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Derangements in the male gonadal activities during aging: A review

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Abstract

The male reproductive system undergoes insidious decremental changes during the advancement of aging process from reproductively active to senescent phase. Aging results in deterioration of vital physiological processes including reproductive performances. Age-related decline in male sex hormones is a direct consequence of testicular aging. These variations in the hormonal complementcause physiological instabilities affecting the quality of life formillions of aging men. Although older males often retain the ability to father children, aging influencesvarious aspects of their gonads. The structure and function of various testicular cell-types (germ cells, Sertoli cells, and Leydig cells) are affected during aging. Also, semen volume, sperm quality, quantity, motility, and morphology got partially disturbed. Testicular metabolism and levels of oxidative stress appear to be significantly altered at different rates during the different stages of lifespan. This review is an amalgamation of physical, hormonal and metabolic changes that might be responsible for the decreased testicular activity during the aging process.

Keywords: Aging; Hypothalamus-pituitary-gonadal axis; Testis; Steroidogenesis; Metabolism; Oxidative stress

Introduction

Aging or senescence is defined as “a persistent decline in the age-specific fitness components of an organism due to deterioration of vital physiological processes including reproductive performances” (Rose, 1991). Aging is an enormously complex, multifactorial, and irreversible process having a significant impact on fertility (Crosnoe and Kim, 2013). The reproductive capabilities of both the sexes were declined with age (Fitzgerald et al., 1998; Harris et al., 2011).The mammalian testes develop to exhibit two important functions: spermatogenesis (the production of haploid germ cells) and steroidogenesis (the production of the steroid hormones that support male reproductive development and function). It has been well reported that during aging regressive changes in spermatogenesis and steroidogenesis occurs, resulting in the decreased androgen production (Perheentupa and Huhtaniemi, 2009). Besides, a plethora of studies had shown that the level of male sex hormone (Testosterone), quality and quantity of spermatogenesisdecline with age (Chen et al., 2003; Kidd et al., 2001; Kuhnert and Nieschlag, 2004; Plas et al., 2000). Moreover, aging males are known to acquire hypogonadism features because of relatively lower testosterone levels and

certain changes within the testis, which are coupled with the loss of gonadal endocrine function and fertility (Hermann et al., 2000). Cocuzza and his colleagues reported that aged individuals showed decreased semen quality (reduced total sperm count, concentration and motility), and decreased normal morphological sperm ratio (Cocuzza et al., 2008). This review describes the cellular, hormonal, and metabolic disturbances found in the male reproductive system during aging.

Impact of aging on Hypothalamic-Pituitary-Gonadal (HPG) axis

The HPG axis in male functions to control the release of male sex hormones and to ensure theformation and maturation of spermatogenic cells. This axis is composed of three essential parts, including the hypothalamus,anterior pituitary, and the testes. The control of male reproductive function initiates with the secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus. The GnRH, in turn, stimulates the anterior pituitary gland to secrete two downstream hormones termed as gonadotropins. These hormones are luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH is the primary stimulus for the testicular secretion of testosterone, while FSH mainly stimulates spermatogenesis. Aging men showed a sign of progressive age-related testicular impairment due to multiple alterations in the hypothalamic-pituitary-testicular axis (Wu et al., 2008). Subsequent studies have shown that multisite impairment occurring during aging might be due to reduced hypothalamicGnRH outflow, reduced response of pituitary gonadotrophs to GnRH, decreased testicular responsiveness to LH and impaired androgenic negative feedback (Harman et al., 2001; Liu et al., 2005a; Veldhuis et al., 2007). Thus, androgen deficiency or hypogonadism leads to reproductive aging.

Impact of aging on testicular histoarchitecture

Dramatic changes occur in the testis during the aging processes, from the neonatal and infantile period to puberty onset, adulthood, and finally senescence (Fink, 2000; Tena-Sempere and Huhtaniemi, 2003). Testicular histomorphology is one of the important parameter studied for observing aging-related defects in the male reproductive system. Histomorphological studies have noticeably revealed a decreased number of germ cells, Sertoli cells, and Leydig cells during aging. In humans, testicular volume tends to rapidly increase during the onset of puberty till 30 years, remains constant between 30 and 60 years of age, and decreases gradually every year after age 60 (Yang et al., 2011). Xu and colleagues observed severe pathological changes in the seminiferous epithelium and interstitial compartment of the aged men. They had shown sections with widespread vacuoles within seminiferous tubules resulted from germ cell degeneration or absence, which lead to loose intercellular spaces and reduced cell-cell communication, and further contributed to low spermatogenesis. Further, the testicular tissue of aged men showed progressive degenerative spermatogenesis with some seminiferous tubules had spermatogenes is while adjacent tubules showed the absence of spermatogenesis (Xu et al., 2013).The study in mice model showed that testicular regression was spontaneously shaped after 6 months of age and prominent regressive

changes were observed after 1.5 years of age. Testicular sections showing atrophied seminiferous tubules with a depletion of germ cells and vacuolization appeared in patches in the aging mice. Also, the age-related deterioration of the Sertoli cells resulted in breakage in the blood-testis barrier and production of antibodies to the germ cells and induction of an autoimmune reaction (Takano and Abe, 1987). The histomorphological study in aged-rat (24 month old) revealed that, the Leydig cells undergo atrophic changes in size rather than reduction in their number and as a consequence the interstitium of aged-rat testes appeared expanded (Barbutska et al., 2013).

Impact of aging on testicular steroidogenesis

Leydig cells are the main source of testicular steroid hormones that control spermatogenesis, the male reproductive tract, and secondary male sexual characteristics. Prominent changes occur in the steroidogenesis during aging in a number of mammalian species, including the human and rodent. It has been well elucidated that serum as well as intra-testicular testosterone levels decrease in the senescence phase of the aging as demonstrated earlier in rodents (Wang and Stocco, 2005; Banerjee et al., 2014). The capacity of Leydig cells to produce testosterone is higher inadult than in old rats. Earlier studies reported the decreased expression of StAR protein in the Leydig cells ofold mice suggesting that there may be deficits in the cholesterol transport to the inner mitochondrial membrane during aging (Chen et al., 1996; Banerjee et al., 2014). There is evidence from earlier study that cholesterol transport machinery got compromised in aged Leydig cells (Culty et al., 2002) In continuation to this, another study performed in rodent had shownasignificantly decreasedexpression of cytochrome p450-SCC enzyme in the senescentmice compared with reproductively-active mice (Anjum et al., 2014).In addition, the decline in the expression of p450 aromatase both at mRNA and protein levels during aging may affect the ability to synthesize male sex hormones in canine an drodent testes (Ogawa et al., 2017; Banerjee et al., 2012). The study performed in the brown Norway rat suggested that the cause of theage-related reduction in steroidogenesis is not due to the decline in LH levels (Gruendelwald et al., 2000).Moreover, it has been suggested earlier that age-related structural and functional alterations in Leydig cells could be considered the primary cause of disturbed steroidogenesis and decreased testosterone production during aging. Also, studies had shown the importance of glucose in testicular steroidogenesis. The inadequate supply of glucose to the testis may be responsible for decline in steroidogenesis in mice during aging (Banerjee et al., 2014).

Impact of aging on testicular metabolism

Germ cells have peculiar nutritional requirements during spermatogenesis, switching their metabolic profile throughout the aging process. Sertoli cells are majorly involved in providing nutritional and physical support to the developing germ cells to achieve successful spermatogenesis (Rato et al., 2012). Energy metabolism and metabolic regulators play pivotal roles in controlling cellular senescence or the aging

process. It is well reported that glucose and its metabolite, lactate, are vital to most mammalian cells including testicular cells, and the transport of glucose across cell membranes is facilitated by a family of integral transport proteins, the glucose transporters (GLUTs) (Simpson et al., 2008). Out of various isoforms of GLUTs known, GLUT8 transporters expressed widely within the testis (Doege et al., 2000). Studies had shown the significant decline in the concentration of intra-testicular glucose as well as the expression of the GL UT8 protein in the aged mice compared with an adult. Also, they have confirmed that the changes in the level of intra-testicular glucose either directly or indirectly lead to changes in testicular steroidogenesis during aging. (Banerjee et al., 2014). In support of this, the earlier study also confirmed that inhibiting testicular glucose uptake resulted in decreased testosterone synthesis (Chen et al., 2003). It has been well documented that lactate serves as preferred energy substrate for the development of spermatocytes and spermatids in the adluminal compartment (Jutte et al., 1981), its testicular content were found to be significantly lower in the aged roosters (67 and 72 weeks) compared to young roosters (aged 27 and 37 weeks) (Weil et al., 1999).

Impact of aging on semen parameters and testicular oxidative stress

Several studies have established that advanced paternal age is linked to a variety of compromised semen parameters including a reduction in seminal fluid volume, percentage of motile sperm and percentage of morphologically normal sperm (Brahem et al., 2011; Oliveira et al., 2014; Harris et al., 2011; Pasqualotto et al., 2005). According to the study conducted on Americanmens, semen analysis were performed on wide range of population (age 16-73 years) and they have concluded that the sperm concentration, total sperm count, proportion of sperm with normal morphology, and sperm motility decline after the age of 45 years (Stone et al., 2013). During the course of aging, body underwent intense imbalance between antioxidant defence machinery and reactive oxygen species (ROS) production. Over accumulation of ROS leads to increased oxidative stress. Thus resulted in enhanced lipid peroxidation, DNA damage and apoptosis, which ultimately culminates in loss of sperm motility and vitality. A study conducted on rats suggested decreased capability for aged spermatozoa to handle oxidative stress due to decreased activity of anti-oxidative enzymes (glutathione peroxidase and superoxide dismutase) in aging spermatozoa (Weir and Robaire, 2007). Despite different studies conducted on the effect of paternal age on increase in testicular oxidative stress, further detail research should be directed to establish the association between aging, oxidative stress and testicular function.

Conclusion

Numerous studies have demonstrated the effects of increasing paternal age on various molecular mechanisms leads to disturbances in male reproductive functions at both central and peripheral level. This molecular aging process was shown to induce changes in male reproductive hormones profiles, decrease sperm quality and contributed to testicular abnormalities. Besides physical and hormonal changes, aging

also exerts metabolic alterations in the male gonad. Therefore, suitable approach pertaining to modulation in the male sex hormones can possibly be an effective approach in managing this aging-related decline in reproductive performances.

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