

Modeling Approaches in Lipid Metabolism

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1 Introduction

Frequent causes of death worldwide are related to arteriosclerotic cardiovascular diseases. It is well known that disorders of the lipid metabolism are a major risk factor for arteriosclerosis [4]. Thus, the investigation of this metabolic pathway may essentially contribute to identify new pharmacological targets and consequently to reduce the risk by developing new drugs.

Systems biology aims at understanding biological processes at a system level by examining the behavior and interactions of all individual components of the biological system under investigation [1]. We apply this general approach to the lipid transport system in the blood plasma transporting water-insoluble lipids assembled in the liver and the intestine in the form of micellar lipoprotein suspensions into the periphery.

In comparison to other well-studied metabolic pathways, such as glycolysis, the structure of the lipoprotein metabolism is more complex in that the metabolites are not homogenous substances in aqueous solution, but rather aggregates of various sub-metabolites with a high heterogeneity in their amount and an individual metabolic fate. Furthermore, almost any metabolic interconversion of these metabolites do not effect the whole metabolite, but rather single sub-metabolites and is accompanied by continuous remodeling of content, shape, core-surface distribution, density and volume of the molecular aggregate.

Due to these peculiarities and based on our previous model [3] we are developing a new type of metabolic model that describes the individual metabolic fate of several sub-metabolites as constituents of a metabolite complex.

2 Modeling Approach

Lipoproteins fulfill the function of transporters for lipids such as neutral fat and cholesterol which are completely insoluble in aqueous-phase media such as blood plasma. Both are indispensable elements of cellular metabolism, the first as a major source of energy metabolism and the second as a component of all cellular membranes. The model of lipid transport metabolism in the blood plasma includes a set of lipoproteins together with their reaction partners, such as enzymes, transfer proteins and receptors. Liver, intestine and periphery represent the system boundaries.

Any such lipoprotein is characterized by the specific apolipoprotein label on its surface serving as a flag for metabolic recognition and by its content of phospholipids, neutral fats (triglycerides, cholesteryl esters) and free cholesterol (Fig.1). It is the actual amount of the various constituents that, by a phase equilibrium, determines the structure, buoyant density, volume and lipid transfer activity of these metabolites. All the physico-chemical features of a micellar particle may at least approximately be calculated if the total content of various constituents is known [2] and assign the particle to a specific lipoprotein density class.

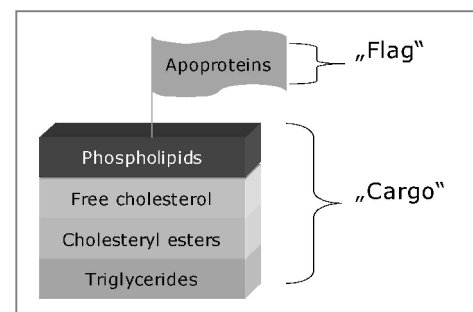


Figure 1: Constituents of a lipoprotein

For example, lipoprotein particles containing apolipoprotein B-100 are subdivided into three main density classes, VLDL (very low density lipoprotein), IDL (intermediate density lipoprotein) and LDL (low density lipoprotein). VLDL is synthesized by the liver and secreted into the blood plasma. IDL and LDL are products of VLDL by a gradual metabolic interconversion. This is mainly caused by the enzyme LPL (lipoprotein lipase) that hydrolyzes almost all triglycerides (TG) and is accompanied by a decrease or increase in the amount of other constituents. The VLDL micelle therefore undergoes a continuous transition leading to a smaller volume and a higher density. Below a certain TG level, the micelle becomes unstable and splits into surface remnants (containing excess PL) and core remnants (containing the core with a reduced surface hull, IDL particles). Fig. 2 illustrates this process schematically.

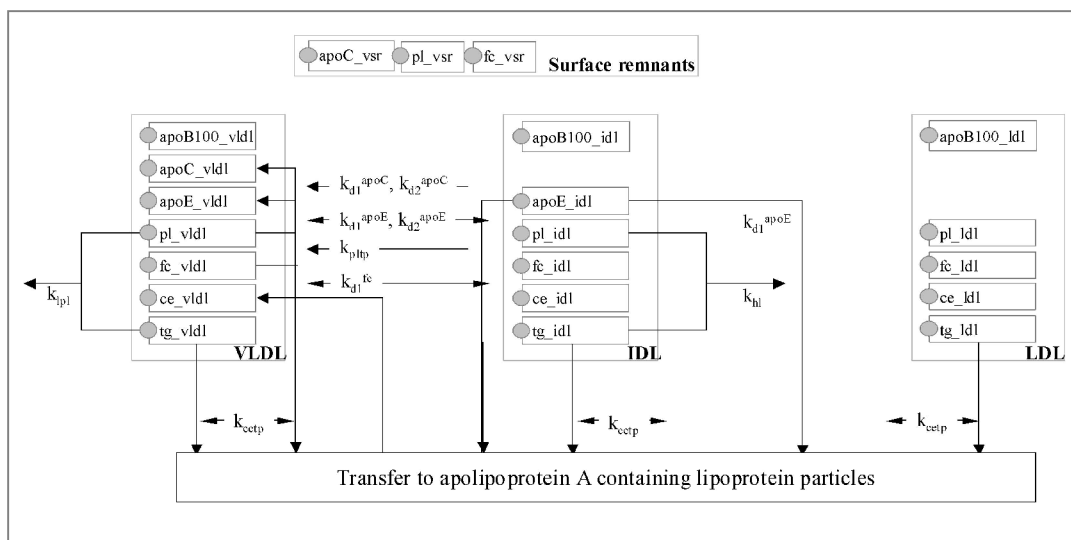


Figure 2: Individual metabolic fate of lipoprotein constituents of apoB containing particles

Starting from the actual content of each constituent, physico-chemical parameters, such as core-surface-distribution, volume and density are calculated and classify the lipoprotein species. Thus, the actual state of the system and e.g. the effect of perturbations after physiological stress or pharmacological treatment could be represented in terms of a lipoprotein profile at any time by calculating these physicochemical properties of the lipoprotein particles.

In a first step, the lipoprotein micelles are formulated as compound metabolites containing sub-metabolites with individual mass balance and kinetic fate. All these individual reactions have been formulated in the framework of a mass balance model with kinetic equations.

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