Chapter 5

The Hypothalamus in Alzheimer's Disease

Stavros J. Baloyannis, Ioannis Mavroudis, Demetrios Mitilineos, Ioannis S. Baloyannis and Vassiliki G. Costa

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.81475

Abstract

Alzheimer's disease is a progressive, irreversible neurodegenerative disorder, characterized by gradual decline of mental faculties, including learning capacity, emotional and behavioral alterations, serious decline of motor skills, and dysfunction of the autonomic nervous system with disruption of circadian rhythms. Among the potential modifiable risk factors, diabetes and obesity may play a considerable role in the pathogenetic background of the disease. We describe some of the morphological alterations of the hypothalamic nuclei in early cases of Alzheimer's disease, using silver impregnation techniques and electron microscopy. The morphological and morphometric study revealed substantial decrease of the neuronal population, which was particularly marked in the suprachiasmatic, the supraoptic, and the paraventricular nuclei of the hypothalamus. The silver staining demonstrated an obvious shortage of the dendritic arborization of neurons, associated with marked spinal pathology and axonal dystrophy. It must be underlined that Alzheimer's pathology, such as neuritic plaques and neurofibrillary degeneration, was minimal in the hypothalamus in comparison with other cortical and subcortical areas of the brain. Mitochondrial alterations and fragmentation of Golgi complex were observed by electron microscopy in a substantial number of neurons and astrocytes in the hypothalamic nuclei. The hypothalamic pathology may be related to instability of autonomic regulation which occurs gradually in Alzheimer's disease.

Keywords: Alzheimer's disease, hypothalamus, Golgi staining, electron microscopy, autonomic dysfunction

1. Introduction

Alzheimer's disease (AD) is a progressive, devastating, irreversible neurodegenerative disorder of the central nervous system, which has been recognized as the most common cause of serious cognitive decline in elderly people, resulting in profound dementia [1, 2] with no effective therapeutic intervention [3]. It is reasonable that AD induces a huge social burden and has a serious economic impact, since it starts frequently as mild cognitive impairment, resulting eventually in dementia, as the time advances [4, 5], affecting over 26 million people worldwide [6, 7].

The pathogenesis of AD involves a considerable number of cellular and molecular underlying mechanisms, as well as many genetic or acquired overlapping risk factors [8], such as diabetes, obesity, and psychosocial stress, which although are among the modifiable factors, may contribute substantially in the rapid mental deterioration, aggravating the clinical phenomenology of the disease [9].

A substantial number of clinical observations and laboratory investigations plead in favor of brain injury [8], stress [10–12], or stress-related psychiatric disorders [13, 14], type 2 diabetes [15, 16], insulin resistance [17, 18], inflammation [19] and depression [20] which may be considered, as probable predisposing factors for AD [21].

The neuropathological findings in AD are numerous. Among them, the amyloid containing neuritic plaques, the neurofibrillary tangles, which consist of intraneuronal aggregation of highly phosphorylated tau proteins, the morphological alterations of dendrites and spines, the synaptic pathology, and the increased neuronal loss in limbic structures and the cortex of the brain hemispheres are considered as hallmarks of the disease [22–24]. The gradual accumulation of Aβ peptide in the brain may induce inflammatory reactions, in which activated microglial cells are mostly involved [24]. It is important that the aggregation of Aβ amyloid peptide may promote selective degeneration of neurons, which are particularly vulnerable to age-related procedures, to oxidative stress, and any other type of energy deficiency [25]. The disruption of the blood brain barrier and the pathology of capillaries play a substantial role in shaping the neuropathological pattern of AD [26, 27], since they can facilitate the infiltration of immune cells promoting the exacerbation of inflammatory reactions in the brain.

The initial clinical manifestations of AD are subtle. However, as the time advances, progressive memory and learning impairment [28]; language disturbances; visuospatial disorientation; ideomotor apraxia; behavioral disturbances; depressive symptoms [29–32]; personality changes [33–35]; and a multitude of non-cognitive symptoms, such as sleep disruption, circadian dysrhythmia, changes in body weight, and autonomic dysfunction, are progressively established as dominant deficits in AD [36]. Sleep disturbances, on the other hand, might have a negative impact on the amyloid burden and the cognitive capacity of the patients, though the entire pathogenetic mechanism in sporadic cases remains unclear and is only approached by various hypotheses. The study of familial cases of AD, on the other hand, advocates in favor of the heterogeneity of the disease, and suggests that the morphological alterations in AD follow an eventual common pathway with many other degenerative conditions of the CNS [37, 38].

Oxidative stress seems to contribute substantially in the pathogenesis of AD [39, 40]. In addition, electron microscopy revealed serious morphological alterations of mitochondria in nerve

cells, astrocytes, and endothelial cells in various brain structures, including the cerebellum [40, 41], which are associated with tremendous spinal loss and loss of dendritic branches. It is important that morphological changes of the Golgi complex [42] have been observed in early cases of AD, in areas of the brain with minimal Alzheimer's pathology, suggesting that the protein trafficking might be impaired from the initial stages of AD, since Golgi apparatus plays a crucial role in trafficking and targeting of the plasma membrane proteins [43, 44].

Autonomic disorders have frequently been observed in patients who suffer from AD. Particularly, autonomic failure frequently occurs under strong emotional or cognitive stimuli during the disease, since the hypothalamus may be seriously involved even in the early stages of the neurodegenerative diseases, including AD [45–49], whereas the suprachiasmatic nucleus (SCN), the main circadian pacemaker, undergoes several continuous alterations during the course of the disease [50].

Stress, which is presumably a potential risk factor, mediated via the hypothalamic-pituitary-adrenal (HPA) pathway, may induce a substantial increase of glucocorticoids [49, 50], affecting seriously the homoeostatic equilibrium of the patients.

An evidence of the involvement of the hypothalamus in cases of AD is the increased volume of the third ventricle, seen in neuroimaging. In addition, there are substantial molecular and cellular differences in the morphological elements in the hypothalamus in cases of AD [51, 52], in correlation with the hippocampus and the involved cortical structures [53]. In addition, they do not contain tau-, neurofilament-, or microtubule-associated protein-reactive epitopes, and do not disrupt the neuropil or induce gliosis [53]. Numerous diffuse neuritic plaques in the hypothalamus in cases of AD are labeled with an antiserum to the Aβ peptide, of the beta-amyloid precursor proteins (beta APPs), whereas Aβ peptide-immunoreactive plaques were uncommon in the hypothalamus of non-AD patients [54]. It was also noticed that the neurofibrillary degeneration in the hypothalamus involves primarily those neurons, which are associated with cortical areas seriously affected by Alzheimer's pathology [55].

We proceeded in studying the morphological changes of the neurons and the neuronal networks of the hypothalamus in early cases of Alzheimer's disease, focusing our observations mainly on the suprachiasmatic (SCN), the supraoptic (SON), and the paraventricular nuclei (PVN) of the hypothalamus.

We described the alterations of dendrites, spines, and dendritic arbors in specimens impregnated by silver nitrate, using light microscope, whereas the mitochondrial alterations as well as the morphological and morphometric changes of Golgi apparatus have been studied and described in electron microscopy.

2. Material and methods

2.1. Material

Our morphological observations are based on the study of 14 brains of patients, aged 54–82 years, who suffered from AD. The brains were excised at autopsy, performed between

4 and 8 hours post mortem at a room temperature of 4°C. All of the patients fulfilled the clinical, neurological, neuropsychological, and neuropsychiatric criteria of AD. All of them died 24–46 months following the clinical diagnosis of the disease (**Table 1**).

Twelve additional macroscopically intact brains of apparently healthy individuals, aged 50–80 years, who died accidentally, were used as normal controls. The definite diagnosis of AD was based on NINCDS-ADRDA criteria [54].

2.2. Methods

Samples from the hypothalamus were excised and processed for electron microscopy and silver impregnation techniques, including rapid Golgi's method, Golgi-Nissl method, and Rio Hortega and Bodian techniques [55, 56].

2.2.1. Electron microscopy

For proceeding to electron microscopy, the specimens were immediately immersed in Sotelo's fixing solution, composed of 1% paraformaldehyde, 2.5% glutaraldehyde in 0.1 M cacodylate buffer adjusted at pH 7.35. Then, they were post fixed in 1% osmium tetroxide for 30 minutes at room temperature. After fixation, the specimens were dehydrated in graded alcohol solutions

Gender	Age at death (years)	Duration of the disease	Length of brain fixation in months	Braak and braak stage
M	55	3 years	1	II/III
F	62	28 months	1	II/III
M	63	37 months	1	II
F	66	40 months	1	II/III
M	72	3 years	1	III
M	74	38 months	1	II/III
F	75	42 months	1	II/III
F	76	46 months	1	III
M	78	42 months	1	II/III
F	80	2 years	1	II/III
M	78	42 months	1	II/III
F	76	36 months	1	III
M	54	2 years	1	III
M	65	37 months	1	II/III

The hypothalamus was excised and studied from 1974 to 2011.
AD, Alzheimer's disease; F, female; M, male. Fixation for silver impregnation techniques.

Table 1. List of the AD brains.

and twice in propylene oxide. Thin sections were cut in a Reichert ultratome, which were contrasted with uranyl acetate and lead citrate and studied in a Zeiss 9aS electron microscope.

2.2.2. Light microscope

2.2.2.1. Silver impregnation techniques

The hypothalamus was processed for silver impregnation techniques, according to rapid Golgi method and Golgi-Nissl method. After a 4-week fixation in solution of 10% fresh formalin, the specimens were immersed in potassium dichromate (7 g potassium dichromate in 300 mL water) for 10 days at room temperature. Then, they were immersed in a solution of 1% silver nitrate for 10 days in a dark environment at a temperature of 16°C. Following rapid dehydration in graded alcohol solutions, the specimens were embedded in paraffin and cut, some of them at 100 μ and some at 25 μ, alternatively. Many sections of 25 μ were stained also with methylene blue, according to Golgi-Nissl technique [57, 58]. Then, the sections were mounted in Entellan (Merck-Millipore, Darmstadt, Germany), between two cover slips and studied in a Zeiss Axiolab Photomicroscope, equipped with digital camera and computer.

We studied extensively, mostly, the suprachiasmatic (SCN), the supraoptic (SON), and the paraventricular nuclei (PVN) of the hypothalamus [45]. For the calculation of the volume of the nuclei, we applied the Cavalieri principle [59, 60]. We estimated the dendritic arborization as a whole and subsequently we described the morphology and calculated the number of the dendritic branches. We studied, in a detailed way, the morphology of the dendritic spines in light microscope, on sections stained according to rapid Golgi and Golgi-Nissl methods.

2.2.3. Morphometry

Morphometric studies were performed with an image analyzer (Image J program). The surface of the neurons and the dendritic arbors of the hypothalamic nuclei were calculated in specimens stained with silver nitrate, according to rapid Golgi method [61].

The morphology and the morphometry of the neurons, the dendrites, and the dendritic spines were estimated, according to Jacobs et al. [62] principles, which concern: (a) the quality of silver impregnation of neurons and dendrites and (b) the sufficient contrast between stained neurons and neuropile space.

Dendritic arbores were quantitatively estimated in a centrifugal way, according to Uylings et al. [63]. The diameter of the neurons was precisely measured, as well as the total length of the apical and basal dendrites. The number of dendritic bifurcations was enumerated as well as the length and number of dendritic segments per dendritic order, and the density of spines on each one of dendritic segments. The dendrites that arise from the neuronal body up to their first symmetrical bifurcation are considered as first-order branches. Subsequently, the dentritic branches, which are located distantly, are considered as second-order segments, third-order segments, and so on. For the morphometric analysis, we applied Image J program after a calibration for the specific types of microscope (Carl Zeiss Axiolab Photomicroscope) and we counted the number and estimated the order of the dendritic branches according to Sholl's

method of concentric circles [64], which were drawn, at intervals of 15 μm, centered on the soma of the neuron. The dendritic spines were counted on three segments of the dendritic field. Thus, we calculated those, which were located: (a) on primary dendrite, 20–30 μm in length; (b) on the secondary dendrite, 20–30 μm in length; and (c) on the tertiary dendrite, 40–50 μm in length.

In electron microscopy, we performed stereological analysis following the Nyengaard [65] and West [66, 67] principles. The number, the length, the total surface area, the volume, the circulatory ratio, and the spatial distribution of mitochondria [68] were precisely counted and estimated as well as the cisternae and vesicles of the Golgi apparatus [69].

We also estimated the mean nuclear area, the dendritic profiles [70], the total number of the dendritic spines per dendritic segment, the pre- and post-synaptic components [71–73], and the number of synaptic vesicles per presynaptic terminal [73].

The statistical analysis of the data was evaluated by Student t tests. p-Values below 0.05 were considered statistically significant, and those below 0.01 were considered as highly significant.

3. Results

3.1. Silver impregnation technique

Topographically, the human hypothalamus is located between the lamina terminalis anteriorly and the posterior commissure and the posterior edge of the mammillary bodies, posteriorly. By rapid Golgi staining, the Golgi-Nissl method, and the other silver impregnation techniques, we could visualize the hypothalamic nuclei entirely and clearly. However, we focused our detailed description and measurement mostly on the suprachiasmatic (SCN), the supraoptic (SON), and the paraventricular nuclei (PVN).

The morphological and morphometric study of the hypothalamic nuclei revealed a substantial decrease of the number of neurons and an impressive loss of dendritic branches in the brains of the patients who suffered from AD (**Figures 1** and **2**), as compared with normal controls (**Figures 3** and **4**). Abbreviation of the dendritic arborization was prominent mostly in the neurons of suprachiasmatic nucleus (SCN). The dendritic alterations were associated with marked decrease in the number of dendritic spines (**Figures 5** and **6**) in comparison with the normal control brains (**Figure 7**). The same morphological alterations concerning the dendritic branches and the spines were also observed in the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus in AD (**Figure 8**).

The morphometric estimation of the dendritic spines of neurons of the SCN and SON revealed a dramatic decrease of spines in AD brains, in comparison with normal controls (**Table 2**).

3.2. Electron microscopy

Detailed study on electron microscope demonstrated substantial morphological changes of the dendritic arbors, concerning mostly the secondary and tertiary dendritic branches, in a substantial number of neurons of the suprachiasmatic (SCN), supraoptic (SON), and

http://dx.doi.org/10.5772/intechopen.81475

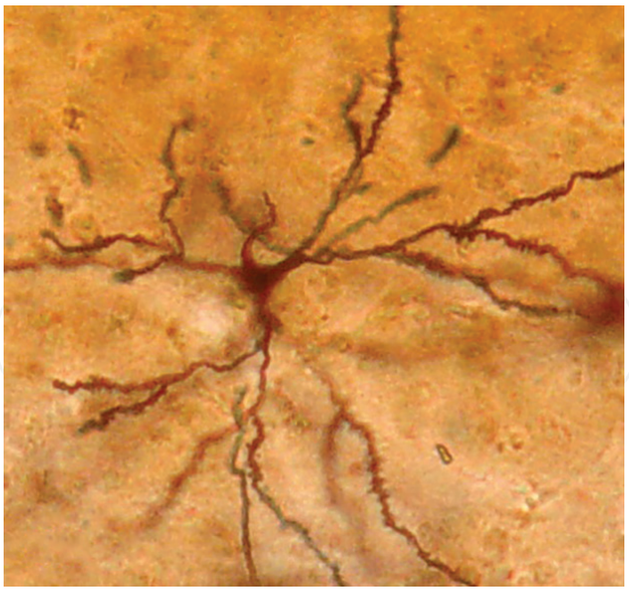


Figure 1. Neuron of the SCN in AD brain. Golgi staining, 1200×.

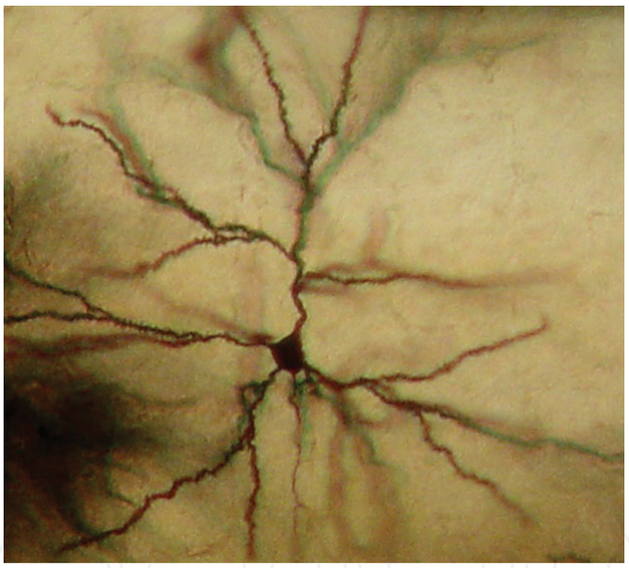


Figure 2. Neuron of SCN of the hypothalamus in a case of AD. The loss of the dendritic branches is obvious. Golgi staining Mag. 1200×.

paraventricular nuclei (PVN) of the hypothalamus in AD brains, in correlation with normal controls. Considerable decrease in spine density was mainly noticed in the secondary and tertiary dendritic branches, which was particularly prominent in the suprachiasmatic nucleus. Small spines and giant spines were also observed in a large number of neurons of the suprachiasmatic nucleus. Many giant spines included large multivesicular bodies.

In a considerable number of dendritic profiles, in the suprachiasmatic and the paraventricular nuclei, the mitochondria demonstrated marked morphological alterations, consisted of wide size diversity, disruption of the cristae, and accumulation of fibrillary material (**Figure 8**).

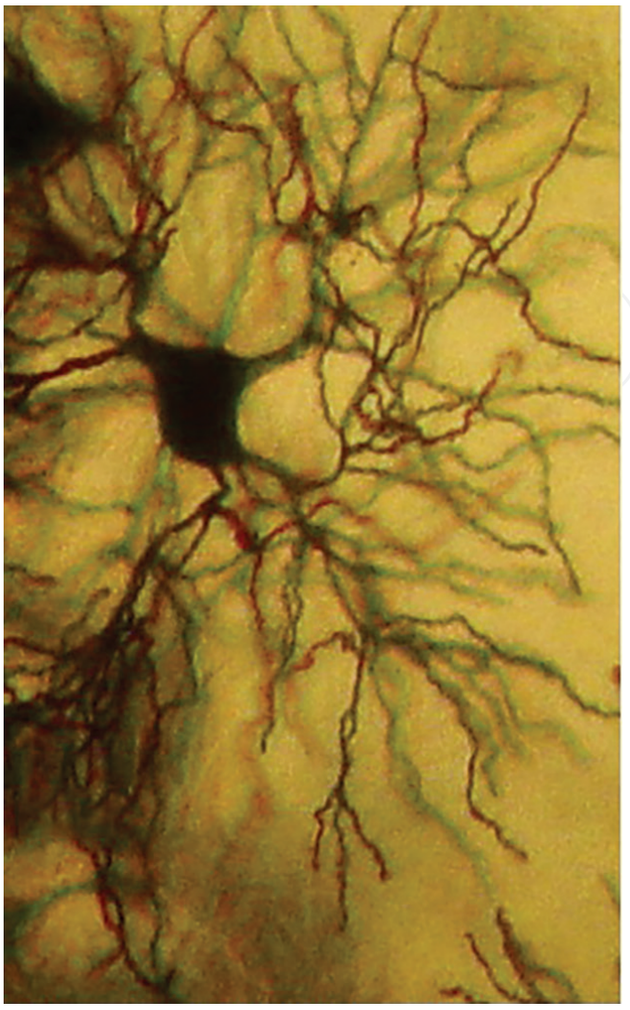


Figure 3. Neuron of the SCN of the hypothalamus of a normal brain aged 75 years.

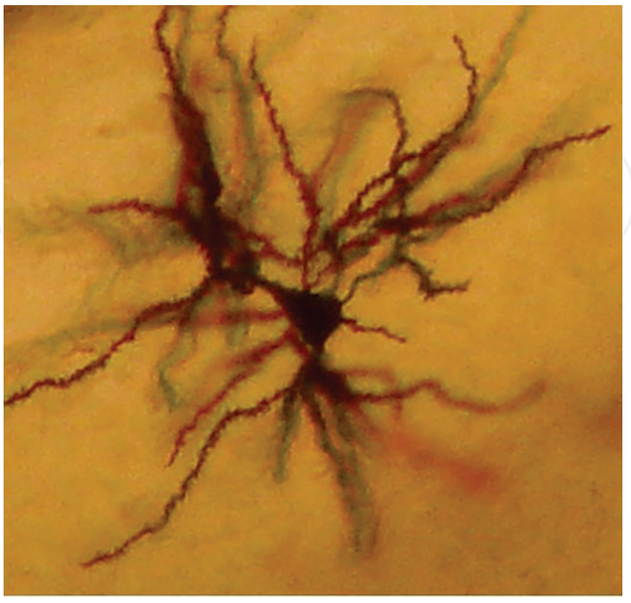


Figure 4. Neuron of the SON of the hypothalamus of a normal brain aged 80 years. The dendritic branches have numerous spines. Golgi staining. Mag. 1200×.

http://dx.doi.org/10.5772/intechopen.81475

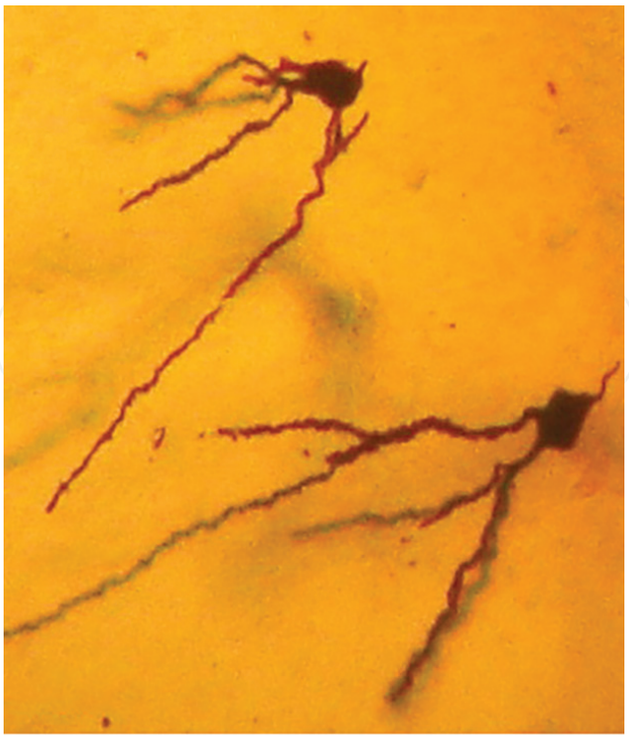


Figure 5. Abbreviations of the dendritic arborization is prominent in the neurons of suprachiasmatic nucleus (SCN) which is associated with marked decrease in the number of dendritic spines. Golgi staining. Mag. 1200×.

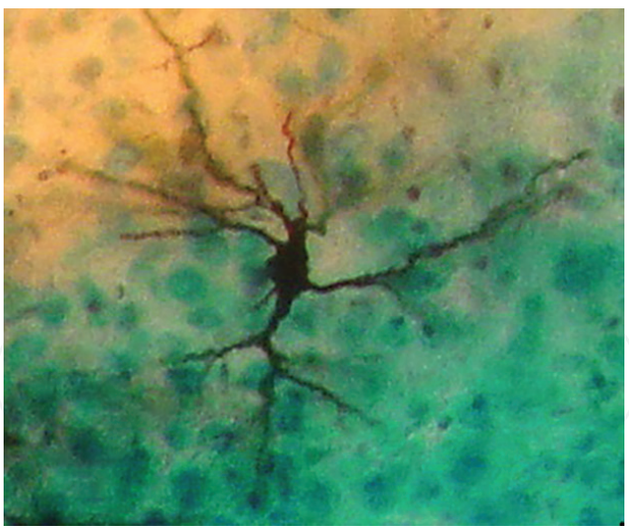


Figure 6. Neuron of the SCN of the hypothalamus of a case of AD. The abbreviation of the dendritic arborization and the poverty of dendritic spines are obvious. Golgi-Nissl staining. Mag. 1200x.

In a morphometric estimation of the mitochondria in dendrites, dendritic spines, and cell body of neurons of the suprachiasmatic nucleus in normal control brains, we concluded that the ellipsoid mitochondria of the spines appear to have an average diameter of 650 ± 250 nm and a mean axial ratio of 1.9 ± 0.2. In addition, the round mitochondria appeared to have a mean diameter of 350 nm. In AD brains, the mitochondria in neurons of

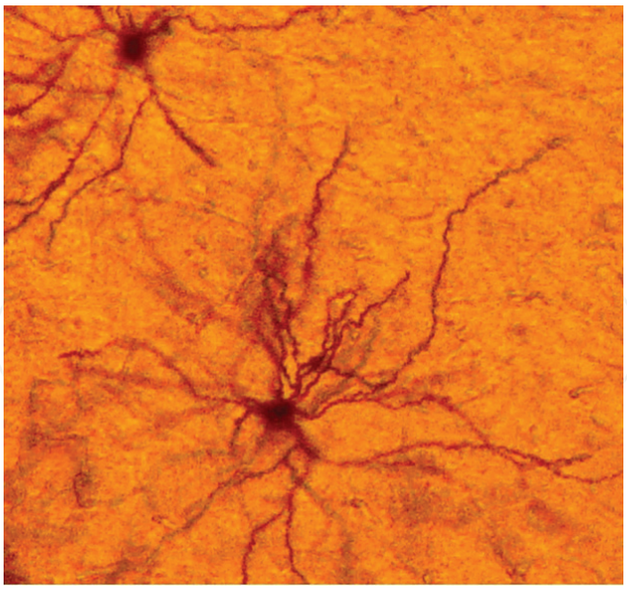


Figure 7. Neuron of the SCN of the hypothalamus of a normal brain aged 80 years. The dendritic branches are covered by spines. Golgi staining. Mag. 1200×.

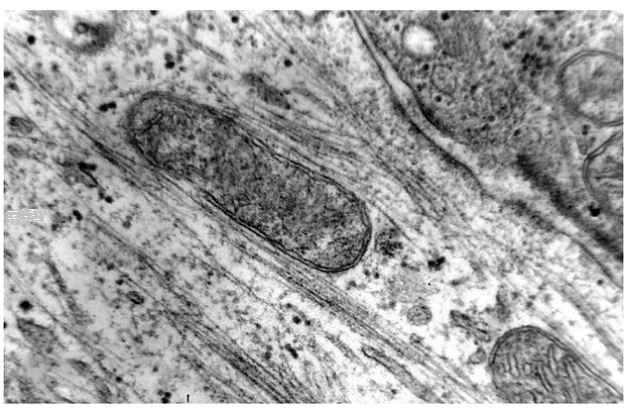
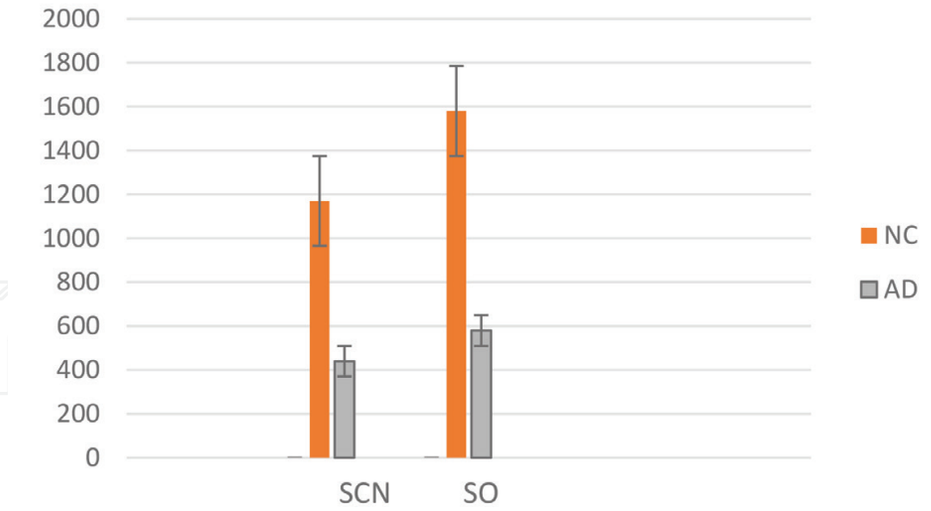


Figure 8. Mitochondrial alterations of a dendritic profile of a neuron of SCN of the hypothalamus of a case of AD. Electron micrograph Mag. 124,000×.

the suprachiasmatic nucleus were estimated as having an average diameter of 440 ± 250 nm and a mean axial ratio of 1.7 ± 0.2 (**Table 3**). The round mitochondria appear to have a mean radius of 235 nm. The changes in the morphology of the cristae were also frequent in the mitochondria of hypothalamic neurons in AD, in comparison with normal controls. Morphological alterations of the mitochondria were also seen in a considerable number of astrocytes and pericytes in AD brains.

In a substantial number of neurons of the suprachiasmatic and paraventricular nuclei of the hypothalamus, the Golgi apparatus appeared to be fragmented and atrophic (**Figure 9**). It

http://dx.doi.org/10.5772/intechopen.81475



AD: Alzheimer's disease, NC: normal control, SCN: suprachiasmatic nucleus, SO: supraoptic nucleus

Table 2. Average dendritic spines per dendritic arbor in SCN and SO neurons, based on measurements of 100 neurons ($p < 0.005$).

Abbreviations: AD, Alzheimer's disease; NC, normal control

Table 3. Mean diameter (in nm) of mitochondria in neurons of mammillary bodies, based on estimation of 500 mitochondria ($p < 0.05$).

was noticed, that the atrophy and fragmentation of Golgi apparatus (**Table 4**) and the mitochondrial alterations coexisted frequently with dendritic and spinal pathology in the majority of neurons.

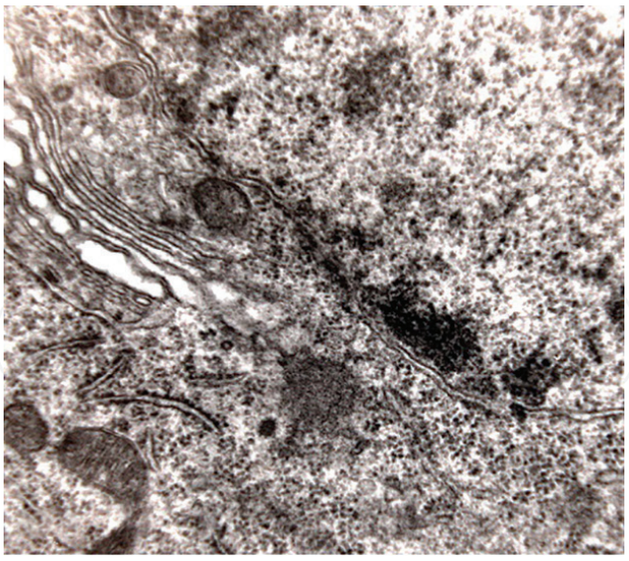
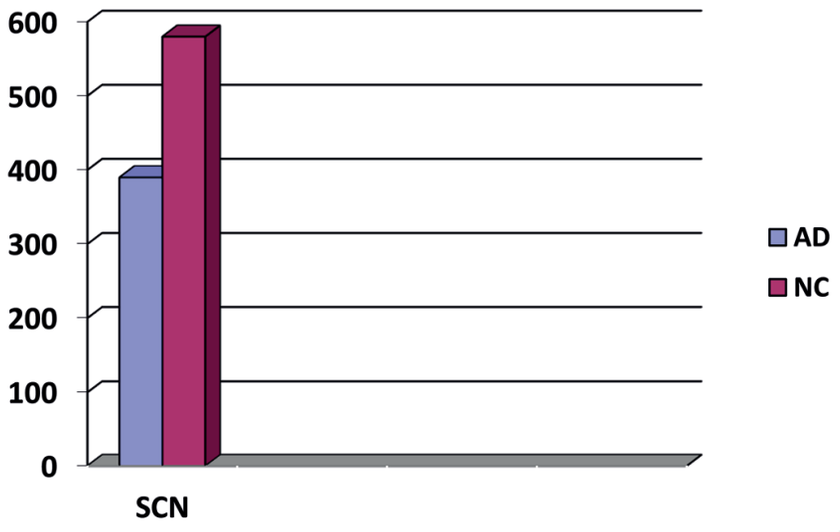


Figure 9. Alteration of Golgi apparatus of a neuron of the SCN of the hypothalamus of a case of AD. Electron micrograph. Mag. 124,000×.



Abbreviations: AD, Alzheimer's disease; NC: normal control
SCN, suprachiasmatic nucleus.

Table 4. The volume of Golgi apparatus in nm^3 based on measurements of 100 neurons of SCN ($p < 0.005$).

4. Discussion

Hypothalamus is a crucial brain structure for the regulation and control of essential homeostatic functions, including the circadian rhythms (CRs) and the sleep-wake cycle. In Alzheimer's disease and other neurodegenerative disorders [74–76], several hypothalamic nuclei are affected. It seems that the hypothalamic nuclei are not involved simultaneously at

the early stages of AD. The suprachiasmatic nucleus seems to be more seriously affected than the others in aging [76] and degenerative disorders. In previous studies, it was clearly revealed that the total cell population of the suprachiasmatic nucleus is decreased both in aging and in AD [76], in which the hypothalamic dysfunction is closely related to sleep disturbances [77].

The hypothalamic nuclei seems to be involved in those neurodegenerative alterations, which would progressively result in AD. In addition, the comparison of the morphological and morphometric alterations of the dendrites in the hypothalamic nuclei with those observed in the cortex of the brain hemispheres and the cerebellum disclosed that the alterations in the hypothalamus were rather modest, in correlation with those of the acoustic and visual cortices, the prefrontal areas of the brain, and the cerebellar cortex [78–81].

The fact that the hypothalamus is the principal subcortical center for the homeostatic and autonomic processes may explain the reason that the supraoptic and the periventricular nuclei, among others, reserve substantial synaptic density, even at the advanced stages of AD.

However, the suprachiasmatic nucleus demonstrated more severe dendritic alterations and synaptic loss than the supraoptic and paraventricular ones, a fact which might explain the phenomenon of desynchronization of circadian rhythms in the majority of the patients, who suffer from AD [82] and cognitive decline [83] in the spectrum of other degenerative brain disorders [84], given that the suprachiasmatic nucleus is indispensable for the generation and synchronization of circadian rhythms in man [85, 86]. It is reported that changes of the circadian rhythm (CR), arterial blood pressure, and body temperature may occur in AD patients [87] especially during the night time [88–90]. Changes also of the melatonin levels are not an unusual phenomenon in advanced senility and AD [91–93]. Sundown syndrome, on the other hand, frequently associated with increased motor activity, is a rather common phenomenon in advanced AD cases [93].

In the majority of neurons of hypothalamic nuclei, mitochondrial alterations were prominent in the cell body as well as in dendrites and synaptic components. As the mitochondria play an essential role in the energy supply of the cell, as ATP-generating organelles, their role is of utmost importance in the alteration of reduction-oxidation potential of the cell, in the free radical formation and scavenging, in the intracellular calcium control and the eventual activation of apoptotic chain [94–96]. Normally, the number of dendritic, axonic, and synaptic mitochondria is very high, especially in pre- and post-synaptic components, since they are the major energy contributor for the synaptic activity.

Mitochondrial dysfunction might induce Aβ peptide neurotoxicity, whereas enhancing mitochondrial proteostasis may reduce amyloid-β proteotoxicity [97]. In addition, impaired mitochondrial biogenesis contributes to mitochondrial dysfunction [98], which is directly associated with oxidative stress, activating furthermore the pathogenic cascade of AD [99–101]. Mitochondrial motility and accumulation are related to the functional state of the neuron, since mitochondria are transported to regions where the necessity for energy is particularly high, as it occurs in the dendritic and axonal profiles and the synapses [102–104]. The shape and size of mitochondria are not stable, since they undergo continual fission and fusion, which are necessary both for the survival of the cell and the harmonious adaptation to changing conditions.

Recent studies reported increased mitochondrial fission and decreased fusion, due to increased Aβ peptide interaction with the mitochondrial fission protein Drp 1, inducing increased mitochondrial fragmentation, impaired axonal transport of mitochondria, and

synaptic degeneration in AD [99]. The consequence of the dynamic fusion and fission processes is the eventual mitophagy of the damaged mitochondria.

A prominent decrease of the size of the mitochondria is observed in aging-related neurodegenerative diseases [95, 96], as well as at the early stages of AD, prior to the onset of a noticeable cognitive dysfunction [105]. Normally, a limited number of dendritic spines contain small and round mitochondria, which are increased in number in the dendritic profiles during the synaptogenesis and hormonal instability [102, 104]. It is important to underline that mitochondrial alterations are mostly associated with synaptic loss in AD patients, due to impairment of mitochondrial energy production [106], seen even before the typical generation of the neuritic plaques and tau pathology [105, 107].

The morphological alteration of the mitochondria, seen in the hypothalamic nuclei in early cases of Alzheimer's disease, pleads in favor of a generalized mitochondrial dysfunction in AD, which may be associated with the dendritic pathology, the tremendous loss of spines, and the marked synaptic alterations [108–110].

The density of the spines on the dendritic branches of a considerable number of neurons of the suprachiasmatic nucleus was decreased. The loss of the dendritic spines causes substantial impairment in neuronal communication and also induces reasonable dysfunction of the neuronal circuits in AD. Previous observations revealed that the loss of dendritic spines coincides with the morphological alterations of the mitochondria and the fragmentation of the cisternae of Golgi apparatus [25, 102, 109, 110]. In an experimental mouse model of Aβ peptide deposition, it was revealed that nonfibrillar Aβ peptide may exert toxicity on the spines, resulting in dramatic decrease of spine density [108, 111].

The role of the hypothalamus in the harmonization of circadian rhythms is crucial for the maintenance of energy homeostasis [25]. The feeding behavior [111–113] and the thermoregulation of the body become gradually unstable during the clinical course of AD [114–116], a fact which was also noticed in experimental models of AD [117] as well as in the behavioral variant of fronto-temporal dementia [118].

In conclusion, the hypothalamic nuclei are involved in AD, inducing autonomic dysfunction and homeostatic disequilibrium, phenomena which are clearly noticeable at the advanced stages of AD.

5. Conclusions

In Alzheimer's disease, silver impregnation technique and electron microscopy revealed a substantial decrease of the neuronal population, which is particularly obvious in the suprachiasmatic nucleus of the hypothalamus.

The silver staining technique demonstrated a marked shortage of the dendritic arborization of neurons, associated with spinal pathology and axonal dystrophy.

It must be underlined that Alzheimer's pathology, such as neuritic plaques and neurofibrillary degeneration, is minimal in hypothalamus in comparison with other areas of the brain.

Mitochondrial alterations and fragmentation of Golgi complex are observed by electron microscopy in a substantial number of neurons and astrocytes in the hypothalamic nuclei.

The hypothalamic pathology may be related to instability of autonomic regulation and homeostatic disequilibrium, which are gradually established in Alzheimer's disease.

Conflict of interest

No conflict of interest.

Nomenclature and abbreviations

AD	Alzheimer's disease
SCN	superchiasmatic nucleus of the hypothalamus
SON	supraoptic nucleus of the hypothalamus
PVN	paraventricular nucleus
HPA	hypothalamic-pituitary-adrenal pathway

Author details

Stavros J. Baloyannis[1,2]*, Ioannis Mavroudis[1], Demetrios Mitilineos[1], Ioannis S. Baloyannis[1] and Vassiliki G. Costa[1,2]

*Address all correspondence to: sibh844@otenet.gr

1 Laboratory of Neuropathology and Electron Microscopy, Department of Neurology, Aristotelian University, Thessaloniki, Greece

2 Institute for Research on Alzheimer's Disease, Iraklion, Greece

References

[1] Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. Allgemeine Zeitschrift für Psychiatrie. 1907;**64**:146-148

[2] Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. The British Journal of Psychiatry. 1968;**114**:797-811

[3] Reitz C, Mayeux R. Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers. Biochemical Pharmacology. 2014;**88**:640-651

[4] Farias ST, Mungas D, Reed BR, Harvey D, DeCarli C. Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. Archives of Neurology. 2009;**66**:1151-1171. DOI: 10.1001/archneurol.2009.106

[5] Alzheimer's Association. 2010 Alzheimer's disease facts and figures. Alzheimer's & Dementia. 2010;**6**:158-194. DOI: 10.1016/j.jalz.2010.01.009

[6] El Gaamouch F, Jing P, Xia J, Cai D. Alzheimer's disease risk genes and lipid regulators. Journal of Alzheimer's Disease. 2016;**53**:15-29. DOI: 10.3233/JAD-160169

[7] Scheltens P, Blennow K, Breteler MM, et al. Alzheimer's disease. Lancet. 2016;**388**(10043):505-517. DOI: 10.1016/S0140-6736(15)01124-1

[8] van Rossuma IA, Vissera PJ, Knolb DL, van der Fliera WM, Teunissenc CE, Barkhofd F, et al. Injury markers but not amyloid markers are associated with rapid progression from mild cognitive impairment to dementia in Alzheimer's disease. Journal of Alzheimer's Disease. 2012;**29**:319-327. DOI: 10.3233/JAD-2011-111694

[9] Pugazhenthi S, Qin L, Reddy PH. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease. 2017;**1863**:1037-1045

[10] Wilson RS, Barnes LL, Bennett DA, Li Y, Bienias JL, Mendes de Leon CF, et al. Proneness to psychological distress and risk of Alzheimer disease in a biracial community. Neurology. 2005;**64**:380-382. DOI: 10.1212/01.WNL.0000149525.53525.E7

[11] Aznar S, Knudsen GM. Depression and Alzheimer's disease: Is stress the initiating factor in a common neuropathological cascade? Journal of Alzheimer's Disease. 2011;**23**:177-193. DOI: 10.3233/JAD-2010-100390

[12] Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. Archives of General Psychiatry. 2006;**63**:530-538. DOI: 10.1001/archpsyc.63.5.530

[13] Mukaetova-Ladinska EB, Abdel-All Z, Andrade J, Alves da Silva J, O'Brien JT, Kalaria RN. Plasma and platelet clusterin ratio is altered in Alzheimer's disease patients with distinct neuropsychiatric symptoms: Findings from a pilot study. International Journal of Geriatric Psychiatry 2015;**30**(4):368-375. DOI: 10.1002/gps.4145

[14] Solas M, Aisa B, Mugueta M, Del Rıo J, Tordera RM, Ramirez MJ. Interactions between age, stress and insulin on cognition: Implications for Alzheimer's disease. Neuropsychopharmacology. 2010;**35**:1664-1673

[15] Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam study. Neurology. 1999;**53**:1937-1942

[16] Haan MN. Therapy insight: Type 2 diabetes mellitus and the risk of late-onset Alzheimer's disease. Nature clinical practice. Neurology. 2006;**2**:159-166

[17] Zhong Y, Miao Y, Jia WP, Yan H, Wang BY, Jin J. Hyperinsulinemia, insulin resistance and cognitive decline in older cohort. Biomedical and Environmental Sciences. 2012;**25**(1):8-14

[18] Mittal K, Katare DP. Shared links between type 2 diabetes mellitus and Alzheimer's disease: A review. Diabetes & Metabolic Syndrome. 2016;**10**(2 Suppl 1):S144-S149

[19] Patel PS, Buras ED, Balasubramanyam A. The role of the immune system in obesity and insulin resistance. Journal of Obesity. 2013;**2013**:616193. DOI: 10.1155/2013/616193

[20] Caracia F, Copania A, Nicolettic F, Dragoe F. Depression and Alzheimer's disease: Neuro biological links and common pharmacological targets. European Journal of Pharmacology. 2010;**626**:64-71. DOI: 10.1016/j.ejphar.2009.10.022

[21] Terry RD. The pathogenesis of Alzheimer disease: An alternative to the amyloid hypothesis. Journal of Neuropathology and Experimental Neurology. 1996;**55**(10):1023-1025

[22] Baloyannis SJ. Neuropathology of Dementia (Monograph). AUTH, Thessaloniki; 1993

[23] Schellenberg GD, Montine TJ. The genetics and neuropathology of Alzheimer's disease. Acta Neuropathologica. 2012;**124**:305-323. DOI: 10.1007/s00401-012-0996-2

[24] Streit WJ, Mrak RE, Griffin WS. Microglia and neuroinflammation: A pathological perspective. Journal of Neuroinflammation. 2004;**1**:14. DOI: 10.1186/1742-2094-1-14

[25] Morawe T, Hiebel C, Kern A, Behl C. Protein homeostasis, aging and Alzheimer's disease. Molecular Neurobiology. 2012;**46**(1):41-54. DOI: 10.1007/s12035-012-8246-0

[26] Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. Acta Neuropathologica. 2009;**118**:103-113. DOI: 10.1007/s00401-009-0522-3

[27] Baloyannis SJ, Baloyannis IS. The vascular factor in Alzheimer's disease: A study in Golgi technique and electron microscopy. Journal of the Neurological Sciences. 2012;**322**: 117-121. DOI: 10.1016/j.jns.2012.07.010

[28] Storandt M, Kaskie B, Von Dras DD. Temporal memory for remote events in healthy aging and dementia. Psychology and Aging. 1998;**13**:4-7

[29] Vida S, Des Rosiers P, Carrier L, Gauthier S. Depression in Alzheimer's disease: Receiver operating characteristic analysis of the Cornell Scale for Depression in Dementia and the Hamilton Depression Scale. Journal of Geriatric Psychiatry and Neurology. 1994;**7**:159-162

[30] Starkstein SE, Mizrahi R, Garau L. Specificity of symptoms of depression in Alzheimer disease: A longitudinal analysis. The American Journal of Geriatric Psychiatry. 2005; **13**(9):802-807. DOI: 10.1176/appi.ajgp.13.9.802

[31] Conde-Sala JL, Reñé-Ramírez R, Turró-Garriga O, Gascón-Bayarri J, Campdelacreu-Fumadó J, Juncadella-Puig M, et al. Severity of dementia, anosognosia and depression in relation to the quality of life of patients with Alzheimer's disease: Discrepancies between patients and caregivers. The American Journal of Geriatric Psychiatry. 2014;**22**:138-147

[32] Patterson MB, Schnell AH, Martin RJ, Mendez MF, Smyth KA, Whitehouse PJ. Assessment of behavioral and affective symptoms in Alzheimer's disease. Journal of Geriatric Psychiatry and Neurology. 1990;**3**:21-30

[33] Ott BR, Noto RB, Fogel BS. Apathy and loss of insight in Alzheimer's disease: A SPECT imaging study. The Journal of Neuropsychiatry and Clinical Neurosciences. 1996;**8**:41-46. DOI: 10.1176/jnp.8.1.41

[34] Reichman WE, Coyne AC, Amireni S, Molino B Jr, Egan S. Negative symptoms in Alzheimer's disease. The American Journal of Psychiatry. 1996;**153**:424-426. DOI: 10.1176/ajp.153.3.424

[35] Talwalker S. The cardinal features of cognitive and noncognitive dysfunction and the differential efficacy of tacrine in Alzheimer's disease patients. Journal of Biopharmaceutical Statistics. 1996;**6**:443-456

[36] Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurology. 2013;**12**:207-216

[37] Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: A review of the literature. Journal of Neuropathology and Experimental Neurology. 2012;**71**:362-381. DOI: 10.1097/NEN.0b013e31825018f7

[38] Atwood CS, Huang X, Moir RD, Tanzi RE, Bush AI. Role of free radicals and metal ions in the pathogenesis of Alzheimer's disease. Metal Ions in Biological Systems. 1999;**36**: 309-364

[39] Baloyannis SJ. Oxidative stress and mitochondria alterations in Alzheimer's disease. Neurobiology of Aging. 2000;**21**:264

[40] Baloyannis SJ. Mitochondrial alterations in Alzheimer's disease. Neurobiology of Aging. 1998;**19**:S241

[41] Baloyannis SJ, Costa V, Michmizos D. Mitochondrial alterations in Alzheimer's disease. American Journal of Alzheimer's Disease and Other Dementias. 2004;**19**(2):89-93

[42] Bannykh S, Balch WE. Membrane dynamics at the endoplasmic reticulum-Golgi interface. The Journal of Cell Biology. 1997;**138**:1-4

[43] Baloyannis SJ. Golgi apparatus and protein trafficking in Alzheimer's disease. Journal of Alzheimer's Disease. 2014;**42** Suppl 3:S153-162. DOI: 10.3233/JAD-132660

[44] Loskutovaa N, Honeab RA, Brooksb WM, Burnsb JM. Reduced limbic and hypothalamic volumes correlate with bone density in early Alzheimer's disease. Journal of Alzheimer's Disease. 2010;**20**(1):313-322. DOI: 10.3233/JAD-2010-1364

[45] Saper CB, German DC. Hypothalamic pathology in Alzheimer's disease. Neuroscience Letters. 1987;**74**(3):364-370

[46] McDuff T, Sumi SM. Subcortical degeneration in Alzheimer's disease. Neurology. 1985;**35**: 123-126

[47] Schultz C, Ghebremedhin E, Braak H, Braak E. Neurofibrillary pathology in the human paraventricular and supraoptic nuclei. Acta Neuropathologica. 1997;**94**:99-102

[48] Joshi YB, Praticò D. Stress and HPA axis dysfunction in Alzheimer's disease. In: Praticò D, Mecocci P, editors. Studies on Alzheimer's Disease Oxidative Stress in Applied Basic Research and Clinical Practice. New York: Springer; 2013. pp. 159-165

[49] Bengtsson S. Stress Steroids as Accelerators of Alzheimer's Disease: Effects of Chronically Elevated Levels of Allopregnanolone in Transgenic AD Models. Umeå, Sweden, University Medical Doctoral Dissertations. 2013. New Series No. 1553. ISBN: 978-91-7459-565-9

[50] Van Erum J, Van Dam D, De Deyn PP. Sleep and Alzheimer's disease: A pivotal role for the suprachiasmatic nucleus? Sleep Medicine Reviews. 2018;**40**:17-27. DOI: 10.1016/j.smrv.2017.07.005

[51] de Lacalle S, Iraizoz I, Gonzalo LM. Cell loss in supraoptic and paraventricular nucleus in Alzheimer's disease. Brain Research. 1993;**609**(1-2):154-158

[52] Berton O, Nestler EJ. New approaches to antidepressant drug discovery: Beyond monoamines. Nature Reviews. Neuroscience. 2006;**7**:137-151. DOI: 10.1038/nrn1846

[53] Standaert DG, Lee VM, Greenberg BD, Lowery DE, Trojanowski JQ. Molecular features of hypothalamic plaques in Alzheimer's disease. The American Journal of Pathology. 1991; **139**(3):681-691

[54] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology. 1984;**34**:939-944

[55] Leonard C. Silver degeneration methods. In: Johnson JE Jr, editor. Current Trends in Morphological Techniques. Florida, Boca Raton: CRC Press; 1981. pp. 93-140

[56] Baloyannis SJ. Recent progress of the Golgi technique and electron microscopy to examine dendritic pathology in Alzheimer's disease. Future Neurology. 2013;**8**:239-242

[57] Baloyannis SJ. Staining neurons with Golgi techniques in degenerative diseases of the brain. Neural Regeneration Research. 2015;**10**(5):693-695. DOI: 10.4103/1673-5374.156950

[58] Baloyannis SJ. Staining of dead neurons by the Golgi method in autopsy material. Methods in Molecular Biology. 2015;**1254**:167-179. DOI: 10.1007/978-1-4939-2152-2_13

[59] Cavalieri B. Geometria Indivisibilibus Continuorum. Bononiae: Typis Clementis Ferronij; 1635. Reprinted as Geometria Degli Indivisibili. Torino: Unione Tipografico-Editrice Torinese; 1966

[60] Gundersen HJ, Jensen EB. The efficiency of systematic sampling in stereology and its prediction. Journal of Microscopy. 1987;**147**:229-263

[61] Abercrombie M. Estimation of nuclear population from microtome sections. The Anatomical Record. 1946;**94**:239-247

[62] Jacobs B, Driscoll L, Schall M. Life-span dendritic and spine changes in areas 10 and 18 of human cortex: A quantitative Golgi study. The Journal of Comparative Neurology. 1997; **386**:661-680

[63] Uylings HBM, Van Eden CG, Parnavelas JG, Kalsbeek A. The prenatal and postnatal development of rat cerebral cortex. In: Kolb E, Tees RC, editors. The Cerebral Cortex of the Rat. Cambridge, Mass: MIT Press; 1990. pp. 35-76

[64] Sholl DA. Dendritic organization in the neurons of the visual and motor cortices of the cat. Journal of Anatomy. 1953;**87**:387-406

[65] Nyengaard JR, Gundersen HJ. Direct and efficient stereological estimation of total cell quantities using electron microscopy. Journal of Microscopy. 2006;**222**(Pt 3):182-187

[66] West MJ. Estimating volume in biological structures. Cold Spring Harbor Protocols. 2012;**2012**(11):1129-1139. DOI: 10.1101/pdb.top071787

[67] West MJ. Counting and measuring ultrastructural features of biological samples. Cold Spring Harbor Protocols. 2013;**2013**(7):593-605. DOI: 10.1101/pdb.top071886

[68] West MJ. Estimating surface area in biological structures. Cold Spring Harbor Protocols. 2013;**2013**(2):77-82. DOI: 10.1101/pdb.top071829

[69] West MJ. The precision of estimates in stereological analyses. Cold Spring Harbor Protocols. 2012;**2012**:937-949. DOI: 10.1101/pdb.top071050

[70] Sterio DC. The unbiased estimation of number and sizes of arbitrary particles using the disector. Journal of Microscopy. 1984;**134**:127-136

[71] Geinisman Y, Gundersen HJ, van der Zee E, West MJ. Unbiased stereological estimation of the total number of synapses in a brain region. Journal of Neurocytology. 1996;**25**:805-881

[72] Fiala JC, Harris KM. Cylindrical diameters method for calibrating section thickness in serial electron microscopy. Journal of Microscopy. 2001;**202**(Pt 3):468-472

[73] Feuerverger A, Menzinger M, Atwood HL, Cooper RL. Statistical methods for assessing the dimensions of synaptic vesicles in nerve terminals. Journal of Neuroscience Methods. 2000;**103**:181-190

[74] Nygard M, Hill RH, Wikstrom MA, Kristensson K. Age-related changes in electrophysiological properties of the mouse suprachiasmatic nucleus in vitro. Brain Research Bulletin. 2005;**65**:149-154

[75] Cai H, Cong W, Ji S, Rothman S, Maudsley S, Martin B. Metabolic dysfunction in Alzheimer's disease and related neurodegenerative disorders. Current Alzheimer Research. 2012;**9**:5-17

[76] Goudsmit E, Hofman MA, Fliers E, Swaab F. The supraoptic and paraventricular nuclei of the human hypothalamus in relation to sex, age and Alzheimer's disease. Neurobiology of Aging. 1990;**11**:529-536

[77] Liguori C, Chiaravalloti A, Nuccetelli M, Izzi F, Sancesario G, Cimini A, et al. Hypothalamic dysfunction is related to sleep impairment and CSF biomarkers in Alzheimer's disease. Journal of Neurology. 2017;**264**(11):2215-2223. DOI: 10.1007/s00415-017-8613-x

[78] Baloyannis SJ. Dendritic pathology in Alzheimer's disease. Journal of the Neurological Sciences. 2009;**283**(1-2):153-157. DOI: 10.1016/j.jns.2009.02.370

[79] Baloyannis SJ, Costa V, Mauroudis I, Psaroulis D, Manolides SL, Manolides LS. Dendritic and spinal pathology in the acoustic cortex in Alzheimer's disease: Morphological and morphometric estimation by Golgi technique and electron microscopy. Acta Oto-Laryngologica. 2007;**127**:351-354

[80] Baloyannis SJ, Manolides SL, Manolides LS. Dendritic and spinal pathology in the acoustic cortex in Alzheimer's disease: Morphological estimation in Golgi technique and electron microscopy. Acta Oto-Laryngologica. 2011;**131**:610-612

[81] Baloyannis SJ. The mossy fibres of the cerebellar cortex in Alzheimer's disease. An electron microscopy study. Neuroscience. 1997;**2**:160-161

[82] Coogan AN, Schutová B, Husung S, Furczyk K, Baune BT, Kropp P, et al. The circadian system in Alzheimer's disease: Disturbances, mechanisms, and opportunities. Biological Psychiatry. 2013;**74**:333-339

[83] Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, Ensrud KE, et al. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Annals of Neurology. 2011;**70**:722-732

[84] Klein DC, Moore RY. Suprachiasmatic Nucleus: The Mind's Clock. New York: Oxford University Press; 1991

[85] Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: Organization and coordination of central and peripheral clocks. Annual Review of Physiology. 2010;**72**: 517-549. DOI: 10.1146/annurev-physiol-021909-135821

[86] Satlin A, Volicer L, Stopa EG, Harper D. Circadian locomotor activity and core-body temperature rhythms in Alzheimer's disease. Neurobiology of Aging. 1995;**16**(5):765-771

[87] Van Someren EJW, Hagebeuk EEO, Lijzenga C, Scheltens P, De Rooij SEA, Jonker G, et al. Circadian rest-activity rhythm disturbances in Alzheimer's disease. Biological Psychiatry. 1996;**40**(4):259-270

[88] Chen HF, Chang-Quan H, You C, Wang ZR, Hui W, Liu QX, et al. The circadian rhythm of arterial blood pressure in Alzheimer disease (AD) patients without hypertension. Blood Pressure. 2013;**22**:101-105

[89] Waterhouse J. Circadian rhythms and cognition. Progress in Brain Research. 2010;**185**: 131-153. DOI: 10.1016/B978-0-444-53702-7.00008-7

[90] Liu RY, Zhou JN, Van Heerikhuize J, Hofman MA, Swaab DF. Decreased melatonin levels in postmortem cerebrospinal fluid in relation to aging, Alzheimer's disease, and apolipoprotein E-ε4/4 genotype. The Journal of Clinical Endocrinology and Metabolism. 1999;**84**:323-327

[91] Wu YH, Swaab DF. The human pineal gland and melatonin in aging and Alzheimer's disease. Journal of Pineal Research. 2005;**38**:145-152. DOI: 10.1111/j.1600-079X.2004.00196.x

[92] Lin L, Huang Q-X, Yang S-S, Chu J, Wang J-Z, Tian Q. Melatonin in Alzheimer's disease. International Journal of Molecular Sciences. 2013;**14**:14575-14593. DOI: 10.3390/ijms140714575

[93] Volicer L, Harper DG, Manning BC, Goldstein R, Satlin A. Sundowning and circadian rhythms in Alzheimer's disease. The American Journal of Psychiatry. 2001;**158**:704-711. DOI: 10.1176/appi.ajp.158.5.704

[94] Beal MF, Hyman BT, Koroshetz W. Do defects in mitochondrial energy metabolism underlie the pathology of neurodegenerative diseases? Trends in Neurosciences. 1993; **16**:125-131

[95] Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. Biochimica et Biophysica Acta. 1998;**1366**(1-2):211-223

[96] Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 2006;**443**(7113):787-795. DOI: 10.1038/nature05292

[97] Sorrentino V, Romani M, Mouchiroud L, Beck JS, Zhang H, D'Amico D, et al. Enhancing mitochondrial proteostasis reduces amyloid-β proteotoxicity. Nature. 2017; **552**(7684):187-193. DOI: 10.1038/nature25143

[98] Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, Reddy PH. Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: Implications for free radical generation and oxidative damage in disease progression. Human Molecular Genetics. 2006;**15**:1437-1449

[99] Manczak M, Reddy PH. Abnormal interaction between the mitochondrial fission protein Drp1 and hyperphosphorylated tau in Alzheimer's disease neurons: Implications for mitochondrial dysfunction and neuronal damage. Human Molecular Genetics. 2012;**15**(9):2538-2547

[100] Sultana R, Butterfield DA. Oxidatively modified, mitochondria-relevant brain proteins in subjects with Alzheimer disease and mild cognitive impairment. Journal of Bioenergetics and Biomembranes. 2009;**41**:441-446

[101] Sheng B, Wang X, Su B, Lee HG, Casadesus G, Perry G, et al. Impaired mitochondrial biogenesis contributes to mitochondrial dysfunction in Alzheimer's disease. Journal of Neurochemistry. 2012;**120**:419-429

[102] Brown MR, Sullivan PG, Geddes JW. Synaptic mitochondria are more susceptible to Ca2+ overload than nonsynaptic mitochondria. The Journal of Biological Chemistry. 2006; **281**(17):11658-11668. DOI: 10.1074/jbc.M510303200

[103] Baloyannis SJ. In: Kishore U, editor. Alterations of Mitochondria and Golgi Apparatus Are Related to Synaptic Pathology in Alzheimer's Disease, Neurodegenerative Diseases. Rijeka, Croatia: InTech Publ; 2013. pp. 101-123

[104] Chang PK-Y, Boridy S, McKinney RA, Maysinger D. Letrozole potentiates mitochondrial and dendritic spine impairments induced by β amyloid. Journal of Aging Research. 2013;**2013**:538979. DOI: 10.1155/2013/538979

[105] Baloyannis SJ. Mitochondria are related to synaptic pathology in Alzheimer's disease. International Journal of Alzheimer's Disease. 2011;**2011**:305395. DOI: 10.4061/2011/305395

[106] Spuch C, Ortolano S, Navarro C. New insights in the amyloid-beta interaction with mitochondria. Journal of Aging Research. 2012;**2012**:324968. DOI: 10.1155/2012/32496897

[107] Reddy PH, Beal MF. Amyloid beta, mitochondrial dysfunction and synaptic damage: Implications for cognitive decline in aging and Alzheimer's disease. Trends in Molecular Medicine. 2008;**14**(2):45-53. DOI: 10.1016/j.molmed.2007.12.002

[108] Kirkwood CM, Ciuchta J, Ikonomovic MD, Fish KN, Abrahamson EE, Murray PS, et al. Dendritic spine density, morphology, and fibrillar actin content surrounding amyloid-[beta] plaques in a mouse model of amyloid-[beta] deposition. Journal of Neuropathology and Experimental Neurology. 2013;**72**:791-800

[109] Budd SL, Nicholls DG. Mitochondria in the life and death of neurons. Essays in Biochemistry. 2017;**33**:43-52

[110] Forner S, Baglietto-Vargas D, Martini AC, Trujillo-Estrada L, LaFerla FM. Synaptic impairment in Alzheimer's disease: A dysregulated symphony. Trends in Neurosciences. 2017;**40**(6):347-357. DOI: 10.1016/j.tins.2017.04.002

[111] Elmquist JK, Elias CF, Saper CB. From lesions to leptin: Hypothalamic control of food intake and body weight. Neuron. 1999;**22**:221-232

[112] Grossberg AJ, Scarlett JM, Marks DL. Hypothalamic mechanisms in cachexia. Physiology & Behavior. 2010;**100**:478-489. DOI: 10.1016/j.physbeh.2010.03.011

[113] Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. Journal of Neurology, Neurosurgery, and Psychiatry. 2002;**73**:371-376

[114] Pascualy M, Petrie EC, Brodkin K, Peskind ER, Wilkinson CW, Raskind MA. Hypothalamic pituitary adrenocortical and sympathetic nervous system responses to the cold pressor test in Alzheimer's disease. Biological Psychiatry. 2000;**48**:247-254

[115] Martín-Maestro P, Gargini R, García E, Perry G, Avila J, García-Escudero V. Slower dynamics and aged mitochondria in sporadic Alzheimer's disease. Oxidative Medicine and Cellular Longevity. 2017;**2017**. DOI: 10.1155/2017/9302761

[116] Brureaua A, Zussya C, Delaira B, Ogiera C, Ixarta G, Mauricea T, et al. Deregulation of hypothalamic-pituitary-adrenal axis functions in an Alzheimer's disease rat model. Neurobiology of Aging. 2013;**34**:1426-1439. DOI: 10.1016/j.neurobiolaging.2012.11.015

[117] Kohjima M, Sun Y, Chan L. Increased food intake leads to obesity and insulin resistance in the Tg2576 Alzheimer's disease mouse model. Endocrinology. 2010;**151**(4):1532-1540. DOI: 10.1210/en.2009-1196

[118] Piguet O, Petersen A, Ka Lam BY, Gabery S, Murphy K, Hodges JR, et al. Eating and hypothalamus changes in behavioral-variant frontotemporal dementia. Annals of Neurology. 2011;**69**:312-319. DOI: 10.1002/ana.22244

IntechOpen