

Perinatal inflammation and adverse outcomes of the intestine and liver

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Impact

Relevance

Preterm birth is a common and major worldwide health issue, contributing to significant neonatal morbidity and mortality. Around one in every ten births are preterm, accounting for approximately 15 million premature newborns each year. Due to complications, over one million premature newborns die shortly after birth.

Survivors of preterm birth have higher rates of adverse long-term health outcomes including cerebral palsy, sensory deficits, learning disabilities, altered intestinal motility and respiratory illnesses, compared with children born at term. The morbidity associated with preterm birth often extends to later in life and have a severe impact on emotional and financial status of patients, their families, caregivers and society.

Spontaneous preterm birth is in up to 40% associated with chorioamnionitis, which is an inflammation of the amniotic membranes. Chorioamnionitis typically results from an ascending bacterial infection from the lower genital tract (cervix and vagina), resulting in microbial colonization of the amniotic membranes, amniotic fluid, and/or umbilical cord. Most frequently, chorioamnionitis is asymptomatic, meaning that pregnant women do not have clinical symptoms and the presence of chorioamnionitis is recognized after delivery.

Chorioamnionitis can also, independently of preterm birth, provoke postnatal adverse effects, of which necrotizing enterocolitis (NEC) is one of the most severe neonatal gastrointestinal emergencies that predominantly affects premature infants. NEC is an inflammatory intestinal disorder, characterized by variable damage to the intestinal tract. The natural history of NEC is a fulminant progression with severe inflammation of the bowel, ischemia and necrosis, leading to septic shock, multiple organ failure, and death within hours or days of onset if appropriate treatment is not timely instituted. Mortality generally ranges from 15 to 30%, but increases up to 50% for extremely low birth weight children treated surgically. Infants that do survive are at increased risk for e.g. intestinal failure, feeding difficulties, growth retardation and developmental delay as they age.

Despite advancing medical care, NEC treatment remains largely symptomatic. Moreover, effective preventative strategies that reduce the prevalence of NEC are lacking. These can only be achieved with a more profound understanding of the pathophysiological mechanisms leading to NEC, since the multifactorial pathogenesis of NEC is still incompletely understood.

Innovation

Firstly, the findings described in this thesis support the concept that intestinal neuropathological lesions found in NEC (loss of enteric neurons and glial cells in the submucosal and myenteric plexus) have their origin far before NEC onset and these enteric nervous system (ENS) alterations are considered to result in dysfunctional intestinal motility facilitating intraluminal bacterial overgrowth and translocation, therewith promoting the multi-factorial pathophysiology of NEC.

Secondly, the data described in this thesis in combination with observations in literature, suggest that the enterohepatic circulation (EHC) alterations (elevated ileal bile acids (BAs) and altered expression of several BAs transporters) and liver inflammation found in NEC have their origin far before the onset of NEC and that both may result in ileal damage contributing to the multi-factorial pathophysiology of NEC.

To the best of our knowledge, we are the first describing the effects of chorioamnionitis on the ENS and EHC and postulate that chorioamnionitis-induced ENS and EHC alterations and liver inflammation may contribute to development of NEC. Moreover, we showed that the vulnerability of the fetus to injurious exposure during intra-uterine development is largest when exposed early in pregnancy, namely in the second trimester, potentially predisposing to NEC.

Ideally, one would like to start therapeutic interventions already *in utero* to prevent intestinal injury later in life and prevent NEC development. In this context, the work in this thesis showed that cyclodextrins, which are highly water-soluble, "ready-made," and commercially available, target liver inflammation and thereby potentially prevent adverse outcomes. Future studies should focus on the correct timing and dose of β -cyclodextrin administration and potential other interventions *in utero* during chorioamnionitis.

All together, the findings in this thesis demonstrate that chorioamnionitis can induce ENS and EHC alterations and liver inflammation which can adversely affect the fetal gut and liver, potentially predisposing to NEC. This increases our understanding of the multifactorial pathophysiology of NEC, which eventually will lead to therapeutic options and also preventative strategies.

Target audience and future activities

The findings in this thesis could be of interest to a wide audience. Firstly, the results are of significant interest for researchers, who could extend this research to further unravel the detrimental effects of chorioamnionitis and the multifactorial pathophysiology of NEC. Moreover, the anti-inflammatory effect of β -cyclodextrin can form the basis for scientists to further investigate the therapeutic effect of β -cyclodextrin in other organs, both in vulnerable neonates but also outside the pediatric setting. Moreover, the potential synergy with other pharmacological interventions should be explored. The described characterization of the *in utero* models facilitate the design of future studies where therapeutic strategies for gut- and liver-associated complications after chorioamnionitis can be tested.

Secondly, the results of this thesis can also be of interest for various clinicians including e.g. neonatologists, pediatricians, perinatologists and gynecologists who are interested in understanding the basic mechanisms underlying liver and gastrointestinal diseases in the newborn.

In conclusion, the studies described in this thesis contribute to the understanding of the effect of chorioamnionitis on the fetus and the multifactorial pathophysiology of NEC. In addition, this thesis presents a potential intervention to protect the fetal liver and gut in

the context of chorioamnionitis. Nevertheless, additional research is required for clinical implementation and our translational ovine model is suitable to test the efficacy and feasibility of more comprehensive therapeutic strategies to prevent and/or treat liver and gastrointestinal complications after chorioamnionitis.