INVITED REVIEW

Age-related changes of the hypothalamic–pituitary–adrenal axis: pathophysiological correlates

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Abstract

The aim of this review was to examine the evidence for age-related changes of the hypothalamic–pituitary–adrenal (HPA) axis in both physiological and pathological aging, on the basis of the many data in the literature, as well as of our personal findings.

A statistically significant circadian rhythmicity of serum cortisol was maintained in elderly subjects, even if with a reduced amplitude of the 24 h fluctuations and a trend to an increase of the serum levels in the evening and at night-time, in comparison with young controls. Furthermore, an age-related impairment of HPA sensitivity to steroid feedback was present in elderly people.

The occurrence of senile dementia amplified the changes already present in physiological aging. While the cortisol secretion was generally well maintained in aging, the adrenal production of dehydroepiandrosterone and of its sulfate (DHEAS) exhibited an age-related decline. Therefore, the cortisol/DHEAS molar ratio was significantly higher in elderly subjects and even more in demented ones, than in young controls.

Due to the opposite effects of cortisol and DHEAS on the brain and particularly on the hippocampal region, the imbalance between glucocorticoids and androgens occurring in physiological and even more in pathological aging, may have adverse effects on the function of this region, whose key role in learning and memory is well known.

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Introduction

The hypothalamic–pituitary–adrenal (HPA) axis is an auto-regulating system with many modulatory mechanisms; due to such regulation, the circulating levels of glucocorticoids are highly variable, according both to the spontaneous rhythmic fluctuations and to the responses towards stressful conditions. Furthermore, the HPA axis realizes a tight integration among the endocrine, nervous and immune systems, being its key point.

In this way, the HPA axis is one of the most important allostatic (or adaptive) systems; when active, it allows the organism to respond to a challenge, or in general to a stressful condition, but its inactivation is equally important, since the allostatic load can over-expose the organism to the mediators of neural, endocrine and immune stress, with different pathophysiological consequences (1, 2).

Significant morphological and functional changes affect with age the HPA axis at different levels both in experimental animals and in human beings. The neural cell impairment and the compensatory gliosis are particularly evident at the level of the hypothalamus and of the hippocampal and limbic system. In particular the neuronal impairment of the suprachiasmatic nucleus (3) may be responsible for alterations of the circadian temporal structure of the aged organism, due to the role played by the same nucleus as central pacemaker of several circadian rhythms. Furthermore, the loss of neurons, especially affecting both the hypothalamus as well as the hippocampus and the limbic region, implies a reduction of the glucocorticoid receptors and hence an impaired regulation of the adrenocortical secretion (4, 5). Indeed, the role played by the hippocampus, both in animals and in humans, in maintaining the adrenocortical circadian rhythmicity (6), as well as in modulating the glucocorticoid feedback control of adrenocorticotropic (ACTH) secretion (7–9) and the adrenocortical responses to stressful conditions (10) is well known.

Consequently, the hippocampal degenerative changes occurring in physiological and even more in pathological aging may be responsible for the impaired sensitivity to
the steroid feedback and for a certain degree of hyperactivity of the HPA axis in elderly subjects (11). However, the heterogeneity of the age-related HPA patterns must be underlined; indeed, some individuals exhibit substantial changes while others maintain an HPA function similar to younger individuals.

Many factors might be potentially involved in the aging process and, in particular, in brain aging, with several metabolic, immune and neuroendocrine changes playing a pathogenic role. Due to the primary role of the adrenal steroids in maintaining the homeostasis and the adaptational organism responses to stress, it seems very interesting to study the link between the corticosteroid secretion and the limbic--hippocampal age-related changes.

In this review we particularly focus on the age-related changes of the glucocorticoid and androgen secretion, by considering separately the two hormonal patterns, due to the peculiar modifications affecting the different adrenocortical zones in aging. For such studies we favored the evaluation of the circadian fluctuations of blood corticosteroids, which may provide better information about the pathophysiology of the endocrine secretions in comparison with the pharmacological tests, which sometimes do not reflect the spontaneous hormonal release. Furthermore, the chronobiological evaluation of neuroendocrine functions in elderly people may represent a clinically reliable tool to investigate the biology of the CNS and particularly of the limbic--hypothalamic system, and hence reveal the pathophysiology of the cerebral aging.

Together with physiological aging, senile dementia represents a clinical model very interesting for chronobiological studies, either for the frequency of changes of the central neurotransmitter pathways, or because of the frequent occurrence of degenerative alterations of the hypothalamic suprachiasmatic nucleus.

**Cortisol secretion and aging**

Much evidence suggests that the primary defect in allostatic systems in aging might be a prolonged response to stressful conditions, due to the inability to shut off the allostatic response after the end of the stress (12–16). Consequently the HPA axis would become less resilient with age in responding to stimulations.

However, in spite of the subtle age-related changes of HPA function, the circulating levels of glucocorticoid show a relative constancy or even a trend toward an increase with aging. Indeed, the blood levels of both cortisol and ACTH usually fall within the normal range in physiological aging, but a trend towards higher nocturnal levels is often reported (17–19).

The possible role of changes of the glucocorticoid signal in the age-related modifications of the CNS has been often suggested. Indeed, since 1968, a link between high glucocorticoid levels and neuronal loss had been hypothesized in Alzheimer’s disease (AD) (20); in the following years much experimental work confirmed this suggestion (21, 22). Similar findings were found both in primates (23) and in humans; in particular, a significant relationship between the increasing cortisol levels over a period of 4 years and the impairment of explicit memory and selective attention performances has been described in a longitudinal study (24).

Furthermore, high cortisol levels with an impaired HPA sensitivity to steroid feedback are often described in senile dementia, both of degenerative and vascular types (25–28).

Besides, a positive relationship of the cortisol response to an i.v. glucose load with the degree of hippocampal atrophy and the severity of dementia has been described in several demented patients (29); moreover the cortisol increase seems to be a very sensitive marker of cognitive decline in AD patients (30).

The conventional measures of total cortisol levels might underestimate the real degree of hypercortisolism in AD patients, since a reduction of corticosteroid-binding globulin (CBG) levels has been found in about 30% of the patients with this kind of dementia (31). In any case, the CBG plasma levels were similar in old subjects with high, low or normal cortisol values, and a strong correlation between total and unbound cortisol levels across subjects has been described (32).

A cross-sectional approach in studying the age-related changes of the HPA axis may offer only tentative suggestions. However, information arising from serial blood samples collected every 4 h during the day and every 2 h during the night, may give a true picture of the hormonal plasma changes in groups of different age which may underline the interindividual variations.

Furthermore, the inclusion in the study of subjects drug-free and without overt acute or chronic disease allowed us to investigate the role of age and dementia in HPA changes, independently of individual health status.

On these basis, we studied the circadian rhythm of serum cortisol in a wide number of healthy old subjects (n = 52, age 69–90 years), of old demented patients, including both AD and multi-infarct dementia (vascular dementia (VD)) (n = 35, age 69–90 years) and of young controls (n = 22, age 19–43 years). The physiological cortisol circadian rhythmicity was maintained, with a significant age-related increase of the nocturnal cortisol levels in physiological aging and even more in senile dementia, in comparison with young subjects (Fig. 1).

Our data agree with other studies, showing the age-related increase of the cortisol nadir values, together with the phase-advance of the onset of the circadian cortisol rise (33). Due to these changes, a reduction of the quiescent period of the cortisol secretion and hence an increase of the cortisol signal throughout the 24 h occur in elderly people in comparison with young one.
The relative increase of cortisol serum levels in the evening and at night-time is responsible for the clear flattening of the cortisol circadian profile. Indeed, the nocturnal increase of serum cortisol (calculated as difference between the values recorded at 0800 and 0000 h) was significantly reduced in both physiological and pathological aging; moreover this reduction was negatively correlated to both the age ($r = -0.3718, P < 0.01$) and the cognitive performance of subjects ($r = 0.3580, P < 0.01$), the latter being evaluated by the Mini Mental State Examination (Table 1).

Since the crucial role played by the central cholinergic and serotonergic pathways in the circadian activation of the ACTH-secreting system at night-time is well known (33, 34), the impairment of the cortisol nocturnal increase in elderly subjects may be a marker of a reduced activity of these pathways.

Figure 1 Serum DHEAS and cortisol circadian rhythm (before and after DXM administration, 1 mg orally at 2300 h) in physiological and pathological brain aging and in young controls (means ± S.E.M.). Old subjects vs young controls: $a = P < 0.05$, $b = P < 0.01$, $c = P < 0.001$. AD patients vs young controls: $d = P < 0.05$, $e = P < 0.01$, $f = P < 0.001$. AD patients vs old subjects $g = P < 0.05$, $h = P < 0.01$, $i = P < 0.001$. L/D, light dark.
A reduction of the melatonin signal, widely described in aging, could also contribute to the changes of cortisol and ACTH nocturnal increase in elderly subjects. Indeed the pineal gland seems to play an inhibitory role on the HPA axis (35, 36), by modulating the adrenal sensitivity to the corticotropic stimulation (37) and even by limiting the corticotropin response to stressful conditions (38). Our data concerning the simultaneous evaluation of cortisol and melatonin secretions in elderly subjects confirm the opposite behavior of the two secretions in both physiological and pathological aging (39, 40) (Table 2).

Age-related changes of the dynamic secretory pattern of HPA axis have also been described. In fact, the cortisol peak values recorded during insulin-induced hypoglycemia were generally higher in old than in young subjects, in spite of the smaller glycemic fall occurring in the elderly (41). Thus, the HPA axis in aged people seems to recover slowly from certain types of stress.

Higher cortisol levels in old than in young subjects have been described during some pharmacological challenges, such as the dexamethasone (DXM) suppression test, the stimulation by human or ovine corticotropin-releasing hormone (CRH) or by physostigmine (12, 42), probably due to the age-related changes of the HPA sensitivity to both exogenous and endogenous stimuli. However, it seems noteworthy that the basal cortisol levels exhibit a high intraperson stability and stimuli. However, it seems noteworthy that the basal cortisol levels exhibit a high intraperson stability and pathological aging (39, 40) (Table 2).

Interesting results have been also reported (44) by the CRH stimulation under DXM suppression. Indeed, in spite of the higher cortisol levels recorded in old subjects under basal conditions, the levels of both ACTH and cortisol after DXM were not different in old and in young subjects, whereas a significantly higher cortisol response to CRH occurred in old subjects.

Some data in the literature (45, 46) suggest that aging does not modify the pituitary and adrenal responsiveness to exogenous CRH. However, other studies concerning cortisol and ACTH response to both CRH and vasopressin, suggest that the pituitary gland might become more sensitive with aging to CRH alone or in association with vasopressin (12, 16, 47) in the presence of stressful conditions and of age-related diseases (48). In our experience (45), the response of cortisol and ACTH to a CRH stimulation test (ovine CRH, 1 μg/kg i.v.) was not significantly different in 14 healthy old women (69–83 years) and in 11 young women (20–40 years) (Table 3).

Age-related changes of the endogenous CRH or vasopressin secretion may also occur (49). Indeed in AD patients the CRH immunoreactivity has been described as increased in the hypothalamus and decreased in other cerebral areas, suggesting the existence of alterations of the glucocorticoid regulation of this peptide (49). Similar neuroendocrine changes may also be suggested in physiological aging (50).

The adrenal sensitivity to exogenous ACTH seems not to be significantly modified during physiological aging and in the early stage of AD (51). In our experience (52) the cortisol response to pulse injection of a small dose of synthetic ACTH (Synacthen, 2500 ng, i.v., at 2030 h) was quite similar in young and old healthy women; however, patients with overt senile dementia exhibited a significant increase of both the duration and the amplitude of cortisol response, as well as a significant delay of the time to peak (73 ± 4.7 min), when compared with old healthy subjects (46 ± 4.9 min) and with young controls (45 ± 5 min).

Since the cortisol response to a pulse injection of a small dose of Synacthen is similar to that induced by a stressor, it is possible to argue that also in humans the adrenocortical responsiveness to stressful conditions is increased and prolonged only when ‘senescence is coupled with pathological conditions’, in agreement with previous studies on old animals (14).

An age-related decrease of the HPA sensitivity to the steroid feedback signal has been reported. In particular both the rate of non-suppression and the residual cortisol levels after DXM were higher in demented patients than in age-matched controls, possibly in relation to anxiety, depression, panic or restlessness (53). Since these clinical symptoms and the high cortisol levels may be modified by the selective serotonin re-uptake blockers, it is possible to suggest that the enhanced activity of the HPA axis in senile dementia may be related to a central neurotransmitter

### Table 1

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<th>Cortisol nocturnal increase in physiological and pathological brain aging and in young controls (means ± S.E.M.)</th>
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<tr>
<td>Young controls</td>
<td>16.10 ± 1.39^a,b</td>
</tr>
<tr>
<td>Old subjects</td>
<td>9.26 ± 0.88</td>
</tr>
<tr>
<td>Demented patients</td>
<td>8.02 ± 1.83</td>
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^a P < 0.001 (Student’s t-test) vs demented patients.
^b P < 0.001 vs old subjects.

### Table 2

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<th>Ratio between cortisol and melatonin circadian mesors</th>
<th>Ratio between cortisol nadir and melatonin peak</th>
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<tr>
<td>Young controls</td>
<td>0.58 ± 0.17^a</td>
<td>0.05 ± 0.01^b</td>
</tr>
<tr>
<td>Old subjects</td>
<td>0.93 ± 0.14</td>
<td>0.34 ± 0.09^c</td>
</tr>
<tr>
<td>AD patients</td>
<td>1.33 ± 0.20</td>
<td>0.58 ± 0.11</td>
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^a AD patients and young controls: age vs cortisol nadir/melatonin peak ratio
^r = 0.64. P < 0.001
^b P < 0.001 vs AD patients.
^c P < 0.001 vs AD patients.

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imbalance, probably responsible also for the impaired sensitivity to the steroid feedback (53, 54).

It is now well established that the glucocorticoid feedback on the HPA axis includes at least three time domains: fast (seconds or minutes), intermediate (usually less than 10 h) and slow (within hours or days) (55), and that for all of them the sites of action are the hypothalamus and the hippocampus (56), two brain areas in which the corticosteroid receptors (both type I and type II) are widely represented (57).

In order to study the first phase of the negative feedback, Boscaro et al. (9) recently evaluated in aged people and in young controls the ACTH and cortisol suppressibility by the infusion of hydrocortisone, which differs from DXM in the affinity for corticosteroid receptors subtypes (16, 58–61). In spite of a similar cortisol increase in both groups of subjects, the old ones exhibited a slight and not significant decrease of ACTH levels during the first phase of the response to hydrocortisone infusion, in comparison with young controls; on the contrary, a pronounced and significant decline of ACTH concentrations occurred thereafter in old subjects.

These findings suggest that the age-related changes of the HPA activity in aging may be related to several factors, namely a decrease with aging of the brain corticosteroid receptor concentration (62), but also the age-related differences in the cerebrospinal fluid (CSF) steroid concentrations (63), probably secondary to changes of the cortisol clearance rate in CSF and/or of the blood–brain barrier (64, 65). Thus, also vascular factors may play a pathogenetic role in the decline of the HPA sensitivity to the steroid feedback.

In physiological and pathological brain aging and in young controls, the study of the circadian rhythm of serum cortisol, both before and after DXM administration (1 mg at 2300 h, orally) (Fig. 1), allowed us to detect a high percentage of 'non-responders' (serum cortisol levels above 5 μg/dl the morning following DXM (66), in healthy old subjects (about 30%) and in old demented patients (50%). Indeed, the mean cortisol values recorded after DXM were significantly higher in elderly subjects and especially in demented patients than in young controls; moreover, patients with senile dementia also exhibited a delay of the cortisol response to DXM (67).

These findings underline the relevance of the ‘age’ factor in the pathogenesis of the impaired HPA sensitivity towards the negative steroid feedback, and the additional effect of the occurrence of senile dementia.

In conclusion, the changes of the cortisol secretory pattern observed in elderly subjects and especially in patients with senile dementia (namely the flattening of the circadian profile and the increase of the nadir levels, together with the impaired sensitivity to the steroid feedback) are reminiscent of the data described in senescent animals or in animals with experimental hippocampal lesions (68).

### Dehydroepiandrosterone sulfate (DHEAS) and aging

Only in humans and a few primates do the adrenals secrete dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) (69, 70); in particular, the zona reticularis of the adrenal cortex is the exclusive source for DHEA and DHEAS, and the level of expression of 3β-hydroxysteroid dehydrogenase is the most important determinant for their biosynthesis (71).

In contrast with the minimal changes of the cortisol secretion occurring with age, the last decades of life are characterized by a progressive reduction of the secretion rate of DHEA and DHEAS, the main adrenal androgens.

In fact, the blood levels of these steroids, very low in the first years of life, begin to rise at the adrenarche and progressively increase till the third decade; after the age of 30 the steroid levels declines at a rate of 1–2% per year, even if with marked interindividual differences, and by the age of 70–80 they correspond only to 20–30% of the peak concentration occurring in young people (72–74). The DHEAS/DHEA ratio does not change with aging.

In spite of the great interindividual variability, the DHEAS levels show a low within-subjects changes; therefore they may be considered as highly specific individual markers (75).

The morphological correlates of the physiological age-related changes of DHEA and DHEAS secretion are the modifications of the zona reticularis. Indeed, the development of this zone of the adrenals begins at the adrenarche and shows a clear width reduction during aging (76). The mechanisms responsible for this reduction are still unknown; furthermore, a significant correlation between the DHEAS decline in aging and the morphological changes of the zona reticularis was never found (77).

However, the zona reticularis is particularly susceptible to the intra-adrenal gradient of autocrine and para-crine factors, as also reported for the zona fasciculata (78, 79).

#### Table 3

<table>
<thead>
<tr>
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<th>Old healthy women (n = 14, age 69–83 years)</th>
<th>Young healthy women (n = 11, age 20–40 years)</th>
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<tbody>
<tr>
<td>ACTH (pg/ml)</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>27.1 ± 3.7</td>
<td>19.4 ± 1.5</td>
</tr>
<tr>
<td>Delta (max.)</td>
<td>29.2 ± 8.4</td>
<td>28.1 ± 10</td>
</tr>
<tr>
<td>Delta (%)</td>
<td>117.9 ± 22.3</td>
<td>144.8 ± 33.5</td>
</tr>
<tr>
<td>Cortisol (μg/dl)</td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>15.7 ± 1.3</td>
<td>9.0 ± 1.1</td>
</tr>
<tr>
<td>Delta (max.)</td>
<td>12.6 ± 2.4</td>
<td>8.4 ± 1.5</td>
</tr>
<tr>
<td>Delta (%)</td>
<td>90.4 ± 18.5</td>
<td>93.3 ± 21.2</td>
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</tbody>
</table>

**Note:** ACTH = adrenocorticotrophin; DHEAS = dehydroepiandrosterone sulfate; DXM = dexamethasone; CSF = cerebrospinal fluid; HPA = hypothalamic–pituitary–adrenal; DHEA = dehydroepiandrosterone; CRH = corticotropin releasing hormone.
paracrine factors created by the blood supply, and to vascular damages, such as multiple microhemorrhagic events, with subsequent necrotic damage. Taken together, all these factors might explain the age-related decline and the interindividual changes in DHEAS secretion.

In addition to the reduced secretion in basal conditions, the DHEAS response to exogenous ACTH is significantly impaired in old subjects, whereas the cortisol response is generally maintained (78). Thus, a specific, but unexplained, defect of the desmolase activity of P450c17 cytochrome in the zona reticularis seems to occur with aging (79).

Extra-adrenal factors may also affect the adrenal androgen biosynthesis. For example, some proopiomelanocortin-related peptides, and in particular the joint peptide and beta-endorphin, could stimulate the androgen secretion (80, 81), although some authors did not confirm such action (82, 83). The possible role of a specific pituitary adrenal androgen-stimulating factor, identified by Parker et al. (81), is still debated.

Furthermore, a possible influence of insulin in the age-related decline of DHEAS has been suggested, due to the inhibitory activity of insulin on DHEAS secretion, and the trend to increase of insulin during aging, but this effect seems well-evident only in men (84).

In addition to the doubts concerning the pathophysiology of the age-related decline of DHEAS secretion, many questions still remain about the central and peripheral effects of adrenal androgens, since no specific cellular or molecular targets for DHEA and DHEAS have until now been identified (79). However, the results of DHEA administration in experimental animals or during clinical trials, suggest a pleiotropic effect of this hormone.

Indeed, DHEAS, but not DHEA, is able to activate the hepatic peroxisome proliferator-activated receptor alpha (85), an intracellular receptor of the steroid receptors family; this activation could modulate the fatty acid metabolism and the expression of peroxisomal enzymes, and thus could explain the DHEAS anticarcinogenic and chemoprotective effects (85).

Antidiabetic and antiobesity activities of DHEAS have been also described in experimental animals, but they are not always confirmed in humans. Furthermore, high DHEAS levels have been related to a significant decrease of mortality for cardiovascular disease in men but not in women (86).

The most important findings, however, concern the effects of DHEAS on the CNS, where these steroids may be synthesized de novo, namely independently from the gonads and the adrenal glands, and thus they are called ‘neurosteroids’ (87). At the present it is unknown if changes in plasma DHEAS levels can directly affect CNS functions. However, at the CNS level, DHEAS and pregnenolone sulfate on the one hand and tetrahydroprogesterone, tetrahydrodeoxy-cortistosterone and androsterone on the other, effect an important homeostatic control mechanism for the neuronal activity, by binding to the γ-aminobutyric acid A (GABA_A) receptor (88). In particular, DHEA and DHEAS, acting as allosteric antagonists of GABA_A receptor, may enhance the neuronal and glial survival and may improve learning and memory capacities (89, 90). Indeed in experimental animals, DHEA administration has a memory-enhancing effect and in vitro studies suggest a neurotropic effect on neurons and glial cells (91).

Furthermore, the noradrenergic release of N-methyl-d-aspartate in the rat hippocampus may be enhanced by DHEA (92). This action, together with the proserotonergic activity of DHEAS, could be responsible for the antidepressive effects, and for the improvement of memory reported after DHEA administration in humans, due to the key role played by noradrenaline on this function (93–95).

In rat primary hippocampal neurons, the addition of DHEAS, but not of DHEA, was able to enhance the neuronal resistance to stress relevant for both acute and chronic neurodegenerative conditions, by the activation of a kB-binding transcription factor (96) which is involved in the neuroprotection against oxidative stress, calcium and β-amyloid (97, 98). Thus, the age-related decline of DHEAS might play a role in the occurrence of AD and other neurodegenerative diseases.

Beside the possible role of DHEA on cognitive functions, many studies suggest an involvement of the adrenal androgens also in the maintenance of functional abilities (99, 100) and in the pathogenesis of several age-related diseases (101). Furthermore, the reported lack of relationship between the age and the DHEAS levels in subjects over 90 years old (102), suggests that high DHEAS levels might be associated with a longer survival. Indeed, when age is factored out by appropriate polynomial regression, a significant component of DHEAS variations seems to exist (103).

The data in the literature concerning DHEAS secretion in senile dementia are still conflicting (104–110), although at the moment strong evidence points to the possible role of DHEAS in limiting the cortisol neurotoxic effect on hippocampal cells, in this way preventing the brain degeneration in AD (108).

In a community-based study, no significant relationships between DHEAS levels and cognitive function have been found (111). In another longitudinal study, lower DHEAS values were recorded in women with functional limitations, depressive symptomatology and poor well-being, but not in men (112).

Our results, obtained by the simultaneous evaluation of the circadian rhythm of blood cortisol and DHEAS in physiological and pathological brain aging, including both AD and VD, indicated a clear decline in DHEAS secretion throughout the 24 h cycle in elderly subjects (n = 23, age 76–96 years), and especially in old demented patients (n = 23, age 68–91 years), without
sex-related differences, in comparison with young controls \((n = 10, \text{ age } 25–32 \text{ years})\). Concerning the type of dementia, patients with VD exhibited the lowest DHEAS levels (Fig. 1).

The statistical analysis of our data by the population mean cosinor method demonstrated the statistical significance of the serum DHEAS circadian rhythm in young and elderly subjects, even if with a marked reduction of both mesor and amplitude in old subjects, particularly if demented. However, a good maintenance of the temporal relationship between the DHEAS and cortisol crest-times persisted in both physiological and pathological brain aging, as already described in children and in young adults (113).

The molar ratio between cortisol and DHEAS levels throughout the 24 h cycle was significantly higher in elderly subjects, particularly if demented, in comparison with young controls. Furthermore, old demented patients exhibited a further increase of this ratio at night-time, when compared with old controls, suggesting the existence of a deeper neurotoxic effect of the adrenocortical secretory imbalance (Fig. 1).

This finding seems particularly interesting if we consider that, in spite of the decline of DHEAS secretion, well evident also in extreme senility, we have recently found similar cortisol levels in healthy centenarians \((n = 20, \text{ age } 100–106 \text{ years})\) and in younger controls. Thus the cortisol/DHEAS molar ratio was similar in centenarians and in healthy old controls (data not shown).

Due to the opposite changes of cortisol and androgen secretions occurring in physiological and even more in pathological brain aging, it seemed interesting to study, by morphometric measures, the cerebral changes occurring in these conditions, in order to try to correlate the neuroendocrinological features with the cerebral volumetric modifications.

In particular we have considered the hippocampal changes, since it is well known that both the age-related neuronal impairment and the degenerative changes of AD are especially evident in this area. Indeed, the hippocampus is a particularly vulnerable brain area, with a high expression of glucocorticoid receptors, and it is deeply involved in the regulation of the HPA axis (114). Thus, it represents a vulnerable link in the regulation of both HPA function and cognition (115).

Both in experimental animals and in humans, the hippocampal volume decreases with aging, due not only to neuronal loss, but also to the effects of neurotransmitters imbalance, excitatory amino acids (116) and adrenal steroids (117, 118). To assess in vivo the main cerebral volumes in healthy young and old subjects and in AD patients, we have recently performed a cerebral morphometric analysis by the magnetic resonance imaging method (119).

In spite of the great interindividual variability, our study demonstrated an age-related decline in hippocampal volumes and a progressive enlargement of the ventricular size, which represents an index of cerebral atrophy and volume loss (120). An important finding to be emphasized is that the reduction of the hippocampal volumes seems to be significantly related to the impairment of the cortisol nocturnal increase and to the mean circadian value of serum DHEAS (Fig. 2). Even if in humans it is hard to demonstrate a relationship between the hippocampal modifications and the adrenal secretion, our data suggest the existence of a link between the reduction of hippocampal volumes occurring with age and the trend to increase of cortisol in the evening and at night-time and the decline of DHEAS secretion.

Among the other cerebral volumes evaluated, only the temporal lobe was significantly lower in AD patients than in age-matched controls, suggesting the specificity for AD of these changes (121).

**Conclusions**

According to the results of our research and of many studies in the literature, a clear dissociation of the adrenocortical secretory pattern occurs with aging, due to good maintenance of cortisol secretion and clear impairment of that of androgens in elderly subjects, with particular evidence in the demented ones.

Consequently, a significant increase of the cortisol/DHEAS molar ratio occurs in both physiological and pathological aging.

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It is now well known that both glucocorticoids and androgens have relevant effects on the brain, most notably on the hippocampus, a critical area for learning and memory, as well as a crucial center for the glucocorticoid inhibition of their own release (115, 122, 123). The effects of the two kinds of steroids on the hippocampus are opposite, since cortisol promotes the neuronal degeneration and death, whereas DHEAS plays a protective role towards the structural damages and the functional impairment due to aging itself or to pathological situations, and stimulates the neuronal long-term potentiation (124). Thus, the age-related decrease of DHEAS secretion necessarily results in an impairment of the DHEAS-mediated antiglucocorticoid activity, and consequently in an enhanced neurotoxicity of glucocorticoids and of excitatory amino acids (123).

As a whole our data suggest that, as in experimental animals (125, 126), the brain aging may depend upon the cumulative exposure to increasing cortisol levels throughout life (32, 127), particularly if parallel to a reduced androgen secretion.

The age-related hormonal changes, such as the opposite modifications of cortisol and melatonin secretion, may play a role in the pathophysiology of the CNS degenerative changes also through the enhancement of 5-lipoxygenase (5-LOX) expression in the CNS (128); this is the key enzyme responsible for the synthesis of inflammatory leukotrienes, and probably involved in neurodegeneration. Indeed, it is well known that 5-LOX expression, prominent in hippocampal and cerebellar neurons, is stimulated by glucocorticoids (129) and depressed by melatonin (130). Therefore, the subtle but significant changes of the hormonal balance occurring in aging may contribute to the onset and progression of the aging-associated neurodegenerative diseases.

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