

Pathophysiological regulation of white adipocyte exocytosis of different adiponectin molecular forms

Akademisk avhandling

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av

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Avhandlingen baseras på följande arbeten:

- I. Komai AM*, Musovic S*, Peris EF, Alrifaiy A, El Hachmane MF, Johansson M, Asterholm IW, Olofsson CS. White adipocyte adiponectin exocytosis is stimulated via β 3-Adrenergic signaling and activation of Epac1: catecholamine resistance in obesity and type 2 diabetes. *Diabetes*. 2016; 65(11):3301-3313
* The authors contributed equally and their names appear in alphabetical order.
- II. Musovic S, Komai AM, Banke EN, Noor UA, Asterholm IW, Olofsson CS. Epinephrine and insulin stimulates white adipocyte secretion of diverse adiponectin forms: evidence for blunted exocytosis of high-molecular weight adiponectin in diabetes-induced catecholamine resistance. *Manuscript*
- III. Musovic S, Komai AM, Micallef P, Wu Y, Asterholm IW, Olofsson CS. Sympathetic innervation and purinergic signaling in regulation of white adipocyte adiponectin secretion. *Manuscript*
- IV. Musovic S, Olofsson CS. Adrenergic stimulation of adiponectin secretion in visceral mouse adipocytes: blunted release in high-fat diet induced obesity. *Submitted*



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ABSTRACT

In this thesis we have identified mechanisms involved in the exocytosis of different adiponectin molecular forms in health and in metabolic disease. We have also studied similarities and differences in depot-specific adipocyte adiponectin release. In **paper I** we show that the physiological regulation of subcutaneous white adipocyte adiponectin exocytosis involves β 3 adrenergic receptors (β 3ARs) and Exchange Protein directly Activated by cAMP isoform 1 (Epac1) signalling. Furthermore, we show that adiponectin secretion is disturbed in obesity/type 2 diabetes induced catecholamine resistance due to reduced abundance of the key proteins β 3ARs and Epac1. This condition of *catecholamine resistance* is further associated with a ~50% reduction of circulating high-molecular weight (HMW) adiponectin. In **paper II** we show that β 3AR-activation rapidly triggers the release of HMW adiponectin-containing vesicle whereas insulin induces release of smaller molecular forms, with delayed time-kinetics. We moreover demonstrate that both catecholamine-triggered exocytosis of HMW adiponectin and the insulin-induced secretion of smaller adiponectin forms is entirely diminished in adipocytes from obese/type 2 diabetic mice. The equivalent regulation of secretion of different adiponectin molecular forms by catecholamines and insulin was confirmed in human adipocytes, thus defining a novel role of β 3ARs in human adipocyte function. In **paper III** we propose that adiponectin exocytosis is regulated by sympathetic nerve endings, co-releasing noradrenaline and ATP within the adipose tissue. Secretion measurements confirmed that noradrenaline (elevates cAMP), like adrenaline in paper I, triggers adiponectin exocytosis. Extracellular ATP was shown to augment the exocytotic process, largely due to its elevation of intracellular Ca^{2+} . We also show that defect purinergic signalling together with reduced white adipose tissue noradrenaline content likely aggravates the catecholamine resistance observed in paper I and II. Finally we describe regulation of mouse visceral adipocyte adiponectin secretion in **paper IV**. As demonstrated in subcutaneous adipocytes (paper I-III), visceral adipocyte adiponectin secretion is also stimulated by activation of β 3AR and Epac1. In obese/diabetic conditions, visceral adipocytes are likewise unresponsive to stimulation with catecholamines, but the underlying molecular defect does not involve reduced levels of neither β 3AR nor Epac1, thus differing from observations in subcutaneous adipocytes. In conclusion, our results suggest that secretory defects in obesity/type 2 diabetes, attributed to catecholamine resistance, underlie the reduced levels of HMW adiponectin in metabolic disease.

Keywords: White adipocytes, adiponectin exocytosis/secretion, health and metabolic disease

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