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Review

Involvement of oxysterols in age-related diseases and ageing processes

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ABSTRACT

Ageing is accompanied by increasing vulnerability to major pathologies (atherosclerosis, Alzheimer's disease, age-related macular degeneration, cataract, and osteoporosis) which can have similar underlying pathoetiologies. All of these diseases involve oxidative stress, inflammation and/or cell death processes, which are triggered by cholesterol oxide derivatives, also named oxysterols. These oxidized lipids result either from spontaneous and/or enzymatic oxidation of cholesterol on the steroid nucleus or on the side chain. The ability of oxysterols to induce severe dysfunctions in organelles (especially mitochondria) plays key roles in RedOx homeostasis, inflammatory status, lipid metabolism, and in the control of cell death induction, which may at least in part contribute to explain the potential participation of these molecules in ageing processes and in age related diseases. As no efficient treatments are currently available for most of these diseases, which are predicted to become more prevalent due to the increasing life expectancy and average age, a better knowledge of the biological activities of the different oxysterols is of interest, and constitutes an important step toward identification of pharmacological targets for the development of new therapeutic strategies.

Contents

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1. Introduction

Ageing is considered as an ineluctable biological process, and the lengthening of life expectancy is mainly due to better hygiene, and to major medical progress. This is in agreement with evolutionary theory which considers ageing as the result from a decline in the force of natural selection. Today, in humans, ageing can be considered as a multifactorial process which will depend on genetic and epigenetic factors. Ageing will be influenced by the environmental conditions and the way of life. From a biological point of view, ageing can be commonly defined as the accumulation of diverse deleterious changes occurring in cells and tissues with advancing age that are responsible for the increased risk of disease and death (Harman, 2003). Currently, the major theories of ageing (free radical, immunologic, inflammation, and mitochondrial theories) cannot be considered as mutually exclusive but rather as complementary, and they can provide useful and important insights for the understanding of physiological changes occurring with ageing (Tosato et al., 2007). Due to the increasing life expectancy and average age, it is important to determine the common denominators between the major theories of ageing in order to prevent age related diseases. Ageing in good health is a new challenge with important economic impacts which lead to the concept of silver economy. It is therefore important to identify molecules, and families of molecules, which could play important roles in different aspects of ageing processes and in the development of age related diseases.

Among potentially deleterious compounds within the body, some cholesterol oxide derivatives (also named oxysterols) formed endogeneously or present in various foodstuffs have been shown to play important roles in the metabolism, RedOx equilibrium and inflammatory status of certain cells, especially vascular cells and nervous cells, which are strongly affected by ageing process, and are associated with major age related diseases such as cardiovascular diseases and dementia (Lordan et al., 2009; Vejux and Lizard, 2009; Leoni and Caccia, 2011; Poli et al., 2013).

Based on experimental data obtained on cell cultures, animal models, and in humans, there are now several lines of evidence that the function of some major organs (brain, eyes, heart and vessels, colon, pancreas, bones, prostate) can be adversely affected by oxysterols, and that these molecules can contribute to the development of age related diseases (Schroepfer, 2000). Indeed, from a physiological point of view, as hypercholesterolemia frequently increases with age, whereas the oxidative defenses and the hepatic metabolism contributing to reducing the circulating level of oxysterols decrease, it is tempting to speculate that some oxysterols could play critical roles in ageing and in the pathophysiology of several age related diseases such as atherosclerosis, type 2 diabetes mellitus, Alzheimer's disease (including vascular dementia), age-related macular degeneration and cataract, osteoporosis, and certain forms of cancers (colon carcinoma and prostate cancer) (Fig. 1).

2. Oxysterols: Origins and structures

Oxysterols are 27-carbon-atom cholesterol oxidation products. They can be produced endogenously by autoxidation and/or by enzymatic reactions that can modify the sterol nucleus or the isooctyl tail (Otaegui-Arrazola et al., 2010; Iuliano, 2011) (Fig. 2). They also can be provided by food (Otaegui-Arrazola et al., 2010).

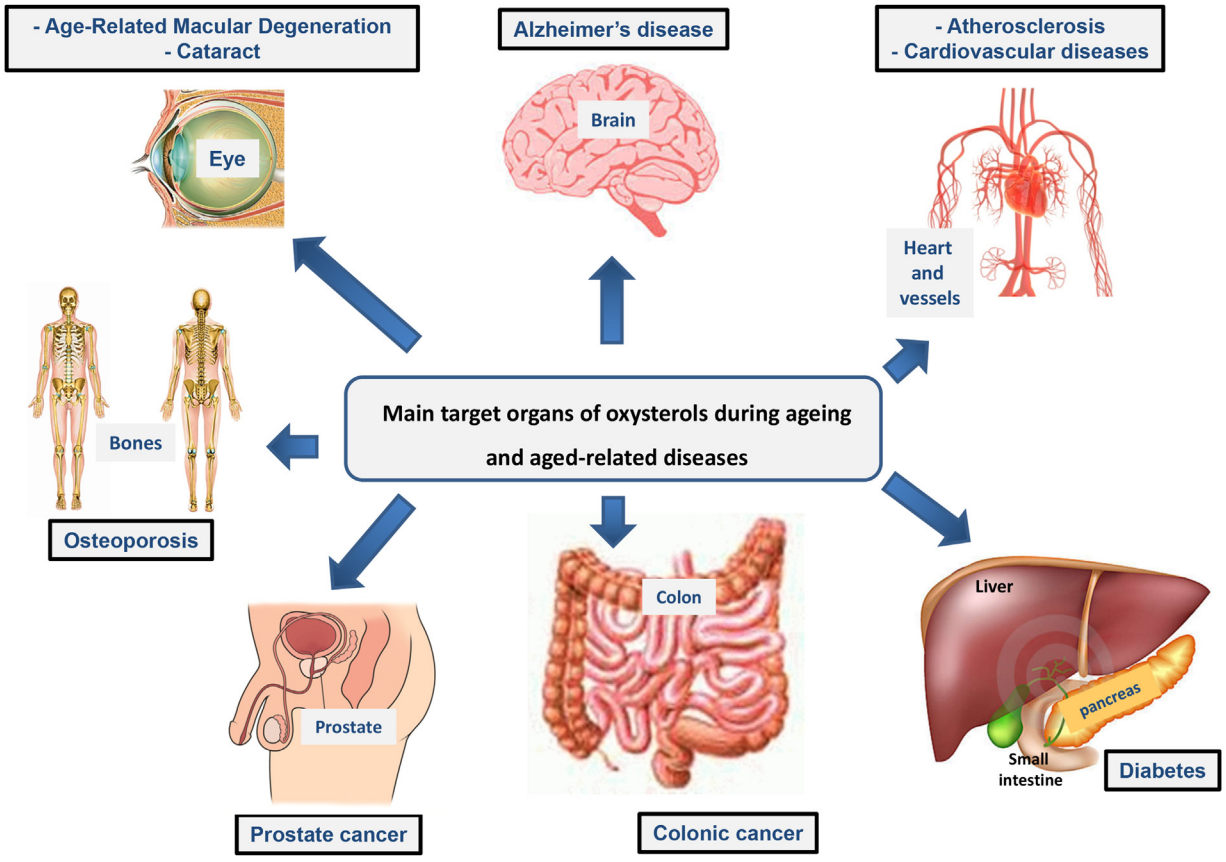

Fig. 1. Oxysterols in various age-related diseases. Based on in vitro studies, animal studies and clinical investigations there are several arguments supporting the critical role of various oxysterols in the pathophysiology of age-related diseases such as atherosclerosis, diabetes (especially type 2 diabetes mellitus), vascular dementia, Alzheimer's disease, age-related macular degeneration and cataract, osteoporosis, and certain forms of cancer (colon carcinoma and prostate cancer).