Interleukin-1: an important target for perinatal neuroprotection?

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Abstract
Perinatal inflammation is a significant risk factor for lifelong neurodevelopmental impairments such as cerebral palsy. Extensive clinical and preclinical evidence links the severity and pattern of perinatal inflammation to impaired maturation of white and grey matters and reduced brain growth. Multiple pathways are involved in the pathogenesis of perinatal inflammation. However, studies of human and experimental perinatal encephalopathy have demonstrated a strong causative link between perinatal encephalopathy and excessive production of the pro-inflammatory effector cytokine interleukin-1. In this review, we summarize clinical and preclinical evidence that underpins interleukin-1 as a critical factor in initiating and perpetuating systemic and central nervous system inflammation and subsequent perinatal brain injury. We also highlight the important role of endogenous interleukin-1 receptor antagonist in mitigating interleukin-1-driven neuroinflammation and tissue damage, and summarize outcomes from clinical and mechanistic animal studies that establish the commercially available interleukin-1 receptor antagonist, anakinra, as a safe and effective therapeutic intervention. We reflect on the evidence supporting clinical translation of interleukin-1 receptor antagonist for infants at the greatest risk of perinatal inflammation and impaired neurodevelopment, and suggest a path to advance interleukin-1 receptor antagonist along the translational path for perinatal neuroprotection.

Key Words: brain; inflammation; interleukin-1 receptor antagonist; interleukin-1; interleukin-1β; neonatal encephalopathy; neuroprotection; preterm brain injury

Perinatal Inflammation Underpins Neurodevelopmental Impairments
Perinatal inflammation is a significant risk factor for neonatal mortality and morbidity, including neurodevelopmental impairments, such as cerebral palsy, which can have a devastating lifelong impact (Wu and Colford, 2000; Honeycutt et al., 2004; Fleischmann et al., 2021). Indeed, perinatal inflammation is associated with a several-fold increase in the risk of cerebral palsy in preterm and near-term/term infants (odds ratio: 2.5–9.3) (Grether and Nelson, 1997; Wu et al., 2003; Soraisham et al., 2013). The cumulative lifetime economic cost of cerebral palsy in the USA was estimated to be over USD11.5 billion in 2003 (Honeycutt et al., 2004). More recent evidence indicates that the cost of disability associated with perinatal brain injury continues to rise, and that prevention of such injury and therefore disability would significantly reduce the socio-economic burden on affected individuals, their families, and society (Shih et al., 2018). No established effective therapy for inflammation-induced brain injury is available and this deficit is a major unmet medical need (Galinsky et al., 2020). Developing more effective therapeutic interventions requires improving our understanding of the underlying pathophysiological mechanisms that lead to impaired neurodevelopment in infants exposed to perinatal inflammation.

There are multiple triggers of perinatal inflammation; however, there is compelling evidence that chronic inflammation caused by perinatal infection, hypoxia-ischemia, pulmonary volutrauma and barotrauma, and oxygen toxicity during postnatal respiratory support can independently or synergistically cause inflammation in the fetus and neonate (Bui et al., 2017; Galinsky et al., 2018). In recent cohort studies, multiple perinatal disturbances were associated with chronic inflammation and diffuse injury in the white matter tracts in both term and preterm infants (Leviton et al., 1999; Wu and Colford, 2000; Wu et al., 2003; O’Shea et al., 2012, 2013; O’Muircheartaigh et al., 2020). As previously reviewed, when unbridled, both systemic and central nervous system inflammation is strongly implicated in the disturbances to neuronal and oligodendrocyte development and reductions in brain growth that lead to reduced white and grey matter volumes and long-term behavioral and intellectual disabilities seen in preterm and term infants (Hagberg et al., 2015; Galinsky et al., 2018).

Search Strategy
PubMed and Ovid MEDLINE databases were searched between September 20, 2021 and November 20, 2021 with no limitations set to the literature search in this narrative review. All years were chosen in the search. Search terms were “preterm brain injury OR neonatal encephalopathy OR neonatal inflammation AND IL-1 receptor antagonist OR anakinra OR kineret”. Other sources used to identify studies included relevant original manuscripts and reviews.

Preterm and Term Encephalopathy: Outcomes and Available Interventions
Encephalopathy in preterm and near-term/term neonates continues to be associated with a high risk of lifelong neurodevelopmental impairment. For example, in a large cohort of preterm infants born between 1997 and 2011 in France, survival without moderate to severe neuromotor or sensory disabilities increased from 46% to 62% in infants born at 25–26 weeks of gestational age but remained unchanged at 22–24 and 32–34 weeks of gestation (Pierrett et al., 2017). Similarly, the Australian cerebral palsy register found no significant change in the overall risk of cerebral palsy from 1993–2006; however, there was a trend for a reduced risk of cerebral palsy after extremely preterm birth (births < 28 weeks of gestation) (Smithers-Sheedy et al., 2016). By contrast, in a population-based study of 8-year-old children who were born preterm in the Australian state of Victoria, rates of major neurosensory disability were similar for cohorts born in 1991–1992, 1997, and 2005. Of concern, academic performance was worse in 2005 than in previous cohorts, after controlling for other factors (Cheong et al., 2017). Meta analyses of large randomized controlled trials have shown that maternal treatment with magnesium sulfate (MgSO4) for threatened preterm labor at <

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30 weeks of gestation is associated with a reduced risk of cerebral palsy and gross motor dysfunction after premature birth (Conde-Agudelo and Romero, 2009). Whilst follow-up to school age is yet to find a long-term clinical benefit (Cantarino et al., 2014; Doyle et al., 2014), antenatal MgSO₄ is currently the only treatment available for preterm neuroprotection. Antenatal corticosteroids and neonatal caffeine administration have been linked to a reduced risk of preterm brain injury (Ment et al., 1995; Schmidt et al., 2007); however, the pathways by which this reduction occurs remain unclear.

Although mild therapeutic hyperventilation, via whole body or head cooling, for example, to prevent neonatal encephalopathy in near-term (≥ 32 weeks of gestation) and term infants is now well established to improve survival without disability, current hypothermia protocols are only partially protective, such that approximately 30% to nearly half of infants still die or survive with disability despite cooling (Jacobs et al., 2013; Shankaran et al., 2017). For example, in a cohort of infants who underwent therapeutic hypothermia from 2000 to 2003 for moderate to severe encephalopathy, neurodevelopmental assessment at 18 months of age showed an improvement in cerebral palsy by 25% of children with subnormal IQ scores. A subnormal IQ was more prevalent in survivors with cerebral palsy (96%) compared to children without cerebral palsy (40%) (Pappas et al., 2015). Furthermore, 20% of children with a normal IQ and 28% of children with a subnormal IQ score received special educational support or were held back ≥ 1-grade level. A recent multicenter cohort study of mild encephalopathy at term showed that cognitive performance at 2 years of age was lower compared to the control group. Neuroprotective interventions for mild encephalopathy are yet to be developed.

Collectively, these data indicate that while progress in perinatal neuroprotection has been made, there is still an urgent unmet need to develop more effective therapies for preventing or minimizing injury to the preterm and near-term/brain.

Interleukin-1: A Promising Target for Perinatal Neuroprotection

There are two IL-1 cytokine agonist isoforms, IL-1α and IL-1β, which both signal via the heterodimeric receptor pair IL-1R1:IL-1R3, augmenting inflammation through activation of downstream effectors such as mitogen-activated protein kinases, nuclear factor kappa B, and activator protein-1. IL-1β is bioactive at femtomolar concentrations (Dinarello et al., 2012; Dinarello, 2018); hence, to curb excessive activation of this potent cytokine, two endogenous IL-1 antagonists (IL-1Ra, with which complex formation of the IL-1 ligands to their receptor, is often co-induced with IL-1α and IL-1β. Another antagonist of IL-1 signaling is IL-1R2, which functions as a decoy receptor that sequesters IL-1 without transducing pro-inflammatory signals (Dinarello et al., 2012; Dinarello, 2018; Figure 1). IL-1 function is furthermore controlled by the requirement of inflammasome activation to render IL-1 bioactivation. Activation of pattern recognition receptors triggers the assembly of the multi-protein inflammasome complex, which converts pro-caspase-1 into active caspase-1, and in turn, cleaves the pro-IL-1β protein. This cleavage generates mature, bioactive IL-1β that is ready for release from the cell (Dinarello, 2018; Figure 1). IL-1 protein abundance is usually minimal in healthy, undisturbed conditions; however, it is rapidly induced in cases of pathological inflammation and tissue injury (Rothwell, 2003). In the brain, IL-1 is produced by astrocytes, microglia, lymphocytes, and infiltrating myeloid cells and is also capable of penetrating the blood-brain barrier from systemic circulation (Prasad et al., 2021).

IL-1β is the main isoform implicated in neural injury (Rothwell, 2003). For example, in term/newborn infants, elevated systemic and cerebrospinal IL-1β on the first 2 days of life were associated with impaired cerebral metabolism and developmentality at 2 years of age (Bartha et al., 2004; Bajnok et al., 2017). Similarly, in extremely preterm infants chronically elevated circulating IL-1β within the first 2 weeks after birth were associated with impaired neurodevelopment at 2 years of age (O’Shea et al., 2012). Furthermore, polymorphisms in the IL1B gene that result in increased production of the IL-1β protein are associated with an increased risk of intraventricular hemorrhage and periventricular leukomalacia (Baier, 2006). In postmortem brain tissue sections from preterm infants, accumulation of IL-1β was primarily localized to areas of white matter inflammation and injury. Furthermore, in areas of periventricular white matter injury, IL-1β was significantly increased in preterm infants compared to term infants, and this imbalance in the ratio of pro- versus anti-inflammatory IL-1 family cytokines was more pronounced in very preterm infants (born < 32 weeks) compared to near-term infants that developed white matter injury (Girard et al. et al., 2010a). Consistent with the evidence linking IL-1β to perinatal brain injury has found a strong link between elevated systemic cytokines was more pronounced in very preterm infants (born < 32 weeks) compared to near-term infants that developed white matter injury (Girard et al. et al., 2010a). Consistent with the evidence linking IL-1β to perinatal brain injury, IL-1Ra was significantly less augmented than IL-1β; consequently, the Pro-IL-1β protein is expressed intracellularly. The NOD-LRR and pyrin domain-containing protein 3 (NLRP3) inflammasome complex cleaves pro-caspase 1 into caspase 1 which in turn cleaves pro-IL-1β into bioactive IL-1β, which is then secreted by the cell. Bioactive IL-1β reacts with the IL-1 heterodimeric receptor (IL-1R1:IL-1R3) on the surface of most cell types including other microglia, astrocytes, oligodendrocytes (olarges), and neurons (pink), and leads to further nuclear factor kappa B regulated transcription of IL-1β and the subsequent release of bioactive IL-1β. Increased protein expression levels of IL-1β cause activation of astrocytes, as well as cell damage and apoptosis of oligodendrocytes and neurons. By contrast, the endogenous IL-1 receptor antagonist (IL-Ra) secreted by microglia, and administration of recombinant IL-1Ra, bind to the IL-1R1:IL-1R3 receptor complex and thereby block activation of transcription factors. In the circulation, LPS is detected by TLR4 on macrophages (purple), and the LPS-IL-1β signaling cascade releases IL-1β into the circulation which recruits additional immune cells and can further damage the endothelium. The endogenous IL-1 receptor antagonist IL-1Ra released by macrophages and other immune cells, and recombiant endogenous IL-1Ra blocks IL-1 signaling. Created with BioRender.com.

In a study designed to test this hypothesis, we used a clinically relevant large animal model to determine whether IL-1 inhibition, using the commercially available recombinant IL-1Ra called anakinra, started 1 hour after the induction of progressive lipopolysaccharide (LPS)-induced systemic inflammation, could mitigate neuroinflammation and brain injury in the late preterm (0.85 gestation) fetal sheep. At this age, brain development in sheep is broadly equivalent to the late preterm human infant (Barlow, 1969). Progressively increasing doses of LPS were used in this study to reflect the progressive inflammation typical of perinatal infection (Kuster et al., 1998; Oh et al., 2019). We showed that IL-1 inhibition during progressive LPS-induced inflammation was associated with reduced microgliosis and apoptosis, and improved pre-oligodendrocyte survival in the intragral and periventricular evidence line, which are among the large white matter tracts that are highly susceptible to neuroinflammation and injury. The reduction in neuroinflammation and pre-oligodendrocyte cell death was associated with reduced circulating pro-inflammatory cytokines (IL-1β, tumor necrosis factor, and IL-6) and improved recovery of electrophysiological brain activity and fetal movement (assessed using electroencephalography and electromyography, respectively (Kelly et al., 2021)). Critically, these data demonstrate that IL-1, and particularly IL-1β, plays a key role in the pathophysiology of white matter injury and injury, that is secondary to systemic inflammation, and that systemic administration of IL-1Ra improves histological and functional outcomes in a clinically relevant large animal model of perinatal inflammation. These data are congruent with recent studies that have reported IL-1Ra-induced reductions in placental inflammation, glosis and microvascular degradation, and improved oligodendrocyte survival, myelination, and neurobehavioral outcomes after exposure to inflammatory and or hypoxic.
Interleukin-1 Receptor Antagonist: an Established Therapeutic Agent

The commercially available IL-1Ra anakinra is a recombinant non-glycosylated form of the human IL-1Ra, and it has been in clinical use for over 20 years (Food and Drug Administration approval in 2001) in a range of autoimmune conditions as well as atherogenic and other hyper-inflammatory syndromes to reduce inflammation-related morbidity. IL-1Ra has a molecular weight of 17 kDa and has been shown to penetrate the blood-brain barrier in human and preclinical animal studies (Galea et al., 2011; Sadowska et al., 2015). After intravenous administration, IL-1Ra has been shown to cross the blood-brain barrier and achieve therapeutic concentrations in the brain within approximately 45 minutes (Galea et al., 2011). Thus, we may reasonably speculate that IL-1Ra exerts its neuroprotective actions through modulating both the central nervous system and systemic inflammation (Figure 1). Experience in an estimated 200,000 patients, including infants and children, has established an excellent safety record for IL-1Ra. Endogenous cytokine expression is important for normal brain development; hence, at least in theory, high dose anti-inflammatory therapy could affect the otherwise normal brain (Deverman and Patterson, 2009). Reassuringly, no effect on organ growth and development has been observed (Pascual et al., 2005; Dinarello et al., 2018). Therefore, the use of IL-1Ra anakinra to pregnancy category B, the second most favorable of 5 categories, signifying that, while there are limited controlled data in human pregnancy, there is no evidence of fetal harm in animal models. Case reports of babies born to mothers on anakinra noted no abnormalities (Berger et al., 2009; Fischer-Betz et al., 2011), despite anakinra crossing the placenta (McDuffie et al., 2001). Importantly, anakinra gained FDA approval in 2013 for the treatment of neonatal-onset multisystem inflammatory disease, and denosumab (Prolia) in 2020 and has since been used successfully and safely in young neonates and children.

Considerations for Clinical Translation: What Is Still Missing?

IL-1Ra is now established as a safe and effective treatment for neonatal-onset multisystem inflammatory disease, deficiency of IL-1Ra, and rheumatoid arthritis in young infants and children. In addition to mitigating systemic and central nervous system inflammation and related brain injury and improving neurological function in small and large animal trials, IL-1Ra has been shown to reduce neonatal pulmonary hypertension, bronchopulmonary dysplasia, and retinopathy of prematurity in preclinical animal studies (Nold et al., 2013; Zhou et al., 2016; Rudloff et al., 2017; Beaudry-Richard et al., 2018; Bui et al., 2019; Sayah et al., 2020). Collectively, these data suggest IL-1Ra is implicated in the pathophysiology of multiple inflammatory driven neonatal diseases and that IL-1Ra has the potential to provide multigorgan protection. However, there are no data in human term or term infants with neonatal encephalopathy, who are often at risk of long-term neurodevelopmental impairment. Thus, before progressing to studies of IL-1Ra for perinatal neuroprotection, it is advisable to conduct pilot trials to establish safety in these at-risk populations. Thus, we strongly suggest that it is now time for a phase 1 safety trial of IL-1Ra for infants at greatest risk of inflammation-induced brain injury, such as extremely preterm infants.

Another consideration in assessing the therapeutic potential of IL-1Ra for perinatal encephalopathy is when to treat. Indeed most of the preclinical trials demonstrating histological and or functional benefits administered IL-1Ra before (Girard et al., 2010b; Leitner et al., 2014) or shortly (1 hour) after (Kelly et al., 2021) inducing inflammation. In a study of neonatal rats (neurodevelopmentally equivalent to extremely preterm humans) exposed to LPS and/or neonatal hypoxia-ischemia, delaying IL-1Ra treatment by approximately 48–72 hours after LPS-induced fetal inflammation was associated with reduced gliosis and improvements in cognition, numbers of neurons in the frontal and myelination (Girard et al., 2012). It is important to note that IL-1Ra was administered repeatedly, every 12 hours for 9 days after birth, suggesting that delayed and prolonged IL-1Ra administration could be an effective therapeutic approach (Girard et al., 2012). By contrast, in a study of normal rats, a model of bronchopulmonary dysplasia, antenatal LPS and 28 days of postnatal hypoxia, both delayed (treatment started on postnatal day 6) and very high-dose IL-1Ra (100 mg/kg, equating to approximately 10x the dose clinically used in humans after correction for interspecies application) were less effective than early (treatment started on postnatal day 1) and standard-dose IL-1Ra (10 mg/kg) at mitigating pulmonary inflammation and tissue injury. Notably, neither intervention was associated with abnormalities in cerebral growth or morphology (Rudloff et al., 2017). Thus, based on the available evidence, early intervention appears to be the most promising strategy. Nevertheless, these data suggest that after establishing safety and efficacy in human neonates, there is scope to further evaluate the therapeutic window and therapeutic range of IL-1Ra for reducing inflammation and injury in future preclinical studies, similar to the strategy by which therapeutic hypothermia was developed (Gunn et al., 2017).

As previously reviewed, inflammation is fundamental to the pathogenesis of neonatal encephalopathy at term (Cho et al., 2020). Identifying adjunct therapies to further improve outcomes for neonatal encephalopathy in near-term/term infants is a key priority area for improving outcomes in neonatal encephalopathy. In a term-equivalent rat model of neonatal encephalopathy, IL-1Ra administered during mild therapeutic hypothermia was associated with reduced expression of cerebral IL-1Ra and a paradoxical upregulation of IL-1 signaling in the brain which underpinned a reduction in the neuroprotective efficacy IL-1Ra (Chevin et al., 2018). Indeed, in a piglet model of neonatal encephalopathy, a delayed rise in circulating cytokines, including IL-1β, was observed following therapeutic hypothermia and was associated with white matter and basal ganglia injury (Rocha-Ferreira et al., 2017). Collectively, these data suggest that the timing of IL-1Ra treatment in the setting of therapeutic hypothermia requires further preclinical evaluation. In conclusion, there is compelling evidence to support the premise that IL-1 is a major culprit in the manifestation of perinatal inflammation and subsequence IL-1Ra, and blocking IL-1 signaling using IL-1Ra could be a safe and effective therapeutic approach. Thus, determining whether IL-1Ra is a safe intervention for extremely preterm infants who are at greatest risk of perinatal inflammation and long-term neurodevelopmental impairments represents a vital next step in progressing IL-1Ra down the translational path for perinatal neuroprotection.

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