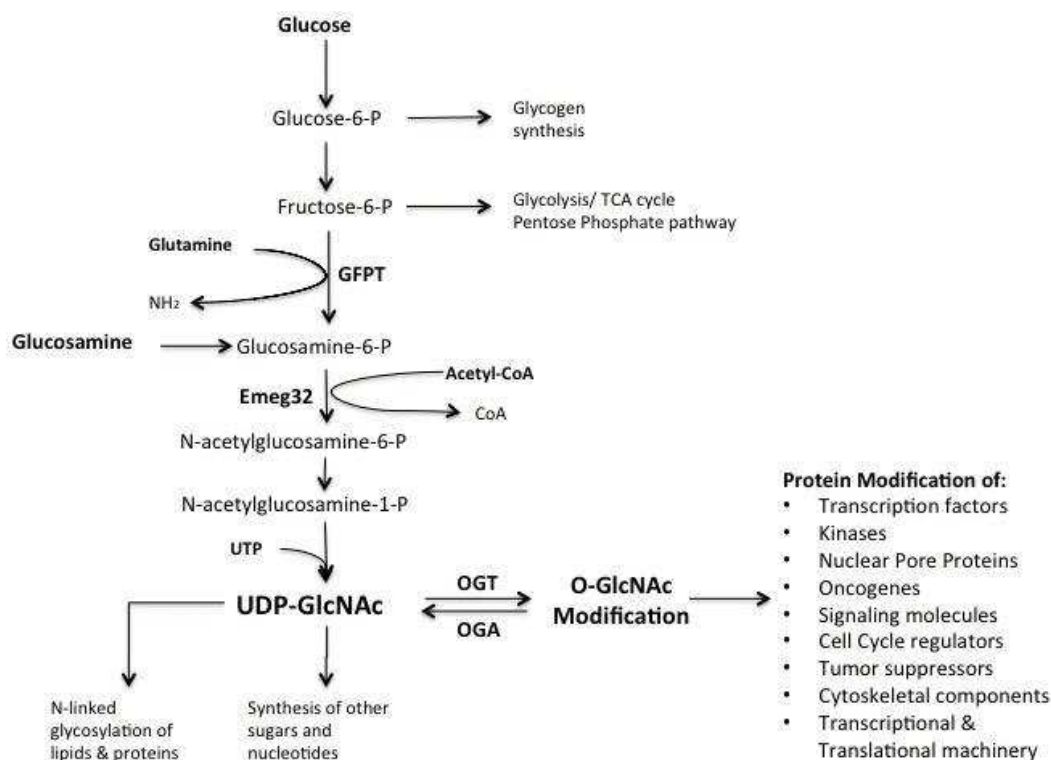


Alterations in key elements of the hexosamine signalling pathway in mouse placenta in response to maternal stress: implications for fetal programming of adult disease

K. McMahon, J.S.M. Cuffe, K.M. Moritz and M. Pantaleon, School of Biomedical Sciences, The University of Queensland, St Lucia, QLD 4072, Australia.

A stressful environment during development can program adult disease propensity in a sexually dimorphic manner. Female offspring appear to be more resistant to an adverse maternal environment whereas male offspring are adversely affected. Our previous studies of short-term (60h) exposure to maternal glucocorticoid during gestation suggest that male offspring susceptibility to adult disease may occur at the level of the placenta (Cuffe *et al.*, 2012). Although the mechanisms by which the fetal/placental unit senses and responds to stressful environments are not understood, the ability of cells to respond to multiple forms of stress is associated with rapidly increased glucose uptake and metabolism through the hexosamine signalling pathway (HSP) outlined in the figure. This is an essential survival response of adaptive importance in healthy cells.



Up to 5% of glucose entering cells is metabolised through this pathway following conversion to glucosamine-6-P (GlcN-6-P) by the rate-limiting enzyme GFPT. The end product of hexosamine biosynthesis, UDP-N-acetyl glucosamine (UDP-GlcNAc) is used in several biosynthetic reactions including O-linked glycosylation by N-acetyl glucosamine (GlcNAc). Addition of GlcNAc is catalysed by the X-linked O-GlcNAc transferase (OGT) and its removal by the O-GlcNAc-selective β -N-acetyl glucosaminidase (OGA). This is regulatory modification responsible for regulating the activity and stability of a diverse group of proteins including survival factors, such as Akt. Using our model of maternal glucocorticoid exposure associated with sexually dimorphic programming and placental outcomes (above) we examined levels of key enzymes of the HSP as well as levels of O-GlcNAcylation in mouse placentae at E14.5 by RT-PCR and western blotting.

Our results demonstrate that the O-GlcNAcylation response to stress is blunted in male placentae relative to female placentae suggesting dysregulation of this signaling pathway may underlie the sexually dimorphic response to a stressful environment *in utero*. Increased levels of the stress-responsive, pro-survival factor Akt2, in placentae from female ($P < 0.05$), but not male fetuses following glucocorticoid administration further supports this notion. Given that dysregulation of O-GlcNAcylation is implicated in a growing number of adult diseases our results suggest that sex-specific alterations in placental OGT levels in response to stress may act to protect the female fetus from propensity to adult disease in later life.

Cuffe JS, O'Sullivan L, Simmons DG, Anderson ST, Moritz KM. (2012). *Endocrinology* **153**: 5500-5511.