ABSTRACT

Charles University
Faculty of Pharmacy in Hradec Králové
Department of Pharmacology and Toxicology

Student: Michaela Medková
Supervisor: PharmDr. Rona Karahoda, Ph.D.
Title of diploma thesis: Targeting placental inflammation: Investigating the effects of glucose, metformin, and LPS on the NLRP3 inflammasome

Gestational diabetes mellitus (GDM) is one of the most common obstetric complications defined as glucose tolerance first detected during pregnancy. Recent research indicates that GDM is associated with chronic low-grade inflammation, a phenomenon observed within the placenta as well. Importantly, the human placenta expresses high levels of NLRP3-inflammasome-associated molecules and secretes large amounts of proinflammatory cytokines IL-1β and IL-18. Elevated circulating levels of these cytokines, including IL-1β, have been linked to GDM. Moreover, metformin, a hypoglycemic agent used in pregnancy, has gained attention for its potential to modulate inflammasome activation. Thus, our study aimed to investigate the inflammatory response of human placental tissue to high glucose levels and LPS exposure and explore the potential anti-inflammatory effects of metformin. The study was conducted in villous placental explants isolated from human term placenta. qPCR and ELISA were used to evaluate the gene expression and cytokine release, respectively. We show a strong and modest effect of LPS and high glucose, respectively, on the placental NLRP3 pathway. This aligns with the evidence linking hyperglycemia with a low-grade inflammatory state. Surprisingly, we observed a proinflammatory effect of metformin in the presence of LPS, challenging the conventional understanding of its anti-inflammatory properties. These findings highlight the complexity in the modulation of inflammatory responses in the placenta. Further research is necessary to identify mechanisms underlying these effects on placental NLRP3 inflammasome regulation.