Clinical Section / Mini-Review

Gerontology

Gerontology 2015;61:291–300
DOI: 10.1159/000367692

Received: March 18, 2014
Accepted: August 19, 2014
Published online: November 27, 2014

The Endocrinology of Ageing: A Mini-Review

Christopher M. Jones Kristien Boelaert

Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK

Key Words
Ageing · Endocrine · Hormone · Elderly · Longevity · Metabolism

Abstract
Significant advances in health and social wellbeing have led to linear gains in life expectancy and an accompanying increase in the burden imposed by age-related morbidities. Complex alterations in hormonal networks which regulate homeostasis and survival may underlie this poor adaptation to later life, as exemplified by an increased fracture risk amongst post-menopausal women. Beyond overt under- or overactivity of hormonal axes, changes in the concentrations of regulatory hormones may also impact on health and disease. Subclinical hyperthyroidism, a disorder characterised by normal thyroxine levels in the presence of decreased thyroid-stimulating hormone, is, for instance, independently associated with an increased risk of atrial fibrillation amongst elderly populations. Both the menopause and subclinical thyroid disease demonstrate the difficulty in reversing endocrine changes in later life, with minimal impact from thyroxine therapy in subclinical hypothyroidism and multiple reports of harm resulting from hormone replacement therapy in peri- and post-menopausal women. Given these findings, strategies to locally regulate hormone bioavailability by altering pre-receptor metabolism may offer greater therapeutic potential in the fight against age-related disease. This review aims to provide an overview of the ageing endocrine system and its potential impact on health and disease in the elderly. It will postulate that strategies to coordinate pre-receptor hormone metabolism and a greater understanding of putative hormonal longevity pathways may offer key new drug targets in the fight against ageing, and will argue against applying the conventional endocrine maxim of 'block and replace' to hormonal changes seen during ageing.
© 2014 S. Karger AG, Basel

Introduction

Despite the contribution of sustained improvements in health and social wellbeing to linear gains in life expectancy within the developed world, much of older age is impaired by detrimental changes in body composition and function [1]. Complex alterations in hormonal networks which maintain homeostasis and regulate reproduction, metabolism, nutrition and growth may underlie this poor adaptation to later life. The secretion of hormones decreases within most axes, the impact of which is augmented by a reduction in the sensitivity of tissues to their action, and normal circadian rhythms are lost. Endocrine axes manifest these changes with clinically identifiable losses of function such as those seen in the ageing of the reproductive system (menopause and andropause), the growth axis (somatopause) and axes involving the adrenal gland (adrenopause).

The clinical sequelae of these changes are variable but include reductions in bone, skin and skeletal muscle mass and strength, derangement of insulin signalling, increases in adipose tissue and effects on immune function. Conse-

KARGER 125

© 2014 S. Karger AG, Basel
0304–324X/14/0614–0291$39.50/0

E-Mail karger@karger.com
www.karger.com/ger

Dr. Kristien Boelaert
Centre for Endocrinology, Diabetes and Metabolism, 2nd Floor
Institute of Biomedical Research, College of Medical and Dental Sciences
University of Birmingham, Edgbaston, Birmingham B15 2TT (UK)
E-Mail k.boelaert@bham.ac.uk

Downloaded by:
198.143.56.33 - 7/1/2015 2:32:05 AM

quently, a number of studies have been carried out to assess the benefits of hormonal supplementation in the elderly, but the efficacy of these interventions remains relatively unclear. It is also increasingly recognised that endocrine adaptation during earlier life may affect longevity and health in older age [2]. Relative decreases in early nutritional intake have, for instance, found associations with both prolonged lifespan and reduced incidence of pathologies such as diabetes and cardiovascular disease via effects mediated by the insulin and insulin-like growth factor-I (IGF-I) pathways [3].

This article will highlight pathways linked to both longevity and variable endocrine function in the elderly as a means to delineating the myriad changes in hormonal signalling seen during the ageing of an individual. It will subsequently evaluate the clinical impact of these changes before arguing that targeted strategies to locally modulate dysregulated hormonal signalling during ageing may be of potential therapeutic benefit.

Endocrine Regulation of the Ageing Process

The recognition that food restriction in animals alters biomarkers associated with longevity may afford the pituitary gland and its downstream pathways additional significance in the control of ageing [2, 3]. The existence of these evolutionarily conserved pituitary-derived longevity pathways is supported by studies undertaken in mice and a raft of simpler organisms. It is recognised, for instance, that mutations of the IGF-I receptor homologue DAF2 which interfere with the functioning of the IGF-I/insulin signalling pathway in *Caenorhabditis elegans* and *Drosophila melanogaster* extend lifespan, as do reductions in signalling through the separate growth hormone (GH)/IGF-I and insulin pathways in mice [4, 5].

The potential role of insulin and GH/IGF-I pathways in controlling longevity is exemplified by the *Ames* dwarf mouse, which lacks the *PROP1* transcription factor. Deletion of this factor, which is crucial to the development of the pituitary, leads to an absence of GH, prolactin and thyroid-stimulating hormone (TSH), in addition to decreased circulating levels of IGF-I [6]. A similar picture is found with mutations of the pituitary-forming transcription factor PIT1 in Snell dwarf mice, yet in both instances, mice live longer even with amelioration of their hypothyroidism by thyroxine replacement [6, 7]. Given that deletions of the GH receptor and GH-releasing hormone (GHRH) receptor have similar consequences and that female mice with cell autonomous IGF-I receptor mutations live longer than their wild-type counterparts, it follows that the GH/IGF-I axis at least partly determines longevity [8]. In these global knockout models, cell autonomous reduced signalling through the insulin and IGF-I pathways leads to a reduction in the phosphorylation of their downstream intracellular targets AKT/protein kinase B (PKB) and serum/glucocorticoid-regulated kinase (SGK). This, in turn, reduces the phosphorylation of the forkhead box transcription factors (FOXO), resulting in their nuclear translocation and both the subsequent transcription of longevity genes and inhibition of their pro-ageing counterparts (fig. 1) [2, 6–8].

Alternatively, numerous studies focussed on the highly conserved insulin/IGF-I signalling pathway have raised the exciting potential of additional non-cell autonomous endocrine regulation of ageing which is succinct from pituitary-derived longevity pathways. It is recognised in a number of species of both flies and worms that control of putative longevity factors such as the insulin/IGF-I pathway may originate at the level of cells such as adipocytes and neurones. In these instances, a mutant cellular genotype is able to exert cell non-autonomous control of the phenotype of other non-mutated tissues by as yet undetermined endocrine factors in order to alter their phenotype to one compatible with a longer lifespan [2]. Whilst it is not yet clear whether these findings are applicable to the mammalian IGF-I receptor, the fat-specific insulin receptor knockout (FIRKO) mouse provides evidence for the existence of mammalian cell non-autonomous control of ageing. In this mouse, specific knockout of the insulin receptor within adipocytes leads to a significantly increased lifespan and phenotypic change within a raft of tissues not carrying the knockout mutation [7].

This raises the prospect of adipocytes producing as yet undetermined humoral factors which trigger the ageing of multiple different tissues. Similarly, the discovery in the human circulation of fragments of the transmembrane protein Klotho, which favours longevity when expressed, lends more evidence to the existence of humoral 'longevity factors', as do a multitude of lipophilic hormone pathways associated with ageing regulation within simple organisms. Should these processes be effectively characterised, novel therapeutic targets to modulate ageing may be on the horizon.

Ageing of the Endocrine System

Given that the most reproducible factor affecting the function of key endocrine regulators of homeostasis, the hypothalamus, is ageing, much of elderly morbidity may

Downloaded by:
198.143.56.33 - 7/1/2015 2:32:05 AM

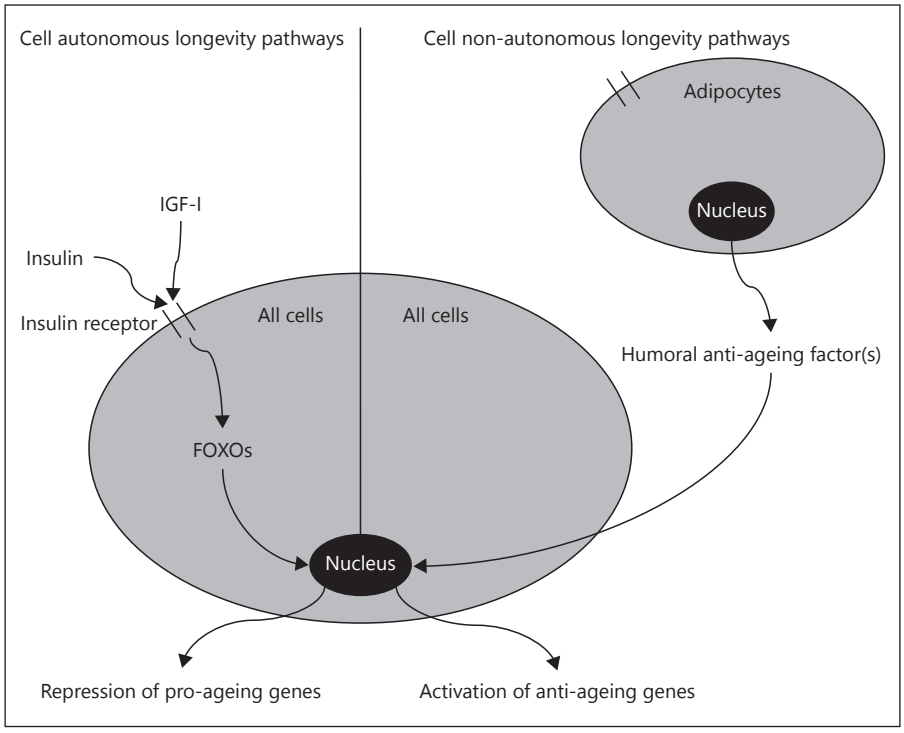

Fig. 1. Putative intracellular mechanisms for the coordination of longevity pathways. Ageing may be determined, at least in part, by evolutionarily conserved longevity pathways. Many of these are 'cell autonomous', meaning that a global mutation in a gene encoding a regulator such as the insulin receptor directly affects all cells in the body via the transcriptional activity of FOXOs. Additional control of longevity may be exerted by specific cellular lineages which produce humoral factors capable of reprogramming gene transcription in response to environmental stressors.

be attributed to more overt and potentially replaceable hormone imbalances. By better understanding the changes undergone by the ageing endocrine hypothalamus and both its downstream pathways and counterpart regulators, the potential utility of hormone supplementation in the elderly will be determined.

The Hypothalamic-Pituitary-Gonadal Axis

The decline in the reproductive capacity of women in the late fourth to fifth decade of life is accompanied by diverse sequelae, including an increased risk of osteoporosis, psychogenic disturbance and a greater burden of cardiovascular and cerebrovascular disease [9]. Attempts to ameliorate losses in oestrogen through hormone replacement therapy (HRT) have, however, courted significant controversy relating both to increased risks of malignancy and vascular events, thereby standing as an exemplar for the difficulty in managing hormone balance during ageing [10, 11]. Recognised changes in female sex steroids are matched by the andropause, a relatively poorly defined process characterised by a progressive age-dependent loss of the anabolic androgen testosterone within males [12]. The reported positive and negative health outcomes associated with reproductive HRTs are summarised in table 1.

Within reproductive life, oestrogen production by the ovaries is tightly controlled by negative feedback mechanisms with limited influence exerted by extra-gonadal synthesis. However, approximately 90% of circulating oestrogen is lost at the time of ovarian failure, during the fourth and fifth decade of life, prompting extra-glandular formation of oestrogens by aromatase expression within adipose and skin to become the predominant source of sex steroid generation, with additional contribution from the adrenals.

Unlike the dramatic changes seen in women, testosterone loss seen during the andropause is both insidious and more contentious. There is no specific age at which this process starts and cross-sectional studies have suggested that it is driven by global reductions in activity across the hypothalamic-pituitary-gonadal axis, though reduced GnRH neuronal release is postulated to be the principal change with primary testicular failure as a contributing factor [8, 13]. Sex hormone-binding globulin (SHBG) levels increase during ageing, meaning that the andropause is biochemically manifest by a relatively greater decrease in free testosterone than its bound counterpart [8, 13].

In both men and women, loss of sex hormones during ageing contributes to changes in body mass, musculoskeletal integrity, sexual dysfunction and long-term risks of

Gerontology 2015;61:291–300
DOI: 10.1159/000367692

Downloaded by:
198.143.56.33 - 7/1/2015 2:32:05 AM

Table 1. Reported positive and negative health outcomes of female and male reproductive hormone replacement treatment

Organ system	Replacement hormone	Reported health outcome
Short-term outcomes		
Vascular	oestrogen	relief of vasomotor symptoms
Brain	oestrogen	improved mood and decreased depression in early menopause
Urogenital	testosterone and oestrogen	increased libido
	oestrogen	proliferative effect on the vaginal and vulval epithelium
	oestrogen	improved vaginal lubrication and reduced dyspareunia
	oestrogen	reduction in urinary frequency and urgency
	oestrogen	putative reduction in urinary tract infection incidence
Musculoskeletal	oestrogen and testosterone	protection against connective tissue loss
Long-term outcomes		
Musculoskeletal	oestrogen and testosterone	preserved bone mineral density reduced risk of osteoporosis-related fractures
Vascular	oestrogen (combined continuous regimes)	increased risk of coronary events
	oestrogen (combined and oestrogen only regimens)	increased risk of venous thromboembolism
	oestrogen (combined and oestrogen only regimens)	increased risk of stroke
Gastrointestinal	oestrogen	increased risk of gallbladder disease no significant impact on colorectal cancer
Cognition	oestrogen (combined regimens)	increased incidence of dementia
	oestrogen (single agent)	no significant change
Female reproductive system	oestrogen	increased risk of breast cancer
	oestrogen	conflicting reports regarding risk of ovarian cancer
	oestrogen (unopposed)	increased risk of endometrial cancer

health and disease. Interestingly, decreased libido in postmenopausal women may be attributed to reductions in testosterone, the additional impact of which in men may be erectile dysfunction [14]. The literature concerning the role of sex hormone changes in a raft of additional cognitive changes within ageing men and postmenopausal women is more disparate, with inconsistent studies within both males and females [15]. Persistently elevated FSH within postmenopausal women has, however, been linked to Alzheimer's disease [15].

Perhaps the most recognised change resulting from the menopause is that of osteoporosis. This appears to be driven by reductions in metabolically active trabecular bone occurring due to uncoupling of the bone remodelling cycle secondary to oestrogen loss and leads to a marked increase in fracture risk amongst elderly women [16]. Whilst men are relatively more protected from the effects of decreased bone mineral density due to the attainment of a higher peak bone mass, the prevalence of osteoporosis is known to increase amongst ageing males [17]. A number of studies have reported both maintenance of bone mineral density following testosterone supplementation during ageing and a positive relationship between endogenous androgen levels and bone mineral density, yet men with defunctioning oestrogen receptor mutations and aromatase deficiency have been identified to have lower bone mineral density [18–21]. This, and research identifying that serum oestrogen correlates more closely with peak bone mass than testosterone, indicates that both male and female sex steroids are required for the maintenance of bone mineral density during ageing. Further, it is not yet known whether testosterone supplementation affords any reduction in the frequency of fractures amongst ageing men.

The significant increase in the risk of heart disease in women undergoing the menopause, coupled with the relatively reduced burden of heart disease amongst premenopausal women when compared to age-matched

Downloaded by:
198.143.56.33 - 7/1/2015 2:32:05 AM

males, indicates a cardioprotective role for oestrogen which is lost in later age [10]. The relationship between testosterone and heart disease in both males and females is less clear. In women, a pooled meta-analysis has suggested that, whilst beneficial for sexual function, the addition of testosterone to HRT may result in an adverse increase in high-density lipoprotein cholesterol. This study was, however, unable to confirm longer-term effects on morbidity. In contrast, whilst studies focussing on testosterone supplementation amongst males have extolled short-term gains in sexual function, strength and well-being, a number of studies have identified significant increases in cardiovascular adverse outcomes amongst men with late-onset hypogonadism who receive testosterone supplementation [22–24]. A less significant but similar effect for testosterone has been recognised amongst ageing men [11]. Although the manner in which sex hormones modulate cardiovascular risk is unclear, it is postulated to include changes in cholesterol and both high- and low-density lipoproteins. It is likely to be additionally, albeit indirectly, related to increases in insulin resistance which follow falling sex hormone concentrations [8]. Testosterone may additionally directly affect the myocardium via androgen receptors.

Despite similarly reduced sex hormone concentrations in ageing men and women, the menopause is set apart from the andropause by the extent to which it induces reproducible symptoms which significantly impair quality of life. It is accompanied by a cacophony of urogenital symptoms and changes, including urinary frequency, dysuria, incontinence and vaginal atrophy, all of which carry significant burden for postmenopausal women [25]. These symptoms are in turn accompanied by those resulting from alterations in the set point of the hypothalamus, including recurrent hot flushes recognised to follow luteinizing hormone (LH) surges, and changes in serotonin levels [26].

Despite these many changes, HRT has met with considerable controversy in females. Its use for the primary or secondary prevention of cardiovascular disease has, for instance, been warranted both ineffective and harmful, at least in its combined continuous form [10]. Analysing thirteen trials incorporating a total of 38,171 women, a recent Cochrane review identified an increased risk of stroke, venous thromboembolic events and pulmonary embolism in patients treated with HRT, revealing relatively low numbers needed to harm [10]. Similarly, although initially considered to be of some excitement as a 'rejuvenating hormone', testosterone therapy remains highly contentious within men. It is on the basis of current evidence entirely unclear as to whether androgen replacement affords any significant advantage to men with testosterone within normal parameters for their age [26].

The balance of risks and benefits for HRT in women is more complex and the British Menopause Society has published extensive guidance relating to its use in peri- and post-menopausal women with or without a uterus [27]. In summary, it appears clear at present that HRT offers support with treating vasomotor, urogenital and some psychogenic symptoms related to the menopause. Whilst it decreases fracture incidence, its risks mean that alternative therapies such as bisphosphonates are preferred for the long-term prophylaxis and treatment of osteoporosis [25, 27, 28]. It has no role in the prevention or treatment of cardiovascular disease and previous links to a significantly reduced risk of colorectal cancer incidence have not been supported by strong evidence [29]. There is, however, a clear increase in the risk of breast cancer, coronary events, venous thromboembolism, gallbladder disease and, putatively, ovarian cancer in women taking HRT, meaning that its use should ideally be curtailed to short-term therapy only [25, 27, 28].

The Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal axis sits as an adaptive regulator of stress response and is integral to homeostasis. It is perhaps the adrenal steroids DHEA and DHEA-S that have evoked the greatest attention in the search for effective anti-ageing hormones [30]. Arguably poorly understood, DHEA and DHEA-S are the most abundant of the steroid hormones and may act as neurosteroids, with postulated immunoprotective, anti-cancer and anti-ageing effects [8, 30]. Unlike other adrenal hormones, the production of DHEA is closely tied to ageing so that secretion is greatest at the beginning of the second decade of life, falling thereafter. This decrease, which results in DHEA levels falling longitudinally by approximately 2–3% each year, is thought to follow involution of the zona reticularis of the adrenal gland [30, 31].

In a large prospective observational study of DHEA, healthy persons were noted to have significantly lower DHEA and DHEA-S concentrations than their more poorly ageing counterparts [32]. Similarly, a number of cross-sectional studies have revealed a close, albeit circumstantial, correlation between DHEA-S levels and a raft of morbidities, including depression, type 2 diabetes and Alzheimer's disease [28]. Whether this relationship is causal remains to be determined, with a large double-blind randomized controlled study revealing only in-

Downloaded by:
198.143.56.33 - 7/1/2015 2:32:05 AM

creased libido and selectively improved skin status and bone turnover in elderly women, and not men, treated with DHEA supplementation [33]. A more recent double-blinded study, which reviewed the effect of DHEA replacement in patients with low levels of the hormone, recognised no beneficial effects from DHEA supplementation on physiological parameters of health. This apparent sexual dimorphism of adrenal hormone release may have greater significance in the pathogenesis of cardiovascular disease and cognitive dysfunction, particularly given suggestions that ageing women exhibit lower DHEA(S) and higher cortisol levels, and thus a higher cortisol/DHEAS ratio, than men [34].

Unlike many other hormones, concentrations of both cortisol and its binding globulin remain relatively consistent throughout ageing [35, 36]. There is, however, some evidence to suggest diminished negative feedback on cortisol production, which may lead to a greater response to corticotropin-releasing hormone (CRH) challenge, particularly in women [26]. Similarly, the mineralocorticosteroid aldosterone demonstrates a moderate decrease during life, and both this and an associated decrease in plasma renin activity are considered to impact minimally on physiological processes in the elderly [35, 36].

The Hypothalamic-Pituitary-Thyroid Axis

Dysfunction of the thyroid axis is common in the general population and even more prevalent in the elderly, with an increased incidence of overt thyroid under- or overactivity [37]. This is augmented by significant numbers of patients with subclinical thyroid pathology, which is found in more than 10% of patients aged over 80 years [37].

The burden imposed by disorders of the thyroid in the elderly is, however, unclear. Confounding factors include the 'nonthyroidal illness syndrome', characterised by decreased serum free triiodothyronine (T3), low or normal TSH, high reverse T3 and relatively normal free thyroxine (T4) concentrations. It is important to make a differential diagnosis between this sick euthyroid syndrome and subclinical hyperthyroidism. The failure of the serum TSH to rise in response to low circulating thyroid hormone concentrations in critical illness arises from a degree of central hypothyroidism caused by alterations in the set point of the hypothalamo-pituitary-thyroid axis [37]. A similar pattern may also be found during treatment with certain drugs including corticosteroids and dopamine agonists.

Primary hypothyroidism, the most common pathological hormone deficiency, occurs more often in women than in men and increases in incidence with age [38]. Like hyperthyroidism, the presentation of hypothyroidism may be overt or subclinical (raised TSH with normal free T4 and free T3 concentrations). Its presentation is both insidious and non-specific, with psychiatric symptoms such as depression particularly common in the elderly, in addition to hair loss, dry skin, cold intolerance, reduced appetite, fatigue and weakness [37]. Within elderly populations, Hashimoto's thyroiditis is the most common cause of hypothyroidism, although the use of radiotherapy, surgery and iodine for thyroid overactivity or malignancy is a significant contributing factor [39, 40]. The increasing use of tyrosine kinase inhibitors (TKIs), such as sunitinib, may also impact on the prevalence of this disorder [38].

Subclinical hypothyroidism, on the other hand, reflects early thyroid failure and its accurate diagnosis depends on the recognition of the physiological shift in the upper limit of TSH towards higher concentrations, which occurs during ageing [41]. This age-specific TSH trend necessitates the use of age-appropriate reference ranges when evaluating thyroid dysfunction in the elderly, although it is broadly classed as mild (serum TSH 4.5–10.0 mIU/l) or severe (TSH >10.0 mIU/l) [41]. The diagnosis of subclinical hypothyroidism is additionally complicated by its paucity of objectively definable symptoms. Two large cross-sectional studies have, for example, failed to demonstrate any association with cognitive dysfunction, anxiety or depression in elderly patients, with an additional study suggesting that walking speed and physical function may in fact be better in patients with subclinical hypothyroidism [37].

There are a number of important postulated long-term impacts of both overt and subclinical hypothyroidism [37, 38, 41]. Overt hypothyroidism is associated with dyslipidaemia and, though the relationship between serum lipid concentrations and subclinical hypothyroidism is more controversial, a recent systematic review demonstrated that levothyroxine replacement results in small beneficial effects on total and low-density lipoprotein cholesterol [38]. An increased risk of heart failure has also been demonstrated in patients with subclinical hypothyroidism aged over 65 years [41]. Despite this, the Leiden study of persons aged over 85 years has associated raised TSH with decreased risk of death from cardiovascular disease and increased longevity, although TSH >10.0 mIU/l has been linked to an increased risk of coronary heart disease events and related mortality in all ages [42].

The prevalence of thyrotoxicosis increases with age and is highest within white populations and in iodine-deficient areas [37]. A reduction in the frequency of classically described symptoms such as heat intolerance,

Downloaded by:
198.143.56.33 - 7/1/2015 2:32:05 AM

Table 2. Postulated long-term consequences of subclinical hyperthyroidism and subclinical hypothyroidism in the elderly

Subclinical hyperthyroidism	
Symptoms	increased palpitation and heat intolerance
Cognition	increased risk of dementia, though findings remain conflicting
Cardiovascular	increased risk of atrial fibrillation increased risk of related mortality
Cerebrovascular	increased risk of related mortality
Musculoskeletal	reduced bone mineral density, particularly in post-menopausal women limited evidence of impact on fracture rates
Subclinical hypothyroidism	
Cognition	little effect, though findings remain conflicting
Cardiovascular	left ventricular diastolic dysfunction increased systemic vascular resistance increased total cholesterol conflicting reports relating to increased mortality

tremor and anxiety is observed in elderly people who often present in an asymptomatic manner [37]. Weight loss and shortness of breath are more commonly reported, and atrial fibrillation is more frequent in people aged more than 60 years [39]. Thyrotoxicosis may be associated with hyperthyroidism when there is increased production and secretion of thyroid hormones or may be due to the release of pre-formed thyroid hormones into the circulation. Whilst Graves' disease accounts for the majority of hyperthyroidism in the general population, the prevalence of toxic nodular hyperthyroidism is disproportionately high in the elderly and may be the principal underlying aetiology [37]. Causes of 'leakage hyperthyroidism' include subacute and drug-induced thyroiditis. Amiodarone may also cause thyrotoxicosis in 6–10% of patients who take it, both by inducing hyperthyroidism (type 1) and by causing thyroiditis (type 2) [37].

The long-term sequelae of subclinical hyperthyroidism are somewhat more contested but summarised within table 2 [37, 43]. Data from three meta-analyses have shown no increase in cardiovascular mortality or all-cause mortality in patients with subclinical hyperthyroidism, although a further three have demonstrated an association [37]. Intriguingly, one meta-analysis highlighted that mild hyperthyroidism was associated with increased cardiovascular mortality only in those with other morbidities, perhaps instead identifying a link with non-thyroidal illness syndrome. Both overt and subclinical hyperthyroidism are additionally associated with reduced bone mineral density, whilst low TSH levels have also been linked to poor cognitive function and dementia, yet underlying mechanisms remain unclear [39, 42, 43].

Overt hypothyroidism is treated with levothyroxine monotherapy and hyperthyroidism is best managed with radioiodine, especially if the underlying aetiology is toxic nodular disease, although thyroidectomy (following induction of euthyroidism) or long-term low-dose antithyroid drugs may be preferred in certain patients. The treatment of subclinical thyroid dysfunction is more controversial and guidelines for treatment in such patients are based on the degree of abnormality in TSH concentrations, the presence of comorbidities and patients' symptom profiles [41, 43]. There is an urgent need for well-conducted clinical trials to indicate the need for intervention in patients with mild thyroid dysfunction and the effects of these therapies on the long-term consequences of subclinical thyroid disease.

Pituitary: GH, IGF and Prolactin

Levels of both GH and IGF-I fall in concert during ageing and may more than halve between early and later life in a process termed the somatopause. Its postulated consequences are extensive and, given that the GH/IGF-I axis represents the principal anabolic hormone axis in females, may differ between sexes. Given that a number of factors are known to differentially stimulate GH/IGF-I action and activity, it is perhaps unsurprising that the clinical impact of altered GH/IGF-I levels in older age remains unclear [44]. In isolation, GH and IGF-I supplementation has been inconsistently linked to improvements in strength training in older individuals [45].

Hormonal links between the ageing pituitary and cognitive, rather than physical, changes have been afforded by prolactin, a hormone secreted by the anterior pituitary lactotrophs [15]. Peak concentrations of this hormone, which occur shortly prior to the onset of sleep, have been demonstrated to negatively correlate with age [46, 47]. This, and reduced pulse amplitude during sleep in older age, indicates decreased dopaminergic inhibitory action on prolactin production in the elderly during the sleep period [15, 26]. This may be restorable with dopaminergic agents such as metoclopramide, potentially assisting in the control of age-related disordered sleep patterns such as early sleep onset and awakening.

Downloaded by:
198.143.56.33 - 7/1/2015 2:32:05 AM

The Gut Hormones

Perhaps the most significant endocrine organ to impact on age-related morbidity is the endocrine pancreas. Insulin secretion is known to be affected by ageing, falling with advancing age by as much as 0.5% per year, independent of its action in peripheral tissues [26]. A decline in both the number of pancreatic islet β cells and their function, occurring independently of peripheral resistance to insulin, is thought to underlie this and may contribute to the elderly population's susceptibility to developing diabetes [48].

The decrease in islet cell function appears to be multifactorial in aetiology, with postulated contributing factors including a loss of expression of β-adrenergic receptors and orphan G-protein-coupled receptors encoded by GPR39, with a consequent reduction in adrenergic stimulation of insulin secretion and pancreatic function [48]. Reduced circulating vitamin D and impaired incretin sensitivity have also been linked to cellular dysfunction [49]. There appears to be an additional age-related decline in cell cycle entry of β cells and a reduction in their regeneration capacity which contributes to a decrease in pancreatic islet β-cell mass [48].

Hormones involved in governing satiety and informing energy expenditure, such as adiponectin, ghrelin and leptin, also undergo a number of age-related changes which are yet to be accurately characterised [50].

Vitamin D

Vitamin D has been linked to a premature ageing phenotype in mouse models with hypervitaminosis D. Seemingly conflictingly, severe vitamin D deficiency demonstrates a similar phenotype. These data demonstrate that vitamin D is linked to ageing, that it may contribute to health and disease in elderly individuals and that there appears to be a U-shaped dependence on its concentration [51]. It should be noted, however, that reports of a U-shaped response to vitamin D levels have recently been extensively critiqued [52].

Pre-Receptor Hormone Metabolism

The activity of a number of hormones is determined by the degree to which they are available to bind at intracellular receptors. For the majority of hormones, the effect of this is masked by significant changes in the humoral level of the hormone during ageing, yet for hormones such as cortisol, the circulating level of which remains relatively stable during ageing, pre-receptor regulation may contribute to significant morbidity in the elderly.

It is now well documented that the glucocorticosteroid-activating enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1), which converts the inactive steroid cortisone to its active catabolic product cortisol, increases in activity and expression during the ageing of bone, skeletal muscle, skin and the central nervous system [53, 54]. It is postulated that this local glucocorticoid excess, occurring despite normal circulating concentrations of cortisol, could underlie conditions including osteoporosis, sarcopenia, skin atrophy and cognitive decline. Whilst work continues to focus on postulated regulatory pathways for this increased enzymatic activity, including those important in the concept of 'inflammaging', specific inhibitors of 11βHSD1 have been developed and are entering study in phase 2 clinical trials following exciting results in mouse models in vivo. Replicating this approach for other hormones may provide yet more targeted avenues for regulating the impact of hormone imbalance on age-related morbidity.

Conclusion

Ageing is associated with significant changes in the regulation of hormonal axes and the downstream availability of their active products. Many of these changes are well characterised, but their precise impact on health and disease remains unclear. Similarly, whilst hormonal deficit and excess has been linked to pathological changes in ageing individuals, the harm imposed by inappropriate HRT administration demonstrates that the conventional endocrine maxim of 'block or replace' is too simple a means to addressing age-related morbidity. Mechanisms to control pre-receptor hormone metabolism may afford significant future therapeutic potential, as may control of longevity pathways through as yet largely undetermined hormonal mediators of cell non-autonomous signalling.

Disclosure Statement

The authors confirm that they have no conflicts of interest relating to this article.

Downloaded by:
198.143.56.33 - 7/1/2015 2:32:05 AM

References

1 Christensen K, Doblhammer G, Rau R, Vaupel JW: Ageing populations: the challenges ahead. Lancet 2009;374:1196–1208.
2 Russell SJ, Kahn CR: Endocrine regulation of ageing. Nat Rev Mol Cell Biol 2007;8:681–691.
3 Masoro EJ: Overview of caloric restriction and ageing. Mech Ageing Dev 2005;126:913–922.
4 Tatar M, Kopelman A, Epstein D, Tu MP, Yin CM, Garofalo RS: A mutant Drosophila insulin receptor homolog that extends life-span and impairs neuroendocrine function. Science 2001;292:107–110.
5 Arantes-Oliveira N, Berman JR, Kenyon C: Healthy animals with extreme longevity. Science 2003;302:611.
6 Brown-Borg HM, Borg KE, Meliska CJ, Bartke A: Dwarf mice and the ageing process. Nature 1996;384:33.
7 Katic M, Kennedy AR, Leykin I, Norris A, McGettrick A, Gesta S, Russell SJ, Bluher M, Maratos-Flier E, Kahn CR: Mitochondrial gene expression and increased oxidative metabolism: role in increased lifespan of fat-specific insulin receptor knock-out mice. Aging Cell 2007;6:827–839.
8 Batrinos ML: The aging of the endocrine hypothalamus and its dependent endocrine glands. Hormones 2012;11:241–253.
9 El Khoudary SR, McClure CK, VoPham T, Karvonen-Gutierrez CA, Sternfeld B, Cauley JA, Khalil N, Sutton-Tyrrell K: Longitudinal assessment of the menopausal transition, endogenous sex hormones, and perception of physical functioning: the Study of Women's Health Across the Nation. J Gerontol A Biol Sci Med Sci 2014;69:1011–1017.
10 Marioribanks J, Farquhar C, Roberts H, Lethaby A: Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2012;7:CD004143.
11 Somboonporn W, Davis S, Seif MW, Bell R: Testosterone for peri- and postmenopausal women. Cochrane Database Syst Rev 2005;4:CD004509.
12 Cunningham GR: Andropause or male menopause? Rationale for testosterone replacement therapy in older men with low testosterone levels. Endocr Pract 2013;19:847–852.
13 Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Lean ME, Pendleton N, Punab M, Boonen S, Vanderschueren D, Labrie F, Huhtaniemi IT; EMAS Group: Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363:123–135.
14 El-Sakka AI, Hassoba HM: Age related testosterone depletion in patients with erectile dysfunction. J Urol 2006;176:2589–2593.
15 Janicki SC, Schupf N: Hormonal influences on cognition and risk for Alzheimer's disease. Curr Neurol Neurosci Rep 2010;10:359–366.
16 Wells G, Tugwell P, Shea B, Guyatt G, Peterson J, Zytaruk N, Robinson V, Henry D, O'Connell D, Cranny A; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group: Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23:529–539.
17 Scopacasa F, Wishart JM, Need AG, Horowitz M, Morris HA, Nordin BE: Bone density and bone-related biochemical variables in normal men: a longitudinal study. J Gerontol A Biol Sci Med Sci 2002;57:M385–M391.
18 Stanworth RD, Jones TH: Testosterone for the aging male; current evidence and recommended practice. Clin Interv Aging 2008;3:25–44.
19 Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J, Korach KS, Simpson ER: Effect of testosterone and estradiol in a man with aromatase deficiency. N Engl J Med 1997;337:91–95.
20 Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, Williams TC, Lubahn DB, Korach KS: Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 1994;331:1056–1061.
21 Khosla S, Melton LJ 3rd, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL: Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab 1998;83:2266–2274.
22 Vigen R, O'Donnell CI, Baron AE, Grunwald GK, Maddox TM, Bradley SM, Barqawi L, Woning G, Wierman ME, Plomondon ME, Rumsfeld JS, Ho PM: Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829–1836.
23 Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, Fraumeni JF Jr, Hoover RN: Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014;9:e85805.
24 Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K, Lakshman KM, Mazer NA, Miciek R, Krasnoff J, Elmi A, Knapp PE, Brooks B, Appleman E, Aggarwal S, Bhasin G, Hede-Brierley L, Bhatia A, Collins L, LeBrasseur N, Fiore LD, Bhasin S: Adverse events associated with testosterone administration. N Engl J Med 2010;363:109–122.
25 Grodstein F, Lifford K, Resnick NM, Gurhan GC: Postmenopausal hormone therapy and risk of developing urinary incontinence. Obstet Gynecol 2004;103:254–260.
26 Chahal HS, Drake WM: The endocrine system and ageing. J Pathol 2007;211:173–180.
27 Panay N, Hamoda H, Arya R, Savvas M; British Menopause Society and Women's Health Concern: The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy. Menopause Int 2013;19:59–68.
28 US Preventive Services Task Force: Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale. Ann Intern Med 2002;137:834–839.
29 Johnson JR, Lacey JV Jr, Lazovich D, Geller MA, Schairer C, Shatzkin A, Flood A: Menopausal hormone therapy and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2009;18:196–203.
30 Perrini S, Laviola L, Natalicchio A, Giorgino F: Associated hormonal declines in aging: DHEAS. J Endocrinol Invest 2005;28(3 suppl):85–93.
31 Salvini S, Stampfer MJ, Barbieri RL, Hennekens CH: Effects of age, smoking and vitamins on plasma DHEAS levels: a cross-sectional study in men. J Clin Endocrinol Metab 1992;74:139–143.
32 Kedziora-Kornatowska K, Beszczynska-Oles R, Kornatowski T, Szadujkis-Szadurski L: The analysis of dehydroepiandrosterone sulphate concentration in elderly age women depending on coexisting disease states. Adv Med Sci 2007;52(suppl 1):126–130.
33 Baulieu EE, Thomas G, Legrain S, Lahlou N, Roger M, Debuire B, Fauconau V, Girard L, Hervy MP, Latour F, Leaud MC, Mokrane A, Pitti-Ferrandi H, Trivalle C, de Lacharriere O, Nouveau S, Rakoto-Arison B, Souberbielle JC, Raison J, Le Bouc Y, Raynaud A, Girerd X, Forette F: Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge study to a sociobiomedical issue. Proc Natl Acad Sci U S A 2000;97:4279–4284.
34 Laughlin GA, Barrett-Connor E: Sexual dimorphism in the influence of advanced aging on adrenal hormone levels: the Rancho Bernardo Study. J Clin Endocrinol Metab 2000;85:3561–3568.
35 Veldhuis JD, Sharma A, Roelfsema F: Age-dependent and gender-dependent regulation of hypothalamic-adrenocorticotropic-adrenal axis. Endocrinol Metab Clin North Am 2013;42:201–225.
36 Zaidi SK, Shen W-J, Azhar S: Impact of aging on steroid hormone biosynthesis and secretion. Open Longev Sci 2012;6:1–30.
37 Boelaert K: Thyroid dysfunction in the elderly. Nat Rev Endocrinol 2013;9:194–204.
38 Roberts CG, Ladenson PW: Hypothyroidism. Lancet 2004;363:793–803.
39 Boelaert K, Torlinska B, Holder RL, Franklyn JA: Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. J Clin Endocrinol Metab 2010;95:2715–2726.

Downloaded by:
198.143.56.33 - 7/1/2015 2:32:05 AM

40 Haugen BR: Drugs that suppress TSH or cause central hypothyroidism. Best Pract Res Clin Endocrinol Metab 2009;23:793–800.
41 Franklyn JA: The thyroid – too much and too little across the ages. The consequences of subclinical thyroid dysfunction. Clin Endocrinol (Oxf) 2013;78:1–8.
42 Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG: Thyroid status, disability and cognitive function, and survival in old age. JAMA 2004;292:2591–2599.
43 Vadiveloo T, Donnan PT, Cochrane L, Leese GP: The Thyroid Epidemiology, Audit, and Research Study (TEARS): the natural history of endogenous subclinical hyperthyroidism. J Clin Endocrinol Metab 2011;96:E1–E8.
44 Rudman D, Kutner MH, Rogers CM, Lubin MF, Fleming GA, Bain RP: Impaired growth hormone secretion in the adult population: relation to age and adiposity. J Clin Invest 1981;67:1361–1369.
45 Junnila RK, List EO, Berryman DE, Murrey JW, Kopchick JJ: The GH/IGF-1 axis in ageing and longevity. Nat Rev Endocrinol 2013;9:366–376.
46 Roelfsema F, Pijl H, Keenan DM, Veldhuis JD: Prolactin secretion in healthy adults is determined by gender, age and body mass index. PLoS One 2012;7:e31305.
47 Bubenik GA, Konturek SJ: Melatonin and aging: prospects for human treatment. J Physiol Pharmacol 2011;62:13–19.
48 Kushner JA: The role of aging upon β cell turnover. J Clin Invest 2013;123:990–995.
49 Gunasekaran U, Gannon M: Type 2 diabetes and the aging pancreatic beta cell. Aging 2011;3:565–575.
50 Atalayer D, Astbury NM: Anorexia of aging and gut hormones. Aging Dis 2013;4:264–275.
51 Tuohimaa P: Vitamin D and aging. J Steroid Biochem Mol Biol 2009;114:78–84.
52 Grant WB: Critique of the U-shaped serum 25-hydroxyvitamin D level-disease response relation. Dermatoendocrinol 2009;1:289–293.
53 Tiganescu A, Tahrani AA, Morgan SA, Ontranto M, Desmoulière A, Abrahams L, Hassan-Smith Z, Walker AE, Rabbitt EH, Cooper MS, Amrein K, Lavery GG, Stewart PM: 11β-Hydroxysteroid dehydrogenase blockade prevents age-induced skin structure and function defects. J Clin Invest 2013;123:3051–3060.
54 Yau JL, Noble J, Seckl JR: 11β-Hydroxysteroid dehydrogenase type 1 deficiency prevents memory deficits with aging by switching from glucocorticoid receptor to mineralocorticoid receptor-mediated cognitive control. J Neurosci 2011;31:4188–4193.

Downloaded by:
198.143.56.33 - 7/1/2015 2:32:05 AM