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Vascular RAGE and AGE binding protein expression and function in gestational diabetes.

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Gestational diabetes (GD) is an increasingly prevalent complication of pregnancy which alters foetal growth patterns and increases the likelihood of future metabolic disease. GD occurs more commonly in women with pre-existing insulin resistance and elevated BMI and is also a risk factor for pre-eclampsia (1). Many of the health impacts of GD may arise from impaired uterine and placental vascular function, including impaired blood flow and increased capillary permeability (2). The hyperglycemia characteristic of GD results in the excessive plasma accumulation of advanced glycated end-products (AGEs) and tissue expression of their binding proteins, principally RAGE (receptor for AGEs) but also including AGER-1 and galectin-3. The AGE-RAGE interaction exerts several pro-inflammatory actions in human gestational tissues, increasing oxidative stress and an inflammatory response with the release of cytokines and adhesion molecules (3). The role of AGEs and RAGE in uterine vascular dysfunction associated with gestational hyperglycaemia and diabetes has not been investigated extensively. This study aimed explore the potential involvement of RAGE in maternal vascular dysfunction in gestational diabetes.

Small arteries (internal diameter ~200 µm) were dissected from pieces of myometrium and omentum obtained at term from consenting normoglycemic (NG) women and others with GD (fasting glucose >8 mmol/L). RAGE, AGER-1, NLRP3 and galectin-3 mRNA and protein expression in these vessels was investigated using rt-qPCR and immunofluorescence (IF), respectively. Functional studies examining the effects of AGEs on vasoreactivity of the arteries were performed using pressure myography. Arteries were pre-constricted with vasopressin (1-10 nM) and endothelium-dependent responses examined using bradykinin. AGEs were generated by incubating human serum albumin (10 mg/ml) with methylglyoxal (9 mM) in phosphate-buffered saline for 4 days at 37°C.

The mRNA expression of RAGE, AGER-1, NLRP3 and galectin-3 was not significantly changed in myometrial arteries from GD women (n = 8) compared with those from NG women (n = 9). IF studies suggested RAGE protein expression was increased in both smooth muscle and the endothelium of myometrial and omental arteries of GD women, while galectin-3 protein expression was also increased in the smooth muscle and endothelium of omental arteries only. Functional studies demonstrated that AGEs (0.1mg/ml) inhibited endothelium-dependent, bradykinin-induced dilation of myometrial arteries from GD women (bradykinin pEC_{50} 6.57 ± 0.08) compared with NT women (7.30 ± 0.16; n = 4 for each, $P<0.05$). AGEs also induced contraction of the myometrial arteries in a time-dependant manner (pre-AGE diameter 96.4 ± 1.8% of max; 120 min post-AGE 74.1 ± 10% of max, n = 4 for both, $P<0.05$). Preliminary studies (n=1) suggest these effects of AGEs were prevented in the presence of the RAGE antagonist FPS-ZM1 (1 µM).

Overall, RAGE and galectin-3 protein (but not mRNA) expression was increased in arteries from GD women, and AGE inhibited endothelium-dependent dilation of myometrial arteries taken from women with GD, but not NG women. These observations imply AGEs inhibit endothelium-dependent hyperpolarization of the myometrial arteries, as GD abolished nitric oxide/prostanoid-mediated dilation in these vessels (4). AGEs also induced contraction of the myometrial arteries; combined with effects on vasodilation, AGEs may interact with RAGE to impair uterine blood flow in GD.

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