Commentary

MOLECULAR METABOLISM

Distinct roles of angiopoietin-like 4 in the regulation of central and peripheral lipid metabolism?*

Matthias Blüher*

Angiopoietin-like 4 (Angptl4), an important regulator of lipoprotein lipase (LPL) activity in a variety of tissues, is under sensitive transcriptional control of fatty acids and the fatty acid-activated peroxisome proliferator activated receptors [1]. The three structurally related proteins Angptl 3, 4 and 8 inhibit LPL activity during different physiological situations, but they differ in their tissue expression pattern and regulation [1]. Angptl3 is predominantly produced by the liver without significant fluctuations, whereas Angptl4 and 8 are more ubiquitously expressed and regulated by various stimuli such as fasting [1]. From the angiopoietin-like proteins involved in plasma triglyceride clearance, Angptl4 has been most extensively studied in the context of lipid metabolism. In addition, Angptl4 seems to play a role in the regulation of endothelial function, tumor biology, wound healing, the extracellular matrix, and also in central mechanisms such as food intake and protection against ischemia-associated brain damage [2]. Angptl4 is primarily secreted from the liver and adipose tissue into circulation where it inhibits LPL activation by preventing its dimerization [1,2]. Noteworthy, the precise biochemical mechanisms behind the inhibition of LPL activity by Angptl4 are not entirely understood [1]. Although it is well accepted that Angptl4 mediates the decrease in adipose tissue LPL activity during fasting, certain aspects of its inhibitory action on LPL activity are still unclear or controversial [1]. In particular, the role of Angptl4 in brain lipid metabolism and regulation of LPL activity remains unknown.

In this issue of *Molecular Metabolism*, Vienberg and co-workers provide novel experimental evidence that Angptl4 in the brain is almost exclusively produced by glial cells, but does not inhibit central LPL activity [3]. Using both an *in vivo* (intracerebroventricular injection) and *in vitro* (glia cells) approach, the authors show consistent down-regulation of Angptl4 expression by insulin in a dose dependent manner [3]. In animal models of insulin-deficient (streptozotocin, STZ, treated C57Bl/6 mice) and obesity-associated (*ob*/*ob* mice) diabetes, Angptl4 was one of the most significantly upregulated genes in the hypothalamus and skeletal muscle, suggesting common mechanisms in the regulation of central and peripheral Angptl4 expression [3] but also an important role of this molecule in linking the effects of hyperglycemia to impaired lipid metabolism. The latter suggestion has been further substantiated by demonstrating that Angptl4 knockout mice have higher LPL mRNA expression in skeletal muscle, and whole body LPL activity is associated with lower serum triglycerides independently of the acute feeding status and the induction of hyperglycemia [3]. Interestingly, increased muscle *LPL* expression in Angptl4 knockout mice was normalized when circulating insulin levels were low in STZ treated mice. It remains an open question whether other insulin-regulated endogenous LPL inhibitors can compensate for the deletion of Angptl4 in this model. Angptl4 independent mechanisms in the regulation of LPL activity are suggested further by the observation that insulin deficiency alone (STZ mice) could increase LPL activity independently of normal or diminished expression of Angptl4 [3]. A better understanding of the interrelationships between Angptl4, Angptl3, and Angptl8, which all have the capacity to inhibit LPL *in vivo* and to modulate plasma TG levels, may guide us further to define the precise mechanisms of LPL regulation *in vivo*. In contrast to the Angptl4-dependent regulation of LPL in muscle and as previously reported in liver and adipose tissue [4], central LPL activity and expression was not affected by Angptl4 [3]. In different brain areas including the hypothalamus, LPL activity was neither altered by the whole body deletion of Angptl4 nor by STZ-induced diabetes or nutritional status [3]. Moreover, the previously reported association between brain LPL activity, appetite and energy expenditure [5] does not appear to be mediated by Angptl4. In this context, the authors could demonstrate that central administration of recombinant Angptl4 does not alter food intake in mice on chow or high fat diet [3].

The work of Vienberg et al. [3] further highlights a potentially important heterogeneity of central Angptl4 expression with a highly predominant expression in glial cells. The authors postulate that central Angptl4 may participate in the metabolic crosstalk between glia and neurons. However, further studies are required to elucidate whether Angptl4 regulates LPL activity locally and whether glia cell derived Angptl4 affects metabolism in neurons. Such cellular crosstalk has been demonstrated already for the delivery of cholesterol from glial cells to neighboring neurons as an essential mechanism for normal neuronal function and formation of synapses [6].

*This commentary refers to "Differential effects of angiopoietin-like 4 in brain and muscle on regulation of lipoprotein lipase activity by Sara Gry Vienberg et al.", 10.1016/j.molmet.2014.11.003.

Department of Medicine, University of Leipzig, Liebigstr. 20, D-04103 Leipzig, Germany

*Tel.: +49 341 9715984; fax: +49 341 9722439. E-mail: bluma@medizin.uni-leipzig.de (M. Blüher).

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The novel data of Vienberg et al. [3] may become relevant in a clinical perspective. Supporting the importance of Angptl4 reported from mouse studies, a relatively frequent (~3% of Caucasian Americans) human genetic loss-of-function variant in the ANGPTL4 gene was found to be associated with lower plasma triglyceride concentrations [7]. The strong triglyceride lowering effect seen in Angptl4 knockout mouse models [3,8] suggested this molecule as a potential target for future lipid-lowering therapies. However, because mice lacking Angptl4 develop a lethal phenotype characterized by peritonitis, ascites, intestinal fibrosis, and cachexia upon intake of saturated fat [9], the road to Angptl4 as a pharmacological treatment target seems to be blocked [1]. In addition, so far there is no evidence from human studies that circulating ANGPTL4 is linked to triglyeride plasma concentrations [1]. Therefore local Angptl4 actions may become the focus of future translational research. Here, the work by Vienberg et al. [3] may stimulate further research aiming to define the cellular locations at which the inhibition of LPL by Angptl4 occurs. Moreover, this article raises (again) the question about the relative contribution of locally produced Angptl4 compared to circulating Angptl4 with respect to inhibition of tissue LPL activity, brain function and brain control of metabolism.

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