Chapter 8
Hormones of Hypothalamus in Aging

Gurcharan Kaur and Jyoti Parkash

Abstract Hypothalamus being the master regulator of the vertebrate endocrine system undergoes many adjustments/alterations which body makes during the course of aging. Moreover, the endocrinological basis of aging in male and female organisms is very complex, with multiple hormones along the hypothalamic-pituitary (HP) axis interacting with each other via different feedback loops to maintain homeodynamic state. Also the sensitivity of the hypothalamus to the external stimuli decreases with age mainly due to its lack of sensitivity towards the feedback system The endocrine system is although severely affected by aging but all the organ systems are not affected at the same time or in the same way. During aging cellular protein synthesis machinery as well as immune functions are diminished and gradually physiological functions decline. There is also an increase in fat mass, a loss of muscle mass and strength, and a decrease in bone mineral density profile that contribute to declining health status with increasing age. The hallmarks of aging such as Genomic instability, Telomere attrition, Epigenetic alterations, Loss of proteostasis, Dysregulated Nutrient Sensing, Mitochondrial dysfunction, Altered intracellular communication, Cellular senescence etc. are well reported in literature. In this chapter we have compiled information and discussed various hormonal changes that occur with age in hypothalamus and pituitary gland and how these two master regulators gradually lose their sensitivity with the increasing age.

Keywords Hypothalamus · Regulation · Receptors · Thyrotropin · Oxytocin · Vasopressin · Somatostatin · Reproduction · Menopause · Neurotransmitters

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8.1 Introduction

Hormones are known as the body's distant messengers/regulators which determine the way the body functions, and are produced by many different parts of the body. The hypothalamus, a part of the basal brain, is the source of many releasing hormones. Understanding these "brainy hormones" will help to take control of our body and health profile. The hypothalamus produces releasing hormones which in turn control the production of trophic hormones from the pituitary gland. These two endocrine regulators work in harmony to control the other endocrine glands to release their respective hormones. Because of these reasons, function of hypothalamus is directly responsible for overall hormone health. So in case the hypothalamus is damaged due to traumatic brain injury or genetic factors, overall hormonal health becomes the target.

The hypothalamus produces different hormones to regulate various endocrine glands in the body (see Fig. 8.1)

- **Thyrotropin-Releasing Hormone**—Stimulates production of the thyroid hormone, which in turn controls the cardiovascular system, brain development, muscle control, digestive health and metabolism

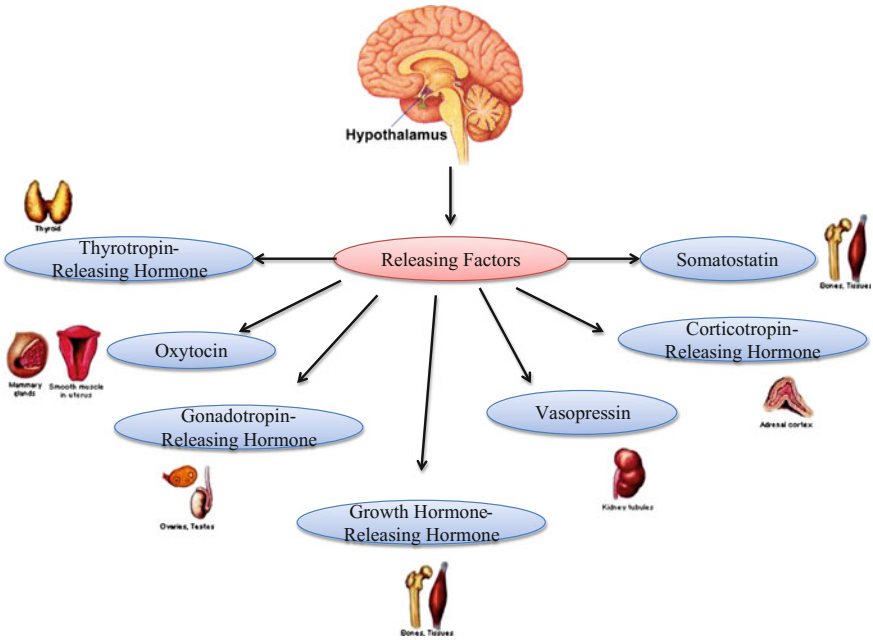

Fig. 8.1 Hypothalamus secretes various releasing hormones, which control the production of trophic hormones from pituitary gland

- **Oxytocin**—A hormone that controls parturition, human behaviors and the reproductive system
- **Gonadotropin-Releasing Hormone**—Stimulates the release of hormones which control reproductive function, puberty and sexual maturation
- **Growth Hormone-Releasing Hormone**—Controls growth and physical development in children as well as metabolism in adults
- **Anti-Diuretic Hormones (Vasopressin)**—The hormones that regulate water levels in the body, including blood volume and blood pressure
- **Corticotropin-Releasing Hormone**—Controls the body's response to physical and emotional stress, and is responsible for suppressing the appetite and stimulating anxiety
- **Somatostatin**—Inhibits growth and thyroid-stimulating hormones

Aging is a multi-faceted and multi-factorial decline of the body functions, and is associated with degenerative changes in multiple organ systems. The rate and extent to which these degenerative changes occur depends on genetics, the presence of other disease processes, and the accumulated effects of socioeconomic factors, lifestyle, and environmental factors (Araujo and Wittert 2011). Aging is very well reported to cause reproductive decline in mammals, including hormonal abnormalities and infertility (Kunimura et al. 2017). Reproductive aging refers specifically to changes in germ cells and the hormone-producing cells that support them, both within the gonad as well as at the hypothalamic and pituitary level. With advanced aging, there are reproductive changes, which are more pronounced in females. In comparison, aging effects on the male reproductive axis are much less pronounced, and reproductive potential is maintained until very late in life. During the reproductive aging process, every level of the hypothalamic-pituitary-gonadal (HPG) axis undergoes changes in structure, function, and synthesis/release of regulatory hormones. In addition, ovarian and testicular hormones exert feedback actions on the hypothalamus and pituitary, which may also change with aging. Although reproductive aging occurs within the broader context of somatic aging, but how the reproductive systems of females and males change with age is also very important in terms of physiological functions, hormones, and underlying mechanisms.

8.2 Aging and Thyroid Hormones

Thyroid gland functioning and Hypothalamo-hypophyseal-thyroid (HPT) axis are known to undergo numerous changes with the ageing process (Maudsley et al. 2012; Stan and Morris 2005). Thyroid functions have been extensively studied in relation to the cognition and its pathological conditions and TSH is the main biomarker in cognition studies. The level of TSH declines with age and impacts the processes such as maturation of neurons, mitochondrial enzyme activity (Tan and Vasan 2009). Congenital hypothyroidism is a common pathological condition related to aging process which is the outcome of insufficient secretion of the thyroid gland hormones and often mental deficiencies are observed (De Escobar et al. 2004). Most of the

animal studies have reported a decrease in circulating T4 levels with old age, whereas, changes in TSH and T3 are less consistent with age and are more gender and strain specific (Stan and Morris 2005).

8.3 Aging and Oxytocin

Literature reports very few studies on the role of ageing on the mammalian oxytocin system and majority of these reports relied on the autopsy studies of the neural tissue of the PVN and the supraoptic nuclei. Autopsy studies of the aged person suffering from Alzheimer's disease showed mixed resuts with some groups showing decrease in oxytonergic activity while others failed to show any such effect (Wierda et al. 1991; North et al. 1992). One more study of the aged rodents showed the decrease in central oxytonergic activity mainly including the reduced oxytocin responses to stress (Keck et al. 2000) as well as the reduction in the oxytocin receptors numbers frome various regions of the brain (Arsenijevic et al. 1995). Moreover, although animal studies have provided sufficient evidence for age-related decreases in oxytonergic activity but human reports have so far provided mixed evidence. There are also reports on age-related changes in hormonal and neurotransmitter systems interacting with the oxytonergic system, particularly reduced levels of gonadal steroids and dopaminergic functions (Rehman and Masson 2001), which may be responsible to alter the functional consequences for the oxytocin system. Huffmeijer et al. (2012) proposed that even if ageing adversely affects the human oxytonergic system, but this does not necessarily reflect that the oxytonergic system is not involved in social behavior and social cognition. Recently Sannino et al. (2016) and Colonnello et al. (2016) have reviewed the role of oxytocin in three temporal distinct periods of life-early postnatal period, puberty/adolescence, and old age. The available literature reports suggest that oxytocin potentially contributes to maintain social capacities of aged people and may help to ameliorate socially emotional deficits as well as symptoms of neurodegenerative diseases.

8.4 Growth Hormone Level as a Marker of the Aging Process

GH is the most widely associated candidate hormone as a biomarker of aging as the level of this hormone decreases with age. Both the secretion of GH by the pituitary gland, and its receptors become unresponsive to the hormone with age. This reduction in the GH level is also suggested to be responsible for age-dependent accumulation of adipose tissue and reduced muscle mass with decrease in the mineral content in bones (Corpas et al. 1993). The existence of a potential

hypothalamic releasing hormone regulating GH secretion from pituitary was demonstrated by Reichlin (1961), who for the first time identified that lesions of the VMN in the rat hypothalamus resulted in poor growth and a reduction in GH content of the pituitary. Further this evidence was supported by observations that the addition of rat hypothalamus extract increased GH secretion from cultured rat pituitaries, but rat cerebral cortex extract had no effect at all (Deuben and Meites 1964). A close association between acromegaly and extra-pituitary tumours was also recognized in the 1960s. It was in 1982 when three different peptides [GH-releasing factors, GRF(1–44)NH_2, GRF(1–40)OH and GRF(1–37)], were purified and sequenced from pancreatic tumours removed from acromegaly patients (Guillemin et al. 1982). Two of these peptides were subsequently identified within the human hypothalamus (Bőhlen et al. 1983) with the major form being GRF (1–44) NH_2 and given the name GHRH. GH plays very important role in controlling IGF-1 biosynthesis and exerts important actions on insulin secretion and also on responsiveness of target tissues to action of insulin. A major role of IGF-1, insulin and homologous molecules in the regulation of lifespan has been conclusively reported in wide range of organisms from worms and insects to mammals.

Suh et al. (2008) reported that mutations of the human IGF-1 receptor which reduced cellular responses to IGF-1 and resistance was associated with shorter stature and extended longevity. These key findings strongly suggests that the reduced somatotropic signaling can lead to increased life expectancy in the human. Further reduced levels of IGF-1, partial IGF-1 resistance and mutations suppressing IGF-1 signaling downstream from the IGF-1 receptor also suggests that GH signaling can accelerate aging and shorten lifespan although reported only in females (Selman et al. 2008). Age-related reductions in GH secretion in rats and humans have been suggested to be the result of decrease in GHRH secretion (Russell-Aulet et al. 1999). Old rats show lower pituitary GH mRNA, GH content as well as down regulation GHRH receptor expression. Many recent studies in animal models and human subjects provide a great body of evidence on the role of an attenuation of the GHRH/GH/Insulin-like growth factor-1 (IGF-1) axis in the control of mammalian aging (Reviewed by Steyn et al. 2016).

8.5 Reproduction and Gonadotropin-Releasing Hormone (GnRH)

Hypothalamus is the key regulation center of reproduction and produces the decapeptide Gonadotropin Releasing Hormone (GnRH). Mammalian reproduction is regulated by interactions between the hypothalamus, pituitary gland and gonads. Each component of the reproductive system is regulated by feedback mechanisms coordinating the processes resulting to gonadotropin secretion, gamete production and maintenance of the species (Conn and Crowley 1994; Ojeda et al. 2006). In most mammalian species, GnRH neurons are distributed in the preoptic area and

adjacent sites in the rostral region of the hypothalamus, rather than concentrated in a discrete nucleus. These scattered neurons are believed to form a diffuse neural network that functions coordinately as a GnRH pulse generator (Knobil 1990). The generation of pulsatile GnRH release at the median eminence is the central and essential element governing reproductive function, and depends on the coordinated activities of the 1500 or so GnRH neurons that are located in the hypothalamus (Wray 2001, 2010; Herbison et al. 2008).

8.6 The GnRH System

GnRH was discovered in the early 70s when two groups, Dr Schally's and Dr Guillemin's, respectively, published the primary structure of a decapeptide, named Luteinizing Hormone Releasing Hormone (LHRH) and capable to release LH. This discovery was rewarded with the Nobel Prize few years later (1977). As this molecule was able also to induce Follicle- Stimulating Hormone (FSH) release, it was called GnRH for gonadotropin-releasing hormone. Pioneer experiments had already started to put in evidence the importance of the GnRH system in the control of reproduction, even before its discovery by Schally and Guillemin. In fact, in 1950s, Donovan and Harris demonstrated that cutting the pituitary stalk in female ferret caused the loss of female cyclicity, but reconnections of the portal vessels between median eminence and pituitary reversed this condition (Donovan and Harris 1954). The expression pattern of GnRH peptide was evidenced by the production of the first GnRH antibody that permitted the presence of GnRH fibers at the level of median eminence (Barry and Dubois 1974).

GnRH cells arise from the nasal placode and migrate into the brain to become integral members of the hypothalamic-pituitary-gonadal axis. Disruption of either the development or regulationof the GnRH system results in reproductive dysfunctions. In 1989, two independent groups (Schwanzel-Fukuda and Pfaff 1989; Wray et al. 1989) proposed that GnRH neurons arise from an extra-CNS region (the olfactory placode) and during prenatal development migrate from nasal regions into the forebrain along olfactory/vomeronasal axons. Once GnRH neurons have reached the hypothalamus, they project their axons to the median eminence. Here they release GnRH hormone into the pituitary portal vessels to induce the secretion of pituitary gonadotropins into the general circulation.

Pulsatile LH release in rodents is altered by aging, and the age-related decrease in pulsatile LH secretion is controlled by LH pulse generator. Pulsatile LH release decreases during aging in ovariectomized female rats, due to absence of feedback pulse and as a result increased LH pulse (Scarbrough and Wise 1990). As gonadectomized aged animals exhibit markedly reduced pulsatile LH secretion, it was proposed that the age-related reduction of LH pulses is not the result of change in sensitivity of the gonadal steroid negative feedback, but rather may be due to deterioration of the LH pulse generating system.

Hypothalamic arcuate nucleus (ARC) express 3 different peptides, kisspeptin, neurokinin B (NKB), and dynorphin, termed KNDy neurons and their coexpression has been reported in several species, including rats, mice, goats, sheep, and humans (Wakabayashi et al. 2010). Several parallel evidence suggests that ARC neurons coexpressing these three different peptides are the LH pulse generator. Kisspeptin, a neuropeptide encoded by the Kiss1 gene, is a strong activator of GnRH neurons and is required for episodic GnRH release (Goodman and Lehman 2012). Recent study revealed that the attenuated LH secretion in aging female and male rats was associated with reduced numbers of kisspeptin, NKB, and dynorphin neurons in the ARC. These results suggest that the decreased NKB and dynorphin expression in aged animals causes the reduction of kisspeptin release from ARC kisspeptin neurons. Therefore, reduced expression of kisspeptin, NKB, and dynorphin in the ARC and/or change in pituitary responsiveness may cause attenuated LH levels in aged rats (Kunimura et al. 2017).

8.7 Aging, Menopause and Reproduction: Role of Steroid Feedback Mechanism

Age-related changes in the hypothalamus and pituitary are known to play a critical role in reproductive aging in rodents, and it has been hypothesized that parallel changes may contribute to reproductive aging in women (Zapantis and Santoro 2002). In this section, we will focus on experimental evidence of what is known about hypothalamic aging and regulation by steroid hormones during reproductive aging in female models. The decline in ovarian function is associated with dramatic fluctuations in ovarian feedback on the central components of the reproductive axis during the menopause transition in women thus making it very difficult to determine the potential contribution of aging of the hypothalamus and/or pituitary per se to reproductive senescence. The cessation of ovarian function may then create an open-loop setting so that the hypothalamic and pituitary components of gonadotropin secretion can be examined as a function of aging. A 30–40% decrease in both LH and FSH levels has been reported after menopause thus providing evidence that aging itself influences the hypothalamic and/or pituitary components of the reproductive axis.

The GnRH system has been investigated for age associated changes and the data suggests little to no loss of GnRH perikarya numbers and no change in their distribution. On the other hand, some properties of GnRH neurons may change with aging such as their morphology, cytoarchitecture, and ultrastructure, thus suggesting that alterations in properties of cells such as their ability to synthesize or release the GnRH peptides may occur. Finally, GnRH transcriptional activity, studied by co-expression of GnRH perikarya with the immediate early gene Fos or its gene product, is decreased in middle-aged compared to young rats during the preovulatory surge (King and Rubin 1994). As a whole, these studies suggest a loss

of activation of GnRH neurons in middle-aged rodents, prior to a loss of ovarian follicular complement. The fact that GnRH changes precede ovarian changes suggests at least some causality of the hypothalamus in reproductive senescence in rodents.

Females of most other spontaneously ovulating species have estrous cycles that may differ substantially in length and in hormonal and physiological changes from these processes in women. Rodents are an established laboratory model of reproductive aging, but rats and mice differ fundamentally from humans both in having a short estrous cycle (4–5 days) compared to the much longer menstrual cycle (−28 days) and in that their ovaries maintain viable follicles until relatively late in life (Kermath and Gore 2012). Despite the presence of viable follicles, rodents undergo a transition from regular reproductive (estrous) cycles to irregular cycles to acyclicity at middle age, (LeFevre and McClintock 1988) indicating that the neuroendocrine system is driving this process independently of follicular loss (Kermath and Gore 2012). Further-more, transplantation studies of ovaries from aged to young ovariectomized rodents show that ovaries from old donors can begin to function in the young hosts, and undergo folliculogenesis and ovulation. These findings suggest that reproductive failure with aging in rodents is not limited by the ovary. Therefore, rat and mouse models are useful in that they have enabled insight into how the hypothalamus changes with aging, both independent of and dependent upon gonadal steroid hormonal changes.

Basic research on reproductive aging is hampered by limitations in the availability of aging animals; the high cost of maintaining and/or purchasing such animals; and morbidity and mortality associated with aging. Thus, alternative models have been developed such as ovariectomy or orchidectomy to model loss of gonadal hormones. While these experimental models are extremely important, they are typically conducted in young animals. Because young and aged animals (and humans) differ in both hormone-dependent and -independent manners, there is a great need to conduct experiments in age-appropriate models. Another experimental limitation in females is that few species experience menstrual cycles or undergo a true menopause, and those that do typically experience menopause relatively later in life than in humans. For example, in the rhesus macaque it has been estimated that females undergo menopause at the equivalent age of a 65–90 year-old woman, compared to the typical age of 45–55 years in women. Thus, new models of menopause are needed that better approximate the hypothalamic, pituitary, and ovarian changes in women.

The onset of irregular cycles marks the transition from the late reproductive years to the menopause transition. Large-scale cohorts have provided important insights into the overall pattern of hormonal changes that occur through this final transition to the end of reproductive life. The fact that the pituitary response to GnRH is attenuated with aging may also contribute to the approximately two-thirds of cycles in the year before the final menstrual period that are either anovulatory or have prolonged follicular phases (Van Voorhis et al. 2008), resulting in irregular bleeding patterns along with varying breast tenderness, hot flashes, sleep disturbance, and possible mood changes.

In women, ovarian aging per se is central to reproductive senescence. Studies to date suggest that both genetic and environmental factors play a role, alone or in combination, but such studies are in their infancy. Future research that seeks to understand the genetic and environmental factors that prolong the health of and their supporting structures or hasten their demise will be required to extend reproductive capacity to meet the social needs of women in industrialized countries. There is now evidence that neuroendocrine aging occurs in women as well as animals. It will be important to determine the degree to which modification of these changes can extend reproductive life. Markers of ovarian aging have been identified in infertility populations, but further studies will be required to determine if these markers can predict menopause in the general population. Finally, further studies on the effects of the loss of reproductive hormones on non-reproductive systems including the brain (cognition, sleep, vasomotor symptoms), metabolism, bone, and cardiovascular disease will be critical to healthy aging in women as will be development of individualized approaches to treatment that optimize risk and benefit based on genetic and environmental information.

Thus, new models of menopause are needed that better approximate the hypothalamic, pituitary, and ovarian changes in women. Aging has more modest effects on the HPG axis of men than women. The most significant changes occur peripherally at the level of the testis, with steroidogenesis being impacted much more than spermatogenesis. Further studies are needed to dissect the impact of age versus age-related diseases on the HPG axis, as well as to determine the role of changes in semen parameters to the modest decline in fertility seen in older men. Further studies will be required to determine whether optimal aging in men is associated with age-related norms or is better achieved with replacement to levels in young men. Perimenopause is a midlife transition state that leads to reproductive senescence in women. Worldwide, >850 million women are currently aged 40–60 years, 88% of whom will transition through perimenopause at an average age of 51.4 years with a Gaussian distribution of 40–58 years. Regardless of ethnicity, geographic loca-tion or culture, all women who reach the age of 60 years with their reproductive organs intact will transition through perimenopause state to menopause with an average duration of 1–5 years from start to completion (Reviewed by Brinton et al. 2015).

8.8 Role Played by Different Neurotransmitters

Glutamate is the predominant excitatory neurotransmitter in the brain, and a well-known stimulatory regulator of GnRH Glutamate's actions on GnRH neurons occur through N-methyl-D-aspartate receptors and non-NMDARs (Eyigor and Jennes 2000). While initially controversial, it is now accepted that GnRH neurons co-express different classes of glutamate receptors (Miller and Gore 2002), and sub-populations of GnRH neurons respond to NMDA and non-NMDA pharmacological agents in electrophysiological studies of relevance (Iremonger et al. 2010).

The co-expression of GnRH neurons with glutamate receptor protein has reported stoichiometric changes in the ratio of receptor subunits, especially NR2a and NR2b, in aging compared to young female rats (Miller and Gore 2002). Thus, the stimulatory drive to GnRH neurons from glutamate decreases in the aging rodent hypothalamus. Interestingly, a pharmacological study on the interplay among glutamate, kisspeptin, and GnRH signaling has reported that glutamate and kisspeptin may modulate each other's activity on GnRH cells and contribute to the loss of GnRH output with aging (Neal-Perry et al. 2009). There are a few reports about another key amino acid neurotransmitter in the brain, GABA, and its regulation of the GnRH system during reproductive aging. In general, this data suggest increased GABAergic signaling in the aging hypothalamus. Measuring GABA release in the POA using microdialysis showed higher levels in middle-aged as compared to young female rats. Elevated gene expression of an enzyme involved in GABA bio-synthesis, glutamic acid decarboxylase 67 (GAD67), was shown in middle-aged compared to young rats (Grove-Strawser et al. 2007).

8.9 Male Reproductive System and Aging

Reproductive aging in men exhibits a number of striking differences from the female. While the association between advanced maternal age and declining fertility has been unequivocally established, the role of paternal age is more controversial (Langheinrich et al. 2012). The impact of aging on fertility and spermatogenesis in men has been comprehensively reviewed in (Handelsman 2006). The most fundamental difference between reproductive aging between males and females is that unlike the fixed complement of follicles seen in women, the germinal epithelium of the male can continue to generate fresh gametes throughout life. Accordingly, the reproductive lifespan of men may be as much as several decades longer than their female counterparts. Second, while aging in the female is characterized by an inexorable decline in ovarian function with follicle exhaustion following a relatively predictable time course, the process in the male is more modest and gradual and shows a high degree of variability. Third, while gametogenesis and steroidogenesis are very tightly coupled in the ovary and are both susceptible to the impact of aging, the same is not true in the male in whom aging tends to have a greater impact on testosterone production than spermatogenesis (Kidd et al. 2001).

Although aging in males cause a modest decline in testosterone levels, data from several studies highlight that age-related increases in obesity and chronic illness as well as smoking and marital status have a significant impact on circulating testosterone levels (Travison et al. 2007). Obesity is considered to have a greater impact on testosterone levels than age alone and that a 4–5 kg/m^2 increase in body mass index (BMI) is associated with declines in total serum testosterone comparable to that seen with approximately 10 years of aging (Travison et al. 2007). These data imply that the apparent age-related decline in testosterone may not be an inevitable consequence of the aging process but rather reflect health and lifestyle

factors and thus be potentially preventable and/or reversible. Aging in men is associated not only with a reduction in absolute levels of testosterone but also a blunting of the characteristic diurnal rhythm in the secretion of this steroid in young, healthy males. The physiological significance of the diurnal rhythm in testosterone secretion is unknown.

Reproduction is the most important function of an organism's life not only for perpetuation but also for species survival. One key feature of the Reproductive-Cell Cycle Theory of aging is that the hormones that regulate reproduction act in an antagonistic pleiotrophic manner through cell cycling signaling to control aging (Atwood and Bowen 2011). Reproductive hormones promote growth and development of species to achieve reproduction early in life, but later in life as age progresses, hormonal control in order to maintain reproduction, become dysregulated and drive senescence and aging. Atwood and his team suggest that since hypothalamic-pituitary-gonadal axis hormones regulate cell division, differentiation and death, therefore may be involved in the regulation of growth and development early in life with an aim to achieve reproduction, but as reproductive function starts declining progressively, the associated endocrine dyscrasia (dyotic signaling) drives senescent phenotype, age asssociated diseases and ultimately removes non-reproductive individuals from the gene pool.

8.10 Aging and Disease: Role of Hormones

Endocrine dyscrasia which is associated with gonadal cell loss is known to initiate senescence and age-related diseases. It is very important to understand the pathophysiology of age-related diseases as they account for ~80% of all deaths, the remainder 20% is largely the result of accidents and infections. Infections again are positively correlated with age (CDC National Vital Statistics Report 2009). Functional HPG hormone signaling is necessary for normal growth and development during embryogenesis, fetal life, childhood, adolescence, and for the maintenance of general health during adult reproductive lifespan. The loss of sex steroids following menopause in females and during andropause in males results in unopposed elevations in GnRH, gonadotropin [LH and follicle-stimulating hormone (FSH)]. This may lead to dysregulation of cell cycle events keeping in view the proliferation and differentiation properties of these hormones (Bowen et al. 2004; Cole 2009; Gallego et al. 2009).

The signaling resulting from reproductive endocrine dyscrasia in women commences around the time of menopause (~51 years of age), while in males andropause commences around 30 years of age when testosterone levels start declining at the rate of 1% every year between the ages of 30–80 (Belanger et al. 1994) with corresponding increases in circulating gonadotropins. Thus, males are under the influence of these lower testosterone and higher LH levels for many decades before they enter into hypogonadism phase (the clinical definition of andropause). Several studies in the recent past present evidence at molecular, epidemiological and clinical

aspects towards reproductive endocrine dyscrasia-induced cell cycle changes as important risk factors of age-related diseases such as AD/dementia (Atwood et al. 2005), stroke (Wilson et al. 2007), osteoporosis (Sun et al. 2006), heart disease (Lee et al. 2009) and cancer. The basis for this association are also attributed to the identification of receptors for HPG axis hormones in many different body tissues (reviewed in: Bowen et al. 2004; Vadakkadath Meethal and Atwood 2005). HPG axis hormones and receptors are evolutionarily conserved throughout reproductive organisms as the orthologs having been identified in flies (*D. melanogaster*), worms (*C. elegans*), yeast (*Saccharomyces cerevisiae*) and plants (Bowen et al. 2004; Vadakkadath Meethal et al. 2006). Therefore reproduction is the most important function of an organism from the perspective of species survival.

8.11 Conclusion

In this chapter we have made an attempt to compile information on the various hormonal changes that occur with age and how hypothalamus and pituitary gland slowly lose their sensitivity with the increasing age. Much is still to be done to understand the basic mechanisms of hormones and aging and to understand the mysterious link of age associated diseases. Neurodegenerative diseases such as AD, PD, and HD may not only due to the changes in some biochemical and molecular factors but also attributed to lack of hormonal activity due to the gradual alterations/loss of the endocrine mechanisms with aging. Several studies in literature affirm that the age related changes in the hypothalamus are manifested in many disorders. We also need to carry out more extensive research to understand how the structure-activity relationship of many commercially available synthetic hormonal drugs correlates to their potential beneficial effects in humans suffering with various age related diseases. Women, as they age, become prone to the cumulative effects of menopause, adiposity, and inflammation that is associated with the depletion of estrogens and bioenergetic dysregulation. The association between hypometabolism and the neurological symptoms of the perimenopause suggests that this transition state is a critical period in the neuroadaptive landscape of ageing in the female brain and may provide a window of opportunity to intervene and prevent age-related neurological diseases in post-menopausal women. This will be of importance when determining the efficacy of sex-hormone replacement strategies and diets rich in sex-hormone active compounds when it comes to preventing AD in women.

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