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Review

Aging and age-related diseases – From endocrine therapy to target therapy

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ABSTRACT

Aging represents an important health issue not only for the individual, but also for society in general. Burdens associated with aging are expanding as longevity increases. This has led to an enhanced focus on issues related to aging and age-related diseases. Until recently, anti-aging endocrine-therapy has been largely limited to hormone-replacement therapy (HRT) that is associated with multiple side effects, including an increased risk of cancer. This has greatly limited the application of HRT in anti-aging therapy. Recently, the focus of anti-aging research has expanded from endocrine signaling pathways to effects on regulatory gene networks. In this regard, the GHRH-GH-IGF-1/Insulin, TOR-S6K1,NAD^+-Sirtuin, *P53*, *Klotho* and *APOE pathways* have been linked to processes associated with age-related diseases, including cancer, cardiovascular disease, diabetes, osteoporosis, and neurodegenerative diseases, all of which directly influence health in aging, and represent key targets in anti-aging therapy.
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Contents

0. Introduction

Aging is a multi-factorial process characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death (Lopez-Otin et al., 2013). Age-related diseases include cancer, cardiovascular disease, diabetes, osteoporosis, and various neurodegenerative diseases such as dementia and Alzheimer's disease (Anton et al., 2005). A reduction in these age-related diseases will enhance the quality of life and reduce the overall burden to society and families. Possible targets for therapeutic interventions leading to aging with relatively healthy status are the focus of this review.

1. Limitations of hormone-replacement therapy

Hormone-replacement therapy remains the most widely applied anti-aging endocrine therapy in use today. The most commonly used hormones are growth hormone (GH), androgen, estrogen and progesterone (Liu et al., 2007; Nair et al., 2006; Rossouw et al., 2002, 2007). We have summarized below some of the more

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systemic analyses that have been performed and discuss the pros and cons of HRT.

Liu et al. have summarized the results of 18 clinical studies relating to GH application for anti-aging therapy (Liu et al., 2007). The results suggest that the advantages of GH include decreased levels of fat mass and total cholesterol, with an overall increased lean body mass. However, differences in total cholesterol were not found to be significant if it was normalized to body composition. Weight, bone density and serum lipid levels were not changed. In addition, GH therapy was associated with side effects, such as soft tissue edema, arthralgias, carpal tunnel syndrome and gynecomastia. The patients were also more likely to experience the onset of diabetes mellitus and impaired fasting glucose. The use of GH for anti-aging purpose has not been approved by the U.S. Food and Drug Administration, and the application of GH as an anti-aging agent is currently illegal in the United States. Nair et al. reported a randomized control double-blind study that compared the use of Dehydroepiandrosterone (DHEA) and testosterone as HRT agents in 87 males and 57 females (Nair et al., 2006). The two-year follow-up study showed that both treatments led to increased bone mineral density (BMD) at the femoral neck in men, and a slight increase in fat-free mass in the men who received testosterone. DHEA treatment in women was found to lead to increased BMD at the ultra-distal radius. Neither hormone altered the peak volume of oxygen consumption per minute, muscle strength, or insulin sensitivity in either men or women. The authors concluded that DHEA and testosterone did not significantly improve quality of life, and did not lead to major adverse side effects.

The use of estrogen and progesterone in HRT is both popular and controversial. The Women's Health Initiative (WHI) conducted a randomized controlled primary prevention trial in which 16,608 postmenopausal women aged 50–79 years were recruited. After a mean of 5.2 years follow-up, the results suggested that a regiment of estrogen with progesterone increased the risk factor for coronary heart disease (CHD), breast cancer, stroke and pulmonary embolism, but showed significant benefit for fractures and colon cancer (Rossouw et al., 2002). Five years later, the WHI published a follow up study that showed that women who initiated hormone therapy closer to menopause (<10 years) tended to have reduced CHD risks as compared to those who received the therapy more distant from menopause, but the risk of stroke was elevated regardless of years since menopause (Rossouw et al., 2007). A RCT trial conducted in Denmark with 1006 healthy women aged from 45 to 58 (mean age 50 y) confirmed the protective effect of estrogen and progesterone on CHD (Schierbeck et al., 2012). The result was consistent with WHI trial within the same age range, which indicated that women receiving hormone replacement therapy early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction. Nonetheless, the results from the Million Women Study (Beral, 2003), Collaborative Group on Hormonal Factors in Breast Cancer Study (Anon., 1997) and Finland Case Control Study (Lyytinen et al., 2010) suggested an increased risk of breast cancer and endometrial cancer in women using HRT. The risk was increased with the onset, duration and combination of estrogen and progesterone use. Lastly, both the ESTHER (Scarabin et al., 2003) and Canonico study groups (Canonico et al., 2008) demonstrated that oral, but not transdermal estrogen replacement treatment (ERT), was associated with the risk of venous thrombo-embolism (VTE) in postmenopausal women. It is well recognized that estrogen plus progesterone treatment can reduce the symptoms of menopause women associated with vasomotor instability, which leads to hot flashes and night sweats, psychological complaints, and urogenital atrophy. The treatment can ameliorate age-related diseases such as osteoporosis, decrease fracture and colon cancer. However, it also increases the risk of breast cancer, endometrial cancer, stroke and venous thrombo-embolism, and shows time-dependent safety-risk effect of coronary heart disease. It is suggested that for the application of estrogen and progesterone treatment in HRT, it is important to use them at the lowest possible dose that alleviates symptoms, for the shortest time period needed, and only by prescription.

Although patients have described "feeling good" after HRT, and most of the long-term controlled randomized studies and case control studies are convincing, the objective data suggested only limited benefits when balanced with the many risks identified. This general strategy is not advised in anti-aging therapy. However, newly identified genes, regulatory pathways and networks that are closely associated with endocrine biology may offer new hope for expanded anti-ageing therapy.

2. Anti-aging research: from endocrine pathway to gene regulation network

As is well known to all, growth hormone is strongly associated with the GHRH-GH-IGF-1/Insulin pathway, and its expression is controlled by the hypothalamus–pituitary-liver/pancreas endocrine axis. An axis now closely associated with the aging process.

A study by Flurkey has shown that, $Ghrhr^{lit/lit}$ mice have reduced signalling through the GHRH-GH-IGF-1/Insulin axis that is accompanied by a decrease in GH expression and IGF-1, with reduced circulating glucose and Insulin. More importantly, the life span of these mice is significantly prolonged as compared to *lit/+* littermates (Flurkey et al., 2001). In fat-specific insulin receptor knockout (FIRKO) mice, the fat tissues are reduced, and the mice show protection from age-related obesity, and longer lifespan than wild-type controls (Bluher et al., 2003). Additionally, $Igf1r^{+/-}$ mice, which showed partial IGF-1 resistance, were found to live a mean of 26% longer than $Igf1r^{+/+}$ littermates ($P < 0.02$) Holzenberger et al., 2003. These results demonstrate that impairment in receptor of GHRH, IGF-1 and insulin axis can lead to enhanced longevity with an associated reduction in age-related disease.

One of the most efficient ways of inhibiting the GHRH-GH-IGF-1/Insulin axis is through caloric restriction (CR). CR is defined as having diet which is 30–50% reduced in calories from normal food intake, and is nutritionally competent. As intake of calories is reduced, carbohydrates that need to be digested are also reduced, which leads to further reduction in insulin secretion, and inhibition of the GHRH-GH-IGF-1/Insulin pathway.

The influence of CR on the lifespan of mammals was first reported by the Wisconsin National Primate Research Center on Science in 2009 (Colman et al., 2009). This was the result of a 20-year longitudinal adult-onset CR study using rhesus monkeys. In this study, moderate CR was found to lower the incidence of aging-related deaths and delayed the onset of age-related diseases. Specifically, CR was found to reduce incidence of diabetes, cancer, cardiovascular disease, and brain atrophy. Later, another CR study using rhesus monkeys was reported by the National Institute on Ageing (NIA), where they show that a CR regimen applied in young and older age groups has not improved survival outcomes, but old-onset CR was beneficial on several measures of metabolic health, such as lower triglycerides, lower cholesterol and lower fasting glucose. Particularly, age-related diseases were detected in control monkeys at an earlier age than in CR monkeys (Mattison et al., 2012).

While the GHRH-GH-IGF-1/Insulin signaling pathway can be seen as one of the most important CR downstream pathways influencing longevity, and another recently identified target is represented by the mTOR-S6 K axis. Selman et al. have shown that in mice with a deletion of ribosomal S6 protein kinase 1 (S6K1), a component of the nutrient-responsive mTOR (mammalian target

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