PRESS RELEASE

Enzyme potential target for fight against obesity and diabetes

Removing an enzyme that controls bile acid and hormone levels significantly protects female mice from weight gain, according to a new study presented today at the Society for Endocrinology annual conference in Edinburgh. The finding offers a new a therapeutic target in the fight against obesity.

Steroid hormones and bile acids have multiple functions that affect appetite, physical activity and how energy is used and stored in the body. For example, the sex hormone oestrogen (a steroid) has previously shown to decrease women's appetite while firing up their metabolism and levels of physical activity. Bile acids are important to digest fats in diets, without which animals could not make the most out of a fatty food's calorific content.

The enzyme 5β-Reductase helps generate bile acid and clears excess levels of steroid hormones in the human body.

In this study, researchers from the University of Oxford compared the effects of feeding wild mice a high calorie, fat-rich diet with mice that lacked the ability to make 5β-Reductase over a period of 30 weeks.

Female mice without 5β-Reductase gained 42% less weight than the wild mice (15.8g vs 27.2g respectively), while males in both experimental groups gained the same amount of weight. Female mice without 5β-Reductase also stored less fat around the gonads, vital organs and under their skin compared to wild mice, while also being more sensitive to insulin and better at controlling their blood glucose levels.

"The gender-specific health outcomes of our experiment are interesting but poorly understood", said lead author of the study Dr Laura Gathercole. "It could be that lacking this key enzyme means female mice are less able to extract energy from their food, spend more energy to power their metabolism, or both at the same time".

"Tweaking steroid and bile acid levels has significant health implications and so 5β-Reductase could be an important potential therapeutic target in metabolic disease", she continued.

The researchers next steps are to pinpoint the mechanisms behind the phenomenon, which could provide insights into the different ways males and females regulate their energy and metabolisms.

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Society for Endocrinology

Abstract

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Female 5β-reductase knockout mice are protected from diet induced obesity, insulin resistance and glucose intolerance

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Steroid hormones and bile acids are potent regulators of metabolic phenotype. The enzyme 5β-Reductase (AKR1D1) has a crucial role in bile acid synthesis and also generates 5β-reduced dihydrosteroid metabolites, regulating intra-cellular steroid availability though the clearance of cortisol, testosterone, androstenedione and progesterone. As AKR1D1 sits at the interface of bile acid synthesis and steroid metabolism, we have hypothesised that it plays a key role in metabolic homeostasis and have generated and characterised an entirely novel, global AKR1D1 knockout (KO) mouse.

As expected AKR1D1KO mice had altered hepatic steroid (*in vitro* cortisone clearance: 100% [WT], 70% [KO]; *in vitro* 5α-cortisone/cortisol metabolite generation increased 3.9-fold [KO]) and bile acid metabolism (hepatic bile acid concentration males: 1164±626 pmol/mg [WT], 122±42 pmol/mg [KO] $p<0.05$; females: 310±67 pmol/mg [WT], 113±23 pmol/mg [KO] $p<0.01$). At 10 weeks, KO animals were the same weight as wildtype (WT) littermates with no differences in glucose tolerance. Mice were challenged with a further 20-weeks of high fat diet feeding whereon female, but not male, AKR1D1KO mice were protected from diet induced weight gain (weight gain males: 21.8g±0.9g [WT], 21.4g±0.7g [KO] p=ns; females: 27.2g±0.5g [WT], 15.8g±1.2g [KO] $p<0.01$), with reduced adipose tissue mass across all depots (gonadal: 4.0g±0.2g [WT], 2.4g±0.4g [KO] $p<0.005$; subcutaneous: 3.9g±0.3g [WT], 2.4g±0.5g [KO] $p<0.05$; mesenteric: 1.9g±0.2g [WT], 1.2g±0.3g [KO] $p<0.05$), but with preserved lean mass. Female AKR1D1KO mice were also protected from the metabolic consequences of the high fat diet, with improved glucose tolerance (ipGTT AUC females: 3216 mMol□min [WT], 2601 mMol□min [KO] $p<0.05$) and enhanced insulin sensitivity (ipITT AUC females: 1171 mMol□min [WT], 947 mMol□min [KO]).

AKR1D1KO mice display a sexually dimorphic metabolic phenotype, where female mice are protected from the adverse metabolic effects of a high fat diet. Although the underpinning mechanisms remain to be fully defined, AKR1D1 may represent a future novel therapeutic target for the treatment of metabolic disease.

Notes for editors

1. The study *Female 5β-reductase knockout mice are protected from diet induced obesity, insulin resistance and glucose intolerance* will be presented by Dr Laura Gathercole at the Society for Endocrinology's annual conference at 17.30 GMT, room OC3.6 on Tuesday 3 November 2015. Please note this is a conference abstract, and this study has not yet been published in a peer-reviewed journal.

2. For press enquiries, please contact the Society for Endocrinology press office:

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3. The Society for Endocrinology's annual conference is held at the Edinburgh International Conference Centre from 2-4 November 2015. The conference features some of the world's leading basic and clinical endocrinologists who present their work. Journalists wishing to attend should contact the Society for Endocrinology press office using the details above. The scientific programme is available on the conference webpage.

4. The Society for Endocrinology is a UK-based membership organisation representing a global community of scientists, clinicians and nurses who work with hormones. Together we aim to improve public health by advancing endocrine education and research, and engaging wider audiences with the science of hormones. www.endocrinology.org