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Chronic inflammation and impaired development of the preterm brain

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ABSTRACT

The preterm newborn is at significant risk of neural injury and impaired neurodevelopment. Infants with mild or no evidence of injury may also be at risk of altered brain development, with evidence impaired cell maturation. The underlying causes are multifactorial and include exposure of both the fetus and newborn to hypoxia-ischemia, inflammation (chorioamnionitis) and infection, adverse maternal lifestyle choices (smoking, drug and alcohol use, diet) and obesity, as well as the significant demand that adaptation to post-natal life places on immature organs. Further, many fetuses and infants may have combinations of these events, and repeated (multi-hit) events that may induce tolerance to injury or sensitize to greater injury. Currently there are no treatments to prevent preterm injury or impaired neurodevelopment. However, inflammation is a common pathway for many of these insults, and clinical and experimental evidence demonstrates that acute and chronic inflammation is associated with impaired brain development. This review examines our current knowledge about the relationship between inflammation and preterm brain development, and the potential for stem cell therapy to provide neuroprotection and neurorepair through reducing inflammation and release of trophic factors, which promote cell maturation and repair.

1. Introduction

Each year around 11% of all babies are born prematurely (before 37 completed weeks of gestation) (Harrison and Goldenberg, 2016). While preterm birth rates are lower than this in most developed countries (~9.4%), the rate varies considerably and has been as high as 12.8% in the USA (1 in 8 babies) in recent years (Harrison and Goldenberg, 2016). Preterm birth is associated with high mortality and is currently the number one cause of neonatal death, with most deaths occurring in babies less than 32 weeks at birth (Harrison and Goldenberg, 2016; Committee on understanding premature birth and assuring healthy outcomes, 2007; Ortinau and Neil, 2015; Kidokoro et al., 2014). Survivors are at risk of a wide range of morbidities such as necrotising enterocolitis, retinopathy, cardio-respiratory complications, brain injury and impaired neurodevelopment (Harrison and Goldenberg, 2016; Committee on understanding premature birth and assuring healthy outcomes, 2007; Ortinau and Neil, 2015; Kidokoro et al., 2014).

To change the outcomes of individuals born preterm requires a significant improvement in our knowledge about the mechanisms mediating injury and illness in order to improve current treatments and therapies and to the facilitate development of new treatments. The focus of this review is on the role of chronic inflammation in mediating impaired perinatal neurodevelopment and injury and the utility of stem cell therapy for neuroprotection and neurorepair.

2. The preterm brain and impaired neurodevelopment

Despite improvements in perinatal care, 5–10% of preterm infants will develop cerebral palsy (CP), and it is conservatively estimated that as many as 50% of preterm infants will go onto to have cognitive and behavioural difficulties (Kidokoro et al., 2014; Ortinau and Neil, 2015). While younger and smaller infants are at greater risk, moderate to late-preterm and near-term infants also have a higher risk of neurodevelopmental disability compared to their full term counterparts (Ortinau and Neil, 2015; Brumbaugh et al., 2016). Underpinning impaired neurodevelopment is an altered cerebral architecture characterized by reduced grey and white matter volumes, diffuse non-cystic white matter loss, and reduced cortical folding and gyral complexity (Ortinau and Neil, 2015; Back, 2015; Brumbaugh et al., 2016). Further, reduced brain growth is associated with impaired cortical arborisation and

Abbreviations: CP, cerebral Palsy; CSF, cerebrospinal fluid; HI, hypoxia-ischemia; HIE, hypoxic-ischemic encephalopathy; hAECs, human amnion epithelial cells; MCAO, middle cerebral artery occlusion; MSCs, mesenchymal stem cells; MRI, magnetic resonance imaging; NSCs, neural stem cells; UCBCs, umbilical cord blood cells; UCO, umbilical cord occlusion; IL, interleukin; TNF-α, tissue necrosis factor; TLR, toll like receptor

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synapse formation, synaptic pruning, and white matter dysmaturation, leading to compromised neuronal integrity and functional capacity (Dean et al., 2013; Vinall et al., 2013; Buser et al., 2010; Riddle et al., 2011; Favrais et al., 2011; Haynes et al., 2008; Segovia et al., 2008; Kesler et al., 2004; Mcclendon et al., 2017).

White matter dysmaturation is characterized by initial cell loss and rapid regeneration of pre-oligodendrocyte populations, but impaired maturation of these cells into their mature form, leading to a reduction in the pool of myelinating cells (Buser et al., 2010; Riddle et al., 2011; Favrais et al., 2011; Haynes et al., 2008; Segovia et al., 2008). While neurodevelopmental outcomes independently correlate with both white matter injury and the magnitude of the grey matter deficits (Woodward et al., 2006), infants born without evident white matter abnormality on MRI have fewer cognitive problems later in life (Woodward et al., 2012). Further, neuronal loss is only seen when there is also evidence of white matter loss (Pierson et al., 2007). The factors which cause impaired white matter maturation include the presence of astrogliotic lesions and accumulation of the proteoglycan hyaluronic acid in these lesion areas, as pre-oligodendrocytes fail to differentiate into areas where there are microcystic or astrogliotic lesions (Back, 2015; Dean et al., 2014; Fowke et al., 2017). More recently prostaglandin E2 (PGE2), a mediator released early after HI which promotes inflammation, has been shown to impair oligodendrocyte maturation (Shiow et al., 2017). Inflammation, however, is postulated to be one of the primary mediators of white matter dysmaturation (Back, 2015; Hagberg et al., 2015).

Altered neural architecture in turn leads to an altered development of the neural network and connectivity, characterized by less complexity, fewer connections and disruption to local and short-path connections and cortical to subcortical relays, all of which impair neurocognitive capacity (Ball et al., 2015; Scheinost et al., 2016; Meng et al., 2016). Reduced brain volumes and the aberrant intrinsic network connectivity seen in neonates persists into adult life (Meng et al., 2016), and is associated with adult neurocognitive dysfunction (Rathbone et al., 2011). While many factors in postnatal life may contribute to impaired brain development, as discussed below, this process may also start before birth. A recent study has shown that altered functional connectivity in the preterm brain, particularly in regions which support language, is identifiable before birth (Thomason et al., 2017). Infants in this study had a high prevalence of inflammatory lesions, and both acute and chronic chorioamnionitis, and funisitis, demonstrating a strong association between perinatal inflammation and impaired neurodevelopment (Thomason et al., 2017).

3. Causes of neuroinflammation

The causes of injury and illness are multifactorial and include exposure of both the fetus and newborn to acute and chronic infection and inflammation and perinatal hypoxia-ischemia (HI). Additional physiological challenges can include maternal lifestyle choices (smoking, drug and alcohol use, diet) and obesity, respiratory compromise and standard clinical care such as mechanical ventilation, invasive clinical procedures, pain and stress and drug therapy (e.g. glucocorticoids, antiseizure and pain medications), neonatal nutrition, hyper- and hypoglycemia, physical handling and the physical environment (noise and light), and more generally the considerable demands that adaptation to postnatal life places on the functioning of immature organs (Kidokoro et al., 2014; Hagberg et al., 2015; Dammann and Leviton, 2014; Leviton et al., 2013; Scheinost et al., 2017; Melville and Moss, 2013; Committee on understanding premature birth and assuring healthy outcomes, 2007). Complicating the issue is the fact that insults seldom occur in isolation, making understanding the mechanisms mediating the pathogenesis of injury or impaired neurodevelopment challenging. In the section below we discuss some of the evidence around the causes of neuroinflammation.

3.1. Hypoxia-ischemia

Early onset HI encephalopathy (HIE) occurs more frequently in preterm than term infants and is associated with impaired neurodevelopmental outcomes (Manuck et al., 2016; Low et al., 2003). Surprisingly, however, the incidence of HIE in preterm births is poorly assessed (Logitharajah et al., 2009), but several reports suggest that it is significantly higher than in full-term infants: 5–9/1000 live births versus 1–3/1000 live births at term (Logitharajah et al., 2009; Chalak et al., 2012; Salhab and Perlman, 2005; Gopagondanahalli et al., 2016). The rate is higher still in younger infants, with recent data showing the HIE rate in infants born before 28 weeks to be around 120/1000 (Manuck et al., 2016).

HI insults are associated with inflammation and consequent adverse neurodevelopmental outcomes (Bartha et al., 2004; Ahearne et al., 2017; Chalak et al., 2014; Savman et al., 1998). For example, recent clinical data in term infants show that elevated umbilical cord blood concentrations of inflammatory mediators such as interleukin (IL)-6, and IL-16 are associated with adverse neurological outcomes in HIE children at three years of age (Ahearne et al., 2017). Clinical and research focus, however, tends to be on moderate-severe HIE cases, and we know far less about the effects of mild hypoxia. However, mild insults may also be associated with adverse outcomes. For example, a recent prospective evaluation of term infants has revealed an unexpectedly higher proportion of mild HIE infants with abnormal outcomes leading clinicians to query whether mild cases of HIE should also be treated with therapeutic hypothermia (TH) (Prempunpong et al., 2017). TH is immunosuppressive, but recent data suggest that there may be rebound pro-inflammatory mediator release during rewarming. In piglets, for example, there was an increase in pro-inflammatory cytokines IL-1β, IL-6, IL-4 and IL-8 36 h after the end of therapeutic hypothermia with elevations in CSF inflammatory cytokines at 48 h were associated with MRS Lac/NAA and white matter cell death (Rocha-Ferreira et al., 2017). Our group has also recently demonstrated that premature rewarming in term fetal sheep is deleterious, potentially through increased inflammation (Davidson et al., 2017).

In neonatal rat studies, a mild HI insult at postnatal day (P)3 (equivalent to brain maturation in a 24–28 week infant) led to compromised cortical growth and selective alteration of cortical myelinated axons with persistent gliosis (Sizonenko et al., 2003). A moderate HI insult in P7 rats (30–34 week human brain equivalent) led to delayed cerebral atrophy and infarction weeks after the insult (Geddes et al., 2001). In neonatal mice, mild, intermittent non-ischemic HI caused evolving non-cystic white matter injury, hypomyelination and sensorimotor deficits (Juliano et al., 2015). In preterm fetal sheep at 0.65–0.7 gestation (28–30 week human brain maturation), transient hypoxia can significantly disrupt maturation of the fetal subplate neuron arborization and activity, and the degree of compromise relates to the level of hypoxia (Mcclendon et al., 2017). Consistent with this, acute lesions are not seen in many infants who develop CP, but there is delayed loss of white matter and hypomyelination (Woodward et al., 2006).

Further, HI insults may occur well before birth, and the preterm fetus is exceptionally tolerant of HI, as recently reviewed (Bennet, 2017). Thus a fetus may be exposed to an HI insult well before birth, survive that insult with evolving brain injury, and go onto experience a normal birth. We have recently demonstrated chronic neural inflammation in preterm fetal sheep left to recover *in utero* after an acute, severe HI insult (see stem cell section below) (Van Den Heuij et al., 2017). Experimental data from fetal rabbit studies suggest that the severity or duration of an insult is not necessary to cause postnatal motor deficits, but rather injury can be elicited with combinations of insults such as brief fetal HI and additional reperfusion–reoxygenation injury just after the cessation of the HI insult (Drobyshevsky et al., 2012). Research strongly supports the concept that the predominance of insults (HI and other) causing CP occur during the antenatal not the intrapartum period (Tan, 2014). However, currently we lack biomarkers