Göteborg, 2023

The role of beta 3 adrenergic receptor in white adipocyte adiponectin exocytosis

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i **Hörsal M106 Karl Isaksson, Medicinaregatan 16, Torsdag den 25 maj 2023 kl. 09:00**

av **Marina Kalds Said**

Fakultetsopponent:
Professor Karin Stenkula
Lund universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. Musovic, S., Komai, A. M., **Said, M. K.**, Shrestha, M. M., Wu, Y., Wernstedt Asterholm, I., & Olofsson, C. S. (2022). Noradrenaline and ATP regulate adiponectin exocytosis in white adipocytes: Disturbed adrenergic and purinergic signalling in obese and insulin-resistant mice. *Molecular and cellular endocrinology*, *549*, 111619.

II. **Kalds Said, M.,** Mohan Shrestha, M., Musovic, S., Begum Samad, M., Dou, H., Wernstedt Asterholm, I., & Olofsson, C. S. Mice genetically ablated for β_3 adrenergic receptor display improved metabolic health despite reduced circulating adiponectin but are prone to develop insulin resistance when challenged with a high-fat diet. *Manuscript*

III. Musovic, S., Shrestha, M. M., Komai, A. M., **Kalds Said, M.,** Maimaiti, S., Banke, E., Skibicka, K., Wernstedt Asterholm, I., Barg, S., Rorsman, P., Blüher, M., & Olofsson, C. S. Beta 3 adrenergic receptor agonists stimulate white adipocyte exocytosis of high molecular weight (HMW) adiponectin in mice and humans and prevent a decrease of circulating HMW adiponectin levels in obese mice. *Manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP & FYSIOLOGI

GÖTEBORGS UNIVERSITET

Göteborg, 2023

The role of beta 3 adrenergic receptor in white adipocyte adiponectin exocytosis

Marina Kalds Said

Department of Physiology/Metabolic physiology,
Institute of Neuroscience and Physiology
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

ABSTRACT

In this thesis we define the physiological and underlying mechanisms involved in the white adipocyte adiponectin exocytosis, with a special focus on the beta 3 adrenergic receptor (β_3AR) in health and metabolic disease. In **paper I,** we define the role of sympathetic innervation and purinergic signaling in the regulation of white adipocyte adiponectin release**.** We hypothesized that adiponectin exocytosis is regulated by sympathetic nerves, co-releasing noradrenaline and ATP within the white adipose tissue, acting on adrenergic and purinergic receptors, elevating cytosolic cAMP and Ca^{2+}, respectively. A combination of electrophysiological recordings and secretion measurements confirmed that NA stimulate the release of adiponectin, whereas ATP augments it. This regulation is abrogated in adipocytes isolated from obese and diabetic mice, due to a reduction of protein expression of both receptors, and that this is associated with reduced circulating high molecular weight adiponectin. In **paper II,** we investigated the role of β_3AR in white adipocyte adiponectin release and in metabolic health in more detail, using mice that are genetically ablated for β_3AR (β_3AR-KO). Our data show that the disturbed signaling mechanism in the KO mice results in abrogated adiponectin release and reduced serum levels of total and HMW adiponectin. Furthermore, fasting insulin and glucose indicate that KO mice have an improved insulin sensitivity and are metabolically healthy, despite the lower adiponectin levels. However, β_3AR-KO mice become insulin resistant when challenged with high fat diet. Finally, in **paper III**, we show that an activation of β_3AR rapidly triggers the release of HMW adiponectin, while insulin induces release of only smaller molecular forms of adiponectin. Adiponectin secretion is diminished in adipocyte isolated from obese individuals, connected to ~50% reduced abundance of β_3ARs in adipocytes and lower circulating HMW adiponectin. Treatment with a β_3AR agonist increased serum HMW adiponectin in both lean and obese mice.

Keywords: White adipocyte, adiponectin exocytosis/secretion, beta 3 adrenergic receptor

ISBN: 978-91-8069-041-6 (PRINT) http://hdl.handle.net/2077/74158
ISBN: 978-91-8069-042-3 (PDF)