Computational and Structural Biotechnology Journal 13 (2015) 38–46

COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL

journal homepage: www.elsevier.com/locate/csbj

Mini Review

Computationally Modeling Lipid Metabolism and Aging: A Mini-review

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ARTICLE INFO

Available online 15 November 2014

Keywords:
Aging
Lipid metabolism
Computational modeling
Deterministic model
Stochastic model
Parameter inference

ABSTRACT

One of the greatest challenges in biology is to improve the understanding of the mechanisms which underpin aging and how these affect health. The need to better understand aging is amplified by demographic changes, which have caused a gradual increase in the global population of older people. Aging western populations have resulted in a rise in the prevalence of age-related pathologies. Of these diseases, cardiovascular disease is the most common underlying condition in older people. The dysregulation of lipid metabolism due to aging impinges significantly on cardiovascular health. However, the multifaceted nature of lipid metabolism and the complexities of its interaction with aging make it challenging to understand by conventional means. To address this challenge computational modeling, a key component of the systems biology paradigm is being used to study the dynamics of lipid metabolism. This mini-review briefly outlines the key regulators of lipid metabolism, their dysregulation, and how computational modeling is being used to gain an increased insight into this system.

Contents

1. What is Aging and why Study it Using Computational Systems Biology?

The progress of biomedical science, together with improvements in nutrition and public heath interventions has resulted in a remarkable demographic shift in favor of older people. It is projected that by 2050, 25% of the world's population will be over 60 years of age [1]. There has also been a staggering rise within western populations of those individuals over 85 years of age. For example, in the UK it is predicted that by 2050 almost 5% of the population will comprise of these individuals that are referred to as the 'oldest old' [2]. Despite such a dramatic change in population demographics, gerontology remains devoid of a reasonable explanation as to what aging is. Irrespective of this ambiguity, aging is generally recognized as a process that gradually results in the progressive decline of an organism over-time which results in its eventual mortality [3,4]. The fact that aging comprises every facet of a biological system makes it an inherently difficult phenomenon to study. Therefore the question arises why study aging? If populations

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http://dx.doi.org/10.1016/j.csbj.2014.11.006

are living longer is there a necessity? The answer is that although we are living longer, the extra few years that are gained are not necessarily spent in optimum health. For example, in the UK 37.1% of individuals ≥85 years have underlying cardiovascular disease (CVD), which hampers their quality of life [5]. For this reason it is imperative to gain a mechanistic understanding of the impact of aging on the regulation of biological systems. Historically investigating the potential mechanisms which underpin aging has been constrained by their complex and multifaceted nature [6]. This has resulted in aging being studied in a reductionist manner. Fortunately, the last decade and a half has witnessed the growth of systems biology, a discipline which is grounded in understanding biology from an integrated perspective [7,8]. Dynamic computational modeling resides firmly within the systems biology paradigm [9–11]. The impact computational modeling is having on lipid metabolism, a system that offers a potential avenue for extending healthy aging will be the focus of this mini-review.

2. Lipid Metabolism and Healthy Aging

Aging is underpinned by changes to a number of complex biological mechanisms [12]. Consequently, it is necessary to investigate this phenomenon holistically and where possible examine the impact of age-related changes to biological systems in an interconnected fashion [13]. Of the diseases associated with old age, CVD remains the most prevalent cause of morbidity among older people [14,15]. The dysregulation of lipid metabolism is known to impact several parameters of cardiovascular health [16]. For instance, there is a well-established relationship between elevated levels of low-density lipoprotein cholesterol (LDL-C) and risk of CVD [17–19]. Elevated levels of plasma triglycerides (TGs) have also been suggested as a risk factor for CVD, although their association remains a controversial one [20]. Intriguingly, it has also been revealed that certain long lived individuals have a 'finely-tuned' lipid profile which may have helped them avoid CVD [21]. From a nutrition perspective adult western diets contain between 30 and 40% of energy from lipids, of which 92–96% are long chain TGs [22]. TGs are composed of a unit of glycerol together with three fatty acids [23]. Long chain TGs are classified on the basis of the number and type of chemical bonds they possess [23]. There are three general classes, saturated fatty acids (SFAs) which have no double bonds, monounsaturated fatty acids (MUFAs) which have one double bond and polyunsaturated fatty acids (PUFAs) which contain two or more double bonds [24,25]. SFAs are usually solid at room temperature and are mainly found in animal sources such as cream, butter, cheese, milk and animal fats [22]. The main fatty acid in MUFA is oleic acid which is found in olive oil, canola and peanuts [26]. The most ubiquitous PUFA is linoleic acid; its double bonds are in the omega n-6 position. Linoleic acid is found mainly in seed oils, such as sunflower and corn oils [27].

The metabolic fate of dietary lipids can significantly impact health. When SFAs predominate in the diet they tend to raise plasma LDL-C [28]. It is suggested that SFAs increase LDL-C by suppressing the activity and reducing the number of LDL-receptors [29,30]; the mechanism responsible for the removal of LDL from the circulation [31–33]. It is also suggested that SFAs cause an increase in the synthesis of LDL-C [34,35]. Conversely, MUFAs and PUFAs decrease plasma LDL-C levels [36,37] with evidence indicating that they increase hepatic LDL receptor number and LDL turnover [32]. Thus, the metabolic impact of dietary fats can be viewed as a combination of SFAs, MUFAs and PUFAs [38,39]. In terms of the metabolic impact of dietary cholesterol, there has been considerable debate as to its effect on plasma cholesterol. For example, dietary cholesterol intake has been shown to result in increases of LDL-C levels even when dietary SFAs are maintained at a low level [40]. On the other hand meta-analysis studies have shown that the effect of dietary cholesterol on plasma cholesterol levels is negligible [41,42]. In addition dietary cholesterol has only a minimal effect on endogenous cholesterol synthesis, as it is thought whole-body balance is mainly regulated via intestinal absorption [43]. Moreover, studies which monitored plasma cholesterol levels have shown that individuals vary significantly in their responses to dietary cholesterol [44,45], possibly due to intrinsic differences in cholesterol absorption [46] and have resulted in normolipidemic individuals being classified as either hypo or hyper responsders [47,48]. Similarly, it has recently been suggested that certain individuals are hyperproducers of cholesterol while others are hyperabsorbers [49]. These findings endorse the view that regulation of whole-body lipid metabolism is underpinned by a variety of extrinsic and intrinsic factors acting simultaneously. It is therefore logical to investigate lipid metabolism using a whole-body framework which is capable of both representing and exploring individual differences in these factors.

A number of processes are responsible for maintaining lipid metabolism and changes to any of these mechanisms can disrupt its dynamics, for example as eluded in the previous section whole-body cholesterol balance can be sensitive to changes in cholesterol absorption [50], synthesis [51] and ingestion [52]. Fig. 1 presents a coarse grained overview of the key components of whole-body lipid metabolism. The diagram commences with the dietary intake of lipids. Due to the insolubility of lipids, specialized carriers known as lipoproteins are required to transport them throughout the body [53]. After digestion lipids are taken up by enterocytes and packaged in a lipoprotein called a chylomicron [54,55]. Absorbed chylomicrons are acted on by lipoprotein lipase (LPL) which hydrolyzes TG releasing free fatty acids (FFAs) and glycerol [56]. The chylomicron remnants are removed hepatically and the FFAs are taken up by muscle and liver for either oxidation or re-esterification [57]. Hormone sensitive lipase (HSL) acts on adipose tissue to release FFAs during lipolysis [58], a process suppressed in fat cells by insulin during the fed state [59]. Hepatic TGs together with cholesterol can be released as part of very low density lipoproteins (VLDLs) [60]. VLDLs are hydrolyzed by LPL, forming VLDL remnants and intermediate density lipoproteins (IDLs). IDLs are either taken up by the liver or hydrolyzed to LDLs, the main cholesterol transporter [60]. LDL is taken up by the liver or by peripheral cells, either independently [61–63] or via the LDL-receptor [64,65]. Reverse cholesterol transport (RCT) is the only route for removal of excess cholesterol from peripheral tissue [66]. Crucial to RCT are high density lipoproteins (HDLs) which uptake cholesterol in the peripheral tissue to become high density lipoprotein cholesterol (HDL-C), the so-called 'good cholesterol'. The excess cholesterol is transferred from the peripheral tissue to the liver where hepatocytes take up the cholesterol and excrete it into the bile either as free cholesterol or as bile salts after conversion [67]. Subsequently, cholesterol and bile salts end up in the feces. Fundamental to RCT is the transport of free cholesterol and phospholipids to lipid-free apo A-I in a process mediated by ATP-binding cassette transporter (ABCA1) [68]. The intimate relationship between ABCA1 and apo A-I leads to the lipidation of apo A-I and generation of a discoid nascent pre-β HDL particle [69,70]. Following this initial event in RCT, the nascent HDL then matures through the esterification of cholesterol which is mediated enzymatically by lecithin-cholesterol acyltransferase (LCAT) [71]. Mature HDLs can transfer cholesterol directly to the liver in a process mediated by scavenger receptor class B, type I (SR-BI) or alternatively it can transfer cholesterol indirectly by using cholesteryl ester transfer protein (CETP) to reallocate cholesterol to other lipoproteins including LDL and VLDL [72].

3. The Impact of Aging and Genetic Variability on the Dynamics of Lipid Metabolism

It is known that plasma lipids increase with age in both males and females [73]. Although the underlying reasons for this rise are not completely delineated, several putative mechanisms have been proposed. For example, in rodents TG absorption can be impaired by as much as 50% with advancing age [74]. This could be due to a defect in lipoprotein assembly or due to a decline in the abundance of fatty acid-binding proteins [74,75]. Moreover the decrease in TG absorption