

Endocrine Society of Australia Postdoctoral Award 2016 – Report

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Project Title: The dietary phytophenol resveratrol as a novel therapeutic for gestational diabetes mellitus.

Summary

Gestational diabetes mellitus (GDM) affects up to 20% of all pregnancies but have an impact that extends well beyond pregnancy and childbirth, with lifelong morbidity or mortality for both mother and baby. Despite the enormous health-impact, little progress has been made with interventions aimed at prevention with the rate of GDM is increasing in parallel with the obesity epidemic.

There is increasing volume and quality of evidence that high fruit and vegetable intake in pregnancy is associated with a decreased risk of adverse pregnancy outcomes. Compounds known as phytophenols are richly sourced in these foods and have been shown to have antidiabetic properties in type 2 diabetes. Thus, the antidiabetic effects of dietary phytophenols may represent an exciting and novel therapeutic approach in the management of women with GDM.

I have previously found the phytophenol resveratrol inhibited inflammation in placenta and omental adipose tissue muscle *in vitro*. The Endocrine Society of Australia Postdoctoral Award has supported my research on the role of resveratrol in the prevention of GDM *in vivo*.

Aims

The aim of this project was to a mouse model of GDM to examine whether resveratrol can prevent the development of GDM. The use of a GDM mouse model (db/+ mouse strain) to test the effects of phytophenols to prevent GDM *in vivo*, was a new avenue of research in our laboratory. We had 3 groups of mice receiving different treatments: 1) db/+ mice with resveratrol; 2) db/+ mice with control vehicle only; 3) wild-type mice (non-diabetic) with control vehicle only. We gave daily doses of the phytophenol resveratrol from day 1 of pregnancy until day 17. On day 17, we performed a GTT to assess whether resveratrol could improve maternal glucose levels in GDM mice. On day 18, after mice have recovered from their GTT, maternal and fetal tissues were collected and pup weights recorded. Maternal weights and fats were also measured daily throughout pregnancy. Analysis on the inflammatory and lipid profiles of the maternal and fetal tissues that have been collected so far have yet to be performed.

Progress/Update

The mouse studies are still on-going. Initiating and optimising the mouse model was more difficult than first expected. Establishing the GDM mouse colony took longer than expected. For our studies only female mice heterozygous for the db gene will develop the GDM phenotype in pregnancy. We are unable to use homozygous db mice for our studies. In addition, the breeding and rate of successful pregnancies in these mice are low. It was expected that 4 out of 6 time-mated mice would be pregnant, however we have been experiencing lower pregnancy success rate of 50% or below. Some tissues were not collected from the first few experiments, and the effect of resveratrol on offspring of GDM mice at 6 months of age has not been performed. Some analysis

is still to be performed on maternal and fetal metabolic profile in fetal and maternal livers that has been collected. Given that the GDM mice strain used in this study only demonstrated mild glucose intolerance, we did not find significant effects of phytophenols on the insulin signalling pathway in skeletal muscle collected.

Given the low success rate of timed-mated pregnant mice, we have recently changed our protocol to start treatment on day 10 instead of day 1 of pregnancy, to prevent any potential miscarriages early in the pregnancy due to stressors from the oral gavage procedure. We have also begun testing a new phytophenol, curcumin which has shown very promising results in improving maternal glucose tolerance in GDM mice using this new treatment protocol.

Conclusions

Excitingly, my *in vivo* data shows resveratrol to improve glucose tolerance in GDM-mice and also decrease maternal fat gain associated with GDM. Tissues collected on day 18 of pregnancy showed resveratrol to improve maternal and placental inflammation associated with GDM. Future studies on the effect of these phytophenols on long-term fetal outcome could lead to establishing a potential therapeutic to prevent the adverse effects associated with GDM.

Conference Oral Presentations:

Phytophenols improves inflammation and insulin resistance associated with gestational diabetes mellitus. Austin Life Sciences Research Week, Austin Health, Heidelberg, Victoria, Australia, 2015

Phytophenols improves inflammation and insulin resistance associated with gestational diabetes mellitus. Endocrine Society of Australia and Society for Reproductive Biology and Australia and New Zealand Bone and Mineral Society Joint (ESA-SRB-ANZBMS) Annual Scientific Meeting, Gold Coast, Queensland, Australia, 2016