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Review

The aging of the endocrine hypothalamus and its dependent endocrine glands

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INTRODUCTION

Clusters of poorly demarcated neurons, called nuclei, situated in the hypothalamic area are the source of hormones which through the succession of their actions on the pituitary and the peripheral endocrine glands, regulate and control major functions of the organism, namely, reproduction, energy, metabolism and adaptation. The significance of these vital functions is obvious; thus our understanding of the course of endocrine hypothalamus functioning throughout the length of life is evidently of paramount importance. Numerous genetic and intrinsic or environmental factors can influence or derange the endocrine function of the hypothalamus. However, the most consistent and inevitable factor, one which we now know commences earlier than was once assumed, is aging.

The onset of aging cannot easily be ascribed to a specific point or phase of the lifespan. In man only two periods of life can be clearly distinguished by definite clinical features: puberty and female menopause. The aging of the organism as a whole as well as the aging of the systems and organs commences without any identifiable clinical or biological sign indicating the beginning of the involutionary process; it then progresses without any essential change in the rate of age-related alterations. The hypofunctioning, however, of the endocrine system governed by the hypothalamus is well documented as starting between the age of 30 and 40 years.

As we age, the anabolic hormones, namely growth hormone, testosterone and dehydroepiandrosterone, as well as the reproductive function of women, enter a period of progressive insufficiency which is characteristically designated as somatopause, andropause and adrenopause respectively for the first three hormones, terms which are used in accordance with the menopause occurring in women. Already at the age of thirty, a steep diminution of the follicles in the ovaries also commences, signaling the beginning of the decline in the reproductive capacity of women.

In the early times of modern endocrinology the amelioration of endocrine insufficiencies through hormonal replacement therapy and the spectacular eradication of the accompanying symptoms of skin changes, fatigue and muscular weakness, characteristics typically observed in older persons, raised anticipation for humanity that an elixir against aging might be available in the form of hormones. This expectation has not been fulfilled; however, there may still be hope that when the degree and extent of endocrine alterations in aging are scientifically precisely established and the consequences of these changes to the organism are meticulously weighted,

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the benefits of modifying them via hormonal replacement therapy might be realistically evaluated.

In this context, the endocrine system presents a unique opportunity compared with other organs. It can provide us with the means and the knowledge to restore the function of damaged or even totally destroyed endocrine glands by the use of hormonal replacement all of which are available with no need for transplantations or immunosuppressives.

The present review attempts to summarize the indirect evidence of endocrine hypothalamus function in aging as this is reflected in the function of the hypophysis and the dependent endocrine glands. No reference is made to the remarkable animal experimental work on this subject, worthy of considerable regard because it was deliberately designed to record only its relevance to human physiology and clinical medicine. To reduce the confusion created by the discrepancies between study results, in the references section large series and longitudinal investigations have been accorded preference on the assumption that large numbers are more likely to represent actuality.

THE GHRH – GH – GHBPS – IGF-I – IGF-IBPS – LIVER AXIS

The pituitary secretes the growth hormone (GH), an essential hormone for the development of the human body and an important protein anabolic factor. GH secretion is stimulated by the hypothalamic growth hormone releasing hormone (GHRH) which, like the other hypothalamic hormones, presents a pulsatile secretory pattern reflected on GH secretion characterized by pulses that have greater amplitude during the first two hours of sleep, this accounting for the 2-4 times greater release of GH at night. Growth hormone is constantly inhibited by the hypothalamic hormone somatostatin and stimulated by the gastrointestinal hormone ghrelin. The GH circulates in the blood bound to proteins (GH-BPs).

The anabolic action of GH is essential in adults, especially in women who have small quantities of the other strong anabolic hormone of the organism, testosterone. Growth hormone stimulates the secretion by the liver of insulin-like growth factor I (IGF-I) or somatomedin C (SmC) which is the effector of its major actions. The receptor of GH in the liver is the extramembranous part of its own receptor. A general estimation of GH action therefore includes the measurement of GH, GHBPs, IGF-I, its binding proteins IGF-IBPs, the receptor of GH and the functional capacity of the liver. Due to its minimal concentrations in the blood, GHRH cannot be assayed, while hypothalamic somatostatin estimation is problematic because of extrahypothalamic production of this hormone, which is also present in the circulation. A number of studies have demonstrated the great decline of GH with advancing age beginning in the second decade of life (Table 1).

In one of the earlier studies of GH secretion during sleep that recruited four volunteers aged 52-73 years (1 men and 3 woman), it was reported that the subjects failed to show a sleep-related peak of GH in blood samples taken every 60-90 minutes.[1] In a well designed study of GH secretory pattern in various age groups from age 6 to 62 years, performed by sampling at 20-minute intervals over a period of 24 hours, it was found that the mean 24hrs secretory rate in eight adults aged 23-42 years was 382 μg/24hrs, whereas in two women and one man aged 47-62 years no measurable secretion of GH was found. Another 55-year old woman had a 505ng secretory rate and one 62-year old man had 57μg/24hrs. The authors explained that calculation of secretion was limited to episodes of 5ng/ml and greater.[2] Growth hormone was measured at half-hour intervals for four hours after sleep and at one-hour intervals from 8.00 am to 4.00 pm in 52 individuals. Average peak GH levels during the night were three times greater than those of the daytime in the group of ten individuals aged 20-29 years. In contrast, 6 of 12 individuals aged 60-70 years with somatomedin C (SmC) 0,64 U/ml had lower day and night GH bursts than those of the young age group, whereas the remaining six with SmC less than 0.64 U/ml had a flat day and night GH curve (Figure 1 of Reference 3). The prevalence of low plasma SmC less than 0.38 U/ml increased progressively from age 20 to 90 years. The decrease from age 20 to 90 was as follows: Third decade 0%, fourth 11%, fifth 20%, sixth 22%, seventh 42%, eighth 55% and ninth 95%, with SmC being inversely related to obesity within each decade.[3]

Table 1. Growth hormone (GH) changes in aged subjects

Authors	N	Age	Method	Results
Carlson J et al 1972[1]	1 M 3 F	52-73yrs	60-90min sampling during sleep	No sleep related peak of GH
Finkelstein et al 1972[2]	**53**	3F 2M 47-62yrs	Integrated 24hrs GH at 20 min sampling	In 2 women and 1 man secretion of GH approached zero. Calculation limited to episodes of ≥5ng/ml
Rudman D et al 1981[3]	**22**	10 men 20-29yrs 12 men 60-70yrs	30min sampling for 4hrs after sleep and at 1hr intervals from 08.00 to 16.00	Average peak GH during sleep was 3 times greater than in the day in young men. SmC less than 0.38 was 0 in the 3rd decade 11% in the 4th, **42%** in the 7th and 55% in the 8th
Zadikt Z et al 1985[4]	173 89 M 84 F	7-65yrs	24hrs integrated GH at 30min sampling	Decreased integrated GH after 2nd decade
Vermeulin A 1987[5]	20	10 M 22-45yrs 10 M 65-85yrs	24hrs integrated GH at 20min sampling SmC at 11.00, 16.00, 21.00, 02.00hrs	45% decrease of integrated GH and of peak amplitude SmC significantly lower in old men
Ho KY et al 1987[6]	36 18F 18M	10F 18-33yrs 8F > 55yrs 10M 18-33yrs 8M > 55yrs	24hrs integrated GH and SmC at 20min sampling	Fraction of GH secreted in pulses reduced from 81% to 29%. No significant difference between the sexes. SmC declined significantly with age
Iranmanesh et al 1991[7]	21	21-71yrs	24hrs integrated GH at 10min sampling	70% decrease of GH
Corpas et al 1992[8]	19	9M 22-33yrs 10M 60-78yrs	24hrs integrated GH at 20min sampling	29% decrease of GH

In a larger study of 173 individuals (89 male and 84 female) aged 7-65 years, a highly significant ($p<0.001$) decline of 24hrs GH secretion was found after the 2nd decade.[4] No significant difference was noted on repeat tests of 12 men and 23 women studied in the follicular phase and again in the luteal phase. Two more studies published in 1987 established the early and great decrease of GH with aging. 24hrs GH sampling at 20min intervals and somatomedin (SmC) sampling at 1100, 1600, 2100 and 02.00hrs in 10 men 22-45 and 10 men 65-85 years old showed a 45% decrease of 24hrs integrated GH secretion and lower peak amplitudes in the old men. Serum SmC also decreased with aging.[5] Calculation of the fraction 24hrs GH secretion in pulses revealed a steep decline of 81% from 29% in eight women and eight men > 55 years old compared to 10 women and 10 men who were 18-33 years old. No difference between the sexes was found in 24hrs GH secretion.[6] A more frequent sampling at 10min intervals in 21 men 21-71 years old showed a 70% decline of 24hrs GH with aging. The production rate of GH decreased by 16% and half-life fell by 6% with each advancing decade.[7] A smaller decline by 29% of 24hrs GH secretion in 10 men aged 60-78 years old compared with nine men 22-33 years old was also reported.[8] GHRH stimulation of GH secretion in 116 women and men (18-95 years old) demonstrated a significant negative correlation between integrated GH response and age in both women and men.[9] Repeated administration of GHRH every 2 days for 12 days restored the attenuated response.[10]

In the published studies of GH response to different stimulatory factors in old age (hypoglycemia, arginine infusion, exercise, GHRH itself) there appear great variations that do not allow the assembling of either direct or indirect information concerning functional GHRH capacity. Moreover, concrete

conclusions on the natural course of GHBPs, IGF-IBPs and GH receptor cannot be drawn because of the paucity of studies on these and the inconsistent results as well as the complex interactions between these parameters.[8-10]

THE PROLACTIN INHIBITING FACTOR (PIF) – PROLACTIN AXIS

Prolactin (PRL) is secreted by the pituitary lactotrops in a pulsatile pattern like the other pituitary hormones. Isolated pituitaries present an innate pulsatility of the lactotrops on which a hypothalamic episodic dopaminergic inhibition is superimposed in normal individuals resulting in 13-14 secretory pulses per day. An increase in the amplitude of the PRL secretory pulses occurs 60-90 minutes after the onset of sleep. Antidopaminergic drugs rapidly liberate the lactotrops from dopamine inhibition, provoking an increase of serum prolactin levels which is more pronounced in woman than in men.

Serum prolactin was assayed in 86 women and 241 men aged 18-65 years. There was a progressive decline of prolactin with age in women from 443 mU/L in women aged 15-25 years to 218 mU/L in women in the sixth decade.[11] In men prolactin increased slightly in the sixth decade. Higher prolactin concentrations in women than in men of the same age groups were found in 315 adult subjects of various age groups with the exception of the sixth decade. The response to TRH stimulation was significantly greater in females than in males both in the young and the aged subjects.[12] This study showed no quantitative difference between young and elderly subjects in the prolactin release induced by TRH, suggesting that the lactotrop is not affected by aging. However, a 4-hour infusion of TRH in three groups of healthy men aged 30-45, 50-69 and 70-96 years showed an age-dependent increase in the magnitude of peak prolactin response.[13] A large-scale study of basal prolactin in 500 men and 384 women found slightly higher levels in women at age 20 to 29 years and a slight rise of the levels in men with aging. Prolactin did not fall after the menopause.[14]

The effect of aging on the pulsatile secretion of prolactin during day and night was tested in young and old men. Pulse frequency remained stable with aging and the pulses during the daytime were similar in young and old subjects. During the night, however, significantly higher amplitude and greater area of the pulses was noted in the younger men than in the older individuals. In contrast, the administration of an antidopaminergic drug provoked significantly higher pulse amplitudes at night in old men than in the younger group.[15] In a large 7 to 10-year longitudinal study of 1156 men from the Massachusetts Male Aging Study (MMAS), prolactin varied only slightly cross-sectionally within both measurements but underwent a sharp longitudinal increase of 5.3%.[16]

The general conclusion that might be drawn from these conflicting results, based on the studies with the larger number of subjects, is that prolactin secretion rises in old age (Table 2).

THE TRH – TSH – T_4 + T_3 AXIS

The evaluation of TRH – TSH – T_4 + T_3 axis in aging presents certain difficulties due to confounding parameters complicating the study results. Numerous factors have been observed to have a varying degree of implications on pituitary-thyroid function in old age, rendering the definition of "healthy" old individuals problematic.[17,18] Chronic diseases and drug therapy frequently occurring in the aged, physical activity, nutrition, obesity, smoking and the statistically more disturbing subclinical thyroid diseases obscure the actual impact of aging itself on the thyroid. Consequently, the truth must be sought again in the large numbers (Table 3).

The normal range of serum TSH has been defined by the Committee on Subclinical Thyroid Disease as 0.45 to 4.5 mU/L based on a large United States population cohort of 13,344 subjects aged 12 years and older.[19] Using the 2.5 and 97.5 percentile the serum TSH in 150 normal men was found to range between 0.5 and 5 mU/L in Britain.[20] The distribution curve of TSH levels shifts toward higher concentrations with age as is indicated by the difference in mean TSH between 6167 individuals aged 20-39 years (1.54 to 1.75 mU/L) and the mean TSH (1.91 to 2.96 mU/L) in the age group of 60-79 years (n = 2431).[21]

TSH and thyroid hormone T_4, T_3, rT_3 and FT_3 levels were measured in 131 subjects (94 women and 37 men aged 18-77 years) and the TSH response to

Table 2. Prolactin changes in aged subjects

Authors	N	Age	Studies	Results
Yamazi T et al 1975[12]	315	Various ages	Cross-sectional	Higher PRL in women than men. No difference between young and older men in response to TRH
Brackman MR et al 1986[13]		30-45yrs 50-69yrs 70-96 yrs	4hrs infusion of TRH	Age-dependent increase in the magnitude of peak prolactin response
Swing CT 1989[14]	501 M 384 F	> 50yrs	Cross-sectional	Slight increase of PRL in men with aging No change in women after the menopause
Vekeman SM, Robyn E 1995[11]	241 M 86 F	18-65yrs	Cross-sectional	Progressive decline in women from 443mU/L to 218mU/L Slight increase in men in the 6th decade
Greenspan et al 1990[15]			24hrs pulsatile secretion	Significantly higher amplitude of PRL pulses in younger group
Feldman et al 2002[16]	1156 M	40-70yrs	7-10 years	Steep longitudinal PRL decrease of 5.6% years

TRH was calculated. Increase of rT_3 in the aged was noted and a decrease in post-stimulation TSH was found with aging in men but not in women.[22] With 15 min intervals sampling at the 24hrs integrated TSH was 1.42±0.37 mU/L in eight young men (20-27 yrs) and 0.78±0.47 mU/L in eight men aged 67-89 yrs.[23] No statistically significant difference in 24hrs TSH was reported between 10 young men (26-35 yrs) and 10 old men aged 78-83 yrs (TSH 3.5mU/L and 3.1mU/L, respectively). However, nighttime TSH was 4.1±0.1 in the young group and 3.2±0.3 mU/L in the old men group.[24]

The relation of physical activity, the number of diseases and mortality with thyroid hormones was studied in 403 independently living men aged 73-94 years. Serum rT_3 increased with age and the presence of disease and lower physical activity. Sixty-three men presented with low T_3 syndrome (low T_3 increased rT_3). Low FT_4 (within the normal range) was associated with a better 4-year survival. Changes in the hepatic deiodination may account for the increase of rT_3.[25]

The observation in animal models that longevity is associated with thyroid hypofunction prompted authors to investigate thyroid function in the very old. Four groups were studied: A) 41 healthy centenarians (100-110 yrs), B) 33 healthy elderly subjects (65-80 yrs), C) 98 normal adult subjects (20-64 yrs) and 52 patients with no thyroid diseases. The centenarians had lower TSH and FT_3 and higher rT_3 than B group subjects but lower rT_3 compared with group C. FT_4 was similar in groups A, B, C.[26]

A recent larger study of three groups was composed of: A) 166 women (median age 97.8yrs) and 166 men (median age 97.1 yrs), Ashkenazi centenarian Jews, B) 95 women (median age 69.5 yrs) and 93 men (median age 72.3 yrs), Ashkenazi of a younger age and C) 605 subjects 60-79 yrs old. TSH was significantly higher in the first group ($p<0.001$) than in groups B and C (1.97 mU/L, 1.55 mU/L and 1.61 mU/L, respectively). FT_4 was similar, but inversely correlated with TSH. The authors hypothesize that changes in negative feedback may contribute to exceptional longevity.[27]

THE CRH – POMC – CORTISOL – DHEA AXIS

Central control of the hypothalamic-pituitary-adrenal (HPA) axis is exerted by the corticotropin releasing hormone (CRH) which, with the antidiuretic hormone, stimulates the corticotrop cells of the pituitary to secrete a long polypeptide, proopiomelanocortin (POMC). The POMC molecule is cleaved intracellularly giving rise to adrenocorticotropic hormone (ACTH) and to other hormonal peptides. CRH is the most sensitive hypothalamic hormone: activated by stress, it is a major regulator of the adaptation responses that ensures homeostasis of

Table 3. TSH and thyroid hormones changes in aged subjects

Authors	N	Age	Studies	Results	
Erfurth EM et al 1984[22]	91	45F ≤39yrs 24F 66-79yrs 14M ≤38yrs 8M 60-79yrs	Cross-sectional	F ≤39 TSH 2.4±20 T_4 106 T_3 2.27 FT_3=2.09 M ≤39 TSH 2.93±0.41 T_4 108.3 T_3 2.49 FT3=2.37	F 60-79 3.79±0.39mU/L T_4 107 nmol/L T_3 2.09nmol/L FT_3=1.99 M 60-79 TSH 2.25±0.7 T_4 107nmol/L T_3 2.09nmol/L FT_3=1.99
Barreca T et al 1985[24]	20	10 (26-35yrs) 10 (78-83yrs)	Cross-sectional	Mean 24hrs TSH Night Time TSH Young 3.5mU/L Young 4.1 mU/L Old 3.1 mU/L Old 3.2 mU/L	
Van Coevorden A 1989[23]	16M	8M 20-27yrs 8M 67-89yrs	Cross-sectional	24hrs sampling at 15min intervals TSH young 1.43±0.41μU/L TSH old 0.78±0.37 μU/L TRH induced TSH (AUC) 42±16.6 μU/L in the young 15.9±6.3 μU/L in the aged	
Perle JV et al 1991[20]	1210 700 F 510 M	≥60yrs	Cross-sectional	TSH above normal (5 IU/ml) 11.6% women 2.9% men (<0.5IU/L) 6.6% women 5.5% men	
Mariotti et al 1993[26]	222	A) 41 (100-110yrs) B) 33 (65-80yrs) C) 98 (20-64yrs) D) 52 (28-82yrs)	Cross-sectional	TSH A 0.97 B 1.17 (1.17mU/L) FT_4 A+B+C no difference A low FT_3 high rT_3	
Committee on Subclinical Thyroid Disease 2004[19]	13334	12yrs and older	Cross-sectional	Normal range of TSH 0.4 to 4mU/L	
Van den Beld AW et al 2005[25]	403	73-94 yrs	Cross-sectional	rT_3 increases with age and disease. 63 men with T_3 low rT_3 increased. FT_4 increase (within the normal range) favourable for a 4-year survival	
Sulcs M et al 2007[21]	8598	20-39yrs 6167 subjects 60-79yrs 2431 subjects	Cross-sectional	TSH in the young group 1.54 to 1.75 mU/L In the old group 1.91 to 2.96 mU/L	
Atzmon G 2009[27]	1124	A) 166F (97.8yrs) 166M (97.1yrs) B) 95F (69.7yrs) 93M (72.3yrs) C) 605 (60-79yrs)	Cross-sectional	A TSH 1.97 (0.42-7.15) B TSH 1.55 (0.46-4.55) C TSH 1.61 (0.39-6.29) A > B and C (p<0.001)	

the organism. CRH is secreted in a pulsatile pattern that is imposed on ACTH secretion showing 12-14 pulses over a 24-hour period with 15 minutes blood sampling. More frequent sampling reveals more frequent pulses. ACTH presents the more intense circadian rhythm, 70% of its secretion taking place between midnight and 07.00 hours. ACTH stimulates the initial step of stereogenesis in the adrenals which is followed by successive enzymatic actions that lead to the production of cortisol, the adrenal androgens dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), Δ_4-androstendione (Δ_4-A), insignificant

quantities of testosterone and part of aldosterone. The natural course of adrenal hormones through the years to old age is of great interest because cortisol is essential for survival and the adrenal androgens that have anabolic action.

DHEA-S is a peculiar hormone that has aroused the interest of scientists, the public and the media. Experimental work in animals has shown that DHEA-S possesses antidiabetic, antimitotic, antiaging and immunoprotective actions. In humans, epidemiologic studies have associated low DHEA-S levels with cardiovascular disease. On the basis of experimental research and clinical observations, DHEA-S, in the form of DHEA with which it is interconvertible, has been used in the treatment of various diseases for the prevention of osteoporosis and as a metabolic agent in the elderly. DHEA has also been used and abused by the public as a supplement for a variety of illnesses, being sold over the counter. DHEA-S is exclusively produced by the adrenals at a rate of 7-14mg daily and has a long half-life of 4 hours and a small clearance rate, resulting in large amounts of circulating DHEA-S. The serum levels of DHEA-S are between 1500 and 4000 ng/mL, whereas DHEA levels are only 1.5-6 ng/mL and those of Δ_4-A 0.8-1.3 ng/mL.[28] DHEA-S, a weak androgen, multiples its androgenic capacity by being transformed in the liver to DHEA and then to Δ_4-A. Δ_4-androstendione gives rise to testosterone, the amount of which in women represents 50% of total circulating testosterone. The biological significance of such enormous circulating concentrations of DHEA-S is a mystery and the implications for the organism of the deprivation of part of this hormone with aging have not been clarified. Cross-sectional and longitudinal studies have shown a significant decrease of DHEA-S with advancing age (Table 4).

A rapid decline of DHEA starting at the age of 30 years was noted in 110 men, which was attenuated after the 6th decade. DHEA in 211 women presented a great decrease with a short intermediate rise in premenopause.[29] A study of 273 men and 341 women aged 20-69 years of age showed that men had higher concentrations of DHEA and a greater decline in serum levels. The rate of decline for DHEA was 5.6% per year and 2% for DHEA-S.[30] The relation of smoking to DHEA-S levels in 543 healthy men demonstrated a strong positive correlation of DHEA-S with smoking habits ($p=0.002$). A marked linear decline of DHEA-S with age was also observed, with an average decrease of 3% per year.[31] The variation in study results due to wide individual variability is illustrated in the report of 97 men, 32-83 years old, from the Baltimore Longitudinal Study of Aging followed every 1.5 years over a period of 13 years. Sixty-seven percent of them showed a decrease in DHEA-S, 12% no change and 19% an increase.[32]

The largest 10-year prospective observational survey in a random sample of 1156 middle-aged men aged 40-70 years old at baseline was reported from the Massachusetts Male Aging Study (MMAS). DHEA and DHEA-S showed a steep longitudinal decline of 2-3% yearly. The authors of this paper make the important observation that good health added 10-15% to the level of DHEA and DHEA-S.[16] The association of DHEA-S with longevity was investigated in 75 men and women 90 years of age and older in a study assessing the possible correlation between DHEA-S levels and several biological, endocrine-metabolic and physical activity parameters. DHEA-S concentration was 3110 ng/mL in men <40 years old, 551 in 90-99 year-olds and 404 in centenarians. The respective values of women of the same age groups was 2824, 364 and 521 ng/ml.[33]

Contrary to the studies of other hormones, which often report divergent results, the course of cortisol secretion throughout the entire lifespan was found to be stable with a slight increase in the older ages due to decreased metabolic clearance. In the paper of Cummings et al,[34] 09.00 hour cortisol was found similar in 53 women aged 22-38 years, 20 with premature ovarian failure (20-35 years old), 34 postmenopausal or post-castration and 94 women 65 years or older. The cross-sectional age trend for cortisol in the 156 men of the MMAS longitudinal study was virtually flat within both measurement times with only a slight longitudinal decline.[16] The finding of stable cortisol levels in old age in contrast to the deep decline of adrenal androgens revived the older theory of a separate stimulatory factor of adrenal androgens, different from ACTH.

Table 4. Adrenal androgen changes in aged subjects

Authors	N	Age	Studies	Results
Cumming DC et al 1982[34]	90F	≥65yrs	Cross-sectional	1st-7th day of cycle DHEA-S 2.17±0.15µg/ml/L Postmenopause 1.29±µgml/L
Ravaglia G et al 1986[33]	**75**	90 to older than 100yrs	Cross-sectional	DHEA-S ng/ml Men <40yrs 3110 Men 90-99yrs 551 Men ≥100yrs 404 Women <45yrs 2824 Women 90-94yrs 364 Women ≥100yrs 521
Salvini S et al 1992[31]	543M		Cross-sectional	Mean DHEA-S 3.47µmol/L Current smokers DHEA-S 4.27µmol/L P=0.002 3% yearly decline of DHEA-S
Sulcova J et al 1997[29]	211F 110M	16-92yrs	Cross-sectional	At 21-25yrs DHEA-S 8µmol/L At 51-60yrs 2µmol/L
Nafziger AN et al 1998[30]	341F 273M	20-69yrs	Longitudinal 5 years	DHEA-S 5.6% DHEA 2% decline per year
Burger HG et al 2000[55]	172F	Mean age at baseline 49.1±2.4yrs	Longitudinal 7 years	DHEA-S 1.5% year decline
Orentreich JL et al 2002[32]	97M	32-83yrs	Longitudinal 13 years	67% DHEA-S decrease 13% no change 19% increase
Feldman et al 2002[16]	1156M	40-70yrs	Longitudinal 7-10 years	DHEA and DHEA-S declined 2-3% yearly

GNRH-LH-TESTOSTERONE AXIS

The aging of the hypothalamic gonadotropin releasing hormone (GnRH) pituitary-testicular axis has been amply documented by a large body of studies of serum total testosterone and free testosterone (FT)[35] (Table 5). The stimulator of testosterone production, luteinizing hormone (LH), increases with advancing age at a rate of 1% over a period of 10 years in men 40-70 years old. FSH during the same period increased by 3% yearly.[16] In another study no correlation of LH with testosterone was found, suggesting an alteration in the normal feedback relationship of these hormones. FSH increases at a higher rate of 3% yearly, probably due to a diminished inhibin feedback from the Sertoli cells of the aging testis.[36]

Large-scale cross-sectional and longitudinal studies have documented the great decrease of testosterone despite the increase of LH, indicating an anomaly in the strong forward and feedback relationship of these hormones. In a cross-sectional study of 300 men aged 20 to 100 years grouped in decades, Vermeulin et al.[37] found a decrease of mean serum free testosterone (FT) beginning in the decade of 35-45 years and of testosterone starting in the decade of 45-55 and progressing up to the last 85-100 years. Mean values of T at 75 years were approximately two thirds of those at the age of 20 years, whereas those of FT decreased by 50% during the same period. Sex hormone binding protein (SHBP) binding 45-50% of circulating testosterone started increasing in the decade of 35-45 years and continued to increase up to the last years of life.[38] The proportion of healthy men having subnormal total testosterone (less than

Table 5. Testosterone changes in aged subjects

Authors	N	Age	Studies	Results
Zumoff B et al 1982[43]	35	21-85yrs		35% decrease between 21 and 85 years of age
Morley JE et al 1987[36]	77	61-87yrs	Longitudinal 1981-1982, 1984, 1989, 1990	Decrease 1.1ngml/L (3.7 nmol/L) decade
Vermeulin A et al 1996[37]	300	20-100yrs	Longitudinal 13 years	At 75yrs mean T 2 thirds and FT 50% of T at 20yrs
Ferrini R et al Rancho Bernardo Study 1998[40]	810	24-90yrs	Longitudinal 1984, 1987, 1993	Testosterone decline by 1.9pgml/L FT decline by 18.5pgml/L
Barret-Connot E et al 1999[42]	856	50-89yrs		Decade 50-59 (n=701) T=10.5±3.07 nmol/L Bioavail T=4.27±1.09 nmol/L Decade 80-89 (n=155) T=10.3±4.4 nmol/L Bioavail T=2.61±1.07 nmol/L
Harman SM et al Baltimore Longitudinal Study on Aging 2001[44]	890	58±15yrs	Cross-sectional 3rd to 9th decade	Testosterone decline 0.124nmol/L yearly T/SHBG – 0.0049nmol/L yearly
Feldman HA et al Massachusetts Male Aging Study 2002[16]	1156	40-69yrs at baseline	Longitudinal 1987+1989	Cross-sectional T= -1.6% FT= -2.3% Multitudinal T= -0.8% FT= -2%

11 nmol/L or 3.17 ngml/L) and free testosterone (less than 0.18 nmol/L or 0.34 ngml/L) in the above 300 subjects was insignificant in men aged 20-40 years and rose to approximately 7%, 22% and 37% in the decades 40-60, 60-80 and more than 80 years of age, respectively.[39] The authors of the above studies comment on the great interindividual variability of serum testosterone, which was marked in the older ages.

An analysis of total and bioavailable testosterone in 810 men aged 24-90 years adjusted for covariates showed a decrease of total testosterone by 1.9pg/mL and of bioavailable T by 18.5pg/mL per year of age between the ages of 50 and more than 85 years.[40] A linear decrease of testosterone and free testosterone beginning during the third decade was noted between the ages of 30 and 90 years in 890 men participating in the Baltimore Longitudinal Study of Aging. The average change for testosterone was 0.110 nmol/L per year and 0.005 nmol/L for free testosterone. SHBG rose at a slightly greater rate in the older than in the younger men.[41] The authors of this study calculated the percentage of men in each decade who were considered hypogonadal, having T values less than 11.3nmol/L (3,25 ng/mL). The prevalence of the so defined hypogonadism increased progressively from relatively low levels for men less than 49 years of age to 12%, 19%, 28% and 49% by total testosterone or to 9%, 34%, 68% and 91% by free T index in men in their 50's, 60's, 70's and 80's, respectively. It is to be noted, however, that the value of 3.25ng/mL taken as a limit for hypogonadism is well within the range of normal values given by many authors (3-10 ng/mL).

The largest study of age trends in testosterone, DHEA, DHEA-S and other hormones was conducted in 1156 participants of Massachusetts male aging study (MMAS) who were at baseline 40-70 years old. It was found that testosterone declined cross-sectionally at 0.8% per year of age, whereas free and albumin-bound testosterone declined at about 2% per year and SHBG increased at 1.6% per year. The finding that good health added 10-15% to the level of androgens and the fact that longitudinal decline was steeper suggests that incident poor health may accelerate the age-related decline in androgen levels.[16]

Dihydrotestosterone levels have not been found to be related with aging.[38,42] The concentration of DHT

was found to be age invariant in 35 men aged 21-85 years.[43] An unexplained rise of 3.5% per year was reported in the MMAS study of 1156 men during a period of 7-10 years.[16] In any case, serum DHT is not a reliable index of this hormone as 95% of testosterone transformation to DHT takes place in the tissues.

The pathophysiology of the great and progressive testosterone decrease in aging is intriguing. The number of Leydig cells are reduced in old age and there is evidence of vascular changes in the testis that might influence the stereogenetic capacity of Leydig cells, suggesting a primary testosterone insufficiency.[38] However, the response of Leydig cells to human chorionic gonadotropin, although diminished, showed that the testis in old men could restore the low levels of testosterone if they were properly stimulated.[44-46] On the other hand, the increase in old age of Luteinizing Hormone (LH), the principal stimulator of Leydig cells, is inappropriately small compared to the great decrease of testosterone, which should provoke a strong negative action.[36] Moreover, the stimulation of LH by GnRH in aged persons showed a normal secretory capacity of the gonadotropins.[47] The existence therefore of adequate LH and testosterone secretory capacity with modestly increased LH and decreased testosterone points to a hypothalamic dysfunction. Corroborating the above is the reported pulsatile pattern of LH, reflecting GnRH stimulation, with less high amplitude pulses.[48] Sampling of LH at frequent intervals of 2-5 minutes in three old men during the hours of sleep clearly displayed the diminution of high amplitude pulses.[49,50] A blunted circadian rhythm of LH in the aged has also been demonstrated.[51,52]

Recent studies have clarified that there are two mechanisms in the aging-related changes of testicular function (Wu et al., JCEM 93:2737, 2008 and Wu et al. N Engl J Med 363:123, 2010). Aging *per se* has a primarily testicular effect where reduced testosterone is accompanied by elevated LH. Aging-related obesity affects the hypothalamic-pituitary function, whereby lower testosterone is accompanied low or inappropriately normal LH. Alterations therefore of GnRH neuronal release, as is monitored by the profile of LH secretion in old age, seem to be the origin of testosterone decrease in aging with a contribution by primary testicular failure.

THE GNRH-LH + FSH – OVARIAN AXIS

The GnRH-LH + FSH – Ovarian axis undergoes a dramatic change occurring at about the age of 50 years. Within a few months the female organism is deprived of 90% of circulating estradiol, the hormone responsible for the development of the female phenotype essential for the reproductive action of the ovary and indispensable for the skin, the bones and many other tissues, including the brain where the estradiol receptors ER1 and ER2 are abundant.[53] The impact from the loss of this hormone is immediately felt by the disregulation of the neurovegetative nervous system, an overt indication of estradiol significance for the brain. Disturbing symptoms arising from the atrophy of the lower urogenital system and the vagina and which necessitate treatment soon occur, adversely affecting women's quality of life. In a study of vaginal smears in 1000 women 1 to 30 years after the last menses, the loss of the protective superficial layers of the vaginal epithelium, the most sensitive tissue to estrogens, was demonstrated by the presence of parabasal cells in a percentage of 75.5% the first four years after the cessation of menses, which rose to 88-92% after 10 years.[54]

The reduction of estradiol in the post-menopausal period of life may have an adverse effect on hypothalamus and the brain in general. Growth hormone (Table 1) and adrenal androgens (Table 4) also decrease in female individuals. A publication from the group of S.S. Yen reported that postmenopausal subjects show an earlier decline in DHEA-S levels, which however was not corrected by replacement treatment, suggesting that ovarian factors separate from estrogenic failure influenced the reduction of DHEA-S.[34] In a longitudinal study of 172 women through the menopausal transition, Australian researchers found that DHEA-S decreased as a function of age and was not time-related to menopause.[55] The ovarian component of Δ_4-androstendione decreases progressively after menopause representing one quarter rather than half of the total 2-3 mg Δ_4-A produced daily during the cycle. The total production of testosterone in women is small, i.e. 0.250 mg/daily, $^1/_4$ originating from the adrenals, $^1/_4$ from the ovaries and $^2/_4$ from the peripheral transformation of Δ_4-A to testosterone.

The most obvious effect of estrogenic activity

loss is the significant increase of FSH and less of LH after menopause, which continues uninfluenced until late in life. In a study of 116 women 1-45 years after the last menses, it was shown that the mean FSH value in 45 women 16-45 years after menopause was 51.6 mU/ml (with a not included aberrant value of 100mU/ml) compared to 56 mU/mL of 27 women 1 to 5 years after the last period.[56] The phenomenon of unexhausted FSH secretion liberated from estradiol and inhibin intense inhibitory action has been poorly investigated. Is the increased FSH secretion until the end of life due to corresponding GnRH hyperactivity or does the gonadotrop cell possess an intrinsic capacity to secrete high levels of FSH in response to regular GnRH stimulator if it is untied from powerful inhibitions? The consequences on the other hand of the flooding of the female organism by FSH for decades have not been considered. The 2-fold elevation of gonadotropins in individuals with Alzheimer disease compared with age-matched controls must be further explored in women.[57]

CONCLUSIONS

A large volume of studies has disclosed numerous facts concerning pituitary alterations in aging and the changes in the thyroid, the adrenals and the gonads. However, despite the abundance of data accumulated over the years, a definitive and clear-cut understanding of the exact state of endocrine hypothalamic function in old age has not as yet been attained.

Given the mystery surrounding the pulsatile and rhythmic activity of these neurons in other periods of life, it was projected that gaining comprehensive insight into the precise workings of neuronal intracellular activity during aging was bound to be a highly challenging task. The incredible complexity involved in hypothalamic neuroendocrine hormone production and release, resulting from the combined action of multiple neurotransmitter pathways, hormones and cytokines acting synergistically or antagonistically, made the perplexity obvious from the outset.

Meanwhile, the more easily accessible findings derived from animal experimentation have enabled significant advances in our knowledge of neuroendocrine hypothalamus function, especially as regards targeted mutagenesis techniques which offer highly useful information for guiding further human research. Moreover, the newly developed discipline of neuroimaging promises to furnish more insight into endocrine nuclei metabolism once such impediments as the difficult visualization of scattered and non-circumscribed endocrine neurons are overcome.

For the present, the light shed on the involvement of the endocrine hypothalamus, the hypophysis and the peripheral glands in the process of aging and the considerable progress made and volume of research accomplished on the effect of advancing age on the hormonal end products of these endocrine glands have created a satisfactorily clear picture of hormonal status in old age, which may allow decisive initiatives. The alterations observed have produced heightened interest in the possibility of an association between these changes and serious pathologic conditions and longevity.

In summary, the increasingly accumulating knowledge on the subject and the availability of GnRH and its analogues and of the sum total of the pituitary, thyroid, adrenal and gonadal hormones are building up a reliable arsenal enabling well conceived and executed therapeutic interventions based on the Hippocratic doctrine of benefiting and not harming.

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