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Review article

Aging and endothelin: Determinants of disease ☆

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ABSTRACT

Since the beginning of the 20th century human life expectancy has doubled to more than 80 years, and growth and aging of the world population now represent major challenges for healthcare providers, political decision makers, and societies. Cellular senescence is associated with a general, pro-inflammatory state, which represents the common denominator between aging and chronic diseases and their progression. Approaches to interfere with these changes and to allow healthy aging involve modulation of the cellular activity of modifiable molecular mediators (MMMs), such as signaling molecules and growth factors. ET-1 – the biologically predominant member of the endothelin peptide family – is an endothelial cell-derived peptide with a wide variety of developmental and physiological functions, which include embryogenesis, nociception, and natriuresis. In addition, ET-1 is a cytokine-like, multifunctional peptide with pro-inflammatory, mitogenic, and vasoconstrictor properties. If produced in excess amounts ET-1 promotes disease — mainly via activation of its ET_A receptor. Because of its multiple disease-promoting functions ET-1 represents an ideal target MMM. Preclinical studies targeting either activity or production of ET-1 – utilizing ERAs, ARBs, or ACEIs, respectively – have demonstrated that partial regression of aging-associated changes in vasculature and kidney is possible. In this article I will review the molecular regulation of ET-1 and its role in the physiology of vascular homeostasis, aging, and cellular senescence. The clinical implications of activators of ET-1 overproduction, modalities for delaying or reversing aging-related cellular changes, as well as interventions to promote healthy aging and early disease prevention – particularly physical activity – are discussed.

Contents

☆ The article is based in part on the lecture "Endothelin is getting older: How aging links endothelin with disease", presented at the *Thirteenth International Conference on Endothelin* (ET-13), in Tokyo, Japan on September 8, 2013. A summary of the lecture has been published in abstract form (*Life Sci* 2013; 93: e1–e2). Lecture and slides presented are available online in the HMTL version of this article on the publisher's website [Appendix A. Supplementary data].

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"A man is as old as his arteries"

THOMAS SYDENHAM, M.D. (1624-1689)

The physiology of human aging: general considerations

The vasculature: a mirror of health and age

Already in the 17th century, physician Thomas Sydenham M.D. (1624–1689), known as the "English Hippocrates" (Bendiner, 1986), recognized that vascular health and aging are interdependent and inversely related. This is reflected by Sydenham's above quote (O'Rourke and Hashimoto, 2007), which has also been attributed to Canadian physician Sir William Osler, M.D. (1849–1919), the father of modern medicine (Barton, 2013d; Sawabe, 2010). The direct relationship between aging and vascular health is clinically apparent in progeria syndromes: These patients show accelerated aging, abnormal endothelium-dependent vascular function, accelerated atherogenesis, and die within the first three decades of life mostly from clinical complications of vascular disease such as myocardial infarction and stroke (Capell et al., 2007; Merideth et al., 2008; Nabel, 2012).

Aging populations: challenge for the future

Today, age-related morbidity – which primarily involves sequelae of vascular disease (Barton, 2005a) – continues to pose great challenges to health care providers, health insurances, political decision makers, and societies (Barton, 2012). Indeed, life expectancy in humans has doubled since the beginning of the 20th century and in most developed countries now exceeds 80 years in both men and women (Barton, 2005b; Barton and Meyer, 2009; Gerland et al, 2014). In addition, as a consequence of a changes in birth rates and increased longevity, the world population is expected to continue to grow over the next decades — particularly among the elderly (Barton, 2005b; U.S. Census Bureau, 2002; Gerland et al, 2014) (Fig. 1). This will result in an overall shift of the world's age profile with the according increase in the oldest-old and their associated multimorbidity and frailty (Dong et al., 2013; Loffler et al., 2012; Gerland et al, 2014). When we are taking care of patients with chronic diseases, we are often facing that advanced age is accompanied with multimorbidity and greater susceptibility to medical complications. Thus, advanced age becomes an important determinant of mortality in critically ill patients (Barton, 2005a). The increased age-related risk may be partly related to changes in immunity and the overall immune defense in the elderly which have been linked to the increased susceptibility for disease (including an increased incidence of cancer) and infection (Franceschi et al., 2000; Gruver et al., 2007; Thoman and Weigle, 1989) (Boraschi et al., 2010). Immunosenescence has been implicated in the clinical course of viral or bacterial infections in the elderly who more often become critically ill than do middle-aged adults (Aw et al., 2007; Girard and Ely, 2007).

Aging and prevalence of chronic, non-communicable disease

In the industrialized world, a number of certain chronic, non-communicable diseases show a much higher prevalence in the elderly (Mokdad et al., 2004). These diseases include vascular disease, stroke, myocardial infarction, heart failure, diabetes, obesity, and cancer (Fig. 2) and dementia. The likelihood to develop or die from these diseases increases as we age (Harman, 1991, 1996; Mokdad et al., 2004). The aging process sets the stage for some of these diseases to develop. Moreover, endocrine changes related to physiological aging such as menopause result in conditions that resemble disease-like states (Barton, 2013b,c; Barton and Meyer, 2009): for instance, women after menopause become prone to develop obesity, insulin resistance, and diabetes, as well as stiffening of the arterial vascular bed and development of arterial hypertension (Barton and Meyer, 2009). All these factors increasing the risk of vascular disease (Virdis et al., 2009). Importantly, the number of postmenopausal women is expected to increase to approximately to 1 billion worldwide by the year 2050 (Barton and Meyer, 2009) (Fig. 1), indicating the need for health and disease prevention also in this group (Lobo et al., 2014).

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