SKELETAL MUSCLE SPECIFIC OF ABCA1 AND ABCG1 IMPACTS BODY COMPOSITION AND METABOLISM AND IS AGE DEPENDENT

Wei Ting Tan, Chantal Kopecky, Bikash Manandhar, Kerry-Anne Rye and **Blake J Cochran**
UNSW Sydney, Sydney, Australia

Background

- Skeletal muscle is the predominant site of insulin-mediated glucose uptake
- Skeletal muscle insulin resistance is considered to be the initiating or primary defect that is evident decades before β -cell failure and overt hyperglycemia develops
- Skeletal muscle cholesterol accumulation has been reported in hypercholesterolemia *in vivo* in both humans and mice
- Dyslipidemia is one of the major risk factors for cardiovascular disease in type 2 diabetes
- Increased plasma membrane cholesterol levels results in defective insulin-dependent GLUT4 trafficking
- Previous studies have manipulated skeletal muscle cholesterol levels by adding or removing cholesterol using cyclodextrin
- We and others have previously used knockout of ABCA1 and ABCG1 to increase tissue specific cholesterol levels

What impact does specific deletion of ABCA1 and ABCG1 have on skeletal muscle function?

Methodology

Skeletal muscle - ABCA1 ABCG1 KO (SM-DKO)

Initially, 16 week old SM-DKO mice were fed chow supplemented with 400 mg/kg doxycycline or chow for 6 weeks

Body Composition

- There was no significant change in bodyweight between control and SM-DKO mice
- Body fat was increased and lean mass decreased in SM-DKO mice ($p < 0.05$ for trend in both)

Exercise capacity

- Exercise capacity was significantly reduced in SM-DKO mice relative to controls ($p < 0.01$)

Control SM-DKO

Glucose metabolism

- Deletion of ABCA1 and ABCG1 in skeletal muscle did not alter fed or fasting blood glucose
- Glucose tolerance was normal in SM-DKO mice
- Insulin tolerance was normal in SM-DKO mice

Age dependence

- When doxycycline treatment is started at 6 weeks, young mice appear to handle increased cholesterol better – muscle still developing and proliferating, cholesterol demand high. No impact on body composition or glucose
- As mice age and muscle matures, cholesterol overload predominates and glucose metabolism becomes impaired. When doxycycline treatment started at 26 weeks, mice became glucose insensitive

Conclusions

- Alterations to muscle function occur before changes in glucose metabolism in this model
- Complete differentiation of muscle fibres occurs around 16 weeks of age in mice
- Accumulation of cholesterol does not appear to be detrimental until differentiation complete

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