

littermate cage-mates. Lipidomic and proteomic analysis was then conducted on metabolic tissues.

**Results:** After 8 weeks of the HFHS diet, the lean mice had an average of 6.69 gms less adipose tissue than their matched controls ( $p \leq 0.001$ ) with a body fat percentage of 17.63% compared to 31.32% ( $p \leq 0.01$ ). Lipidomic analysis identified that the lean mice had a decrease in multiple lysophosphatidylcholine (LPC) and an increase in ceramide (CER) sphingomyelin (SM) and triacylglycerol (TG) species in the adipose. LPC and SM species were elevated in the muscle of the lean mice. In the liver, diacylglycerols (DG) and TG species were decreased, while SM species were elevated in the lean group. Plasma analysis indicated a decrease in cholesterol esters (CE) and SM species. Proteomic analysis in the muscle and adipose revealed no differences between groups after catering for multiple hypotheses. In the liver Gene Ontology enrichment analysis indicated an overrepresentation of genes/proteins associated with fatty acid transport and metabolic processes in the lean animals.

**Conclusion:** Despite the same genetics and environment, discordance for adiposity in HFHS-fed mice is associated with specific changes in the tissue lipidomic signature. Further studies into the potential processes behind these alterations such as epigenetic or post-translational modifications are warranted.

<https://doi.org/10.1016/j.orcp.2018.11.138>

216

### Fatty acid binding protein 4 inhibitor corrects metabolic disturbance in MKR mouse of Type 2 diabetes



Lili Huang<sup>1,\*</sup>, Weizhuo Dominique Tan<sup>1</sup>, Chengjian Wang<sup>2</sup>, Zhengxiang Huang<sup>1</sup>, Johannes D. Veldhuis<sup>3</sup>, Shanli Zhu<sup>4</sup>, Chen Chen<sup>1</sup>

<sup>1</sup> School of Biomedical Sciences, The University of Queensland, St Lucia, Queensland, Australia

<sup>2</sup> Department of Endocrinology, ChongQing General Hospital, ChongQing, China

<sup>3</sup> Department of Medicine, Endocrine Research Unit, Mayo Clinic, Rochester, MN, USA

<sup>4</sup> Department of Microbiology and immunology, Wenzhou Medical University, Wenzhou, China

Fatty acid binding protein 4 (FABP4) is one of the key adipokines that can serve as an important biomarker predicting the risk of developing metabolic syndrome, type 2 diabetes (T2DM) and atherosclerosis (1). Genetic deficiency of FABP4 improves glucose homeostasis and reduces atherosclerosis in mouse models (2). The associated underlying mechanisms seem to be pleiotropic and request further characterization.

Here we reported that inhibition of FABP4 by a small molecule compound, BMS309403, corrected metabolic disturbance in a lean Type 2 diabetic MKR mouse model. Oral application of BMS309403 (15 mg/kg) in MKR mice for 10 weeks improved insulin sensitivity and glucose tolerance (ITT AUC  $896.3 \pm 107.3$  mmol/l·min vs  $688 \pm 115.1$  mmol/l·min and GTT  $1741 \pm 250.4$  mmol/l·min vs  $1459 \pm 239.6$  mmol/l·min, vehicle vs BMS309403) regardless of an increase in adipose fat mass (gonadal fat  $0.28 \pm 0.02$  g vs  $0.41 \pm 0.04$ ; inguinal fat  $0.28 \pm 0.01$  vs  $0.39 \pm 0.04$  g and brown fat  $0.12 \pm 0.01$  vs  $0.22 \pm 0.02$ ). These changes correlate well with an increase in genes responsible for lipogenesis (*ppar gamma*) and glucose transport (*glu4*) in adipose tissue, and a reduction of gluconeogenesis gene in muscle and liver (*g6pases*). In addition, treatment of BMS309403 significantly increased heat production alongside an increase in genes responsible for transcriptional activation of brown adipocytes (*ucp-1* and *pgc1-alpha*). Furthermore,

inhibition of FABP4 tends to alleviate age-associated decline of pulsatile growth hormone (GH) secretion in MKR mice (total GH  $358.1 \pm 36.18$  ng/ml·min vs  $181.4 \pm 54.46$  ng/ml·min, vehicle mice, pre vs post treatment; and  $469.1 \pm 61.94$  ng/ml·min vs  $392.6 \pm 32.94$  ng/ml·min, BMS309403 treated mice, pre vs post treatment).

To conclude, inhibition of FABP4 improves glucose homeostasis in MKR mice, possibly by re-balancing fat/glucose metabolism and promoting adipose browning. The corresponding improvement in metabolism in diabetic MKR mice may also contribute to the relief of age-associated decline in GH secretion.

This work was supported by the Australian NHMRC and UQ.

<https://doi.org/10.1016/j.orcp.2018.11.139>

217

### Metabolic effects of mirabegron in primary adipocytes in vitro, and on metabolic parameters in vivo



Dana S. Hutchinson<sup>1,\*</sup>, Nodi Dehvari<sup>2</sup>, Masaaki Sato<sup>1</sup>, Jie Gao<sup>1</sup>, Lynda Whiting<sup>1</sup>, Anastasia Kalinovich<sup>2</sup>, Saori Mukaida<sup>1</sup>, Jon Merlin<sup>1</sup>, Denise Wootten<sup>1</sup>, Roger J. Summers<sup>1</sup>, Bronwyn A. Evans<sup>1</sup>, Tore Bengtsson<sup>2</sup>

<sup>1</sup> Monash University, Parkville, VIC, Australia

<sup>2</sup> Physiology, Wenner-Gren Institute, Stockholm, Sweden

**Introduction:** The  $\beta_3$ -adrenoceptor was initially a target for obesity and diabetes treatment, but several  $\beta_3$ -adrenoceptor agonists failed in clinical trials due to their lack of efficacy at the human  $\beta_3$ -adrenoceptor. Recently, the  $\beta_3$ -adrenoceptor agonist mirabegron has been approved for use in humans for overactive bladder, but there is very limited knowledge of any effects mirabegron has on metabolic parameters in model systems.

**Methods:** We have investigated the actions of mirabegron in brown, white and brite adipocytes from mice, using cAMP assays, qPCR for Ucp1 mRNA content, glucose uptake using <sup>3</sup>H-2-deoxyglucose, Seahorse xF96 analysis for in vitro oxygen consumption and glycolysis measurements. We have assessed whether the effects of mirabegron *in vivo* (glucose uptake, oxygen consumption, glucose tolerance tests) are due to activation of the  $\beta_3$ -adrenoceptor with the use of  $\beta_3$ -adrenoceptor knockout mice.

**Results:** Mirabegron increases cyclic AMP levels, Ucp1 mRNA content, glucose uptake and cellular glycolysis in brown adipocytes, and this effect is significantly absent/reduced in white adipocytes. In brite adipocytes, mirabegron increases cyclic AMP levels, Ucp1 mRNA content leading to increased UCP1 mediated oxygen consumption, glucose uptake and cellular glycolysis. Mirabegron *in vivo* increases whole body oxygen consumption rates, glucose uptake into brown and inguinal white adipose tissue, and improves glucose tolerance, which are dependent upon the presence of the  $\beta_3$ -adrenoceptor.

**Conclusion:** Mirabegron has the potential to be used for further studies examining its effects in metabolic disease, specifically in humans.

<https://doi.org/10.1016/j.orcp.2018.11.140>