REVIEW

Neuroendocrinology of ageing

HABIB U. REHMAN, EWAN A. MASSON

Departments of Medicine and Diabetes and Endocrinology, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, UK

Address correspondence to: H. U. Rehman. Fax: (+44) 1482 675370. Email: habib786@aol.com

Abstract

Many common problems encountered in the ageing patient can be related to neuroendocrine phenomena. These include Alzheimer's disease, dementia and cognitive dysfunction, depression, Parkinson's disease, hypotension, and the postmenopausal increase in both vascular risk and osteoporosis. This review concentrates on the hypothalamic neuroendocrine system, including the dopaminergic, noradrenergic, serotonergic, cholinergic and neurohypophyseal systems and the roles of the anterior pituitary and monoamine oxidases, luteinizing hormone-releasing hormone, corticotrophin-releasing factor, the pro-opiomelanocortin-derived and opioid peptides, peptides involved in growth hormone and thyrotropin regulation, and amino acid transmitters.

Keywords: ageing, hypothalamic neuroendocrine system

Introduction

The consequences of ageing of the neuroendocrine system have been incriminated in the development of various age-dependent conditions, such as insulin resistance, osteoporosis, muscular atrophy and abnormalities of fat deposition. Ageing affects the endocrine system by altering endocrine cells, the hormones produced by these cells and hormone receptors or post-receptor processes in the target cells. (Table 1 indicates some of the changes that have been reported in hormones and their receptors.) Here, we summarize the effects of ageing on the hypothalamic neuroendocrine system.

The dopaminergic system

Dopaminergic innervation of the hypothalamus comprises at least three neuronal systems. These are the tuberoinfundibular dopamine system, the tuberohypophyseal dopamine system, and the incertohypothalamic dopamine system. These three systems differ in basal activity, responsiveness to peripheral hormones and in the physiological processes that they regulate [1].

The tuberoinfundibular dopamine system shows the most dramatic age-related changes. Marked decreases in dopamine concentrations with age have been observed in the medial basal hypothalamus [2] and in the median eminence in the animal model. These regions contain primarily tuberoinfundibular dopamine neurones. In contrast to the tuberoinfundibular system, the tubero-hypophyseal and incertohypothalamic dopamine systems show varying responses to ageing [3, 4].

Dopamine receptors can be divided into two major subtypes: D-1 and D-2. Age-related decreases in D-2 receptor subtypes occur in both rodents and humans [5], especially in the caudate nucleus, putamen, substantia nigra and globus pallidus. In contrast, D-1 receptors have been reported to increase or show no change with age [3].

There is a steady decline in dopaminergic cells in the substantia nigra with age in humans. The number of dopaminergic neurones in each substantia nigra declines from 400,000 at birth to 250,000 at age 60. In Parkinson's disease, cell counts range from 60,000 to 120,000. Parkinson's disease may result from a combination of age-related loss of dopaminergic neurones and environmentally-induced damage to the substantia nigra. However, the pattern of striatal cell loss in normal ageing differs substantially from that of Parkinson's disease [4]. Moreover, moderate (<50%) decreases in pre- and postsynaptic dopaminergic indices in the basal ganglia of humans contrast with studies of post mortem material from Parkinson's disease patients, which suggest that a dopamine depletion of >80% is required before functional impairment occurs. Nonetheless, the age-related loss of dopamine from the striatum contributes to the emergence of symptoms in Parkinson's disease.
Age-related deficits in neurotransmitters may be functionally important in relation to compensatory capabilities in response to pharmacological challenges. For example, tardive dyskinesia occurs almost exclusively in older people, in whom age-related changes in the basal ganglia dopaminergic and cholinergic systems may lower the threshold for the appearance of symptoms.

The monoamine oxidase system

Monoamine oxidases (MAOs) are the main enzymes responsible for the catabolism of monoamine neurotransmitters. On the basis of substrate selectivity, two forms are recognized: MAO-A and MAO-B. Most studies have reported no change or decrease of MAO-A in the ageing brain [6]. All brain structures showed an age-related increase in MAO-B in human brain [7]. This increase may reflect an age-associated increase in glial cells. Specific dopamine D-2 receptor binding is reduced in human studies [8].

Increased activity of MAO-B may reduce the synaptic concentration of dopamine with age and exacerbate the functional consequences of age-related loss of dopamine neurones. The age-related loss of D-2 receptors may underlie the increasing incidence of tardive dyskinesia with ageing [9].

The noradrenergic system

Noradrenaline concentrations decline with increasing age in the hypothalamus [10]. The largest group of noradrenergic neurones is located in the locus caeruleus, where marked age-related loss of neurones has been observed [11]. These changes are related to the reduced noradrenaline turnover in the hypothalamus [5].

The age-related decline in noradrenergic function in the hypothalamus influences the secretion of luteinizing hormone (LH), growth hormone (GH) and thyroid-stimulating hormone, and results in a reduction in protein synthesis and development of mammary and pituitary tumours. Administration of drugs that increase hypothalamic catecholamines to old rats can reverse this decline in reproductive function, increase protein synthesis and induce regression of mammary and pituitary tumours [12].

Noradrenaline is catabolized largely by MAO-B. Noradrenergic function may, therefore, be affected by the age-related increase in MAO activity. Reduced concentrations of noradrenaline are found post mortem in the brains of people with Alzheimer’s disease. In addition, high-affinity uptake of noradrenaline is reduced in the temporal cortex in Alzheimer’s disease [13]. Reduced noradrenaline concentrations in three cortical areas have been proposed to underlie behavioural problems in dementia with major depression [14].

The serotoninergic neurones

The serotonin (5-HT) responses to increasing age are variable. Total brain 5-HT levels decrease with age [15], but hindbrain 5-HT levels do not change [9]. A significant reduction in the number of 5-HT1D and 5-HT2 sites, together with a decrease in the 5-HT2 binding affinity has been found in the frontal cortex [16].

Depression is associated with a depletion of noradrenaline and serotonin. Age-related increase in MAO in the brain, which breaks down 5-HT and noradrenaline to 5-hydroxyindoleacetic acid and 4-hydroxy-3-methoxy D-mandelic acid, may predispose elderly people to depression. Serotonin is one of the main regulators of circadian sleep/wake cycles, and deficiency of serotonin is associated with many psychiatric and neurological disorders, including sleep disorders and some forms of dementia.

Amino acid transmitters

The activity of glutamic acid decarboxylase and the concentration of γ-aminobutyric acid (GABA) fall

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Table 1. Neuroendocrine changes with ageing

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<thead>
<tr>
<th>Hormone/receptor</th>
<th>Change</th>
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<tr>
<td></td>
<td>Increase</td>
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<tr>
<td>Dopamine</td>
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<tr>
<td>Dopamine receptor 1</td>
<td>+</td>
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<tr>
<td>Dopamine receptor 2</td>
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<tr>
<td>Monoamine oxidase A</td>
<td>–</td>
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<tr>
<td>Monoamine oxidase B</td>
<td>+</td>
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<tr>
<td>Noradrenaline</td>
<td>–</td>
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<td>Serotonin</td>
<td>–</td>
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<tr>
<td>γ-Aminobutyric acid</td>
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<tr>
<td>Muscarinic receptor</td>
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<tr>
<td>Nicotinic receptor</td>
<td>–</td>
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<tr>
<td>Choline acetyltransferase</td>
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<td>β-Endorphin</td>
<td>–</td>
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<td>α-Melanocyte-stimulating hormone</td>
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<td>Adrenocorticotropic hormone</td>
<td>–</td>
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<tr>
<td>β-Lipotropin</td>
<td>–</td>
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<tr>
<td>Follicle-stimulating hormone</td>
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<td>Luteinizing hormone</td>
<td>+</td>
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<tr>
<td>Inhibin</td>
<td>–</td>
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<tr>
<td>Testosterone</td>
<td>–</td>
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<tr>
<td>Luteinizing hormone-releasing hormone</td>
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<td>Aldosterone</td>
<td>–</td>
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<tr>
<td>Growth hormone</td>
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<td>Thyroid-stimulating hormone</td>
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<td>Thyroxin</td>
<td>–</td>
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<tr>
<td>Tri-iodothyronine</td>
<td>–</td>
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<td>Antidiuretic hormone</td>
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<td>Oxytocin</td>
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<td>Prolactin</td>
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<td>Melatonin</td>
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with age in a number of cerebral cortical areas [17], whereas the numbers of GABA-receptor-binding sites are increased or unchanged [18]. These decreases have been implicated in the pathogenesis of loss of speech understanding in elderly people. Age appears to have no effect on glutamate levels in small control groups that have been studied in relation to other diseases [7].

Age-related changes in GABAergic system and benzodiazepine receptors may play a part in sleep disorders.

The cholinergic system

Pre- and postsynaptic neurochemical markers of the brain cholinergic system decline with age [19]. Decreases in muscarinic receptors are found in brains of humans during ageing. A decline in muscarinic receptor number (50–60%) has been found in the caudate nucleus, putamen, hippocampus and frontal cortex [20].

The cognitive deficits in ageing and Alzheimer’s disease are attributable to deficits in the cholinergic system. Choline acetyltransferase is reduced in Alzheimer’s disease, particularly in the temporal cortex and the hippocampus [21]. The densities of forebrain cholinergic neurones are markedly decreased in cortical and hippocampal areas in Alzheimer’s disease. Cerebrospinal fluid acetylcholine concentrations are reduced in Alzheimer’s disease patients and show a positive correlation with dementia scale scores [22]. These findings, together with results of studies showing that anticholinergic drugs interfere with performance on tasks of memory, suggest that cholinergic deficits are responsible for the cognitive deficits associated with ageing and Alzheimer’s disease.

Maintenance of nicotinic receptors may be important for neuronal survival. Chronic smokers are less likely to develop Alzheimer’s disease or idiopathic Parkinson’s disease [23]. However, cholinergic deficits do not fully account for the cognitive deficits of Alzheimer’s disease. Despite similar degrees of dementia, no deficits in cholinergic markers have been found among subjects with multi-infarct dementia [24]. On the other hand, patients with olivopontocerebellar atrophy have deficits of cortical choline acetyltransferase activity as severe as those of people with Alzheimer’s disease, yet have only mild cognitive impairment [25]. It is likely that more than one neurotransmitter is involved in the cognitive deficits of ageing and Alzheimer’s disease, as marked deficiencies of noradrenergic, dopaminergic, serotonergic, and several peptidergic systems occur in the brains of patients who died with Alzheimer’s disease [26, 27].

Pro-opiomelanocortin-derived peptides and opioid peptides

The concentrations of the major pro-opiomelanocortin-derived peptides decrease with age. Chronic oestradiol exposure results in the destruction of more than 60% of all β-endorphin neurones in the arcuate nucleus [28]. In the hypothalamus, in addition to the reduced concentrations of β-endorphin, marked alterations in the post-translational processing of the peptides occur. Concentrations of β-melanocyte-stimulating hormone, adrenocorticotropic hormone and β-lipotropin are also reduced in the hypothalamus [29]. Inconsistent results have been observed in the response of encephalins to ageing [30].

LH-releasing hormone

Deterioration of the reproductive function with ageing is complex, comprising alterations in all three components of the reproductive axis—the gonads, the pituitary and the hypothalamus.

Blood concentrations of both basal LH and follicle-stimulating hormone (FSH) increase with age [31]. A rise in FSH is accompanied by a fall in inhibin levels with ageing [32]. The mean LH pulse amplitude and the maximal pulse amplitude are lower in elderly than young men [33]. The LH secretory burst frequency tends to increase, with a prolongation of the LH secretory burst duration [34].

Several authors have reported a decrease in free and total testosterone concentrations with ageing [35, 36], whereas others have failed to find age-related changes [37, 38]. Testosterone production by Leydig cells shows loss of its circadian rhythm with ageing [39]. The production rate and plasma clearance of testosterone decrease in older men. In young men, serum testosterone levels have a circadian variation that is blunted or lost with normal ageing, while the inhibin biorhythm is maintained in elderly men [40]. The testosterone response to chorionic gonadotrophin stimulation is diminished in older men, suggesting a decrease in Leydig cell function [41]. The basal elevations in FSH levels are proportionate to the degree of seminiferous tubular atrophy [37]. Pituitary gonadotropic secretory capacity is reduced with advancing age, as suggested by a decrease in the magnitude of LH and/or FSH responses to gonadotrophin-releasing hormone [42]. Increased sensitivity of the hypothalamic pituitary axis to exogenous androgens occurs with age [43]. Contrary to the commonly held belief, secondary hypogonadism seems to be the rule rather than the exception with ageing [44].

Women show reduced concentrations of LH-releasing hormone with advancing age. The sensitivity of the hypothalamic–pituitary axis to negative feedback is also attenuated in postmenopausal women, perhaps due to a hypothalamic decline rather than to a pituitary hypofunction [45].

The observed changes in the LH response to ageing may be due to effects of ageing on the catecholamine responses in the hypothalamus [24].
Drugs that stimulate brain catecholamine neurotransmission reinstate the oestrous cycle in old female rats [46]. Naloxone, when administered to old rats, partially restores the LH surge, suggesting that hypothalamic opiates may be partly responsible for reduction in LH secretion [47].

Chronic caloric restriction retards both neural and ovarian reproductive ageing processes, as well as age-related changes in many other physiological systems [48]. Oestrogen may influence cognition in postmenopausal women. In animal models, pretreatment with oestrogen reduces the extent of injury caused by stroke, suggesting a neuroprotective role of oestrogen. This raised the hopes that oestrogens might ameliorate the decline in function in women with Alzheimer’s disease. However, while some studies have suggested benefit from oestrogens, others have shown no effect [49–51].

Replacement of male sex hormones in elderly subjects is more controversial. Replacement of testosterone in both hypogonadal younger men and older men is associated with an increase in grip and leg strength, as well as increased muscle mass and protein synthesis [52, 53]. Very large doses of dehydroepiandrosterone (DHEA) have demonstrated antitumoral effects in animals [54]. DHEA prevents diabetes mellitus—both of genetic origin and induced by streptozotocin in old rats [55]. DHEA decreases the development of arterial lesions in rabbits on an atherogenic diet [55]. Experiments with animals and human cells suggest a role for DHEA in modulating immunological mechanisms [55]. DHEA increases retention of learning in rats.

However, blood levels of DHEA are not abnormal in patients with neurodegenerative diseases [55]. In nursing-home patients, low levels of DHEA relate to degree of dependence [56]. Whether prolonged DHEA substitution in healthy elderly individuals corrects any age-related phenomena remains to be seen.

**Corticotrophin-releasing factor**

The circadian rhythm of adrenocorticotropic hormone and cortisol secretion is flattened in old people. The cortisol circadian profile is higher in the evening and night time in elderly subjects [57]. The capacity to respond to stressors is preserved, with a normal corticotrophin-releasing factor–adrenocorticotropic hormone response. In contrast to glucocorticoids, the level of aldosterone in blood is decreased with advancing age. There is a diminution with age in the responsiveness of the renin–aldosterone system to changes in posture and variations in salt intake [58].

Alterations in cortisol control may have a number of adverse clinical consequences. For example, depression is associated with elevated levels of cortisol. There is evidence of long-term damage to the hippocampal neurones from a chronically elevated cortisol stress response that may result in memory impairment [59].

**Hypothalamic peptides**

**Peptides involved in GH regulation**

Episodic GH secretion becomes markedly impaired with ageing [60]. This is due to a reduction in pulse amplitude, although pulse frequency remains unchanged. In men, about 70% of the daily GH output occurs during early sleep. In women, the contribution of sleep-dependent GH release to the daily output is lower. During ageing, slow-wave sleep and GH secretion decrease in the same proportion [61]. Sleep-related secretion of GH appears to be primarily dependent on the release of GH-releasing hormone. Age-related decrements in sleep-related GH secretion may play a role in the hyposomatotropism of senescence. Other factors, such as changes in nutrition and reduction of physical exercise, may be important. Adiposity and ageing are independently associated with decreased plasma insulin-like growth factor (IGF)-1 concentrations [62]. The hyposomatotropism associated with ageing is partially reversed by fasting [63]. The response of pituitary somatotrophs to GH-releasing hormone has shown conflicting results. The response of IGF-1 to both exogenous GH administration [64] and GH-releasing-hormone-mediated increases in endogenous secretion are unaltered with increasing age [65].

A decline in pulsatile release of GH may be directly or indirectly responsible for the age-related decline in protein synthesis. The somatotroph cell mass appears to be preserved in older subjects. However, there is a negative correlation between the density of GH-binding sites in the human brain and increasing age [66]. This reduction in the density of GH binding is found in several areas of the brain, including the choroid plexus, the hippocampus, the hypothalamus, the pituitary and the putamen.

Catecholaminergic alterations in the hypothalamus may be responsible for the reduced GH secretion in old age, as suggested by the restoration of GH pulse amplitudes in old male rats by repetitive injections of catecholamine precursors [67]. Since acetylcholine inhibits hypothalamic somatostatin release, the reduced cholinergic tone in elderly subjects may result in an increased somatostatinergic tone [68]. Most evidence supports the concept that norepinephrine’s stimulatory effect on gonadotrophin-releasing hormone release is mediated by α₁-adrenergic receptors [69]. Age-related variations in the activity of other neurotransmitters, such as arginine and galanin, could affect the reduced activity of the GH–IGF-1 axis.
Healthy older people have decreased muscle mass, increased fat mass, and decreased strength. The risk of falls and fractures increases with age-related decreases in muscle strength. The decrease in GH and IGF-1 levels may be partially responsible for the loss of muscle and bone mass in elderly people. Decreased serum concentrations of IGF-1 are strongly associated with an increased risk of osteoporotic fracture in postmenopausal women [70]. Rudman et al. [71] reported an increase in lean body mass and vertebral bone density with a decrease in fat mass in a group of healthy old men who were given 30 μg GH per kg body weight three times a week. This study raised the questions of whether long-term administration of GH might prevent physiological decline in old age, and whether GH might be used in the treatment of osteoporosis and muscle atrophy in elderly patients. Both whole-body and muscle protein synthesis increases in subjects given GH [72, 73]. Another study in GH-deficient adults showed that GH supplementation resulted in increased circulating osteocalcin and procollagen 1 levels, along with a longer-lasting increase in alkaline phosphatase levels and urinary excretion of hydroxyproline and calcium [74]. This increase in markers of bone resorption as well as bone formation indicates an activation of bone remodelling by GH.

GH may also have beneficial effects on myocardial contractility in elderly patients with heart failure. In patients with childhood and adulthood-onset GH deficiency, the impairment of cardiac performance is manifest primarily as a reduction in the left ventricular mass, reduced left ventricular ejection fraction and abnormalities of left ventricular diastolic filling. As in normal subjects, the rate and extent of left ventricular filling are reduced with age, so GH deficiency in older patients may contribute to the development of cardiac failure. GH triggers cardiac tissue growth, augments cardiac contractility, improves myocardial energetics and mechanical efficiency and decreases peripheral vascular resistance. GH may also raise preload through its sodium-retaining action. GH-deficient patients have hypercholesterolaemia, and GH treatment reduces plasma cholesterol [75]. In healthy subjects, GH administration increases heart rate, cardiac output and myocardial contractility [76]. Animal studies and preliminary human trials have confirmed the validity of the GH approach to the treatment of heart failure. However, in a double-blind, placebo-controlled study of recombinant human GH administration in 22 patients with congestive heart failure, no beneficial effect on cardiac function or structure was demonstrated [77]. Larger placebo-controlled human studies are needed.

Questions about the safety of long-term use of pharmacological doses of GH remain to be answered. There is epidemiological evidence for an increased risk of neoplasia—especially of the colon—in untreated acromegalic patients [78]. GH therapy may have detrimental effects on osteoarthritis. IGF-1 and osteophyte growth in the knee are shown to be closely related [79]. The diabetogenic effect of long-term GH therapy remains a concern.

**Peptides involved in thyrotropin regulation**

Circulating levels of thyroxin and tri-iodothyronine are unaltered with advancing age and the thyroid-stimulating hormone levels remain normal or increase slightly. Low concentrations of tri-iodothyronine are better correlated with a quantitative measure of severity of illness rather than with age [80] and no changes were noted in tri-iodothyronine or reverse tri-iodothyronine values with increasing age [81]. There is also a reduction in peripheral utilization of thyroid hormones with age, thereby maintaining plasma thyroxin levels. Degradation of thyroxin and tri-iodothyronine also gradually declines with increasing age. Hypothalamic thyrotropin-releasing hormone concentrations are not reduced in elderly women [82].

In elderly men, there is a decrease in pituitary gland responsiveness to thyrotropin-releasing hormone. The results of thyrotropin-releasing hormone testing may be misleading in old men, since a depressed thyrotropin-releasing hormone responsiveness may not indicate any pathological process.

**The neurohypophyseal system**

In elderly people, cells in the hypothalamic paraventricular and supraoptic nuclei show changes characteristic of augmented hormone synthesis. This is consistent with normal to increased hypothalamic antidiuretic hormone content and baseline plasma antidiuretic hormone levels in elderly subjects [83].

Osmoreceptor sensitivity appears to be increased, as shown by a sharper rise in blood antidiuretic hormone levels in response to an increase in serum osmolality in older people. However, the renal collecting tubule sensitivity to vasopressin is decreased. After infusion of hypertonic saline, older people have a 2- to 2.5-fold greater rise in plasma antidiuretic hormone levels, but similar increases in plasma osmolalities [84]. The response of antidiuretic hormone to orthostatic challenge is blunted [85]. Older people have a higher peak arginine vasopressin response to metoclopramide and cigarette smoking than young subjects, but a similar response to insulin-induced hypoglycaemia [86]. Administration of a water load to young and elderly subjects showed that older people had a decreased ability to excrete this water load despite similar decreases in arginine vasopressin concentrations [87].

Oxytocin content is also decreased. The sexually dimorphic nucleus is between the supraoptic and
paraventricular nuclei. During ageing, a decrease in cell number is found in both sexes [88].

The age-related changes in control of antidiuretic hormone secretion must be considered in the evaluation of fluid balance problems in elderly people and may play a part in the development of hyponatraemia and postural hypotension.

The anterior pituitary and prolactin

There is increased patchy fibrosis, focal necrosis, iron deposition and adenoma formation in the anterior pituitary of the ageing man. There is a moderate decrease in the size of the pituitary [89]. There are no age-related alterations in the total numbers of prolactin cells. The circadian rhythms of plasma melatonin, GH and prolactin are flattened, and the nocturnal secretion of these hormones is impaired in elderly people [90].

In women, baseline serum prolactin levels begin to fall around menopause [91]. In men, both unaltered and augmented serum concentrations of prolactin have been reported [49]. The results of the prolactin secretory response to bolus intravenous injections of thyrotropin-releasing hormone in older men are also inconsistent [92, 93].

The decrease in night-time serum melatonin concentrations with ageing suggests that melatonin may have a role in ageing and age-related diseases [94]. Studies in rats [95] and mice [96] suggest that diminished melatonin secretion may be associated with accelerated ageing, but there are no data supporting an anti-ageing effect of melatonin in humans. The role of melatonin in the regulation of sexual reproductive physiology is suggested by the observation that melatonin administration and young-to-old pineal grafting has a positive effect on the size and function of testes and maintenance of juvenile hippocampal and testicular LH-releasing hormone receptors and β-adrenergic receptors in the testes of old rats and mice [97].

Conclusions

Ageing results in a decline of neuroendocrine function. This has been implicated as a potential factor in the development of several age-related diseases. Although the ageing process itself may not have a neuroendocrine basis, identification and correction of the associated neuroendocrine dysfunction may be important in enhancing the quality of life.

There is much interest in the preventive and therapeutic potential of hormonal substitution therapy for these age-related diseases. Whereas numerous beneficial effects of GH replacement on body composition, strength and quality of life have been reported, other studies have reported only marginal functional improvements. Initial results are promising but further studies are required to elucidate potential risks.

Key points

- Many common problems encountered in the ageing patient can be related to neuroendocrine phenomena. Clues to their aetiology may inform rational treatment.
- Such problems include:
  1. Menopause and vascular risk.
  2. Parkinson’s disease—an exaggeration of the age-related change in the hypothalamic/dopaminergic system?
  3. Alzheimer’s disease—related to the reduction of hypothalamic/noradrenergic function?
  4. Depression—loss of serotoninergic neurones?
  5. Insomnia—loss of functional γ-aminobutyric acid activity?
  6. Dementia or lesser degrees of cognitive dysfunction—a cholinergic problem?
  7. Weakness and loss of energy—growth hormone deficiency?
  8. Hyponatraemia—the compensating system operates but the body is not capable of responding?
  9. Osteoporosis—growth hormone and sex steroid deficiency?

References


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