ELSEVIER

Ageing Research Reviews
5 (2006) 144–164

ageing
research
reviews

www.elsevier.com/locate/arr

Review

Lipotoxicity, overnutrition and energy metabolism in aging

Marc Slawik [1], Antonio J. Vidal-Puig *

Department of Clinical Biochemistry, University of Cambridge, UK

Abstract

The safest place to store lipids is the white adipose tissue, but its storage capacity may become saturated resulting in excess of fat ''overspilled'' to non-adipose tissues. This overspill of fat occurs in apparently opposite pathological states such as lipodistrophy or obesity. When the excess of energy is redirected towards peripheral organs, their initial response is to facilitate the storage of the surplus in the form of triacylglycerol, but the limited triacylglycerol buffer capacity becomes saturated soon. Under these conditions excess of lipids enter alternative non-oxidative pathways that result in production of toxic reactive lipid species that induce organ-specific toxic responses leading to apoptosis. Reactive lipids can accumulate in non-adipose tissues of metabolically relevant organs such as pancreatic β-cells, liver, heart and skeletal muscle leading to lipotoxicity, a process that contributes substantially to the pathophysiology of insulin resistance, type 2 diabetes, steatotic liver disease and heart failure. The effects of this lipotoxic insult can be minimised by several strategies: (a) decreased incorporation of energy, (b) a less orthodox approach such as increased adipose tissue expandability and/or (c) increased oxidation of fat in peripheral organs. Aging should be considered as physiological degenerative process potentially accelerated by concomitant lipotoxic insults. Conversely, the process of aging can sensitise cells to effects of lipid toxicity.
© 2006 Elsevier Ireland Ltd. All rights reserved.

Keywords: Energy homoeostasis; Leptin; Lipoapoptosis; Fatty acid oxidation; de novo lipogenesis; SREBP1c

1. Introduction

Aging is a physiological degenerative process that in the presence of pre-existing pathological conditions may act as an accelerating factor of these diseases. Similarly pre-

* Corresponding author at: Clinical Biochemistry, Box 232, Addenbrooke's Hospital, Cambridge CB2 2QR, UK. Tel.: +44 1223 762790.

E-mail address: ajv22@cam.ac.uk (A.J. Vidal-Puig).

[1] Marc Slawik has been supported by a fellowship from the ''Fritz Thyssen Foundation'', Germany.

1568-1637/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.arr.2006.03.004

existing medical conditions may accelerate the physiological decay experienced during aging. Energy homeostasis is a highly integrated, redundant network that ensures the maintenance of the entropy of the biological system. In this respect, maintenance of energy homeostasis during aging requires biological allostatic changes to maintain the function of progressively inefficient systems. These adaptive allostatic mechanisms increase the stress load of the homeostatic mechanisms increasing their vulnerability to further stress load. Obesity is one of these diseases that can modify the dynamics of the aging process by increasing the allostatic load of the energy homeostatic mechanisms. In fact, the current epidemic of obesity has been suggested as the leading cause for the decreased life expectancy forecasted for the next generation (Olshansky et al., 2005). How obesity contributes to the development of age-related diseases such as diabetes and cardiovascular diseases remains an important question. Roger Unger in the mid 1990s (Unger et al., 1999), suggested that an important causative link between fat distribution and the metabolic syndrome reside in the accumulation of lipids in extra adipocyte sites, in cells that constitute the organs and tissues traditionally recognised as lean body mass—notably in the pancreas, liver, skeletal muscle and heart. As Unger elegantly argues (Unger et al., 1999), the small intracellular reserve of lipids for essential housekeeping functions in non-adipocytes – such as for the maintenance of membrane structure, fluidity and intracellular signalling – is tightly regulated, and if overloaded would lead to cell dysfunction (lipotoxicity) and lipid-induced programmed cell death (lipoapoptosis). The theme ''lipotoxicity'' encompasses toxicity that results not only from lipid overloading induced by excess delivery versus oxidation of circulating FFA (free fatty acids) but also from lipids synthesized from an overload of glucose by the process of de novo lipogenesis occurring in adipocytes or in non-adipocytes. In our opinion, overnutrition defined as a chronic state of positive energy balance can saturate the adipose tissue normal storage capacity of the organism resulting in ectopic deposition of reactive lipid species outside adipose tissues depots. Accumulation of lipids in skeletal muscle, heart, liver, pancreas, kidneys, or blood vessels has the potential to cause organ-specific toxic reactions that compromise their normal functionality. This process caused by lipids and its moieties in non-adipose tissue is referred to as lipotoxicity. Intriguingly, aging is associated with a ''physiological'' increase in lipid accumulation in non-adipose tissues, even in lean individuals. This might be a causal link for increased prevalence of chronic diseases like type 2 diabetes, fatty liver and cardiovascular disease which also substantially increase in prevalence with age. Conversely, obesity could be considered as a potentiating factor of processes normally associated with aging through its effects promoting lipotoxicity. The causes of increased lipid accumulation in non-adipose tissues with special reference to aging are addressed in this review.

Our point of view is that aging can be considered as a physiological degenerative process that potentially can be accelerated by the degenerative processes associated with lipotoxic insults. Similarly aging may increase the susceptibility to the toxic effects of lipid overload associated with overnutrition. Thus individuals that have been able to deal efficiently with excess of fuel (e.g. by being very active) may, as they age and lose their fitness become more sensitive to the deleterious metabolic effects associated with lipotoxicity. For instance the well-recognised age-related reduction in lean body mass may facilitate changes in energy balance favouring fat deposition versus fatty acid oxidation. We have proposed three therapeutic strategies to minimise the effects of overnutrition

Download English Version:

https://daneshyari.com/en/article/1902553

Download Persian Version:

https://daneshyari.com/article/1902553

Daneshyari.com