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Review Article

A Possible Beneficial Effect of Sex Hormones on Vascular Aging through Expression of Sirtuin 1 Gene: A Narrative Review of the Literature

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ABSTRACT

Sirtuin 1 (SIRT1) is a NAD^+–dependent class III histone deacetylase, and a key gene linked to control of longevity, gene silencing, cell cycle progression, apoptosis, inflammation, stress resistance and energy homeostasis. SIRT1 is activated in response to low cellular energy stores and have been implicated in the control of many physiological processes including senescence. SIRT1 also regulates steroid hormone signaling through a variety of molecular mechanisms and modulate pathways that modify steroid hormone receptors. Declining of sex steroid hormones, including estrogens and androgens, is involved in the aging process and age-related diseases such as sarcopenia, falling, osteoporosis, cognitive and mood disorders, cardiovascular diseases, and sexual disturbance.

In this review, we will focus on the effects of sex steroid hormones on SIRT1 gene expression in endothelial cells and the advantages in the treatments with each hormone will be discussed in terms of understanding mammalian aging and longevity control.

Keywords: SIRT1; Estrogen; Androgen; Endothelial cells

INTRODUCTION

Sirtuin family

The sirtuins comprise a family of enzymes belonging to class III histone deacetylase (HDAC), which operate by removing acetyl groups from histones and other protein regulatory factors, resulting infunctional consequences on chromatin remodeling and gene expression profiles [1]. Moreover, the sirtuin family is highly conserved from archaebacteria to eukaryotes [2,3].

The life-prolonging effects of sirtuins were first described in yeast [4]. It was also shown that yeast sirtuin, silent information regulator 2 (Sir2), deficiency caused the short life span [5]. Sir2 is a NAD^+–dependent histone deacetylase and its activity accounts for silencing, recombination suppression and extension of life span in *vivo* [4]. The mammalian sirtuin family consists of seven HDACs, sirtuin 1 (SIRT1) through sirtuin 7 (SIRT7), that share a conserved catalytic core domain and are expressed ubiquitously [6]. SIRT1, 6 and 7 localize to the nucleus, whereas SIRT3, 4 and 5 locate in mitochondria, and SIRT2 is primarily cytoplasmic [7]. Of seven mammalian proteins homologous to Sir2, SIRT1 and SIRT6 have been reported to be involved with longevity [8-10]. Sirtuins are activated in response to low cellular energy stores and have been implicated in the control of many physiological processes including senescence [11].

Sirtuin 1 (SURT1) and longevity

Energy metabolism is deeply involved in cellular aging. It is widely known that calorie restriction has the effect of suppressing aging and extending life span across species [12,13]. In particular, moderate calorie restriction in humans ameliorates multiple metabolic and hormonal factors that are implicated in the pathogenesis of type 2 diabetes, cardiovascular diseases and cancer, that are the leading causes of morbidity, disability and mortality [13]. Sirtuin 1 is a key gene linked to control of longevity, gene silencing, cell cycle progression, apoptosis, inflammation, stress resistance and energy homeostasis [14-19]. Sirtuin 1 transcription is activated during fasting, and triggers changes in metabolism that switches from gluconeogenesis to fat mobilization and fatty acid oxidation when fasting is prolonged [20]. Transgenic mice with whole-body overexpression of SIRT1

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display phenotypes with metabolic features that protect against disorders associated with diet-induced obesity such as metabolic syndrome, type 2 diabetes and liver steatosis, although these effects are not sufficiently potent to affect longevity [21-23]. However, brain-specific SIRT1-overexpressing (BRASTO) transgenic mice show significant life span extension in both males and females, and aged BRASTO mice exhibit phenotypes consistent with a delay in aging [8]. These phenotypes are mediated by enhanced neural activity specifically in the dorsomedial and lateral hypothalamic nuclei (DMH and LH, respectively), indicating the importance of DMH/LH-predominant SIRT1 activity in theregulation of aging and longevity in mammals. Recently, adipose-tissue-specific overexpression of nicotinamide phosphoribosyl transferase (NAMPT) mice exhibit significant extension of median lifespan and delay in aging [24]. In mammals, NAMPT is the rate-limiting enzyme in a major NAD^+ biosynthetic pathway, an essential substrate for SIRT1 activity [25]. It is suggested that the mammalian NAD^+–dependent protein deacetylase SIRT1 and the key NAD^+–biosynthetic enzyme NAMPT mediate an inter-tissue communications [26]. Although the relationship between SIRT1 and human life span is still controversial [27], there are a few reports that SIRT1 polymorphisms may be associated with body mass index and long-term weight changes [28,29].

SEX HORMONES AND AGING

SIRT1 also regulates steroid hormone signaling through a variety of molecular mechanisms and modulate pathways that modify steroid hormone receptors [30]. Declining of sex steroid hormones, including estrogens and androgens, is involved in the aging process and age-related diseases such as sarcopenia, falling, osteoporosis, cognitive and mood disorders, cardiovascular diseases, and sexual disturbance [31]. Estrogen- and testosterone-dependent actions play a vital role in mitochondrial process implicated in aging [32]. The incidence of cardiovascular and vascular diseases is greater in men compared with age-matched premenopausal women [33]. Reduction of endogenous estrogen levels increases risk of bone fracture, cardiovascular diseases and Alzheimer's disease (AD) in postmenopausal women [34]. Therefore, during menopause the incidence in women dramatically increases, supporting a long-standing hypothesis that estrogens might provide vascular protection [35]. However, studies showed that estrogen therapy plays osteoprotective roles in both osteoporotic humans and rodents [36], while whether estrogen therapy can protect against heart diseases or AD remains controversial [37]. Estrogen reduces the risk of developing atherosclerosis in premenopausal women, whereas in post-menopausal women who may have established atherosclerotic diseases, estrogen increases the risk of myocardial diseases through the effects on plaque stability and clot formation [38]. Estrogens may also modulate cardiovascular health through expression of SIRT1, possibly in the AKT and ERK signal pathways [39]. It is also known that SIRT1 is the binding partner of estrogen receptor α (ER_α) in mammary epithelial cells and that the ER_α SIRT1 complex functions as a transcriptional activator of superoxide dismutase (SOD) and glutathione peroxidase (Gpx) and as a transcriptional repressor of p53 and cyclin G2, whereas ER_α bound to the promoter for SIRT1 and increased its transcription in breast cancer cells [40].

On the other hand, it has been known that a decrease in androgens, particularly testosterone, as a result of aging in men or bilateral ovariectomy in women, is associated with hypertension, diabetes, and atherosclerosis and that testosterone replacement therapy may benefit these people [41], although there is evidence that androgen use has been associated with premature coronary diseases in athletes and impaired vascular reactivity in female-to-male trans-sexuals [42]. Studies have also shown alterations in mood, libido, and cognition resulting from testosterone deficiency [43]. Dehydroepiandrostendione (DHEA) may have beneficial effects that have been shown *in vitro* and *in vivo*, including the stimulation of immunity and then the suppression of diabetes, atherosclerosis, dementia, obesity and osteoporosis [44]. Delineating hormonal signaling changes that occur across a lifespan and searching interventions may improve the quality of life (QOL) of elderly people and extend longevity [45].

SIRT1 AND VASCULAR AGING

Atherogenic stimuli, including diabetes, dyslipidemia, and oxidative stress, induce vascular dysfunction, leading to atherosclerosis, which is a key pathological basis for cardiovascular diseases such as ischemic heart diseases and strokes [46]. SIRT1 is highly expressed in human vascular endothelial cells [47] and has a potential antioxidative stress activity in vascular endothelial cells. The inhibition of SIRT1 with pharmacological agents or siRNA leads to an elevation of reactive oxygen species (ROS) levels in an animal model [48]. In human umbilical vein endothelial cells (HUVEC), SIRT1 inhibition increased p53 acetylation and induced premature senescence-like phenotype in parallel with increased plasminogen activator inhibitor-1 (PAI-1) and decreased endothelial nitric oxide synthase (eNOS) expression, whereas overexpression of SIRT1 deranged expression of PAI-1 and eNOS and reversed premature senescence induced by oxidative stress [49]. Those data have indicated a definite relationship between SIRT1 and ROS. The signaling networks of SIRT1 involved in ROS resistance include SIRT1/Forkhead Box class O transcription factors (FOXOs), SIRT1/Nuclear Factor-$_\kappa$B (NF-$_\kappa$B), SIRT1/NADPH oxidase (NOX), SIRT1/SOD, and SIRT1/eNOS pathways [50]. A previous study demonstrated that calorie restriction increased SIRT1 in the white adipose tissue of wild type mice, and this effect was abolished in eNOS-knockout mice [51], suggesting that ROS might control SIRT1 expression as well.

VASCULAR AGING AND SEX HORMONES

It has been reported that ER_α expression modulated by estrogen in endothelial cells is related to eNOS activation [52]. Another report described that ER_β expression in the endothelium was reduced in aging mice, and the expression of ER_α and SIRT1 was not changed, while SIRT1 activity was declined [53]. Estrogens include estrone (E1), estradiol (E2), and estriol (E3). E2 partially suppressed angiotensin II-induced contractions, restored the protein expression of SIRT1/P-AMPK and suppressed histone H3 acetylation in aorta of a post-

menopausal metabolic syndrome model induced in ovariectomized rats by feeding a high-fat diet [54]. Recently, it is reported that either E2 or selective estrogen receptor modulator (SERM) administration increased SIRT1 in endothelial cells and activated eNOS, resulting in decreased vascular senescence and atherosclerotic lesions [55]. The effect of SERM on upregulating SIRT1 was abolished in eNOS-knockout underwent ovariectomy (OVX) mice, OVX+SERM mice treated with a NOS inhibitor also showed no differences in arterial SIRT1 expression and senescence, suggesting that SIRT1 expression is regulated by estrogen-induced eNOS activation. Treatment of human endothelial cells with E2 has been reported to induce SIRT1 gene expression [55,56]. In our own study, treatmentof human aortic endothelial cells (HAEC) with E1 showed similar effects of E2 treatment, while E3 failed to induce SIRT1 gene expression [56]. The beneficial effects of E2 appear to occur from some properties including antioxidant and to imply an overall anti-aging action [57]. On the other hand, transvaginal E3 potentially offers a suitable physiologic delivery as a clinical benefit, however, E3 might be a weak activator of longevity, in contrast to E1 and E2 [58]. Then, the E1- and E2-induced SIRT1 expression was not diminished by high glucose levels [56]. It is consistent with a previous finding that control of oxidative stress by AMPK activation or antioxidants could restore normal estrogen responses, even in hyperglycemia [59], suggesting a possible benefit of anti-atherogenic effects of estrogens in female patients with diabetes.

Androgen receptor (AR) is also expressed in endothelial cells [35]. Epidemiological and clinical data have indicated that androgens are independent factors that contribute to the higher male susceptibility to atherosclerosis through adverse effects on lipids, blood pressure, and glucose metabolism [41,60].

A retrospective national cohort study showed the association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels [61], indicating that excessive testosterone exposure may be detrimental to the cardiovascular system [62-64]. There are a few reports to investigate the effect of androgens on SIRT1 expression in endothelial cells. In human umbilical vein endothelial cells (HUVEC), it is shown that oxidative stress decreases eNOS and SIRT1 and increases PAI-1 expression, and dihydrotestosterone (DHT) or testosterone treatment prevented these changes and increases the phosphorylation of eNOS at Ser1177 [65]. Another report evaluated the endothelial function of the corpus cavernosum in Otsuka Long-Evans Tokushima Fatty (OLETF) rats, which recapitulate type 2 diabetes [66]. The expression of eNOS and Sirt1 mRNA was decreased and that of inducible NO synthase (iNOS), IL-6, and TNF-mRNA was increased, while androgen replacement therapy improved the mRNA expression in OLETF rats. They concluded that androgen replacement therapy suppressed inflammation in rats with type 2 diabtetes and metabolic disorders and improved their endothelial and erectile functions. In our own study, treatments of HAEC with testosterone and DHEA have been also shown to induce SIRT1 mRNA expression, and those effects were not inhibited under culture condition with high glucose levels [56]. However, treatment with androstenedione exerted little effects on SIRT1 mRNA expression in HAEC, which is consistent with a report showing that androstenedione had no effects on development of bones, including sternebrae and soft tissues [67]. Androstenedione is a metabolite of the androgen pathway, suggesting that it may have a relatively weak bioactivity in cultured cells (Table 1).

Table 1: The effects of sex steroid hormones on SIRT1 expression in endothelial cells and tissues [54-56, 65,66].

	Estrogens			**Androgens**			
Condition	E1	E2	E3	Testosterone	Androstenedione	DHT	DHEA
Normal glucose	↑ ↑ ↑	↑ ↑ ↑	→	↑ ↑	→	↑ ↑	↑
High glucose	↑ ↑ ↑	↑ ↑ ↑	→	↑ ↑	→	N. A.	↑

N. A. indicates that data were not available; E1: Estrone; E2: Estradiol; E3: Estriol; DHT: Dihydrotestosterone; DHEA:Dehydroepiandrostendione.

CONCULUSION

We have reviewed the recent progresses related to SIRT1-mediated beneficial effects of sex steroid hormones on vascular aging and discussed the possibility of the sex hormone treatment on endothelial cells. However, sex hormones appear to be at a significantly increased risk to have or to develop specific cancers, although we did not mention it in this review. Thus, we should pay attention to both the advantages and disadvantages of sex hormone treatment and further understanding of the molecular mechanism of the protective effects of sex hormones against aging and to extend longevity should be required.

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