Abstract: 44O

The Effects of Maternal Hyperglycaemia During Pregnancy on One-Carbon Metabolism

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BACKGROUND: Gestational diabetes mellitus (GDM) is the most common metabolic disturbance during pregnancy. GDM is defined as the onset of hyperglycaemia for the first-time during pregnancy and usually resolves soon after birth. The relationship between GDM and the placenta is complex. Placental dysfunction is a known contributor to GDM but the hyperglycaemia in GDM is also known to cause placental dysfunction. It is possible that placental dysfunction may occur as a consequence of changes in essential biological processes, such as one-carbon metabolism. Numerous clinical studies have demonstrated that women with GDM have altered concentrations of circulating one-carbon metabolites and cofactors such as vitamin B12, B6, folate and homocysteine (Barzilay et al., 2018, Lai et al., 2018). Since these metabolites are vital for processes such as methylation of DNA, redox defences and amino acid homeostasis, imbalances have been linked with poor placental development and adverse fetal outcomes (Vanhees et al., 2014). Currently, it is unknown if the hyperglycaemia caused by GDM results in lower concentrations of one-carbon metabolites or if reduced concentrations of one-carbon metabolites increase women's risk of GDM. This study therefore examined the effects of maternal hyperglycaemia on one-carbon metabolism.

METHODS: Gestational hyperglycaemia was induced in pregnant C57BL/6 mice via D-glucose (1.55g/mL) filled osmotic mini-pumps (release rate of 0.5µl/hr) inserted subcutaneously at embryonic day 7 (E7). Control animals received 0.9% saline mini-pumps. An oral glucose tolerance test (OGTT) was performed at E17.5 and mice were euthanised via cervical dislocation the following day (E18.5). Maternal plasma and placentas were collected. Maternal plasma concentrations of one-carbon metabolites and cofactors were measured using liquid chromatography-mass spectrometry. Placental gene expression of enzymes involved in one-carbon metabolism and associated processes were measured using real-time PCR

RESULTS: Hyperglycaemia increased concentrations of several one-carbon metabolites and cofactors in maternal plasma at E18. This included 5-methyl-THF, methionine, vitamin B6 and vitamin B12, with a subsequent decrease in homocysteine. Furthermore, relative S-Adenosyl methionine (SAM) concentrations were higher in the hyperglycaemic group compared to control, with no change in S-Adenosyl-L-homocysteine (SAH) levels. This ultimately led to a two-fold increase in methylation capacity as determined by the SAM/SAH ratio. This was accompanied by increased gene expression of a few key one-carbon enzymes within the placenta, including methionine synthase and methylenetetrahydrofolate reductase. However, there was no change in the expression of DNA methyltransferases.

DISCUSSION: This study demonstrated that maternal hyperglycaemia can induce changes in maternal one-carbon metabolite concentrations and in placental one-carbon metabolism enzymes. Hyperglycaemia increased one-carbon metabolites which contrasts with the decrease in one-carbon metabolites commonly seen clinically in women with GDM. Findings contribute to current literature by suggesting that the hyperglycaemia alone as a result of GDM is not responsible for the decrease in one-carbon metabolites and cofactors demonstrated clinically.

References

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