Interleukin-1 receptor blockade in perinatal brain injury

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**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 physiological 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). There is also evidence that IL-1RA binds to 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 activity (13). Additionally, an endogenous IL-1 receptor antagonist, discussed in greater detail below, has a much lower affinity for IL-1R2. Together, the decoy receptor and antagonist provide a potent mechanism of regulating IL-1 signaling.

**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 TIR/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. However, while pro-IL-1β requires proteolytic cleavage to become the mature, active form of the cytokine, pro-IL-1α 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.

**Keywords:** IL-1, rIL-RA, perinatal brain injury, IL-1beta, Kineret
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), extracellular 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-1RαCp, 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.

**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 niluzol 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 AD(HF))                      | 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/VO2 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*  | 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*                                |
| 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              |

aData 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 intracerebrinjection 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 post-natally (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.

REFERENCES

1. Beeson PB. Temperature-elevating effect of a substance obtained from polymorphonuclear leucocytes. J Clin Invest (1948) 27(4):524.
2. Atkins E. Pathogenesis of fever. Physiol Rev (1960) 40:580–646.

3. Dinarello CA. Interleukin-1 and interleukin-1 antagonism. Blood (1991) 77(1):1672–52.

4. Simms JE, Smith DE. The IL-1 family: regulators of immunity. Nat Rev Immunol (2010) 10(2):89–102. doi:10.1038/nri2691

5. Dinarello CA, Simon A, van der Meer JW. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Nat Rev Drug Discov (2012) 11(8):533–52. doi:10.1038/nrd3800

6. Garlanda C, Dinarello CA, Mantovani A. The interleukin-1 family: back to the future. Immunity (2013) 39(6):1003–18. doi:10.1016/j.immuni.2013.11.010

7. Girard S, Seibre H, Brochu ME, Briotas S, Sarret P, Sebire G. Postnatal administration of IL-1Ra exerts neuroprotective effects following perinatal inflammation and/or hypoxic-ischemic injuries. Brain Behav Immun (2012) 26(8):1331–9. doi:10.1016/j.bbi.2012.09.001

8. Leitner K, Al Shammary M, McLane M, Johnston MV, Elovitz MA, Burd I. IL-1 in perinatal brain injury. Am J Reprod Immunol (2013) 67(7):277–85. doi:10.1111/aji.12216

9. Dunne A, O’Neill LA. The interleukin-1 receptor/Toll-like receptor superfamily: signal transduction during inflammation and host defense. Sci STKE (2003) 2003(171):re3. doi:10.1126/stke.171.re3

10. Watters TM, Kenny EF, O’Neill LA. Structure, function and regulation of the Toll/IL-1 receptor adaptor proteins. Immunol Cell Biol (2007) 85(6):411–9. doi:10.1038/sj.icb.7000955

11. Casanova JL, Abel L, Quintana-Murci L. Human TLRs and IL-1Rs in host defense: natural insights from evolutionary, epidemiological, and clinical genetics. Ann Rev Immunol (2011) 29:487–491. doi:10.1146/annurev-immunol-030409-101335

12. McMahen CJ, Slack JL, Mosley B, Cosman D, Lupondo SD, Brunton LL, et al. A novel IL-1 receptor, cloned from B cells by mammalian expression, is expressed in many cell types. EMBO J (1991) 10:2821–32.

13. Hansum CH, Wilson CJ, Arend WP, Joslin FG, Dripps DJ, Heidmal PL, et al. Interleukin-1 receptor antagonist activity of a human interleukin-1 inhibitor. Nature (1993) 364(6425):336–40. doi:10.1038/364336a0

14. Mariahassan S, Newton K, Monack DM, Tyrrell PJ, Rothwell NJ. Rapid brain penetration of interleukin-1 receptor antagonist 1-alpha/beta, and IL-1 receptor antagonist shows that IL-1beta is crucial in turpentine-induced fever development and glucocorticoid secretion. J Exp Med (2009) 202(2):213–20. doi:10.1084/jem.20081796

15. Tschopp J, Schroder K. NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production? Nature (2004) 430(6996):213–8. doi:10.1038/nature02664

16. Leitner K, Al Shammary M, McLane M, Johnston MV, Elovitz MA, Burd I. IL-1 in perinatal brain injury. Am J Reprod Immunol (2013) 67(7):277–85. doi:10.1111/aji.12216

17. Mariathasan S, Newton K, Monack DM, Vucic D, Strober S, Hussein P. The transfer of interleukin-1 alpha across the human placenta perfused in vitro. Obstet Gynecol (1996) 87(4):613–6. doi:10.1016/0029-8484(95)00473-4

18. Zaretsky MV, Alexander JM, Byrd W, Bawdon RE. Transfer of inflammatory cytokines across the placenta. Obstet Gynecol (2004) 103(3):546–50. doi:10.1097/01.AOG.0000114980.44045.83

19. Aaltenen R, Heikkinen T, Hakala K, Laine K, Alalen A. Transfer of proinflammatory cytokines across term placenta. Obstet Gynecol (2005) 106(4):802–7. doi:10.1097/01.AOG.0000114980.44045.83

20. Ali SH, Tania S, Elahi S, Shehzad T, Ali F, Boksa P. Effects of prenatal infection on brain development and behaviour: a review of findings from animal models. Prog Brain Res (2010) 187:201–20. doi:10.1016/j.pneuro.2011.01.003

21. Zhenzhen J, Kertesz G, Karpov A. Interleukin 1 and interleukin 1 receptor antagonist in preeclampsia: effect of magnesium sulfate. J Interferon Cytokine Res (2012) 32(9):432–41. doi:10.1089/jirf.2012.0013

22. Genovese MC, Cohen S, Moreland L, DuPont J, Smolen JS, Kavanaugh A, et al. Treatment of rheumatoid arthritis with anakinra human interleukin-1 receptor antagonist. Arthritis Rheum (1998) 41(2):196–204. doi:10.1002/1529-0131(199812)41:2<196::AID-ART15>3.3.CO;2-U

23. Cohen S, Hurd E, Cusik J, Schif F, Weimann ME, Moreland LW, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. Arthritis Rheum (2002) 46(3):614–24. doi:10.1002/art.10103

24. Leitner K, Al Shammary M, McLane M, Johnston MV, Elovitz MA, Burd I. IL-1 in perinatal brain injury. Am J Reprod Immunol (2013) 67(7):277–85. doi:10.1111/aji.12216

25. Galea J, Ogungbenro K, Hulme S, Greenhalgh A, Aarons L, Scarth S, et al. Intravenous anakinra can achieve experimentally effective concentrations in the central nervous system within a therapeutic time window: results of a dose-ranging study. J Cereb Blood Flow Metab (2011) 31(2):349–57. doi:10.1038/jcbf.2010.103

26. Amash A, Holberg G, Sapir O, Huleihel M. Placental secretion of interleukin-1 and interleukin-1 receptor antagonist in preeclampsia: effect of magnesium sulfate. J Interferon Cytokine Res (2012) 32(9):432–41. doi:10.1089/jirf.2012.0013

27. Banks WA, Kastin AJ, Broadwell RD. Passage of cytokines across the blood-brain barrier. Neuroimmunomodulation (1995) 2(4):241–8. doi:10.1159/000969887

28. Greenhalgh AD, Galea J, Denes A, Tyrrell PJ, Rothwell NJ. Rapid brain penetration of interleukin-1 receptor antagonist in rat cerebral ischaemia: pharmacokinetics, distribution, protection. Br J Pharmacol (2010) 160(1):153–9. doi:10.1111/j.1364-5810.2010.06944.x
45. Rothwell N. Interleukin-1 and neuronal injury: mechanisms, modification, and therapeutic potential. Brain Behav Immun (2003) 17(3):152–7. doi:10.1016/S0889-1591(02)00098-3
46. Cai Z, Lin S, Pang Y, Rhodes PG. Brain injury induced by intracerebral injection of interleukin-1 beta and tumor necrosis factor-alpha in the neonatal rat. Pediatr Res (2004) 56(5):377–84. doi:10.1203/01.PDR.0000134249.92944.14
47. Allan SM, Tyrrell PJ, Rothwell NJ. Interleukin-1 and neuronal injury. Nat Rev Neurosci (2005) 6(5):689–90. doi:10.1038/nrn1664
48. Thornton P, Pinteaux E, Gibson RM, Allan SM, Rothwell NJ. Interleukin-1-induced neurotoxicity is mediated by glia and requires caspase activation and free radical release. J Neurochem (2006) 98(1):258–66. doi:10.1111/j.1471-4159.2006.03872.x
49. Denes A, Pinteaux E, Rothwell NJ, Allan SM, Interleukin-1 and stroke: bio marker, harbinger of damage, and therapeutic target. Cerebrovasc Dis (2011) 32(6):57–27. doi:10.1159/00033205
50. Savard A, Lavioe K, Brochu ME, Gribsci D, Legape M, Gris D, et al. Involvement of neuronal IL-1 beta in acquired brain lesions in a rat model of neonatal encephalopathy. J Neuroinflammation (2013) 10:110. doi:10.1186/1742-2094-10-110
51. Green HF, Treacy E, Keoshane AK, Sullivan AM, O’Keefe GW, Nolan YM. A role for interleukin-1 beta in determining the lineage fate of embryonic rat hippocampal neural precursor cells. Mol Cell Neurosci (2012) 49(3):311–21. doi:10.1016/j.mcn.2012.01.001
52. Fatemi SH, Emamian ES, Sidwell RW, Kist DA, Stary JM, Earle JA, et al. Human influenza viral infection in utero alters glial fibrillary acidic protein immunoreactivity in the developing brains of neonatal mice. Mol Psychiatry (2002) 7(6):633–40. doi:10.1038/sj.mp.4001046
53. Aden U, Favrais G, Plaisant F, Winerdal M, Felderhoff-Mueser U, Lampa J, et al. Systemic inflammation sensitizes the neonatal brain to excitotoxicity through a pro-/anti-inflammatory imbalance: key role of TNFalpha pathway and protection by etanercept. Brain Behav Immun (2010) 24(5):757–58. doi:10.1016/j.bbi.2009.10.010
54. Chang EY, Zhang J, Sullivan S, Newman R, Singh J. N-acetylcysteine attenuates the maternal and fetal proinflammatory response to intratracheal LPS injection in an animal model for preterm birth and brain injury. J Matern Fetal Neonatal Med (2011) 24(5):732–40. doi:10.3109/14767058.2010.528089
55. Burd I, Balakrishnan B, Kannan S. Models of fetal brain injury, intratracheal inflammation, and preterm birth. Am J Reprod Immunol (2012) 67(4):287–94. doi:10.1111/j.1600-8897.2012.0110x.x
56. Dada T, Rosenweig JM, Al Shammary M, Firdaus W, Al Rebh S, Borbiev T, et al. A mouse model of intrauterine inflammation: sex-specific differences in long-term neurologic and immune sequelae. Brain Behav Immun (2014) 38:142–50. doi:10.1016/j.bbi.2014.01.014
57. Boll MJ, Hallenneck JM. Effects of intratracheal inflammation on developing rat brain. J Neurosci Res (2002) 70(4):570–9. doi:10.1002/jnr.10423
58. Auvin S, Shin D, Mazzarati A, Nakagawa J, Miyamoto J, Sankar R. Inflammation exacerbates seizure-induced injury in the immature brain. Epilepsia (2007) 48(59):27–34. doi:10.1111/j.1528-1167.2007.01239.x
59. Beloosesky R, Ginsburg Y, Khathi N, Maravi N, Ross MG, Hiskowitz-Elder J, et al. Prophylactic maternal N-acetylcysteine in rats prevents maternal inflammation-induced offspring cerebral injury shown on magnetic resonance imaging. Am J Obstet Gynecol (2013) 208(3):e221–6. doi:10.1016/j.ajog.2013.01.023
60. Hagberg H, Peebles D, Mallard C. Models of white matter injury: comparison of infectious, hypoxic-ischemic, and excitotoxic insults. Ment Retard Dev Disabil Res Rev (2002) 8(2):130–8. doi:10.1002/mdrr.10020
61. Kannan S, Saadann-Makkii F, Muzak C, Chakraborty P, Mangner TJ, Janisse J, et al. Microglial activation in perinatal rabbit brain induced by intratracheal inflammation: detection with 11C-(R)-PK11195 and small-animal PET. J Nucl Med (2007) 48(6):946–54. doi:10.2967/jnumed.106.038539
62. Young RS, Hernandez MJ, Yagle SK. Selective reduction of blood flow to white matter during hypotension in newborns: a possible mechanism of periventricular leukomalacia. Ann Neurol (1982) 12(5):445–8. doi:10.1002/ana.19820120506
63. Yaseno T, Schuwerlve J, Moss TJ, Vosdoganes P, Westover AI, Afanadi E, et al. Human amniotic epithelial cells reduce fetal brain injury in response to intratracheal inflammation. Dev Neurosci (2013) 35(2–3):272–82. doi:10.1159/000346883
64. Debillelon T, Gras-Leguen C, Verielle V, Winer N, Calion J, Rove CJ, et al. Intratracheal infection induces programmed cell death in rabbit
83. Carlsson Y, Leverin AL, Hedtjarn M, Wang X, Mallard C, Hagberg H. Role of mixed lineage kinase inhibition in neonatal hypoxia-ischemia. *Dev Neurosci* (2009) 31(5):420–6. doi:10.1159/000252560

84. Park EM, Cho BP, Volpe BT, Cruz MO, Joh TH, Cho S. Ibpuprofen protects ischemia-induced neuronal injury via up-regulating interleukin-1 receptor antagonist expression. *Neuroscience* (2005) 132(3):625–31. doi:10.1016/j.neuroscience.2005.01.021

85. Quiniou C, Kooli E, Joyal JS, Sapieha P, Sennlaub F, Lahaie I, et al. Interleukin-1 mixed lineage kinase inhibition in neonatal hypoxia-ischemia. *Dev Neurosci* (2013) 35(1):26–37. doi:10.1111/j.1471-4159.2004.02968.x

86. Wang CH, Wang WT, Cheng SY, Hung WT, Wu TL, Hsueh CM. Leptin and interleukin-1beta modulate neuronal glutamate release and protect against glucose-oxygen-serum deprivation. *Curr Neurovasc Res* (2010) 7(3):223–37. doi:10.2174/156720210791184925

87. Martin D, Chinooskowong N, Miller G. The interleukin-1 receptor antagonist (rhIL-1ra) protects against cerebral infarction in a rat model of hypoxia-ischemia. *Exp Neurol* (1994) 130(2):362–7. doi:10.1006/exnr.1994.1215

88. Hu X, Nesci-Taylor G, Qiu J, Rea HC, Fabian R, Rassin DK, et al. Activation of nuclear factor-kappaB signaling pathway by interleukin-1 after hypoxia/ischemia in neonatal rat hippocampus and cortex. *J Neurochem* (2005) 93(1):26–37. doi:10.1111/j.1471-4159.2004.02968.x

89. Campion GV, Lebsack ME, Lookabaugh J, Gordon G, Catalano M. Dose-range and dose-frequency study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. The IL-1ra Arthritis Study Group. *Arthritis Rheum* (1996) 39(7):1092–101. doi:10.1002/art.1780390704

90. Nakai G, Bresnahan B, Bear MB, McCabe D. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* (2002) 46(11):2838–46. doi:10.1002/art.10578

91. Ferriero DM. Neonatal brain injury. *N Engl J Med* (2004) 351(19):1985–95. doi:10.1056/NEJMra041996

92. Pierrat V, Haouari N, Liska A, Thomas D, Subtel D, Truffert P. Prevalence, causes, and outcome at 2 years of age of neonatal encephalopathy: population based study. *Arch Dis Child Fetal Neonatal Ed* (2005) 90(3):F257–61. doi:10.1136/adc.2003.047985

93. Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE. A systematic review of the role of intrapartum hypoxia-ischaemia in the causation of neonatal encephalopathy. *Arch Dis Child Fetal Neonatal Ed* (2008) 93(6):587–95. doi:10.1136/adc.2008.160944

94. D’Alton ME, Hankins GDV, Berkowitz RL, Bienstock I, Ghidini A, Goldsmith J, et al. Executive summary: neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists’ task force on neonatal encephalopathy. *Obstet Gynecol* (2014) 123(4):896–901.

95. Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ* (2010) 340:c363. doi:10.1136/bmj.c363

96. Fan X, van Bel F, van der Kooij MA, Heijnen CJ, Groenendaal F. Hypothermia and erythropoietin for neuroprotection after neonatal brain damage. *Pediatr Res* (2013) 73(1):18–23. doi:10.1038/pr.2012.139

97. Fang AY, Gonzalez FE, Sheldon RA, Ferriero DM. Effects of combination therapy using hypothermia and erythropoietin in a rat model of neonatal hypoxic-ischemia. *Pediatr Res* (2013) 73(1):12–7. doi:10.1038/pr.2012.138

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