

Molecular and physiological regulation of adiponectin exocytosis in white adipocytes

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av

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- I. Komai AM, Brännmark C, Musovic S, Olofsson CS. (2014). PKA-independent cAMP stimulation of white adipocyte exocytosis and adipokine secretion: modulations by Ca²⁺ and ATP. *J Physiol* 592, 5169-5186
- II. El Hachmane MF *, Komai AM *, Olofsson CS. (2015). Cooling reduces cAMP-stimulated exocytosis and adiponectin secretion at a Ca²⁺-dependent step in 3T3-L1 adipocytes. *PLoS ONE*, 10(3): e0119530
- III. Komai AM, Musovic S, El Hachmane MF, Johansson M, Peris E, Asterholm IW, Olofsson CS. White adipocyte adiponectin exocytosis is stimulated via β_3 adrenergic signalling and activation of Epacl – catecholamine resistance in obesity and type-2 diabetes. *Submitted*

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ABSTRACT

In this thesis we have investigated the mechanisms of white adipocyte regulated exocytosis in health and disease, with a special focus on adiponectin. We have applied a combination of electrophysiological membrane capacitance measurements, biochemical measurements of released adipokines and gene expression analysis. Our work hypothesis was that since white adipocytes are endocrine cells, secretion of adipocyte hormones should be regulated in a way resembling how hormone secretion is controlled in other endocrine cell types. In **paper I** we show that adipocyte exocytosis is triggered by cAMP via activation of exchange proteins directly activated by cAMP (Epac). cAMP triggers secretion of a readily releasable pool of vesicles in a Ca^{2+} -independent manner. However, a combination of Ca^{2+} and ATP augments exocytosis via a direct effect on the release process and by recruitment of new releasable vesicles. We further demonstrate that recorded membrane capacitance increases can be largely correlated to release of adiponectin containing vesicles and that the regulation of adiponectin exocytosis is similarly controlled in primary human subcutaneous adipocytes. In **paper II** we show that the Ca^{2+} /ATP-dependent maturation of adiponectin vesicles is a temperature-dependent step and thus reduced by cooling. We suggest that the temperature-dependent effects reflect the need of ATP hydrolysis in order to provide energy for recruitment of new releasable vesicles as well as for phosphorylation of exocytotic proteins. Our study provides important mechanistic information about the regulation of white adipocyte stimulus-secretion coupling. In **paper III** we show that adiponectin exocytosis is physiologically stimulated via adrenergic signalling chiefly involving catecholamine activation of $\beta 3$ -adrenergic receptors. We also demonstrate that Epac1 is the isoform expressed in white adipocytes. We moreover show that adrenergic stimulation of adiponectin exocytosis is disturbed in adipocytes isolated from obese/type-2 diabetic mice and that the disruption is due to a low abundance of $\beta 3$ -adrenergic receptors in combination with a reduced expression of Epac1.

Keywords: White adipocytes, adiponectin secretion, exocytosis, stimulus-secretion coupling

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