

# Changes in pituitary function with ageing and implications for patient care

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**Abstract** | The pituitary gland has a role in puberty, reproduction, stress-adaptive responses, sodium and water balance, uterine contractions, lactation, thyroid function, growth, body composition and skin pigmentation. Ageing is marked by initially subtle erosion of physiological signalling mechanisms, resulting in lower incremental secretory-burst amplitude, more disorderly patterns of pituitary hormone release and blunted 24 h rhythmic secretion. Almost all pituitary hormones are altered by ageing in humans, often in a manner dependent on sex, body composition, stress, comorbidity, intercurrent illness, medication use, physical frailty, caloric intake, immune status, level of exercise, and neurocognitive decline. The aim of this article is to critically discuss the mechanisms mediating clinical facets of changes in the hypothalamic–pituitary axis during ageing, and the extent to which confounding factors operate to obscure ageing-related effects.

Veldhuis, J. D. *Nat. Rev. Endocrinol.* 9, 205–215 (2013); published online 26 February 2013; doi:10.1038/nrendo.2013.38

## Introduction

Ageing is marked by subtle incremental changes in all biological systems, including endocrine ensembles. A central regulator of endocrine axes is the hypothalamic–pituitary unit, comprising brain neurotransmitters classified as releasing and inhibitory factors that drive or restrain pituitary hormone synthesis and secretion. The mechanism by which ageing influences pituitary function is complex. Comorbidities and adaptations that accompany ageing strongly modify pituitary secretion.

In particular, the effects of age on endocrine axes depend on hormone type, inhibitor or stimulus tested, concomitant illness, underlying stress, body composition and sex (Supplementary Table 1 online). This critical Review highlights such interactions, thus enabling clinical scientists to parse the implications of endocrine measurements in various clinical contexts in ageing individuals.

## TSH axis in ageing

The TSH–thyroidal axis comprises an array of signalling centres and corresponding signals. Key components are hypothalamic TSH-releasing hormone (TRH) neurons in the paraventricular nuclei, pituitary thyrotropes (TSH-secreting cells) and thyroid hormones ( $T_3$  and  $T_4$ ), along with monocarboxylate  $T_3$  transporters, thyroxine binding globulin (TBG) and pre-albumin. Key mechanistic changes occur in the TSH axis as humans age (Figure 1). Whereas ageing was construed formerly as a threshold event (for example, >60 years of age), data in the past decade establish that ageing-related hormonal changes are continuous variables with rather distinct slopes in relation to age. Moreover, sex, exercise, fasting,

concomitant illness, medications, iodine availability, brief light exposure, sleep stage, exercise training and the assay platform used to measure TSH also influence absolute TSH values. In relation to sex differences, a tendency for baseline (unstimulated) TSH concentrations and thyroid autoantibodies to rise with age is more evident in women,<sup>1–4</sup> whereas a decrease in baseline, overnight and TRH-stimulated TSH release with age is better demonstrated in men.<sup>5–7</sup> These collective factors contribute to the debate about absolute TSH reference ranges in the elderly. Therefore, more precise studies are needed to separate out the effects of comorbidities from those related to ageing.

Reduced serum  $T_3$  concentrations occur in ageing individuals of both sexes. Clinical uncertainty remains concerning the extent to which low  $T_3$  levels in ageing contribute to cognitive decline or depression.<sup>8–11</sup> Serum  $T_3$  levels are especially low in patients with organ failure, undernutrition, systemic inflammation or debilitating illness. Increased reverse  $T_3$  levels emerge particularly when energy intake is restricted.<sup>12</sup> Reductions in mean and 24 h rhythmic (nycthemeral) TSH concentrations in small cohorts become prominent after the eighth decade of life.<sup>5</sup> Typically, serum  $T_4$  levels are preserved in healthy ageing adults whilst free  $T_3$  levels fall, yielding reduced free  $T_3$ :free  $T_4$  ratios. Hypothesized mechanisms mediating these changes include augmented inhibition by  $T_3$  of, or diminished hypothalamic TRH drive to, TSH output.<sup>13</sup>

A near consensus exists that overall, TSH levels tend to rise with age.<sup>14–18</sup> However, confounding issues in elderly adults that can inhibit TSH secretion include decreased exercise; reduced caloric intake;<sup>19</sup> muted symptoms and signs of deficient or excessive  $T_3$ : $T_4$  production; exposure to glucocorticoids;<sup>20</sup> iodine or L-dopa; supervening systemic illness;<sup>21</sup> traumatic brain injury;<sup>22</sup> inanition; and

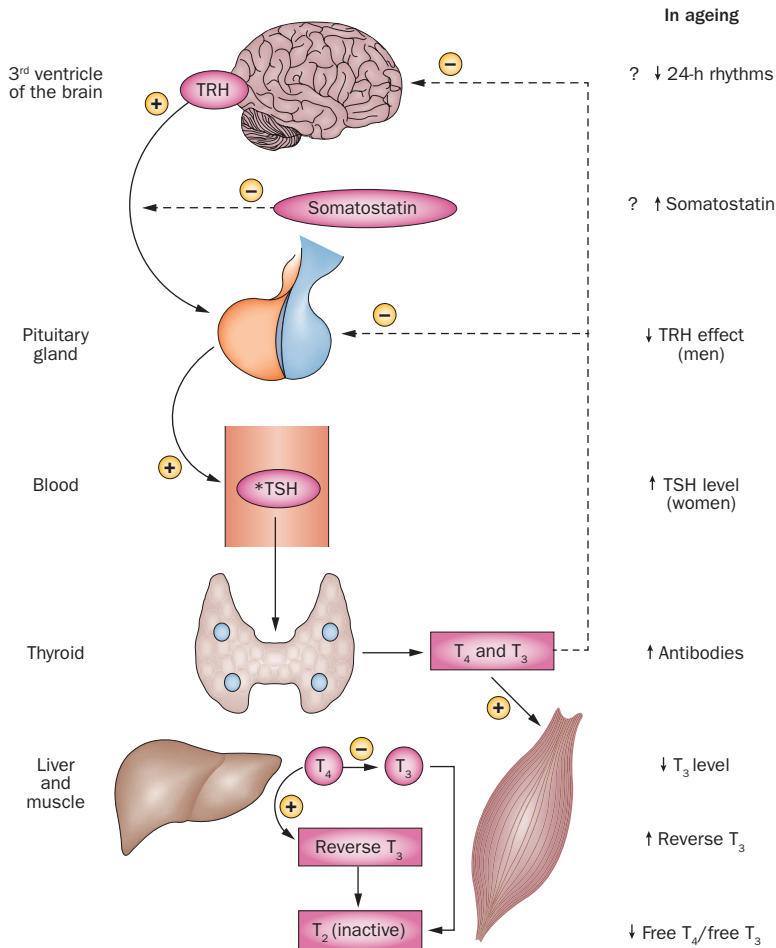
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## Competing interests

The author declares no competing interests.

**Key points**

- Growth hormone responses to most, but not all, stimuli decline markedly with ageing
- Adrenocorticotrophic hormone–cortisol dynamics change with age in a sex-related fashion
- Water and electrolyte homeostasis is precarious in ageing
- TSH tends to rise with age, especially in women
- Gonadotropins increase more in women during ageing than in men
- Multiple factors co-determine ageing effects on pituitary hormones



**Figure 1** | Human thyrotropic axis in ageing. The thyrotropic axis exhibits multiple alterations in healthy ageing individuals, at the levels of the brain, pituitary and thyroid gland, as well as the liver and muscle (in which T<sub>4</sub> is converted to T<sub>3</sub>). Key components include TRH secretion by the paraventricular nuclei surrounding the third ventricle of the brain. In turn, TRH activates pituitary TSH synthesis and secretion. By contrast, somatostatin inhibits TSH release, albeit not TSH synthesis. TSH acts upon thyroid epithelial cells to promote both synthesis and release of T<sub>3</sub> and T<sub>4</sub>, which enter the blood and act on peripheral tissue like bone, adipose tissue, muscle and liver. Peripheral tissues also inactivate T<sub>4</sub> by converting it to reverse T<sub>3</sub>, and inactivate T<sub>3</sub> by converting it to T<sub>2</sub>. Not shown is blood thyroid hormone binding globulin, which is controlled by multiple systemic factors, thus directing the local availability of free T<sub>4</sub> and free T<sub>3</sub>. Upward arrows denote increases in the signalling factor or effector with ageing, and downward arrows denote decreases observed with ageing. The plus and minus signs denote stimulation and inhibition, respectively. The interrupted lines signify negative feedback or inhibition, and the continuous lines positive feedforward or stimulation. \*The hormone value is increased by obesity, and decreased by systemic illness and undernutrition, especially in ageing individuals. Abbreviation: TRH, TSH-releasing hormone.

psychiatric depression. These comorbidities might mask a rise in TSH with age. Conversely, chronic fatigue syndrome, morbid obesity, type 2 diabetes mellitus, use of certain drugs and autoimmune disease<sup>2–4</sup> might potentiate TSH secretion, thus potentially heightening an age-related populational tendency for TSH to increase.

Clinical implications for patient care include a lower threshold for evaluating the thyrotropic axis in ageing individuals than young patients. When an individual measurement is borderline, sequential TSH and free T<sub>4</sub> measurements are helpful.<sup>21,23</sup> However, the clinical pathological significance of minimal (<30%) laboratory deviations is uncertain. From a technical standpoint alone, the least significant change in TSH assays can approach 40%, and in free T<sub>4</sub> assays, this change can approach 15% at 90% confidence intervals. In absolute terms, most thyroidologists agree that a confirmed serum TSH level of >10 mIU/l should prompt T<sub>4</sub> replacement therapy. By contrast, therapy in patients with a TSH level >4 mIU/l but <10 mIU/l without demonstrable symptoms or signs of hypothyroidism (including high-titre thyroid antibodies and a low free T<sub>4</sub> level) is controversial. The clinical implications of this subclinical hypothyroid state remain uncertain. The author suggests that ageing patients who have neither symptoms nor signs of thyroid disease can be reassessed in 2–4 months.<sup>24</sup>

A common scenario in elderly patients is a normal free T<sub>4</sub> level and low T<sub>3</sub> level with low-normal but detectable TSH level of >0.1 mIU/l but <4 mIU/l. This laboratory triad is likely to reflect a combination of medication-associated and illness-associated inhibition of both TSH secretion and 5'-deiodinase activity, which could normalize over 3–12 months.<sup>25</sup> The proof that low-normal TSH level represents sick euthyroidism is retrospective, whereby TSH normalizes after recovery from acute illness, restoration of caloric intake, or reduction in cytokines, glucocorticoids, dopamine and use of other drugs. However, radiation-induced, traumatic and vascular hypothalamic injury, pituitary adenoma, metastatic cancer, hypophysitis, craniopharyngioma, granulomatous processes, infection, and other aetiologies of a suppressed TSH thyroidal axis must not be overlooked, requiring evaluation by an endocrinologist and relevant treatment and follow-up.

An undetectable TSH level (<0.1 mIU/l) suggests possible hyperthyroidism at any age. Further assessment includes measurements of both free T<sub>3</sub> and free T<sub>4</sub>, as untreated hyperthyroidism, particularly in elderly people, increases the risk of heart failure,<sup>26</sup> cardiovascular disease mortality<sup>27</sup> and bone fractures.<sup>28</sup> Challenges to recognizing the diagnosis of hyperthyroidism in ageing individuals are that other causes of hyperthyroid-like symptoms and signs, such as fatigue, sleeplessness, proximal muscle weakness, osteopaenia, neurocognitive loss and atrial fibrillation, are more prevalent in ageing individuals even without a suppressed TSH level and elevated free T<sub>4</sub> concentrations.<sup>8,28</sup> Thus, a close follow-up with clinical and biochemical reassessment is essential.

What remains difficult to investigate is the exact extent to which minimal thyroid axis dysfunction contributes

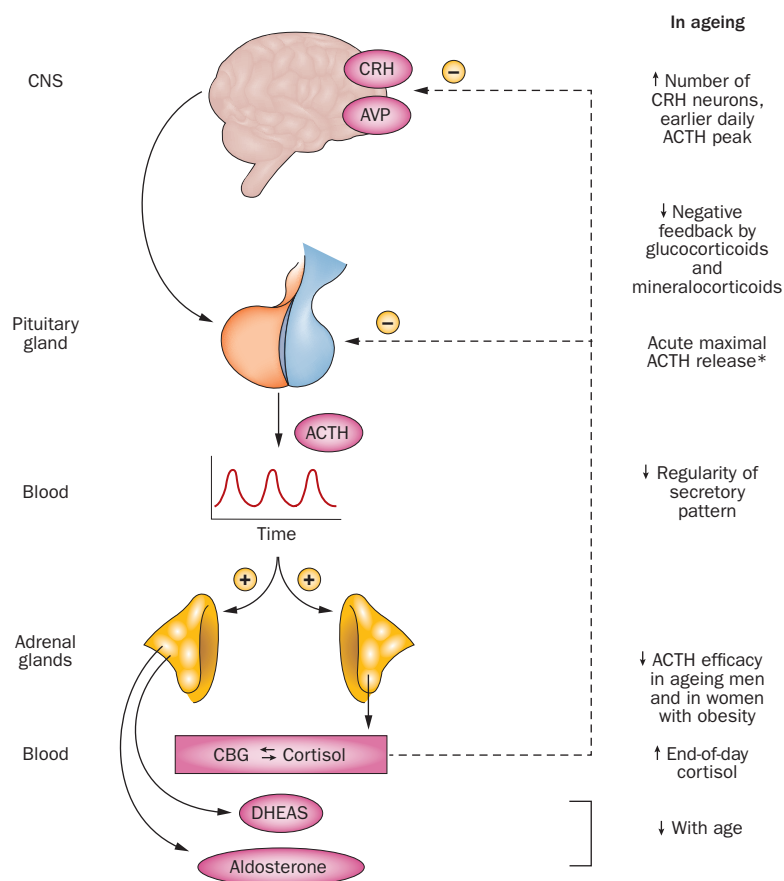
to the ageing phenotype and/or to comorbidity (or even mortality) in ageing individuals. Given this uncertainty and the finite, albeit small, risk associated with treatments for thyroid disorders, consensus treatment guidelines should be helpful to practitioners.

### HPA axis in ageing

The stress-responsive hypothalamic–pituitary–adrenal (HPA) axis is a vital neuroendocrine system regulating cognition, well-being, memory, behaviour, appetite, work capacity, inflammation, glucose metabolism, adipose tissue, muscle and skeletal mass, blood pressure, insulin sensitivity, immune responses, and water and electrolyte balance. The HPA axis comprises the hippocampus and frontal cortex, catecholaminergic tracts, hypothalamically released corticotropin-releasing hormone (CRH) and the antidiuretic hormone arginine vasopressin (AVP), pituitary corticotropes secreting adrenocorticotrophic hormone (ACTH), and cortisol secreted from the adrenal zona fasciculata cells. No part of this dynamic array operates or functions alone. Cortisol is a potent agonist of glucocorticoid receptors and a partial agonist of mineralocorticoid receptors, and the activation of these receptors mediate the tissue effects of cortisol, including negative feedback onto brain CRH and AVP neurones and onto pituitary ACTH secretion. Extensive studies reveal that the effects of age on the HPA axis are modulated by obesity and sex and the type of stress activating the system (Figure 2).

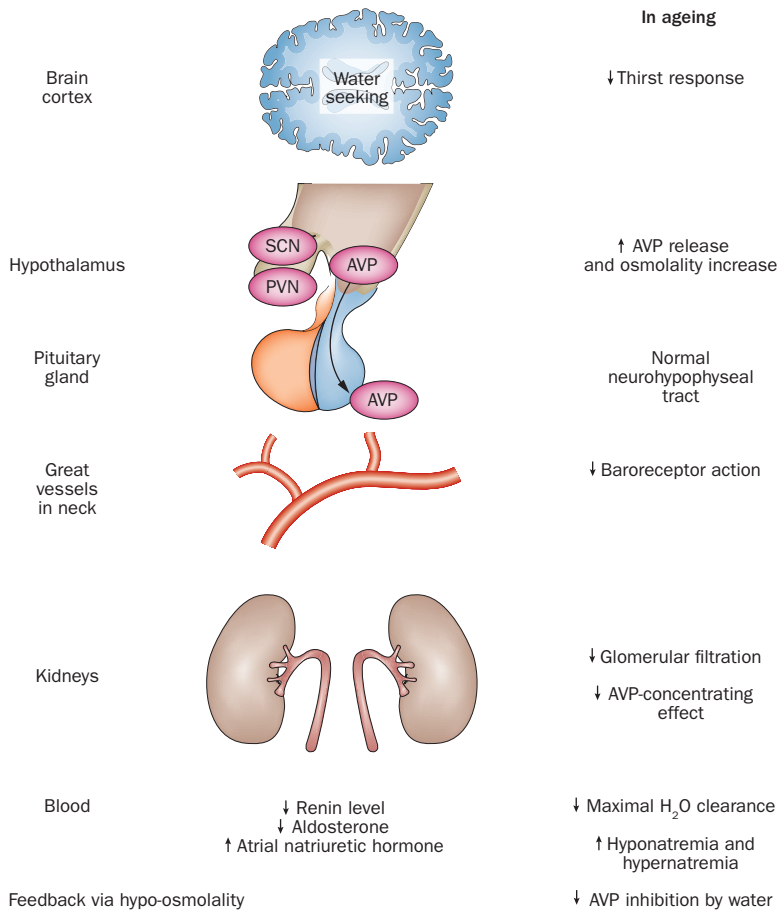
Certain amplifiers of ACTH and/or cortisol secretion seem to be more effective in ageing than young adults, including cholinergic agonists, CRH and/or AVP injection and hypertonic saline infusion.<sup>29–31</sup> At the mechanistic level, feedback disinhibition using a mineralocorticoid receptor antagonist also augments ACTH release more in ageing than young individuals.<sup>32</sup> Other factors that elicit ACTH secretion are equally effective in young and ageing volunteers, namely major surgery, insulin-induced hypoglycaemia, feedback disinhibition,<sup>33–35</sup> and opiate-receptor antagonism.<sup>33,35</sup> Ipsapirone (a serotonin receptor agonist) stimulates more ACTH release in ageing women than older men,<sup>36</sup> as do human CRH and naloxone.<sup>29</sup> Feedback suppression via glucocorticoid receptor agonists or a mineralocorticoid receptor agonist is less effective in ageing than young volunteers.<sup>37–39</sup> Controversy exists regarding unstressed mean ACTH concentrations, which are reportedly unchanged across the age span of 20–100 years,<sup>35,40</sup> or decreased with age or increased with age.<sup>41</sup> Comorbidities, assay nonuniformities and sampling inconsistencies might, in part, explain the discrepant reports. Similar uncertainty applies to plasma, urinary or salivary (free) cortisol concentrations in ageing individuals.<sup>42,43</sup> Intra-abdominal adipose tissue mass is a major confounder of ACTH and/or cortisol output with high intra-abdominal adipose tissue mass predicting increased sympathetic outflow, cortisol production and cortisol inactivation, and increased mean ACTH concentrations in women.<sup>42,44,45</sup>

The 24 h (circadian) rhythm of ACTH and cortisol concentrations is blunted in absolute amplitude



**Figure 2** | Adrenocorticotrophic hormone secretion in ageing individuals. The CNS controls pituitary ACTH secretion into blood by synthesizing and releasing CRH and AVP. The CNS and pituitary are under negative feedback control or inhibition by glucocorticoids and/or mineralocorticoids. However, ACTH release is decreased in ageing after stimulation with CRH, a cholinergic agonist, or hypertonic saline. Conversely, ACTH release is increased in ageing individuals after serotonin-receptor 1A stimulation in women and after mineralocorticoid receptor blockade in men. Up and down arrows indicate increases and decreases in the pathway or regulatory factor with age. Upward arrows denote feedforward drive, and downward arrows feedback inhibition. \*Maximal ACTH release is normal after surgery, during critical illness, during hypoglycaemia, and after administration of metyrapone. Abbreviations: ACTH, adrenocorticotrophic hormone; AVP, arginine vasopressin; CBG, corticosteroid binding protein; CNS, central nervous system; CRH, corticotropin-releasing hormone; DHEAS, dehydroepiandrosterone sulphate.

(the algebraic difference between peak and nadir) owing to high late-day cortisol nadirs in elderly individuals.<sup>40,43</sup> Additionally, the timing of the nycthemeral ACTH and cortisol peak and nadir is earlier in the day (by about 2 h) in ageing compared with young adults. In ageing rats, high nadirs reflect attenuation of negative feedback, arising from decreased glucocorticoid receptor and mineralocorticoid receptor expression in the brain,<sup>46</sup> and activation of CRH and AVP neurons.<sup>47</sup> Ageing-related changes in the HPA axis are more prominent in women than in men, and in patients with Alzheimer disease or major depression.<sup>29</sup> Diabetes mellitus, inflammation, hypertension, obstructive sleep apnoea and genetic polymorphisms can also potentiate ACTH and cortisol release.<sup>48</sup> Confounding factors are anxiety, trauma, stress, illness, sleep loss, inanition,



**Figure 3** | Effects of ageing on water balance. Ageing influences virtually all known physiological steps in the pathway of cortical and hypothalamic regulation of thirst and water balance, including posterior pituitary secretion of AVP, baroreceptor action mediated by pressure sensors in great vessels in the neck, concentrating capacity of renal tubules, and coregulators of salt and water balance, such as renin, aldosterone, and atrial natriuretic hormone. Ageing seems to blunt water-seeking behaviour and augment brain output of AVP. Ageing is associated with a decrease in total body water of approximately 7%, and a decrease in plasma volume of approximately 10%. Abbreviations: AVP, arginine vasopressin; PVN, paraventricular nucleus; SCN, supra-chiasmatic nucleus.

systemic disease, day-to-night schedule,<sup>49</sup> and use of medications,<sup>50</sup> such as benzodiazepines, antidepressants, synthetic progestins and glucocorticoids. In addition, interactions between the pituitary gland and the immune system constitute a growing focus in ageing research.<sup>51–53</sup>

Some clinical implications follow from the changes in the HPA axis that occur in the ageing population. First, for a valid assessment of ACTH regulation with age, patients must be matched for sex, mental health status, obesity status, medication exposure, comorbidities, systemic illness and time of day that ACTH was measured. Second, higher glucocorticoid doses are not required due to ageing *per se*.<sup>33,54</sup> Third, obesity often elevates urinary but not plasma free cortisol levels.<sup>42,44</sup> Fourth, ACTH deficiency does not cause low levels of adrenal dehydroepiandrosterone (DHEA) in the ageing population.<sup>55</sup> An unresolved issue is that comorbidities lead to conflicting findings in terms of the influence of ageing on the HPA axis.

### Arginine vasopressin in ageing

AVP is secreted by hypothalamic neurons, and acts locally on pituitary cells to potentiate CRH-stimulated ACTH secretion and systemically upon kidney tubules to trigger water reabsorption, thereby increasing the osmolality of urine. The mechanisms of AVP regulation have been extensively studied. Deficient AVP secretion or action, albeit not a cause of ACTH deficiency when CRH is present, results in diabetes insipidus with hypernatraemia and inappropriately dilute urine, unless thirst mechanisms compensate for water loss. Conversely, an excess of AVP secretion or of water intake causes (dilutional) hyponatraemia with attendant neuropsychological signs and symptoms.<sup>56–58</sup> Disorders of sodium and water balance tend to be more frequent, less well-defined aetiologically, and are more often multifactorial and more severe in ageing individuals than in young adults.<sup>58,59</sup> The theory behind this difference is that age reduces homeostatic adjustments to both low and high fluid or salt intake.<sup>60</sup>

In the ageing population, deficits exist in renin-aldosterone secretion,<sup>59,61</sup> plasma volume, thirst,<sup>60</sup> baroreceptor reflexes,<sup>62</sup> expression of the AVP receptor and aquaporin 2,<sup>63</sup> and hypothalamic osmoregulation (Figure 3). By contrast, exaggerated AVP release (and possibly atrial natriuretic peptide release) occurs during experimentally imposed hypertonicity, water deprivation, ethanol exposure or volume contraction in humans.<sup>60,64</sup> Thus, the risks of both low and high sodium concentrations are increased in elderly individuals, especially in relation to anaesthesia, surgery, coma, acute myocardial infarction or stroke, fever, glycosuria, diarrhoea, diuresis, emesis, burn injury, blood loss and acute tubulopathies.

The clinical syndrome of inappropriate (autonomous) antidiuretic hormone release (SIADH), which seems more common in elderly cohorts, can cause severe dilutional hyponatraemia by impairing free water clearance.<sup>65</sup> Causes of SIADH include medications such as cyclophosphamide and anaesthetics, neoplasms, pulmonary processes and intracranial lesions.<sup>57,66</sup> Less severe hyponatraemia than that in SIADH occurs with elevated, but nonautonomous, AVP secretion in hypothyroidism,<sup>67</sup> glucocorticoid deficiency, hypovolaemic and hypoperfusional states, and salt-wasting disorders.<sup>58,68</sup> Thus, condition-specific therapy entails replacing T<sub>4</sub> and/or cortisol (in endocrine deficiency), enhancing perfusion or repleting salt (in low-volume state), and restricting water intake or blocking AVP action (in euvoalamic state).<sup>58,65,68</sup> Treatment goals in elderly patients with SIADH or hyponatraemia include averting and/or ameliorating signs and symptoms of hyponatraemic encephalopathy.<sup>58,68</sup> Morbidity and mortality in hyponatraemic individuals are due to cerebral vasoconstriction, tissue hypoxia, brain oedema, and/or the underlying disease.<sup>57,66</sup> Inasmuch as rapid reversal or overcorrection of hyponatraemia or hypernatraemia carries the risk of iatrogenic neurological injury at any age,<sup>69</sup> repeated in-hospital assessments and attendant fluid adjustments are particularly important in frail elderly patients.<sup>69</sup>

### GH-IGF-I axis in ageing

Clinical features of organic or structural growth hormone (GH) deficiency are less vivid in elderly individuals, who already often have decreased insulin-like growth factor I (IGF-I) levels, increased waist to hip ratios, a reduced quality of life, impaired glucose metabolism, unfavourable lipid profiles, and reductions in muscle and bone mass, physical endurance and fitness.<sup>70</sup> Aged adults secrete less GH during fasting, exercise or sleep and in response to nearly all secretagogues than young individuals.<sup>71</sup> However, in response to insulin-induced hypoglycaemia or to the triple combination of L-arginine plus GH-releasing hormone (GHRH) plus ghrelin (the naturally occurring form of GH-releasing peptides), secretion of GH in the elderly is the same as that in young individuals (Box 1).<sup>72,73</sup> Sex, body composition and sex steroids further determine 24-h GH secretion in elderly individuals. Specifically, GH output declines more with increasing age in young men than in premenopausal women, and more when ageing is accompanied by abdominal visceral adiposity, hyperinsulinaemia; and oestrogen and testosterone (acting via oestrogen) deprivation.<sup>70,74–76</sup>

The age-related decrement in pulsatile GH secretion, and thereby IGF-I production, in ageing is due to smaller GH pulses, which reflect diminished secretory-burst mass with no change in pulse frequency.<sup>75,77</sup> Mechanistically, GH secretory-burst mass is under the hypothalamic control of somatostatin (an inhibitory peptide), GHRH and possibly GHRP/ghrelin, which are both stimulatory, and under systemic negative feedback control by circulating GH, IGF-I and free fatty acids, and under systemic positive feedback control by gastric ghrelin.<sup>70</sup> Thus, the reported capability of L-arginine, which is a somatostatin antagonist, combined with both GHRH and GHRP/ghrelin to normalize GH secretion acutely suggests attenuation of hypothalamic drive to pituitary somatotropes in ageing.<sup>73</sup> However, the action of GH on the liver to generate IGF-I is preserved in ageing.<sup>78</sup> Whether the effect of GH on the immune system, brain, bone, muscle and adipose cells change with age is unknown. This issue is an important one to resolve, as patients are concerned about both lifespan and 'healthspan'.<sup>79</sup>

The clinical impact of age-related hyposomatotropism (decreased GH and IGF-I availability) has been explored indirectly by assessing the effects of short-term GH supplementation in ageing individuals. These investigations are deemed experimental, as relative GH deficiency in the elderly does not necessarily constitute a disease.<sup>79</sup> Consistent effects of GH repletion in structural GH deficiency are 2–3 kg loss of total-body fat (and especially visceral fat), 1–2 kg gain of lean body mass (water, bone and muscle), and a reduction of LDL cholesterol levels and an elevation of IGF-I levels.<sup>70</sup> In elderly GH-treated patients, balance, strength, coordination and endurance are often not improved compared with untreated, age-matched individuals.<sup>80,81</sup> At any age, adverse effects such as oedema, heart failure, carpal tunnel syndrome, intracranial hypertension, myalgia, arthralgia

#### Box 1 | Changes in human GH-IGF-I axis in ageing

- Decrease in pulsatile GH secretion via decrease in burst mass
- Decrease in IGF-I, increase in IGFBP-1, increase in IGFBP-3
- Preserved hepatic IGF-I response to exogenous GH<sup>78</sup>
- Decrease in GH accompanies and/or causes the metabolic syndrome
- Decrease in lean body mass (muscle bulk and BMD)
- Hypopituitarism still occurs in the elderly

Abbreviations: GH, growth hormone; IGF-I, insulin-like growth factor I; IGFBP, insulin-like growth factor binding protein.

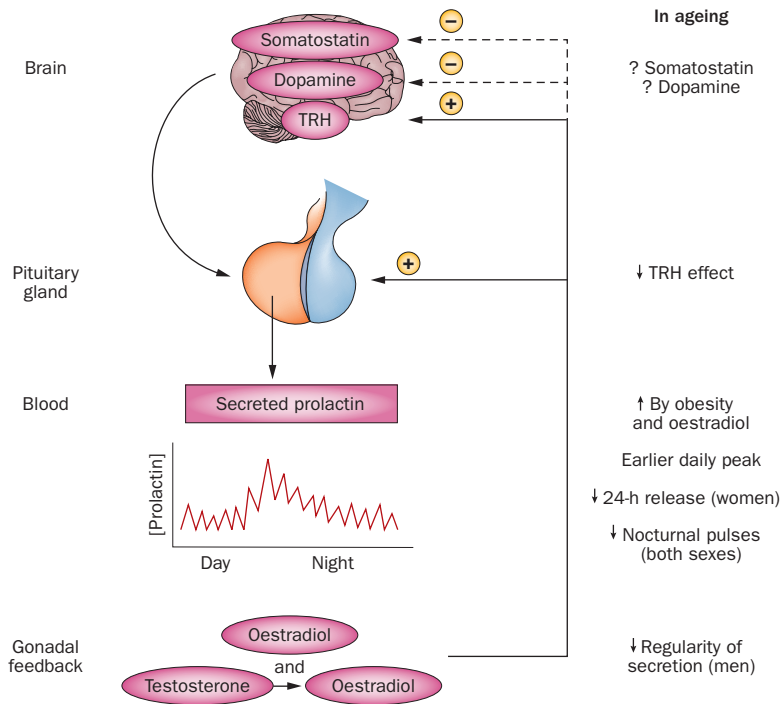
or gynaecomastia and glucose intolerance, are more frequent at high GH doses, prompting IGF-I-targeted GH dosing.<sup>82,83</sup> Whether the risk of neoplasia increases with long-term supplementation with GH and IGF-I in ageing individuals, as suggested in animal models,<sup>79</sup> is not known. Moreover, GH treatment after the eighth decade of life has not been assessed in any study. In view of these deficiencies in the field, supplementation with GH and IGF-I directly or indirectly via administration of GHRH and/or GHRP in healthy elderly adults without hypopituitarism cannot be recommended at present.<sup>84,85</sup>

### Prolactin secretion in ageing

Isolated hypoprolactinaemia is rare, because prolactin deficiency usually signifies panhypopituitarism.<sup>86</sup> By contrast, multiple factors elicit hyperprolactinaemia. Factors that stimulate prolactin secretion acutely include psychological and physical stress, breast stimulation, hypoglycaemia, certain amino acids, oestrogen, dopamine-2-receptor blockers, sexual activity, hyperthermia, TRH infusion, food intake, sleep and exercise.<sup>87–89</sup> Pituitary stalk injury, end-stage renal disease, primary hypothyroidism, prolactinoma, pregnancy, visceral obesity and high leptin levels increase prolactin concentrations chronically.<sup>90–92</sup>

Prolactin is released approximately 50% in pulses and 50% tonically. Both modes of secretion show 24h rhythmicity with higher output at night than during the day.<sup>93</sup> In individuals <50 years of age, prolactin concentrations are higher in women than men.<sup>88,94</sup> Prolactin secretion during the night falls by about 40% after menopause, but declines less markedly in ageing men (Figure 4).<sup>95</sup> Results of clinical studies examining mechanisms of altered prolactin secretion in ageing indicate that TRH-stimulated prolactin secretion may decrease with age,<sup>92,96</sup> prolactin secretion patterns become more irregular with age in men, and oestrogen and adiposity accentuate pulsatile prolactin production in ageing individuals.<sup>87,91,94</sup> Potential mechanisms involved in changes in prolactin secretion during ageing include increased dopamine inhibition, reduced prolactin-releasing-factor stimulation and/or increased adipokine inhibition of lactotropes.<sup>95</sup>

A clinical implication in postmenopausal compared with premenopausal women is that generally lower prolactin concentrations should be interpreted in light of menopausal hypo-oestrogenaemia. Lower prolactin concentrations might favour longevity, given a possible



**Figure 4** | Ageing-related effects on prolactin secretion. An ensemble comprising the brain, pituitary gland, blood circulation, and gonadal feedback directs prolactin secretion. In general, prolactin secretion decreases with ageing (downward arrows), but this decrease is opposed by obesity and oestrogen (upward arrow). Precisely how somatostatin and dopamine, key negative regulators of prolactin secretion, change with ageing is less clear in the human, as denoted by the interrogative marks. Negative feedback is shown by the interrupted arrows and minus sign, and positive feedforward by oestrogen through the continuous arrow and positive sign. Abbreviation: TRH, TSH-releasing hormone.

increase in breast-cancer risk in ageing women in the upper versus lower quartile of prolactin concentrations,<sup>97</sup> albeit not in frankly hyperprolactinaemic women.<sup>98</sup> Technical caveats with regard to the findings of prolactin assays are pseudohyperprolactinaemia caused by prolactin macroaggregates,<sup>99</sup> and pseudohypoprolactinaemia caused by very high prolactin levels or heterophile antibodies.<sup>100</sup>

**LH and FSH secretion in ageing**

The principal known function of the gonadotropins is maintenance of gonadal steroidogenesis (oestrogen, progesterone and testosterone secretion) and gametogenesis (sperm and egg maturation). Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels rise gradually in ageing men, putatively reflecting reduced secretion of androgen and oestrogen from Leydig cells and decreased secretion of inhibin B from Sertoli cells.<sup>101</sup> However, spermatogenesis is relatively preserved in ageing.<sup>102</sup> FSH concentrations begin to increase in late premenopausal women owing to decreased ovarian follicle reserve, inferable by ultrasonography and falling concentrations of oestradiol, anti-Müllerian hormone and inhibin B.<sup>103</sup> The initial elevation of FSH concentration might precede clinical menopause by 5–10 years. After menopause, levels of LH fall by twofold–threefold and levels of FSH fall by threefold to 20-fold; these falls

exceed those in ageing men.<sup>104</sup> A confounding factor is obesity, which increases with age and decreases LH pulse size in both sexes.<sup>105</sup> The mechanism behind this effect in humans is not known.

The primary drive to human gonadotropes is hypothalamic neuronal secretion of gonadotropin-releasing hormone (GnRH). GnRH secretion in turn is under multifold control by sex steroids, kisspeptin, neurokinin B and dynorphin.<sup>106,107</sup> Hypothalamic adaptations in ageing favour enhanced GnRH release.<sup>108,109</sup> This enhanced GnRH release also occurs in gonadectomized animals, creating gonadotrope ‘castration cells’ and pituitary pericyte hyperplasia.<sup>110</sup> The degree of menopause-associated hypergonadotropism seems to wane after age 65 years,<sup>109,111</sup> possibly reflecting hypothalamic changes in the secretion of neurokinin B, glutamate, nitric oxide and GABA.<sup>112,113</sup> In addition, ageing is associated with longer half-lives of more acidic LH and FSH isoforms,<sup>114</sup> increased basal gonadotropin secretion,<sup>115,116</sup> blunted night-time LH and FSH increments,<sup>117</sup> more frequent smaller LH pulses<sup>115,118</sup> and less regular LH secretion patterns.<sup>119</sup> Similar changes typify sex-steroid feedback withdrawal in young adults, which suggests that gonadoprivation is a proximate mechanism.<sup>120</sup>

Ageing of the gonadotropic axis is important clinically because sex-steroid privation adversely affects muscle and bone mass, visceral adipose tissue accumulation, insulin sensitivity, LDL metabolism, and possibly, mood, libido, cognition and memory.<sup>121,122</sup> Direct brain effects of LH and human chorionic gonadotropin, although demonstrable in the rodent, are not inferable in women.<sup>123</sup> Likewise, whereas high FSH levels contribute to osteopaenia in ovariectomized and aged mice,<sup>124,125</sup> this concept does not seem to apply in women, in whom age, weight, ethnicity, inflammation and oestrogen availability are the confirmed crucial factors.<sup>126,127</sup> Hot flushes occur in menopausal women, and their timing matches the onset of LH pulses, providing an indirect window into hypothalamic GnRH neuronal activity.<sup>128</sup> The high FSH concentrations after menopause mean that serum FSH measurements provide suitable initial screening for suspected panhypopituitarism in older women (aged >55 years), except in protracted critical illness, which suppresses gonadotropin output.<sup>129</sup> A clinical caveat is that ageing augments secretion of free (dissociated) alpha and beta subunits, especially of FSH, in both sexes,<sup>113,130,131</sup> necessitating age-dependent norms when assessing pituitary incidentaloma and possible gonadotropinomas in the elderly.<sup>131,132</sup>

**Hypopituitarism in ageing**

Hypopituitarism might be overlooked or confused with natural frailty in elderly individuals. Older patients must be treated with replacement amounts of the life-sustaining hormones, cortisol, thyroxine and AVP, when so indicated by corresponding deficiencies of ACTH, TSH and AVP. Hydrocortisone is a suitable replacement for ACTH deficiency, given the absence of known extra-adrenal effects of ACTH. Low initial T<sub>4</sub> doses (0.025 to 0.050 mg daily) with gradual increments

are often preferred in older hypothyroid patients with myocardial ischemia or cardiac arrhythmias.<sup>133</sup> The presence of congestive heart failure does not contraindicate physiological T<sub>4</sub> replacement. However, especially in ageing patients, chronic over-replacement of thyroid hormone may be associated with atrial fibrillation, bone loss, proximal muscle weakness, tremor and glucose intolerance.<sup>134,135</sup>

Replacement of GH deficiency *per se* in the elderly with documented hypopituitarism is discussed elsewhere.<sup>136</sup> Concerns in aged individuals are fluid retention, hypertension, arthralgias, glucose intolerance, which are all more common in frail elderly patients even without GH treatment. The risks and benefits of sex-steroid replacement should be discussed in clinically hypogonadal older individuals in accordance with good clinical practice.<sup>137–139</sup>

### Pituitary tumours in ageing

Ageing is accompanied by an increased prevalence of pituitary tumours, including incidentaloma of the pituitary gland,<sup>132</sup> macroadenoma, gonadotropinoma, and metastatic carcinoma. Lesions in older patients often present silently (clinically nonsecretory and without mass-lesion effects) or with hormone excess (Cushing disease, acromegaly), visual impairment, headache and/or hypopituitarism.<sup>140–142</sup> Pituitary haemorrhage (apoplexy) heralded by acute headache and visual deficits also occurs in the elderly. Trans-sphenoidal endoscopic surgery remains an effective and safe treatment option in otherwise healthy older individuals,<sup>143</sup> with similar risks of cerebrospinal-fluid leakage, meningitis, haemorrhage, tumour recurrence and hypopituitarism. Dopamine agonists may be used as primary therapy for prolactinomas, albeit cautiously because of orthostatic hypotension in the elderly. Observation alone is acceptable in some surgically high-risk patients without clinically threatening mass-lesion effects.

### Limitations of pituitary studies in ageing

Target tissues of the hypothalamic–pituitary axis are regulated by combined pulsatile signalling and circadian inputs. The complex physiological dynamics can be quantified only by frequent sampling and specialized time-series analysis over 24 h.<sup>144</sup> Such analyses have been sparse in the ageing population, especially in patients >80 years. Interpretative limitations of pituitary studies in an ageing population include prevalent comorbidities, sex-specific effects, sex hormone deficiency or replacement, disrupted sleep, altered body composition, reduced physical activity, elevated inflammatory mediators, increased medication use and methodological inconsistencies (Box 2).<sup>50</sup> Moreover, rigorous evidence-based decisions require adequately powered, longitudinal, double-blind, randomized, placebo-controlled interventions replicated across multiple centres.

Several key unresolved queries exist in research of pituitary function changes in ageing (Box 3). Issues requiring clarification comprise the nature, degree and specificity of age-related alterations in hormone

#### Box 2 | Limitations of pituitary function ageing studies

##### Technical limitations

- Sex-specific effects often not examined
- Few healthy individuals aged 80–100 years
- Variable sex-hormone replacement regimens
- Methodological inconsistencies

##### Comorbidities

- Cardiovascular
- Neural
- Hepatic
- Infectious
- Inflammatory
- Neoplastic
- Sleep disturbances

##### Individual factors

- Disability
- Frailty
- Reduced exercise
- Poor nutrition
- Medication use
- Genetic factors
- Body composition changes

The subtle incremental changes in hypothalamic–pituitary function with ageing are subject to confounding by technical limitations as well as comorbidities that accompany ageing. Several critical factors are listed, which must be individually and collectively controlled for to discern the underlying influence of ageing *per se*. In general, this stringency often requires longitudinal studies, as well as precise comparisons with well-defined control groups.

#### Box 3 | Questions related to pituitary function ageing

- Are endocrine changes that occur during ageing adaptive (for example, a decrease in IGF-I concentrations) or maladaptive (for example, stress-induced atrophy of hippocampus)?
- To what degree are glandular changes that occur during ageing compensated by feedback adjustments?
- What are the sequences of failure within axis components and among different axes during ageing?
- What are the cellular and molecular mechanisms involved in changes in pituitary function during ageing?
- How do comorbidities affect the pituitary function changes that occur during ageing?

Abbreviation: IGF-I, insulin-like growth factor I.

secretion, target-cell responsiveness, and feedback control. The adaptational benefits or liabilities of such alterations are also largely unknown. Incisive methods are needed to define cause-and-effect relationships between comorbidities and age-associated changes, and to elucidate the longitudinal sequence and inevitability of age-associated endocrine changes. For example, sleep-disrupting disorders alter GH, LH, testosterone, ACTH and cortisol secretion, but the exact manner and extent to which ageing and sleep apnoea interact adversely is difficult to ascertain.<sup>40,43,145</sup> Likewise, the anorexia and hypoleptinaemia that accompany ageing could putatively affect multiple endocrine axes. Moreover, age might influence pathological responses to genetic polymorphisms in endocrine signalling. Lastly, whether seemingly minimal pituitary

histologic and microcirculatory changes in ageing disrupt neuroendocrine activity is not known.<sup>146–149</sup>

**Conclusions**

Ageing is associated with multiple subtle changes in pituitary secretion in humans. Concomitant morbidities, such as obesity, diabetes mellitus, reduced nutrition, systemic illness and medication use, alter how ageing affects individual pituitary hormones. Sex also influences the affect of ageing on pituitary function. The fundamental implications of pituitary changes with age require further investigation, as some age-related adaptation could

favour longevity. To achieve maximal healthy life spans, a thorough understanding of age-related adaptations is required.

**Review criteria**

A PubMed search for original articles focused on the ageing pituitary that were published between 1960 and 2012 was performed. The search terms used were “pituitary” AND “hormone” AND (“age OR ageing OR old OR elderly”) AND “human”. The selection of articles reflects the authors’ opinion as to originality and importance in the context of the Review.

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#### Acknowledgements

The author thanks J. Smith of the Endocrine Research Unit, Mayo Clinic, for support of

manuscript preparation. Supported in part via AG019695, DK073148, AG029362, AG031763 and DK050456 (Metabolic Studies Core of the Minnesota Obesity Center) from the National Institutes of Health (Bethesda, MD). The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institute on ageing or the National Institutes of Health. Certain cited studies were supported by the National Center for Research Resources and by Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCTS).

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