Regulation of Lipoprotein Lipase Activity: an In-vitro Study of a Complex and Dynamic System

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Abstract

The progress of human society outpaces our biological evolution, and this brings unexpected health problems. The industrial revolution brought up dramatic changes in nutrition and lifestyle – we are increasingly shifting towards a nutrient-rich Western-patterned diet and to a sedentary lifestyle. Unfortunately, our energy metabolism is not fully capable to adapt to these changes. The excess of nutrients has led to global epidemics in obesity, type 2 diabetes, and cardiovascular diseases. To battle this, medical research has focused on the metabolism of sugars and cholesterol, whereas the fate of triglycerides, the major dietary lipid, has received less attention. Recently it became clear that blood triglycerides are connected to the development of type 2 diabetes and cardiovascular diseases. As a result, triglyceride metabolism became a focus of attention in both basic and clinical research.

Lipoprotein lipase (LPL) is the cornerstone of blood triglyceride metabolism. This means that LPL must be tightly regulated in response to the nutritional state of the body, and to the needs of particular tissues. LPL is produced and secreted by cells that store triglycerides or use them for generation of energy. After secretion, LPL stays attached to the capillary endothelium where it hydrolysates triglycerides from the triglyceride-rich lipoproteins. LPL is relatively unstable and the instability is a key property in its physiological regulation since transcriptional control of LPL does not respond to the metabolic changes fast enough. Instead, LPL is regulated by two groups of proteins – plasma apolipoproteins, which serve as activators or inhibitors of LPL, and angiopoietin-like (ANGPTL) proteins, which irreversibly inactivate LPL in the tissues which do not require triglycerides.

One aim of my thesis was to study the effects of ANGPTL proteins on LPL structure and function. In papers I and II, using various biophysical and biochemical methods, we studied the effects of ANGPTL3, 4 and 8 on LPL structure and function. All data supported the concept that LPL is inactivated by dissociation of active dimers to monomers. Additionally, we describe the molecular basis for complex formation between ANGPTL3 and 8, as well as a novel complex between ANGPTL4 and 8 with unique properties. The other aim of my thesis was to perform an in-depth study of rate-limiting factors that control the activity of LPL in human plasma. In papers III and IV we study LPL activity using an isothermal titration calorimetry-based assay directly in plasma samples. We found that the normal variation in plasma levels of either ANGPTL proteins or apolipoproteins had no significant impact on LPL activity. Instead, the strongest determinant for LPL action was the size of the triglyceride-rich plasma lipoproteins.

Keywords
Lipoprotein lipase, triglyceride metabolism, lipoprotein metabolism, angiopoietin-like proteins, apolipoproteins, hypertriglyceridemia, isothermal titration calorimetry