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Novel intracellular mediator of adiponectin secretion from adipocytes

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Mature white fat cells (adipocytes) are unusual terminally differentiated cells because of their large spherical shape, the fact that their presence is not fixed at a particular location in the body, the fact that they can proliferate in various ways and the weird intracellular structures that permit a unilocular lipid droplet to occupy a large part of the intracellular space, allowing only a small crescent-shaped cytoplasmic space in which all cellular events occur (Sugihara *et al.* 1987).

Since the verification of the hypothesis that insulin stimulates the translocation of glucose transporter (GLUT4) vesicles from intracellular storage to the plasma membrane in isolated rat adipocytes, thus increasing the cellular uptake of glucose (Cushman & Wardzala, 1980; Suzuki & Kono, 1980), the mechanism(s) of vesicular trafficking in fat cells have been the subject of many research studies. Over 10 years later, the discoveries of a number of biologically active cytokines derived from adipocytes, generally named adipokines, have changed the viewpoint, with adipocytes now being considered an endocrine organ rather than a simple energy storage organ. Of the various adipokines, adiponectin has attracted the most studies because of its protective roles against obesity-related diseases, including type-2 diabetes and cardiovascular diseases, and the reports that the reduction in the plasma level of adiponectin in obese subjects precedes the reduction in insulin sensitivity and onset of diabetes (Trujillo & Scherer, 2005; Smith & Minson, 2012; Yamauchi & Kadowaki, 2013). Most of the studies concerning adiponectin secretion have therefore been focused on the long-term chronic regulation, whereas the short-term ($\leq$30 min) regulation of adipocyte exocytosis by intracellular mediators is not well understood.

In this issue of *The Journal of Physiology*, Komai *et al.* (2014) describe a novel mechanism underlying the short-term regulation of adiponectin secretion, in 3T3-L1 adipocytes derived from mice, using a combination of membrane capacitance patch-clamp recordings and measurements of secreted adiponectin. The mechanism regulating adiponectin secretion is fundamentally different from that occurring in other endocrine cells. The authors demonstrate that the final step of adiponectin secretion in mature adipocytes, the release of adipokines from vesicles fused with the plasma membrane, is stimulated by cAMP and an exchange protein activated by cAMP (Epac), without depending on Ca^{2+} or protein kinase A (PKA).

Biochemical measurements showed that adiponectin is the dominant adipokine secreted in a cAMP/Epac-dependent manner, whereas the amounts of other secreted adipokines, such as leptin, resistin and apelin, are very low. Interestingly, Ca^{2+} was shown to have no apparent effect on the final step of adipokine release, although most neurotransmitter release is considered to be Ca^{2+} dependent. However, the role of Ca^{2+} is important in the early steps of exocytosis when the secretion vesicles are recruited and refilled with adiponectin to form ready-to-release vesicles. The regulation of the entire process of adiponectin secretion in adipocytes is thus proposed to be a sequential regulation by Ca^{2+} and cAMP, and ATP may provide energy and substrates for the phosphorylation of proteins that play a role in exocytosis. The findings thus indicate that all three intracellular mediators, Ca^{2+}, ATP and cAMP, are required to accomplish the short-term secretion of adiponectin, through Ca^{2+} and ATP, and cAMP regulates different steps of the exocytosis. In human subcutaneous adipocytes, the adiponectin secretion was also shown to be cAMP-dependent, similar to that observed in 3T3-L1 adipocytes.

There is increasing evidence that obesity is associated with not only metabolic syndrome and atherosclerosis, but also non-alcoholic steatohepatitis (NASH), cancer and Alzheimer's disease, and adiponectin plays a pleiotropic role in protecting against such diseases (Smith & Minson, 2012; Yamauchi & Kadowaki, 2013). Adiponectin is thus expected to be a valuable target molecule for therapeutics supporting a healthy, long life in humans. The key findings that each step of the short-term regulation of adiponectin secretion and the packaging of vesicles is individually regulated by cAMP, Ca^{2+} and ATP would provide a pin-point therapeutic approach for obesity-related diseases.

In white adipocytes, the binding of insulin to the receptor located on the plasma membrane is a trigger for a number of dynamic cellular events, including translocation of GLUT4 vesicles, the secretion of adiponectin and other adipokines, which are controlled in different ways. It is amazing that these complex mechanisms are well organized in the small crescent-shaped cytoplasmic space of the fat cells.

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Additional information

Competing interests

None declared.

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