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Neuroendocrine features in extreme longevity

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Abstract

In order to evaluate the effects of some neuro-endocrine changes during aging we have studied adrenal, thyroid and pineal secretion in young, healthy old and centenarians. The number of subjects in each hormone group varied. The following parameters were evaluated: serum levels of cortisol, dehydroepiandrosterone-sulfate (DHEAS), free triiodothyronine (FT3), thyroxine (FT4), reverse triiodothyronine (rT3) and thyroid-stimulating hormone (TSH). Urinary 6-hydroxymelatonin sulfate (aMT6s) and free cortisol were measured twice daily. Centenarians exhibited significantly lower TSH levels together with slightly higher rT3 levels than old controls. These changes could be due to reduced 5′-deiodinase activity occurring also in absence of substantial changes of the nutritional pattern. Morning serum cortisol levels were found to be similar in the 3 age groups, whereas the decline of serum DHEAS levels was well evident also after the ninth decade of life. The cortisol/DHEAS molar ratio, which usually increases with age and considered to be an expression of a neurotoxic pattern of the steroidal milieu in the central nervous system, did not shown any further increase in centenarians. The urinary free cortisol and aMT6s excretion declined with age; however only in centenarians and in young controls aMT6s excretion was significantly higher at night than during the day. These findings suggest that the circadian rhythm of melatonin secretion is maintained in centenarians and, based on the limitations of this study, could be considered one factor in successful aging.

Keywords: Centenarians; Melatonin; TSH; Thyroid hormones; Cortisol; DHEA-S

1. Introduction

Physiological aging involves both the central nervous system [CNS] and the endocrine system. Both of these systems are essential for the maintenance of the homeostasis. Age-related changes in the CNS include progressive neuronal loss with compensatory gliosis, particularly marked in the hypothalamus, hippocampus and limbic system and imbalance among neurotransmitters and other neuro-modulatory molecules. These features may play a role in the patho-physiology of the neuro-endocrine changes observed during aging and appear to be more related to disorders of the relationship between neural and hormonal signals than to alterations of specific structures. The age-related modifications affecting the secretion as well as the transport and metabolism of various hormones and the relationships between hormones and their specific receptors may not always be clinical apparent. However such changes may affect multiple biological functions, and in particular may be responsible for the reduced adaptability of aged organisms to environmental changes and to stressful conditions. Evaluation of hormonal patterns in elderly subjects, is not always easily to interpret. This is due both to the absence of any recognizable pattern of endocrine change in senility and the great inter-individual variability of the aging process. In addition, there is difficulty distinguishing between strictly age-related changes from those linked to pathological conditions and to pharmacologic interventions which are frequently observed in elderly people (Andersen–Ramberg et al., 1999).

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Accordingly, the study of extreme longevity is particularly valuable since the data derived from such studies, can permit the assessment and evaluation of the role played by age itself on health conditions.

We have recently studied the neuro-endocrine features of a number of healthy centenarian subjects gathered by the Italian Multicenter Study on Centenarians. The qualification of "healthy" centenarians has often been disputed since the chronic pathological conditions and sensory disturbances which occur in these subjects, often interfere with the evaluation of their cognitive performance. However a number of biological functions are found to be within normal limits in many centenarians and therefore their health conditions may be better than those of relatively younger subjects and such individuals may be considered examples of successful aging. For the subjects belonging to such group the definition of "clinically healthy" or "autonomous" centenarians has been proposed (Andersen-Ranberg et al., 2001). The group of centenarians we have studied included 59 subjects (7 males and 52 females) aged 100–107 y (mean age = 101.8 ± 0.4 SD). The clinical and hormonal data of the centenarians were compared to the ones of healthy old ($n = 24$, mean age = 84.7 ± 1.25 y) and young controls ($n = 20$, mean age = 27.8 ± 0.64). All subjects, old and very old, underwent multidimensional geriatric assessment, anthropometric measurements (body mass index, waist and hip circumference and body composition by bioelectric impedance), and blood sample taking for the determination of some nutritional markers such as hemoglobin, total lymphocyte count, transferrin, total protein, albumin, glycaemia, total and HDL cholesterol, tryglicerides, azotemia, creatinine and uric acid. The centenarians were living at home or in nursing homes. While they did not have significant pathology, they frequently experienced sensory disturbances, e.g., sight and hearing.

For the assessment and evaluation of the neuroendocrine features of centenarian subjects, we analyzed the pituitary–thyroid axis, the circadian pattern of melatonin, cortisol and DHEAS. These hormonal functions have a role in the adaptive responses of the organism to environmental changes and to stressful conditions. Furthermore, the evaluation of hormonal circadian fluctuations may better reflect the patho-physiology of the endocrine system better than the responses to provocative tests.

2. Results

2.1. Pituitary–thyroid axis

Changes in thyroid function are of interest because of the similarities of the clinical features of thyroid failure with those associated with aging. The results of numerous works in the literature concerning both the morphological (Berghout et al., 1987; Hintze et al., 1991) and the hormonal secretory changes (Gregrman et al., 1962; Kunikate et al., 1992) of the thyroid gland during aging are rather discordant. In particular there are data showing that no changes occurred in thyrotropin basal secretion (Felicetta, 1998) or that serum TSH levels increased in elderly people (Harman et al., 1984), when compared to young controls; likewise the serum TSH response to the specific TRH stimulation has been reported as unchanged (Herrmann et al., 1974), increased (Ohara et al., 1974) or reduced, respectively, (Chakraborti et al., 1999) in different clinical studies.

These differences in reports may be related to the general exclusion of very old subjects from these studies and to the possible effects on the hormonal parameters of eating behaviour, malnutrition, pathological conditions and medications (Morley, 1986). For the above mentioned reasons, studying the pituitary–thyroid axis in centenarian subjects seems to be of a particular interest, since thyroid function is usually reported as being well maintained until the eighth decade, while in extreme senescence certain complex and not easily interpreted alterations are described (Mariotti et al., 1993).

The thyroid studies involved 24 centenarian subjects (mean age 101.69 ± 0.38 y) (14), compared with 24 clinically healthy old subjects (mean age 84.75 ± 1.25 y) and 20 young controls (mean age 27.84 ± 0.64 y). Figs. 1 and 2 summarize the thyroid axis data. No significant

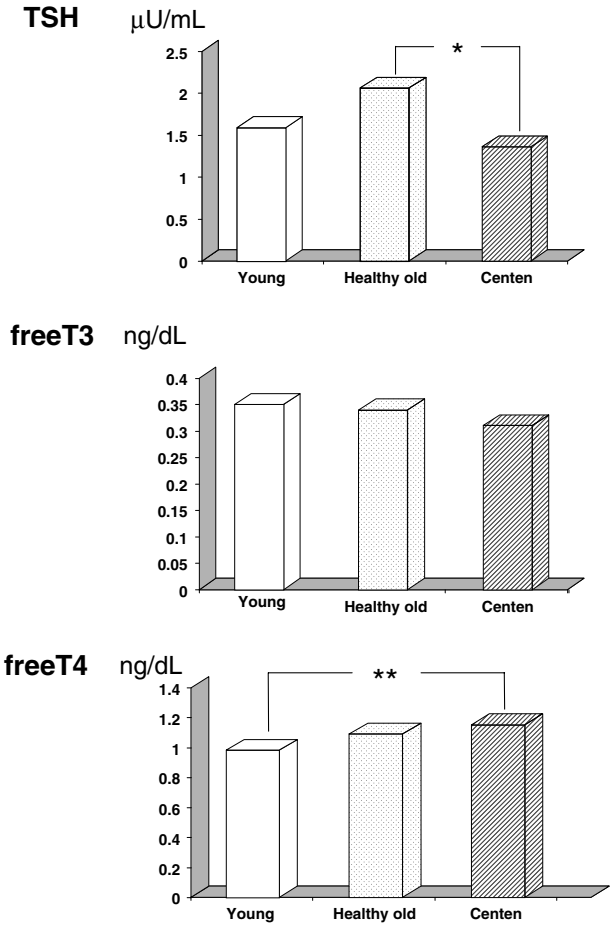

Fig. 1. Mean levels of serum TSH, free T3 and free T4 in young ($n = 20$) and old subjects ($n = 24$) and in centenarians ($n = 24$) ($^{*}p < 0.05$; $^{**}p < 0.01$).

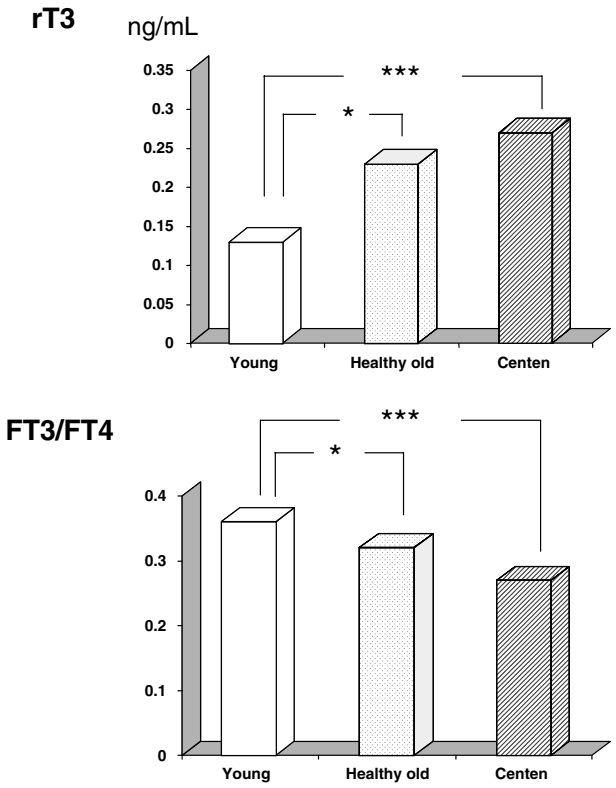

Fig. 2. Mean levels of serum reverse T3 and FT3/FT4 ratio in young ($n = 20$) and old subjects ($n = 24$) and in centenarians ($n = 24$) ($^{*}p < 0.05$; $^{***}p < 0.001$).

differences between the two groups of old subjects were found for both FT3 and FT4 serum levels. The prevalence of positivity for auto-antibodies was also similar in old subjects and centenarians.

On the other hand, the concentration of serum TSH was significantly lower in centenarians than in healthy old and young controls. This reduction of serum TSH concentration in extreme longevity could be due to an enhanced sensitivity of pituitary thyrotrophs to the negative feedback of thyroid hormones, or to complex changes in the neuroendocrine pathways regulating the TRH–TSH–thyroid axis (Mariotti et al., 1993).

The FT3/FT4 ratio, a marker of the 5′-deiodinasis enzymatic activity, was significantly lower in elderly subjects and centenarians when compared to young controls. Furthermore, higher levels of reverse T3 (rT3) were found in centenarian, when compared to both old and young controls. The rT3, derived from 5-deiodination (inner ring deiodination) is an inactive metabolite of thyroid hormones. Increased levels of rT3 are typically observed in non-thyroidal illness (NTI) or euthyroid sick syndrome, terms describing various clinical conditions not due to thyroid diseases. Thus, patients with NTI are in general considered euthyroid. The illness more frequently associated with NTI are metabolic diseases, such as fasting or protein-calorie-malnutrition, infective, renal, liver, cardiac or pulmonary diseases, tumors or primary depression. The decline of 5′- deiodination activity, resulting in increased rT3 levels observed in centenarians, might be related to the complex process of senescence, often characterized by sub-clinical changes in neuroendocrine activity, such as a reduced stimulatory effect of TSH (Bermudez et al., 1975; Olsen et al., 1978; Kabadi, 1989; Greenspan et al., 1991; Magri et al., 2002) or to an age-related increase of cytokines such as TNF-<alpha>, IL-1 and IL-6, which may induce an inhibitory action on the 5′-deiodination activity (Pekary et al., 1994; Tang et al., 1995).

On the other hand, the enhanced production of r-T3 could be related to non- thyroidal illness or to malnutrition. In our centenarian subjects there was no evidence of pathological conditions and, although thinner than old controls, they had biochemical nutritional markers within the normal limits. In addition, they exhibited a body composition of a ''juvenile type'', namely with a percentage of fat free mass similar to the one of young controls. In conclusion, our findings suggest that both physiological aging and extreme longevity do not significantly affect thyroid function, even though peripheral changes of thyroxine metabolism occur, leading to an increased rT3 production which possibly is an energy conserving response.

2.2. Hypothalamo–pituitary–adrenal axis

The adrenocortical secretory pattern undergoes qualitative and quantitative changes with aging, while not clinically apparent, could play a role in the pathogenesis of age-related diseases and especially cognitive decline.

In particular, beside a relatively steady level of cortisol secretion (Jensen and Blichert-Toft, 1971), even if with a trend towards higher plasma levels during evening- and night-time (Ferrari et al., 2001a,b), DHEA and DHEAS production dramatically declines with aging, and during the eighth decade is only 10–20 % of the maximal value usually recorded at 30 y.

Consequently, an imbalance between glucocorticoids and androgens occurs in the elderly. It is well known that cortisol and DHEAS have opposite activities both at peripheral and central levels. In particular cortisol has CNS neurotoxic effects, which is expressed as less complex branching and reduction dendritic length (Magarinos et al., 1996), enhanced vulnerability to vascular and metabolic injuries (Lawrence and Sapolsky, 1994) and cell death probably involving apoptotic mechanisms (McEwen, 1999). On the contrary, androgens and particularly DHEAS, produced both from the adrenal glands and directly from the CNS, by acting as an allosteric antagonist of GABAA receptors (Majewska et al., 1990), may enhance neuronal and glial survival and enhance learning and memory.

Therefore the changes of the brain steroidal milieu with absolutely or relatively higher cortisol than DHEAS levels may foster the occurrence of brain neurotoxic changes observed during aging.

Thus the evaluation of the adrenocortical secretory pattern in centenarians appears of particular interest since

data about extreme longevity are rather scanty in the literature.

Our data and that of others show that by taking serial blood samples throughout the 24 h cycle, evening- and night-time cortisol levels were significantly higher in clinically healthy elderly subjects and even higher in patients with senile dementia than in young controls (Ferrari et al., 1995).

Ultimately the amplitude of the hormonal fluctuations throughout the 24 h cycle was significantly reduced in elderly subjects, as compared to young subjects. Furthermore, in elderly subjects relatively higher blood levels of both cortisol and ACTH coexist during evening- and night hours, namely at the moment of the maximal sensitivity of the hypothalamic–pituitary–adrenal axis to steroid feedback.

These findings suggest the existence in old subjects of an impaired sensitivity of the HPA axis to the steroid feedback, as already demonstrated by the results of the dexamethasone (DXM) suppression test (Ferrari et al., 2001a,b). In our centenarian subjects, due to ethical and technical limitations, it has not been possible to carry out the study of the adrenocortical pattern based on serial blood samples. Thus this study was carried out by the measurement of urinary free cortisol (20 healthy centenarians, mean age = 101.5 ± 1.8 y) and the assay of serum cortisol and DHEAS in a blood sample collected between 08:00 and 09:00 ($n = 59$ healthy centenarians, mean age 101.8 ± 0.4), and by comparing the results with the ones of consistent groups of elderly and young controls.

The 24 h urinary free cortisol excretion exhibited a statistically significant reduction ($r = -0.592$, $p < 0.001$) in the group of centenarians. This finding was independent of renal function: indeed urinary volume and creatinine clearance, although lower than in controls, were within the normal limits in centenarians (cfr. Fig. 3).

On the contrary the morning serum cortisol levels were quite similar in centenarians and in healthy old and young controls (cfr. Fig. 4). For the interpretation of the apparently conflicting results between serum and urinary cortisol data, it seems important to consider the different biological significance of these two parameters. Indeed, the urinary free cortisol excretion, although representing less than 1% of the hormonal production over 24 h, is a valid index of cortisol secretion, reflecting the 24 h integrated hormonal concentrations. On the other hand, the morning serum hormonal levels provide information about only an instant time. Taken together, our data suggest that changes of the cortisol half-life and of its metabolic clearance rate can occur during physiological aging (Ferrari et al., 1987; Tsagarakis and Grossman, 1993).

In contrast the secretory pattern for DHEAS showed significant age-related reduction (cfr. Fig. 4) in both healthy old and centenarians when compared to young subjects. While it has been suggested that chronic DHEA administration can prevent obesity onset, diabetes, neoplastic and cardiovascular diseases and improve immune function in the elderly, the clinical results of DHEA administration in humans are rather discordant and longitudinal studies in healthy old men did not find any significant link between DHEAS decline and cognitive function (Yen, 2001).

According to our preliminary findings, the age-related decline of DHEAS secretion persisting also in centenarians, is not deemed to be a negative factor with respect to successful aging. Indeed, the molar ratio between cortisol and DHEAS, considered as a marker of the central steroidal milieu, showed an age-related increase due to the adrenocortical biosynthetic dissociation, but the value of this

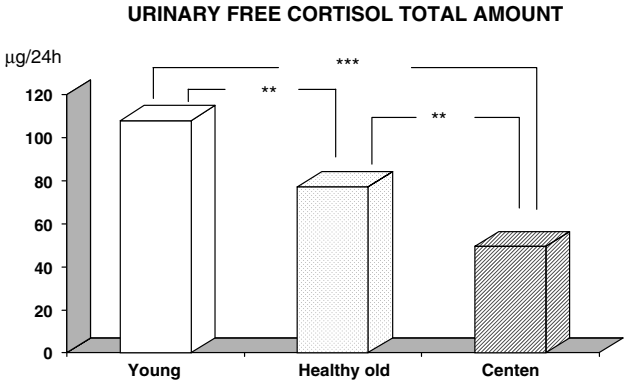

Fig. 3. Mean levels of urinary free cortisol in young ($n = 17$) and old subjects ($n = 20$) and in centenarians ($n = 20$) ($^{**}p < 0.01$; $^{***}p < 0.001$).

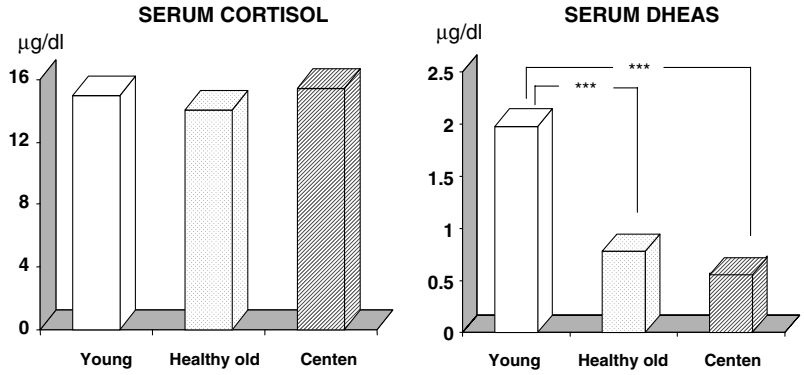

Fig. 4. Mean serum levels of cortisol and DHEAS in young ($n = 17$) and old subjects ($n = 20$) and in centenarians ($n = 59$) ($^{***}p < 0.001$).

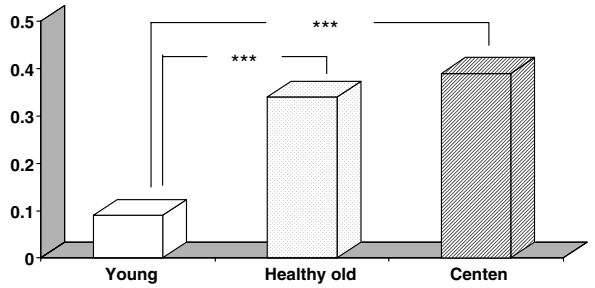

Fig. 5. Cortisolo/DHEAS molar ratio in young ($n = 17$) and old subjects ($n = 20$) and in centenarians ($n = 59$) ($^{***}p < 0.001$).

ratio did not further increase after the threshold of 100 y. Since the cortisol to DHEAS ratio expresses the relationship between neurotoxic and neuroprotective factors, these findings suggest that in centenarians the steroidal neurotoxic pattern did not further increase, when compared to relatively younger controls (cfr. Fig. 5).

2.3. Melatonin secretion

The pineal gland is directly connected to both the hypothalamic suprachiasmatic nucleus (SCN) and to the retina, from which it receives information related to the light-darkness cycle. Hence the pineal gland is considered as a neuro-endocrine transducer, being able to convert a photic input into an endocrine signal, namely the melatonin secretion. Melatonin is the main indolic compound secreted by the pineal gland and its circadian secretion is strictly linked to the light-darkness cycle since it is inhibited by light and stimulated by darkness. Indeed, in a constant photo-periodic schedule, the plasma melatonin chronogram shows a well evident nocturnal peak, which in most subjects attains its highest values between 01:00 and 03:00 h.

The melatonin circadian rhythm may be considered as an endogenous synchronizer for several bio-periodic functions, such as body temperature and cortisol secretion; as a whole, the melatonin circadian rhythmicity contributes to the maintenance of the temporal structure of the organism within the physiological limits. It has been proposed that the response of the circadian system to endogenous and/or exogenous changes diminishes with aging and that when melatonin rhythm deteriorates other circadian function weaken and become desynchronized.

The plasma melatonin concentrations show an age-related increase from birth to puberty; thereafter they are relatively constant in adulthood and then significantly decline during the progression to senescence, by showing a selective reduction of the nocturnal peak. According to some recent data concerning the nocturnal melatonin assay in a wide group of Chinese subjects, the decline of melatonin secretion starts at 60 y (Zhao et al., 2002). The age-related decline of melatonin secretion primarily depends on a reduction of both the central noradrenergic activity and the number or sensitivity of the noradrenergic receptors on the pinealocytes, while the role of the regressive changes affecting the pineal gland in aging seem to be less relevant.

The onset and progression of some age-related diseases such as senile dementia might amplify the physiological melatonin reduction linked to aging (Ferrari et al., 2000), as confirmed by the findings of significant correlations of the melatonin parameters with the results of cognitive performance tests, behavioral changes and wake–sleep cycle abnormalities in demented patients (Mishima et al., 1999) as well as by the evidence that melatonin administration can improve the quality of sleep and the sundowning in patients with Alzheimer's disease (Brusco et al., 1998; Jean-Luis, 1998). Therefore, the age-related changes of melatonin secretion may be considered as a marker of brain physiological and pathological aging.

The peculiar circadian organization of melatonin secretion characterized by very low levels during the day and by high concentrations during a short period at night, implies that an effective evaluation of melatonin secretion requires the measurement of plasma melatonin in several samples collected throughout the 24 h or the assay of 6-hydroxymelatonin sulfate (aMT6s), its main urinary metabolite, in different urine samples. In fact it is well known that in physiological conditions the aMT6s excretion over 24 h parallels the plasma melatonin levels, being higher during the night than during the day (Lynch et al., 1975).

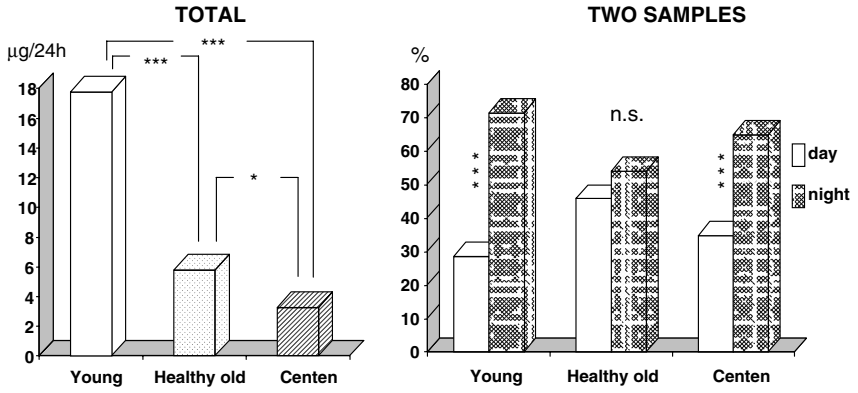

Fig. 6. Mean values of urinary aMT6s, total and in two different samples (day and night % of 24 h) in young ($n = 17$) and old subjects ($n = 20$) and in centenarians ($n = 20$) ($^{*}p < 0.05$; $^{***}p < 0.001$).

In recent years we studied the circadian organization of melatonin secretion in consistent groups of healthy old subjects and in old demented patients (Magri et al., 2004). By the evaluation of serial blood samples obtained during day- and night-time, a selective impairment of the nocturnal melatonin secretion was demonstrated in both groups of elderly subjects, when compared to young controls. Furthermore, the melatonin circadian peak was significantly related to the subjects' age and to the degree of cognitive impairment, evaluated by the MMSE score, suggesting that both age and cognitive decline can affect melatonin secretion.

Only a few data are present in the literature about the melatonin circadian rhythm in long-living subjects or in centenarians. Thus we studied the circadian organization of melatonin secretion in 20 clinically healthy centenarians (mean age $= 101.5 \pm 1.87$ y) by measuring the urinary aMT6s excretion in two different urine samples collected between 08:00 to 20:00 (day-time) and from 20:00 to 08:00 (night-time). The data of centenarians have been compared to the ones of 22 old healthy subjects (mean age $= 83.6 \pm 6.09$ y) and 17 young healthy controls (mean age $= 28.7 \pm 3.34$) (cfr. Fig. 6).

From a quantitative point of view, the age-related reduction of aMT6s excretion was clearly evident when moving from young controls to old subjects and centenarians, suggesting that the weakening of melatonin secretion persists also in extreme senescence. When expressing both the diurnal and nocturnal aMT6s urinary excretion as percent of the total 24 h amount, also after correction for urine volumes and creatinine clearance the nocturnal rate was significantly higher than the diurnal one in young subjects and in centenarians, while no difference between day and night aMT6s urinary levels were found in the group of old controls. Taken together, these findings suggest the maintenance of a better melatonin circadian organization in centenarians than in healthy old individuals but similar to that seen in the young. Since melatonin plays an important role as an endogenous synchronizer of multiple biological systems, the persistence of a physiological circadian organization of melatonin secretion may be considered as a marker of longevity which allows the aging organism to response more appropriately to both stressful events and environmental changes.

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