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Interleukin-1 receptor blockade in perinatal brain injury

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Interleukin-1 (IL-1) is a potent inflammatory cytokine that can be produced by a variety of cell types throughout the body. While IL-1 is a central mediator of inflammation and response to infection, the role of IL-1 signaling in adult and pediatric brain injury is becoming increasingly clear. Although the mechanisms of IL-1 expression are largely understood, the downstream effects and contributions to excitotoxicity and oxidative stress are poorly defined. Here, we present a review of mechanisms of IL-1 signaling with a focus on the role of IL-1 in perinatal brain injury. We highlight research models of perinatal brain injury and the use of interleukin-1 receptor antagonist (IL-1RA) as an agent of therapeutic potential in preventing perinatal brain injury due to exposure to inflammation.

Keywords: IL-1, rIL-RA, perinatal brain injury, IL-1beta, Kineret

INTRODUCTION

Interleukin-1 (IL-1) is the name given to two cytokine peptides, IL-1α and IL-1β, that bind and activate the IL-1 receptor (IL-1R). IL-1 was first called endogenous pyrogen and described as a protein isolated from polymorphonuclear leukocytes, that, when injected into humans or animals, causes fever (1, 2). IL-1 is a pro-inflammatory cytokine that mediates the immune response to infection and inflammation and influences a broad range of physiologic activity that includes acute-phase response gene expression, T and B lymphocyte stimulation, cell survival, glial activation, fever, hypotension, and leukopenia (3–6).

Mounting evidence suggests that IL-1 signaling plays a central role in mediating chronic and acute brain injury in both adult and pediatric populations. IL-1 receptor antagonist (IL-1RA) is an endogenous inhibitor of IL-1 signaling and recombinant IL-1RA is widely used in adults for treatment of autoimmune and inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease (5). There is emerging evidence that perinatal administration of IL-1RA may confer neuroprotective effects during births at high risk for brain injury (7, 8). Here, we offer a review of IL-1 and the therapeutic potential of IL-1RA in preventing brain injury in neonates following exposure to inflammation [either intrauterine inflammation preceding preterm birth, chorioamnionitis, or birth following hypoxia–ischemia (HI)].

IL-1 RECEPTOR

The IL-1R is comprised of two membrane proteins, IL-1R1 and IL-1R accessory protein (IL-1RAcP), and binds IL-1α, IL-1β, IL-1RA, and IL-38. IL-1R1 and IL-1RAcP contain an intracellular Toll/interleukin-1 receptor (TIR) homology domain that recruits myeloid differentiation primary response protein 88 (MyD88) upon receptor heterodimerization (4, 9). MyD88, an adapter protein, recruits the IL-1R associated kinase 4 (IRAK4), which initiates a signaling cascade by phosphorylating and activating IRAK1, which, in turn, activates and recruits TRAF6 to the IL-1R complex. TRAF6 mediates signaling through two pathways. One pathway leads to the activation of the transcription factor NFκB through the activation of TAB2 and TAK1. The other pathway leads to the activation of the c-jun/c-fos heterodimeric activating protein 1 (AP-1) transcription factor complex through the MAPK/JNK pathway. NFκB and AP-1 activation drives expression of the pro-inflammatory genes TNF-α, IL-6, and IL-1, generating an acute-phase response (10, 11).

A decoy receptor made up of IL-1R2 and IL-1RAcP also binds IL-1β but IL-1R2 lacks an intracellular activation domain (12). IL-1α and IL-1β bind IL-1R2 with much greater affinity than IL-1R1. The difference in affinity for the decoy receptor effectively creates a cytokine trap that neutralizes free IL-1 without inflammatory signaling (13). Additionally, an endogenous receptor antagonist, discussed in greater detail below, has a much lower affinity for IL-R2. Together, the decoy receptor and antagonist provide a potent mechanism of regulating IL-1 signaling.

IL-1α AND IL-1β

Both IL-1α and IL-1β transcripts are translated into precursor peptides. However, while pro-IL-1β requires proteolytic cleavage to generate the mature, active form of the cytokine, pro-IL-α is functionally active. Thus, IL-1α, which is expressed in epithelial cells of the gastrointestinal tract, kidney, liver, lung, endothelial cells, and astrocytes, rapidly initiates inflammatory responses when released by necrotic cell death, as occurs following ischemic events.

IL-1β is expressed in hematopoietic cells, including macrophages, dendritic cells, monocytes, and microglia, and in endothelial cells. Expression of IL-1β is triggered by Toll-like receptor 4 (TLR4) signaling, IL-6 signaling, or by IL-1β itself. As many cell types express the IL-1R, IL-1 signaling can be paracrine or autocrine. The production and release of IL-1β is highly regulated by cells. TLR signaling is required for the expression and translation of pro-IL-1β. Maturation of IL-1β requires cleavage of pro-IL-1β by Caspase 1. Caspase 1 activity is regulated by the NLRP3 inflammasome. The inflammasome can be activated by numerous stimuli, including pathogen associate molecular patterns (PAMPS), external ATP and glucose, and molecules that signal of stress or danger (14, 15).

IL-1 RECEPTOR ANTAGONIST

The IL-1 receptor antagonist (IL-1RA) is an endogenous ligand that binds the IL-1R but does not recruit the IL-1RAcP, thereby preventing activation of the receptor (**Figure 1**). IL-1RA also has a higher affinity for the IL-1R than IL-1α or IL-1β and serves to limit pro-inflammatory IL-1 signaling by blocking binding of the active cytokines (16). Deficiencies in IL-1RA result in a reduction of regulatory function and can result in severe inflammation and autoinflammatory disorders such as arthritis, vasculitis, and skin lesions in humans (17–19). IL-1RA knockout mice develop similar phenotypes to those seen in human disease, including arthropathy and arterial inflammation (20–22).

IL-1RA, IL-1α, and IL-1β have been shown to cross the blood–brain barrier by a saturable mechanism (23). In rat models of stroke, rIL-RA, delivered subcutaneously or intravenously, can reach therapeutic concentrations in the cerebrospinal fluid within 45 min (24, 25). While the placenta can secrete IL-RA in response to lipopolysaccharide, to date, no studies have addressed placental transfer of rIL-1RA (26). Placental perfusion studies have found that several cytokines, including IL-1β, TNF-α, and IL-6, do not cross the placenta and this may hold true for rIL-1RA (27–29). Pharmacokinetic studies are warranted to determine the potential efficacy of maternally administered rIL-1RA in the setting of preterm birth. In considering possible future clinical applications, rIL-1RA may need to be delivered via amniocentesis if placental transfer is insufficient to generate therapeutic doses in the fetal compartment. With future advances and knowledge of molecular action of IL-1RA, we speculate that small molecules may be designed that will mimic IL-1RA activity and would be able to cross the placenta.

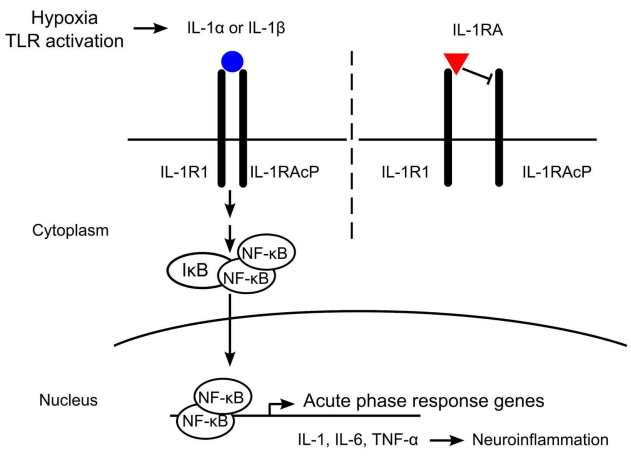

FIGURE 1 | Mechanism of interleukin-1 (IL-1) receptor antagonist (IL-1RA) blockade. IL-1 is produced in response to hypoxia or Toll-like receptor (TLR) activation. The IL-1 receptor (IL-1R) is comprised of an IL-1R1 subunit and an IL-1R accessory protein (IL-1RAcP). IL-1RA binds IL-1R1 with a higher affinity than IL-1α or IL-1β, but does not recruit IL-1RAcP. Without heterodimerization of the IL-1 receptor complex, no signaling occurs. Binding of IL-1α or IL-1β to IL-1R1 recruits IL-1RAcP and intracellular signaling is initiated, leading to the expression of acute-phase response genes such as IL-1, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). In the brain, these pro-inflammatory cytokines induce neuroinflammation, including neuronal injury and astrogliosis.

CLINICAL TRIALS WITH IL-1RA

In 1993, Amgen introduced the first drug targeting IL-1 signaling, a recombinant IL-1RA (rIL-1RA), Anakinra (Kineret). rIL-1RA is produced in *E. coli* and was approved by the FDA for treatment of rheumatoid arthritis in 2001. In 2012, rIL-RA was approved for treatment of neonatal-onset multisystem inflammatory disease (NOMID). Five randomized, double-blind, placebo-controlled trials that included over 3000 patients were conducted (30–34). Mertens and Singh offer a critical review of the rIL-1RA clinical trials (35). Briefly, the trials found rIL-1RA to be significantly more effective than placebo in improving outcomes with no difference in adverse events, deaths, and study withdrawals.

Interest in recombinant rIL-1RA therapy for additional diseases continues, and at this time there are 21 ongoing clinical trials to treat a range of diseases including diabetes, breast cancer, chronic fatigue, and heart failure (**Table 1**). Recent mechanistic studies have reported that rIL-1RA has neuroprotective effects in rodent models of perinatal brain injury (7, 8, 24, 25).

IL-1RA IN BRAIN INJURY

Many antenatal, perinatal, or postnatal factors, whether genetic or environmental, can lead to postnatal brain injury. Chronic events prior to parturition may be of greater importance than acute events, as the chronic conditions may be overlooked until postnatal clinical symptoms are evident. Additionally, the timing of the insult influences the nature of the brain injury. Preterm infants are more likely to suffer from intraventricular hemorrhage and periventricular leukomalacia, while term infants experience focal ischemia, injury to basal ganglia, and subcortical hemorrhage (36).

Pathogen-induced inflammation and/or HI are the major insults resulting in postnatal neurological impairment through the release of inflammatory mediators, such as members of the IL-1 family (37–43). Human neuropathological studies and experimental animal models of postnatal brain injury reveal that pro-inflammatory cytokines, especially IL-1β, are implicated in the cascade leading to brain damage at different developmental stages (41, 44–50). Therefore, postnatal systemic administration of IL-1RA may be a potential therapeutic intervention of postnatal brain injury (7, 51).

Table 1 | Ongoing rIL-1RA clinical trials.

Study title	Phase	Primary outcome measures	Anakinra dose
Anakinra combined with chemotherapy and dendritic cell vaccine to treat breast cancer	1/2	Safety of DC vaccine combined with chemotherapy, and DC vaccine combined with chemotherapy and anakinra	100 mg/day subcutaneous
Infants and children with coronary artery abnormalities in acute Kawasaki disease	1/2	Safety of a 6-week course of anakinra	2 mg/kg/day 4 mg/kg/day
Adult patients with colchicine-resistant familial Mediterranean fever	3	Number of patients with less than a mean of one FMF attack per month	100 mg/day subcutaneous
Safety and blood immune cell study of anakinra in metastatic breast cancer patients	1	Safety – adverse events in participants	100 mg/day subcutaneous
Anakinra or denosumab and everolimus in advanced cancer	1	Maximum tolerated dose (MTD)	100 mg/day subcutaneous
Efficacy study of anakinra, pentoxifylline, and zinc compared to methylprednisolone in severe acute alcoholic hepatitis	2/3	Death|MELD score	100 mg/day subcutaneous
Safety and tolerability of anakinra in combination with riluzol in amyotrophic lateral sclerosis	2	Number and severity of adverse events, pathological laboratory parameters	100 mg/day subcutaneous
IL-1 blockade in acute myocardial infarction (VCU-ART3)	2/3	Acute response (CRP levels)	100 mg/day subcutaneous
Study evaluating the influence of LV5FU2 bevacizumab plus anakinra association on metastatic colorectal cancer	2	Response rate after 2 months in patients with colorectal cancer with liver metastases treated with anakinra and LV5FU2/bevacizumab	100 mg/day subcutaneous
Evaluation of the safety of anakinra plus standard chemotherapy	1	The number of participants with serious adverse events and adverse events	100 mg/day subcutaneous
IL-1 blockade in acute heart failure (anakinra ADHF)	2/3	C reactive protein	200 mg/day for 3 days (high dose) 100 mg/day (standard dose)
Interleukin-1 blockade in recently decompensated heart failure	2/3	Placebo-corrected interval changes in peak VO2 and VE/VCO2 slope	100 mg/day subcutaneous
Inflammatory pustular skin diseases	2	Obtain an estimate of the response rate to treatment	100–300 mg/day subcutaneous
Effect of anakinra on insulin sensitivity in type 1 diabetes mellitus	2	Insulin sensitivity as determined by euglycemic hyperinsulinemic clamp	100 mg/day subcutaneous
Gene expression profiling in PBMCs as a tool for prediction of anakinra responsiveness in rheumatoid arthritis	4	Observational	100 mg/day subcutaneous
Role of interleukin-1 in postprandial fatigue	1	Postprandial fatigue	100 mg subcutaneous
Immunomodulation, IL-1 inhibition, and postoperative incisional pain	N/A[a]	Concentration levels of inflammatory mediators (IL-1, IL-6, IL-8, and TNF-α) present in human wounds following surgery with and without the use of anakinra	N/A[a]
Cytokine inhibition in chronic fatigue syndrome patients	2/3	CIS (checklist individual strength, compared to baseline)	100 mg/day subcutaneous
A dose-block randomized, placebo controlled (double-blind), active controlled(open-label), dose-escalation study	1	Tolerability, pharmacokinetics of HL2351, Immunogenicity of HL2351, Tolerability, pharmacokinetics, and pharmacodynamics of HL2351 in comparison with kineret (anakinra), IL-6 inhibition assay	100 mg/day subcutaneous
Anti-IL-1 treatment in children DKA at diagnosis of type 1 diabetes	2	Number of adverse events	2 mg/kg bolus followed by 2 mg/kg/h infusion
Interleukin-1 blockade in HF with preserved EF	2	Aerobic exercise capacity, ventilatory efficiency	100 mg/day subcutaneous

[a] *Data not available.*

IL-1RA AND PATHOGENIC MODELS OF POSTNATAL BRAIN INJURY

Several models of inflammatory postnatal brain injury have been developed in different species, including mouse (52–56), rat (57–59), rabbit (60, 61), dog (62), and others (63). Rodent models are most widely used due to ease of use and relatively short reproductive cycle. Administration of pathogens, such as virus (52), bacteria (64), pathogenic infectious components (57, 61), and pro-inflammatory cytokines (46, 65) varies widely between models in timing, from prenatal to postnatal stage, and route of delivery, whether intranasal (52, 66), intravenous (67), intrauterine (68, 69), intraperitoneal (59), or intracerebral injection (70).

IL-1RA has been shown to be neuroprotective (71–73) in animal models of traumatic brain injury and excitotoxicity *in vivo* and *in vitro*, in which IL-1β exerts a dominant role pathologically. In rodent models of postnatal brain injury, the elevation of IL-1β and other pro-inflammatory cytokines was observed (69, 74, 75), indicating the importance of the IL-1β signaling pathway in postnatal brain injury. Leitner et al. applied rIL-1RA systemically at embryonic day 15, 30 min prior to administration of intrauterine injection of lipopolysaccharide. They found rIL-1RA improved fetal cortical neuronal injury without affecting the rate of preterm birth. This might be via the blockade of neuronal nitric oxide synthase (8). Furthermore, Girard et al. administrated a low dose of rIL-1RA to pups in a systemic inflammatory animal model and a hypoxic-ischemia model postnatally (7, 76). This treatment preserved motor function and exploratory behavior. Neuroprotective effects were evident by increased neural stem cell populations, prevention of myelin loss, and decreased gliosis. This study provides a potential candidate for postnatal treatment of brain injury, especially in the earliest days of life in the term infant. Savard et al. used systemic infection–inflammation combined with HI in a rat model at postnatal day 12, which exerted a synergistic detrimental effect on rat brain, leading to a peculiar pattern of parasagittal cortical–subcortical infarcts mimicking those in the human full-term newborn with subsequent severe neurodevelopmental impairments. rIL-1RA administration reduced the extent of brain lesions by MRI observation (50).

IL-1RA AND HYPOXIA–ISCHEMIA ASSOCIATED POSTNATAL BRAIN INJURY MODEL

Hypoxia–ischemia is another common cause of postnatal brain injury. The most widely used HI model is the Vannucci model, which combines permanent unilateral ligation of the carotid artery in 7-day-old rat pups, along with exposure to hypoxia (77–80). Increased expression of pro-inflammatory cytokines including IL-1β is associated with HI-induced postnatal brain injury (81–83).

Experimental administration of rIL-1RA has been demonstrated to reduce HI-induced postnatal brain injury (84–86). Martin et al. injected rIL-1RA subcutaneously in a postnatal rat HI model and found prior to or after HI, rIL-1RA ameliorated the ischemia damage as measured by hemisphere dry weights and prevented neuronal loss in the striatum (87). Hu et al. injected 2 μg rIL-1RA intra-cerebroventricularly 2 h after HI and found a significant reduction in cell death and Caspase 3 activity. The observed increase in cytoplasmic NFκB activation and nuclear translocation of Bcl-3 24 h after HI was also significantly attenuated by IL-1 blockade, suggesting that HI-induced IL-1 activation is via both the NFκB activation and the nuclear translocation of Bcl-3 (88).

Though a rapidly expanding body of evidence indicates that rIL-1RA is a promising therapeutic for postnatal brain injury, the specific signaling mechanisms triggered by rIL-1RA responsible for the effects are still not fully known. A number of drawbacks of rIL-1RA limit its broader use; these include injection site reactions (89, 90), broad immunosuppression (90), and high costs. Trials to test safety in a pediatric population are sorely needed as a lack of efficacy and safety data limits the adoption of rIL-1RA for perinatal brain injury.

CONCLUDING REMARKS

During infection and inflammation, the potent effects of IL-1 signaling can lead to devastating tissue damage with long-lasting effects. Therapies that block IL-1 signaling have been successful in reducing negative outcomes in autoinflammatory diseases in adults for over a decade now. Exciting research in the area of neonatal encephalopathy suggests that the benefits of IL-1 blockade in reducing injury in autoinflammatory diseases may be extended to neonatal brain injury and offer much needed neuroprotection for a population with limited effective treatment options.

Neonatal encephalopathy affects up to 1% of live births (91–93) and the causes can vary from hypoxic–ischemic events to intrauterine inflammation (37, 38, 40–43). Treatment options are limited and the current standard of care prescribes therapeutic hypothermia (94). Hypothermia, however, does not confer complete neuroprotection and as many as 50% of treated neonates will experience moderate to severe neurologic disability (95). Common processes that contribute to neuronal injury, including oxidative stress, apoptosis, inflammation, and excitotoxicity, are increasingly the targets of emerging therapies for neonatal encephalopathy.

As a Class B drug, rIL-1RA is approved for use in pregnant women and may be offered in the future as a perinatal intervention to prevent perinatal brain injury due to neonatal encephalopathy or due to exposure to intrauterine inflammation. However, rIL-1RA is not approved for the treatment or prevention of perinatal brain injury, and further studies are needed to determine its safety and efficacy. At this time, little is known in regards to the importance of IL-1 in brain formation or the development of the immature immune system; therefore, further evaluation of this molecule is necessary to establish appropriate safe timing of its administration for variety of etiologies of perinatal brain injury. Furthermore, no studies have yet been conducted to assess the efficacy of rIL-1RA in combination with other therapies, such as hypothermia, although other combination therapies (hypothermia and erythropoietin) have shown promise in rodent models (96, 97). Mechanistic studies of r-IL1RA, as we are conducting, are ongoing to evaluate maternal–fetal transfer and developmental effects in animal models.

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