sheep seems to cause COX inhibition by stimulation of breathing movements, showing that PGs are able to modulate respiratory activity [67].

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