

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



The Hypothalamus in Alzheimer's Disease: A Golgi and Electron and Microscope Study

Stavros Ioannou Baloyannis, Ioannis Mavroudis,
Demetrios Mitilineos, Ioannis S. Baloyannis and
Vasiliki G. Costa

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.75887>

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 hypothalamus in comparison with other 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 non reversible 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 therapy [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 [12, 20] as probable causative factors in the pathogenetic spectrum of AD [21].

The neuropathological profile of AD includes the formation of neuritic plaques, the neurofibrillary degeneration in the form of tangles of highly phosphorylated tau proteins, the dendritic alterations, the spinal pathology, the marked alterations of dendritic spines, the dramatic reduce of the number of synapses, the substantial neuronal loss [22, 23], which is quite prominent mostly in limbic structures and selectively in various areas of the cortex of the brain hemispheres, as well as the phenomena of inflammation [24]. The prolonged gathering of the A β peptide in the brain activates microglial cells and pericytes reasonably, inducing neuroinflammation, which participates obviously in the ongoing pathogenic cascade of AD [24]. Coarse aggregations of A β amyloid peptide in the brain may consequently promote degenerations of neurons and astrocytes, which are particularly sensitive in changes of protein homeostasis, energy decline and oxidative stress [25]. The vascular factor is an additional component of the pathogenetic cascade of AD, since the disruption of the BBB and the alterations of the brain capillaries [26, 27] could lead to infiltration of the perivascular space by immune cells, promoting reasonably the exacerbation of inflammatory reactions [24].

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 progressively establish as principal 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 etiopathogenic mechanisms of the sporadic cases of AD remain yet unclear.

Many hypotheses have been submitted concerning the various mechanisms of the pathogenetic process of AD, based mostly on the neuropathological investigation and the experimental models of AD. Moreover the genetic investigation of the familial AD underline the heterogenetic character of AD, though the clinical investigation suggests that the disease at the advanced stages follows a common pathway with many other degenerative conditions of the brain [37, 38].

The oxidative stress correlated with the cortical and subcortical deposits of A β peptide can obviously play an important pathogenetic role in AD [39, 40]. In addition, the marked mitochondrial alterations in neurons and glial cells in cortical and subcortical structures and in cerebellum [40, 41], which are mostly observed in dendrites deprived of spines, may contribute in shaping the pathogenetic pattern of the disease. On the other hand electron microscopy in early cases of AD revealed fragmentation of the cisternae of Golgi apparatus [42] even in areas where the characteristic Alzheimer's pathology was unremarkable. The morphological alteration of Golgi complex may be associated with the impairment of protein trafficking, acting as an additional pathogenetic component of AD. It is well recognized that Golgi complex is of instrumental importance in sorting and trafficking of the plasma proteins toward their final membranaric target [43].

The autonomic nervous system participates in the brain dysfunction in case of AD either in the form of autonomic hyperactivity or of autonomic failure under the influence of strong exterior emotional inputs. The hypothalamus, the principal autonomic center is involved in advanced stages of AD [44–49], whereas the suprachiasmatic nucleus (SCN), which is the main circadian pacemaker, undergoes several continuous alterations during the course of the disease [50]. The activation of the hypothalamic-pituitary-adrenal (HPA) pathway by exterior stimuli, inducing stress increase substantially the glucocorticoid release [49], which may modify the emotional and autonomic reactions of the patients who suffer from AD.

The modification of the volume of the third ventricle in AD may be considered as an evidence of the involvement of the hypothalamus, which would undergo pathological alterations in AD [51, 52], that may have a different molecular and cellular character in comparison with those observed in the hippocampus and in the cortex of the brain hemispheres [53], since hypothalamic plaques are not associated with increased gliosis or prominent disruption of the neuropile [53]. In addition the majority of diffuse plaques in the hypothalamus in case of AD may be labeled with an antiserum to the A β peptide, of the beta-amyloid precursor proteins (beta APPs), whereas A β peptide-immunoreactive plaques are rather uncommon in the hypothalamus of patients without AD [54]. It was also noticed that the neurofibrillary degeneration in the hypothalamus involves primarily those neurons that are associated with cortical areas which show prominent Alzheimer's pathology [53].

Following our previous study [54] on the morphological alterations of the hypothalamus in AD, in this study we attempted to describe some additional morphological findings, concerning the hypothalamic nuclei and the dendritic and spinal pathology in early cases of Alzheimer's disease.

2. Material and methods

2.1. Material

The morphological study of the hypothalamus concerns 14 autopsy cases of patients suffered from AD [54], at early stages according NINCDS-ADRDA criteria [55] and Braak and Braak staging [56] (**Table 1**). Twelve additional intact brains of apparently healthy individuals, who died accidentally, were used as normal controls [54].

Samples from the hypothalamus were excised and processed for electron microscopy and silver impregnation techniques including rapid Golgi's method, Rio Hortega's and Bodian's techniques [57, 58].

2.2. Methods

2.2.1. Electron microscopy

For the electron microscopy the fixation of the specimens was performed in Sotelo's fixing solution, according to method, which was described in previous article [54]. Then they were post-fixed in 1% osmium tetroxide, dehydrated in graded alcohol solutions and propylene oxide [54]. Thin sections were cut in a Reichert ultratome, contrasted with uranyl acetate and lead citrate and studied in a Zeiss 9aS electron microscope [54].

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

2.2.2. Light microscope

2.2.2.1. Silver impregnation techniques

For the rapid Golgi staining, the hypothalamus, after 1 month's fixation in fresh prepared formalin, was immersed in potassium dichromate for 10 days and in 1% silver nitrate for additional 10 days. Following 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 [54]. Sections of 25 μ were stained also with methylene blue, according to Golgi-Nissl method [57–60]. All 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 the suprachiasmatic (SCN), the supraoptic (SON) and the paraventricular nuclei (PVN) of the hypothalamus [45]. The volume of the nuclei was estimated according to Cavalieri principle [61, 62]. We described the type of dendritic arborization, the morphology of the dendritic branches and spines, and then we estimated the number of dendritic branches, as well as the spinal density, 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 mean surface area of the neurons, as well as the dendritic arborization, was calculated in silver staining [63]. The morphology of the soma and the dendrites was estimated on the basis of the criteria posed by Jacobs et al. [64], concerning the quality of staining of dendrites and the contrast between neurons and neuropile.

The estimation of the in space distribution of the dendritic branches was performed in a centrifugal way according to Uylings et al. [65]. We estimated the diameter of the soma, the length of the dendrites, the number and the type of the dendritic branches, the length of dendritic segments per dendritic order and the spinal density per segment, given that each dendrite which arises from the neuronal body up to the first bifurcation is considered as first-order dendritic branch.

For the quantitation we applied Image J program, which was properly adjusted for the used microscope (Carl Zeiss Axiolab Photomicroscope). The dendritic arborization was assessed on the basis of the method of concentric cycles introduced by Sholl [66].

The dendritic spines were counted on three sequent segments of the dendritic field. The first segment, 20–30 μ m in length, was located on the primary dendrite, the second segment, 20–30 μ m in length, on the secondary one and the third segment of 40–50 μ m, on the tertiary dendrite.

At the level of electron microscopy we applied the stereological estimation introduced by Nyengaard [67] and West [68–70]. We estimated the number, the length, the surface area, the volume and the spatial distribution for the mitochondria [54, 70] and for the cisternae and the vesicles of the Golgi complex [71].

We estimated also the mean nuclear area, the dendritic profiles of the neurons [72], the spinal density per dendritic segment, the areas of the pre- and postsynaptic terminals [73–75] and the number of synaptic vesicles per presynaptic component [54, 75].

The statistical evaluation of the data was based on the Student t tests. P-values below 0.05 were considered statistically significant, and those below 0.01, highly significant.

3. Results

3.1. Silver impregnation technique

From the anatomical point of view the human hypothalamus is extended from the level of lamina terminalis anteriorly to a level through the posterior commissure and the posterior edge of the mammillary bodies, posteriorly. Using the silver impregnation techniques, including Golgi-Nissl method, we could clearly visualize the neuronal population of the hypothalamic nuclei. We studied all the hypothalamic nuclei extensively; however we focused our description particularly on the suprachiasmatic (SCN), the supraoptic (SON) and the paraventricular nuclei (PVN).

In rapid Golgi method, the morphological and morphometric study of the neurons, demonstrated a considerable decrease of the number of neurons, and a substantial loss of dendritic branches in 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) which was 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 the neurons of the SCN and SON revealed a dramatic decrease of their number in AD brains in comparison with normal controls (**Figure 9**).

3.2. Electron microscopy

Detailed study on electron microscope revealed marked morphological changes of the neuronal dendrites, which were prominent mostly in the secondary and tertiary dendritic branches of a considerable neuronal population of the suprachiasmatic (SCN), supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus of patients who suffered from AD. Marked decrease in spine density was noticed in the dendritic branches of the neuronal networks of the hypothalamic nuclei, a phenomenon, which was particularly prominent in the suprachiasmatic nucleus. Small spines and giant spines were also observed in a considerable number of neurons of the suprachiasmatic nucleus. Many large and giant dendritic spines were observed, which included multivesicular bodies.

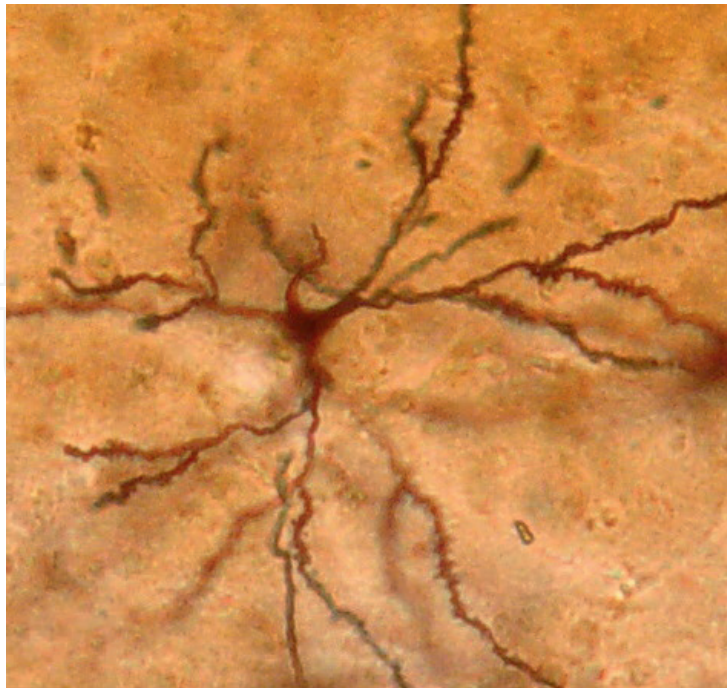


Figure 1. Neuron of the SCN nucleus in AD brain. Golgi staining 1200X.

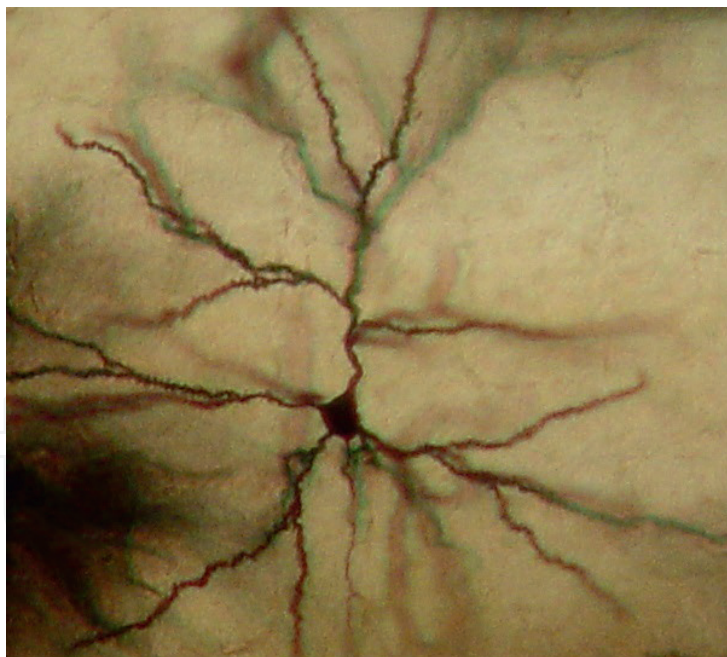


Figure 2. Neuron of SCN of the hypothalamus in a case of AD. The loss of the dendritic branches is obvious. Golgi staining, magnification 1200x.

Mitochondrial pathology was observed in many dendritic profiles in the suprachiasmatic and the paraventricular hypothalamic nuclei, of AD brains. The most frequent findings were the disruption of the cristae and the accumulation either fibrillary or osmiophilic material in the

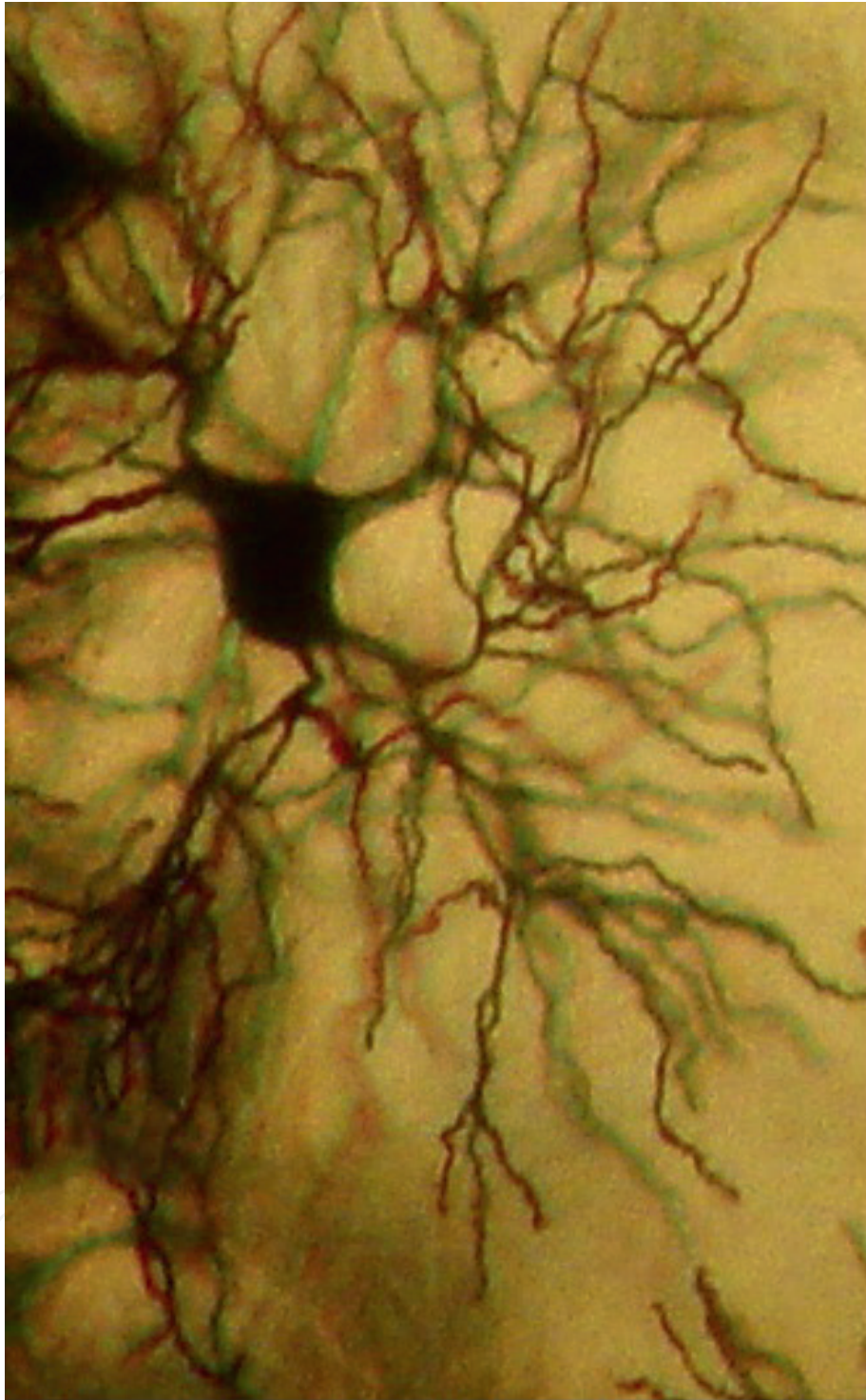


Figure 3. Neuron of the SCN of the hypothalamus of a normal brain aged 75 years.

mitochondria (**Figure 8**). The polymorphism of the mitochondria was also impressive, some of them being giant and very elongated and some being small and round.

The morphometric estimation of the mitochondria in the soma, the dendrites and the dendritic spines of a substantial number of neurons of the suprachiasmatic nucleus in AD brains

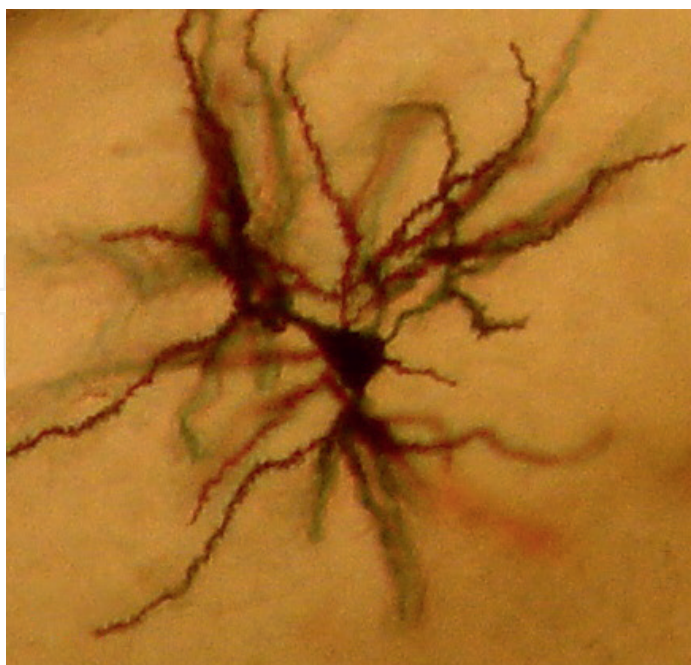


Figure 4. Neuron of the SON of the hypothalamus of a normal brain aged 80 years. The dendritic branches have numerous spines. Golgi staining, magnification 1200 \times .

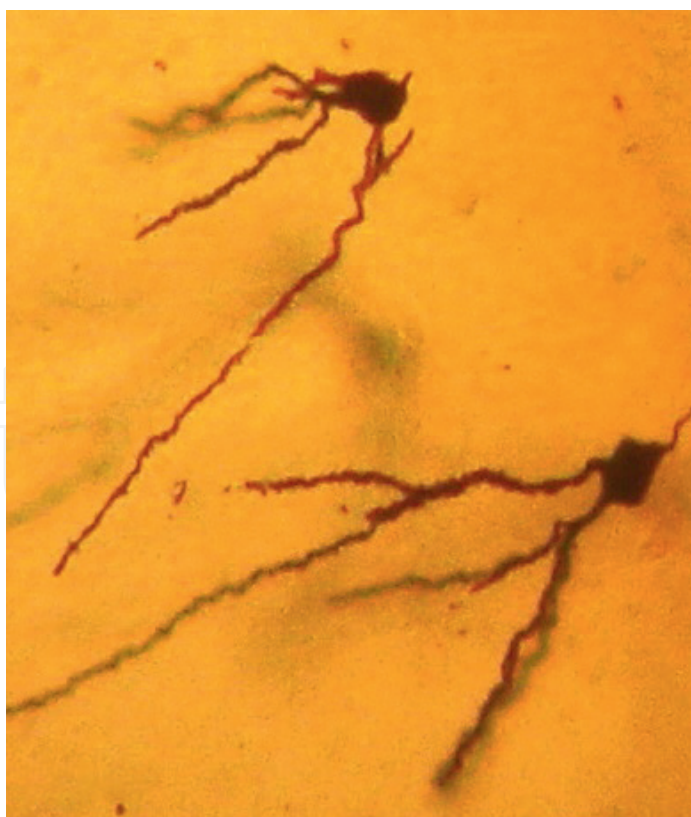


Figure 5. Abbreviation of the dendritic arborization is prominent in the neurons of suprachiasmatic nucleus (SCN) which is associated with marked decrease in the number of dendritic spines. Golgi staining, magnification 1200 \times .

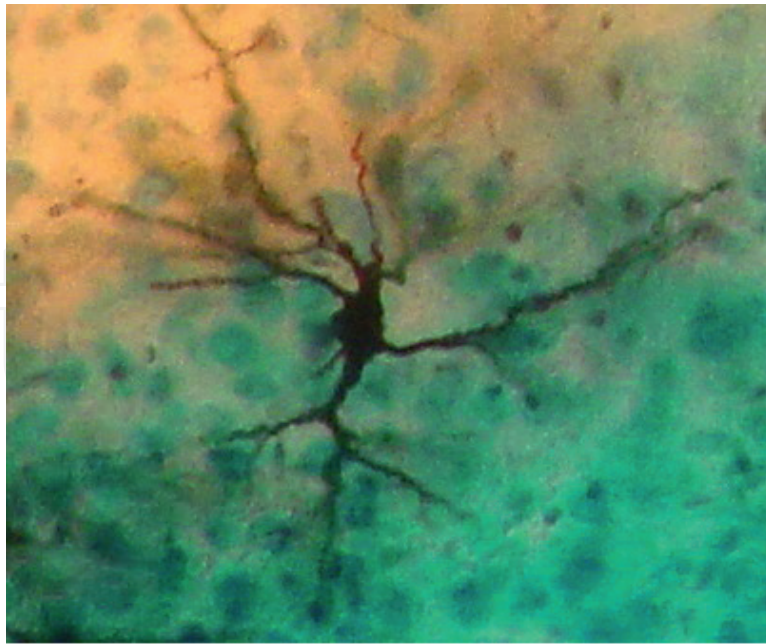


Figure 6. Neuron of the SCN of the hypothalamus of a case of AD. The abbreviation of the dendritic arborization and the poverty of dendritic spines is obvious. Golgi-Nissl staining, magnification 1200 \times .

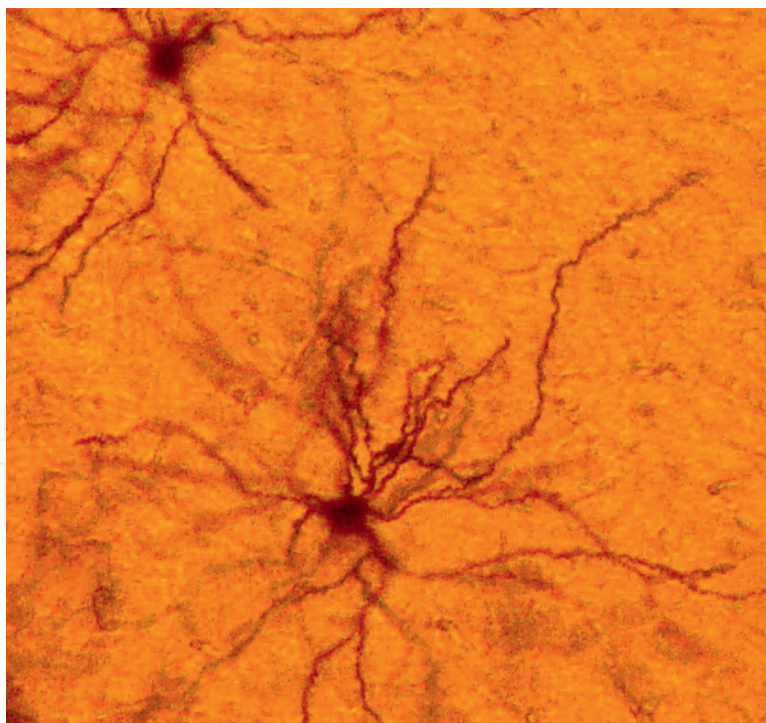


Figure 7. Neuron of the SCN of the hypothalamus of a normal brain 80 years. The dendritic branches are covered by spines. Golgi staining, magnification 1200 \times .

revealed that they have an average diameter of 440 ± 250 nm and a mean axial ratio of 1.7 ± 0.2 . (**Figure 10**). In the same area the ellipsoid mitochondria of the dendritic spines of normal control brains have an average diameter of 650 ± 250 nm and a mean axial ratio of 1.9 ± 0.2 , though the round mitochondria have a mean diameter of 350 nm. The mitochondrial cristae in

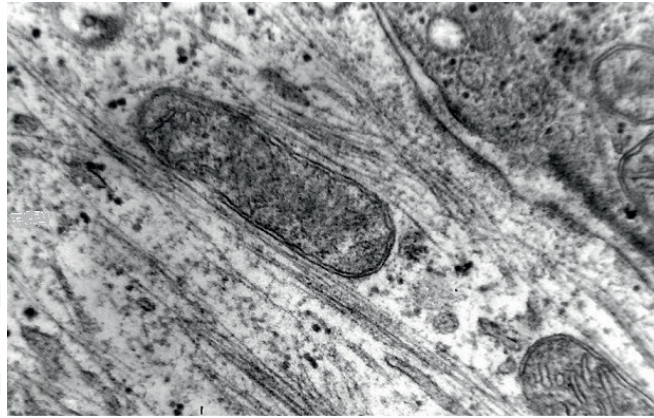


Figure 8. Mitochondrial alterations of a dendritic profile of a neuron of SCN of the hypothalamus of a case of AD. Electron micrograph, magnification 124,000 \times .

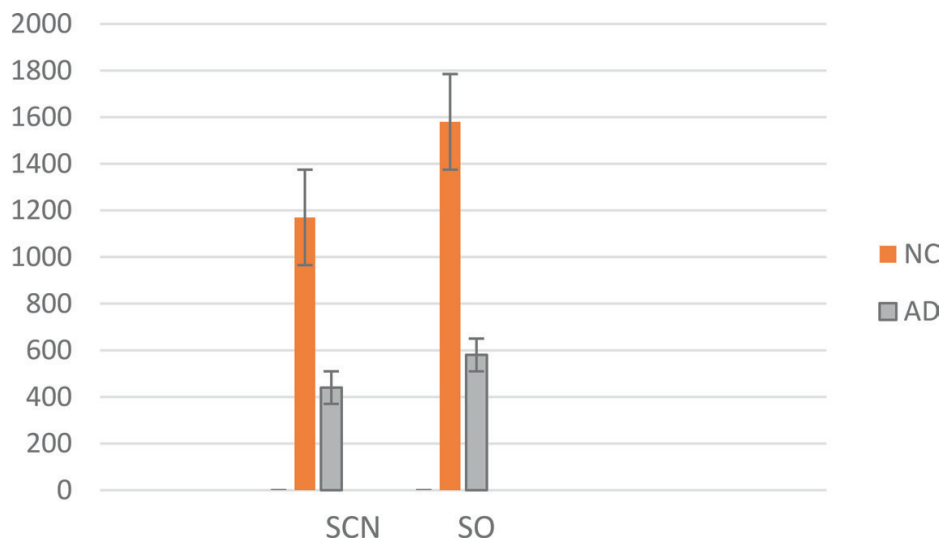


Figure 9. Average dendritic spines per dendritic arbor in SCN and SO neurons, based on measurements of 100 neurons ($p < 0.005$). AD: Alzheimer's disease, NC: normal control, SCN: suprachiasmatic nucleus, SO: supraoptic nucleus.



Figure 10. Mean diameter (in nm) of mitochondria in neurons of suprachiasmatic nucleus, based on estimation of 500 mitochondria ($p < 0.05$). AD, Alzheimer's disease; NC, normal control.

AD brains demonstrated serious changes such as disorientation, fragmentation and globular deformation. Mitochondrial alteration was also a frequent phenomenon in numerous 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 11**). It was noticed that the atrophy or the fragmentation of Golgi apparatus (**Figure 12**) and the mitochondrial alterations coexisted with dendritic and spinal pathology in the majority of neurons.

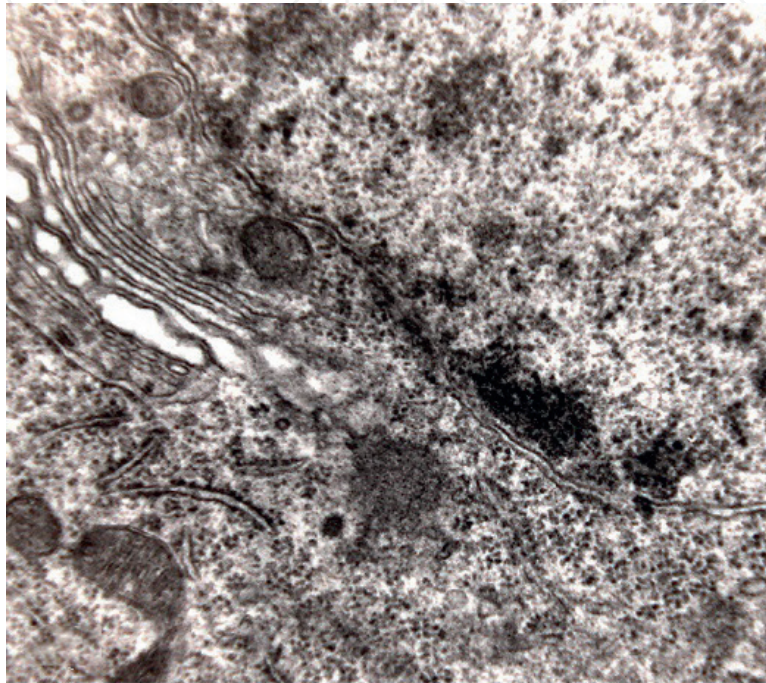


Figure 11. Alteration of Golgi apparatus of a neuron of the SCN nucleus of the hypothalamus of a case of AD. Electron micrograph, magnification 124,000 \times .

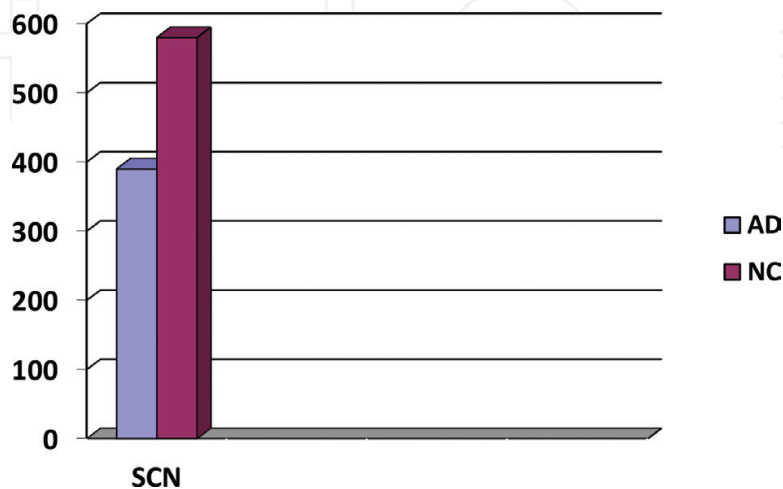


Figure 12. The volume of Golgi apparatus in nm³. Based on measurements of 100 neurons of SCN ($P < 0.005$). AD, Alzheimer's disease; NC: normal control, SCN, suprachiasmatic nucleus.

4. Discussion

Hypothalamus is a crucial brain region for the regulation of substantial homeostatic functions, including the circadian rhythms and the sleep–wake cycle. In Alzheimer's disease and other neurodegenerative disorders [76–78] 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]. In previous studies, it was clearly revealed that the total cell population in the suprachiasmatic nucleus is substantially decreased in aging and dramatically in AD [78] in which the hypothalamic dysfunction is closely related to sleep disturbances [79].

The hypothalamic nuclei seem to be involved with various severities in the neurodegenerative process, which progressively results in AD. In addition, the correlation of the alterations of the neuronal dendrites in the hypothalamic nuclei with those seen in the neocortex and the cerebellum, results in concluding that the hypothalamic alterations are modest in comparison with those, which are established in the acoustic area of the cortex, the visual cortex, the prefrontal areas and the cerebellar cortex [80–83].

The fact that the hypothalamus is the essential subcortical center of the homeostatic and autonomic processes, may explain the reason why some nuclei such as the supraoptic and the periventricular ones reserve substantial synaptic density, even in the advanced stages of AD, in correlation with other subcortical and neocortical neurons.

However, the suprachiasmatic nucleus demonstrated more severe dendritic alterations and synaptic loss than the supraoptic and paraventricular nuclei, a fact which might explain the phenomenon of desynchronization of circadian rhythms in the majority of the patients, who suffer from AD [84] or cognitive decline [85] in the spectrum of other degenerative conditions of the brain [86], given that suprachiasmatic nucleus is of crucial importance for the generation and synchronization of circadian rhythms in man [86, 87]. It is reported that changes of the circadian rhythm (CR), arterial blood pressure and circadian temperature may occur in AD patients [88], especially during the night time [89–91]. Changes also of the melatonin levels are not an unusual phenomenon in advanced senility and AD [92–94]. Sundown syndrome on the other hand, frequently associated with increased motor activity is a rather common condition in advanced AD cases [95].

In a large number of neurons of the hypothalamic nuclei mitochondrial alterations were seen mostly in the soma and the dendrites. Mitochondria play an essential role in the energy supply of the cell, which is crucial in the alteration of reduction-oxidation potential of the cell, in the formation of free radicals, in scavenging activity, as well as in the intracellular calcium control and the activation of apoptotic cascade [96–98]. Normally the mitochondria are numerous in the dendritic profiles and the axons, which have a continuous increased activity during the neuronal interactions. Mitochondrial density is also substantially high in the synaptic components, since mitochondria are the main energy generators for the ceaseless activity of the synapses.

Mitochondrial dysfunction may play an important role for enhancing the neurotoxicity of the A β peptide, though increased mitochondrial proteostasis may reduce amyloid- β

proteotoxicity [99, 100]. In addition, impaired mitochondrial biogenesis contributes to mitochondrial dysfunction [101], which is directly associated with the oxidative stress, the main activator of the pathogenic cascade of AD [101–103].

Mitochondrial motility and accumulation are related to the functional state of the neuron, since mitochondria are transported to regions where necessity for energy is particularly high, as it occurs in the dendritic and axonal profiles and the synapses [103–105]. The shape and size of mitochondria are not stable, since they undergo continual fission and fusion which are necessary for cell survival and harmonious adaptation to changing conditions. Recent studies reported increased mitochondrial fission and decreased fusion, due to increased A β peptide interaction with the mitochondrial fission protein Drp 1, inducing increased mitochondrial fragmentation, impaired axonal transport of mitochondria and synaptic degeneration in AD [106, 107]. The consequence of the dynamic fusion and fission processes is the eventual mitophagy of the damaged mitochondria.

Nevertheless, a considerable diminution of the mitochondria is also seen in aging-related neurodegeneration [97, 98], as well as in the early stages of AD, when the mental decline is subtly detected [107]. In normal brains, few spines only contain small round mitochondria in contrast to dendritic branches which mostly include large mitochondria that become numerous during synaptogenesis and in various conditions of hormonal disequilibrium [104, 106]. In AD, marked morphological changes of the mitochondria have been observed in neurons, which show an extensive loss of dendritic spines, associated with giant spines, distortion of spines and synaptic loss. The association of mitochondrial pathology with the synaptic loss is reasonably attributed to a sharp decrease of energy supply by the defected mitochondria [106, 108], a fact which occurs even at the initial stages of AD, when the typical Alzheimer pathology, consisted of the neuritic plaques and the neurofibrillary tangles is still minimal [109, 110].

The mitochondrial pathology, which is observed in the neurons of the hypothalamic nuclei are additional evidences of the causative role that mitochondrial dysfunction play in synaptic degeneration and loss of dendritic arbors in AD [111, 112]. In the suprachiasmatic nucleus of the hypothalamus a substantial number of neurons made evident the marked decrease of the spine density at the secondary and tertiary dendritic branches, which affects reasonably the neuronal interactions in AD. A substantial body of evidence plead also in favor of the important role that mitochondria and Golgi complex play in the morphological and the quantitative stability of the dendritic spines in neuronal networks [105, 109–112], whereas experimental studies underline the spinal vulnerability to nonfibrillar A β peptide [110].

The hypothalamus play a central role in autonomic functions, including the generation and control of the circadian rhythms, the thermoregulation, the homeostasis of proteins [25], the maintenance of energy supply and the feeding behavior [113–115]. The pathological alterations of hypothalamic nuclei in AD would induce the autonomic instability, which would be particularly prominent at the advanced stages of the disease, aggravating the clinical condition of the patients exceedingly [116–118], a fact which is also observed in experimental models of AD [119] as well as in the behavioral variant of frontotemporal dementia [120].

In conclusion, the serious autonomic dysfunction in advanced stages of AD composes the tragic epilogue of the disease which is related with the involvement of the hypothalamus during the continuous pathological process of the disease.

Author details

Stavros Ioannou Baloyannis^{1,2*}, Ioannis Mavroudis¹, Demetrios Mitilineos¹,
Ioannis S. Baloyannis¹ and Vasiliki G. Costa^{1,2}

*Address all correspondence to: sibh844@otenet.gr

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

2 Institute for Research on Alzheimer's disease, Iraklion, Lagada, 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. *British Journal of Psychology*. 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
- [6] El Gaamouch FP, Jing P, Xia J, Cai D. Alzheimer's disease risk genes and lipid regulators. *Journal of Alzheimer's Disease*. 2016;**53**:15-29
- [7] Scheltens P, Blennow K, Breteler MM, et al. Alzheimer's disease. *Lancet*. 2016;**388** (10043):505-517
- [8] van Rossuma IA, Vissera PJ, Knolb DL, van der Fliera WM, Teunissenc CE, Barkhofd F, Blankensteinc MA, Scheltense P. 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

- [9] Pugazhenth 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
- [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
- [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
- [13] Mukaetova-Ladinska EB, Abdel-All Z, Andrade J, Alves da Silva J, O'Brien JT, Kalaria RN. Plasma and platelet clustering ratio is altered in Alzheimer's disease patients with distinct neuropsychiatric symptoms: Findings from a pilot study. *International Journal of Geriatric Psychiatry*. 2015;**30**:368-375. DOI: 10.1002/gps.4145
- [14] Solas M, Aisa B, Mugueta M, Del Rio J, Tordera RM, Ramirez MJ. Interactions between age, stress and insulin on cognition: Implications for Alzheimer's disease. *Neuropsychopharmacology*. 2010;**35**(8):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: BES*. 2012;**25**: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
- [20] Caracia F, Copania A, Nicolettic F, Dragoe F. Depression and Alzheimer's disease: Neurobiological links and common pharmacological targets. *European Journal of Pharmacology*. 2010;**626**:64-71
- [21] Terry RD. The pathogenesis of Alzheimer disease: An alternative to the amyloid hypothesis. *Journal of Neuropathology and Experimental Neurology*. 1996;**55**: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

- [24] Streit WJ, Mrak RE, Griffin WS. Microglia and neuroinflammation: A pathological perspective. *Journal of Neuroinflammation*. 2004;**1**:14
- [25] Morawe T, Hiebel C, Kern A, Behl C. Protein homeostasis, aging and Alzheimer's disease. *Molecular Neurobiology*. 2012;**46**:41-54
- [26] Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. *Acta Neuropathologica*. 2009;**118**:103-113
- [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
- [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**:802-807
- [31] Conde-Sala JL, Reñé-Ramírez R, Turró-Garriga O, Gascón-Bayarri J, Campdelacreu-Fumadó J, Juncadella-Puig M, Rico-Pons I, Garre-Olmo J. 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
- [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
- [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, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowsk JQ. 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, Castellani RJ, Crain BJ, Davies P, Del Tredici K, Duyckaerts C, Frosch MP, Haroutunian V, Hof PR, Hulette CM,

- Hyman BT, Iwatsubo T, Jellinger KA, Jicha GA, Kövari E, Kukull WA, Leverenz JB, Love S, Mackenzie IR, Mann DM, Masliah E, McKee AC, Montine TJ, Morris JC, Schneider JA, Sonnen JA, Thal DR, Trojanowski JQ, Troncoso JC, Wisniewski T, Woltjer RL, Beach TG. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *Journal of Neuropathology and Experimental Neurology*. 2012;**71**:362-381
- [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**: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):153-162
- [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**:313-322
- [45] Saper CB, German DC. Hypothalamic pathology in Alzheimer's disease. *Neuroscience Letters*. 1987;**74**: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; University Medical Dissertations. 2013. pp. 1-66
- [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*. 2017; pii S 1087-0792 (17)30105-3 DOI: 10.1016 bmr2017.07.005

- [51] de Lacalle S, Iraizoz I, Gonzalo LM. Cell loss in supraoptic and paraventricular nucleus in Alzheimer's disease. *Brain Research*. 1993;**609**:154-158
- [52] Berton O, Nestler EJ. New approaches to antidepressant drug discovery: Beyond monoamines. *Nature Reviews. Neuroscience*. 2006;**7**:137-151
- [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**:681-691
- [54] Baloyannis SJ, Mavroudis I, Mitilineos D, Baloyannis IS, Costa VG. The hypothalamus in Alzheimer's disease: A Golgi and electron microscope study. *American Journal of Alzheimer's Disease and Other Dementias*. 2015;**30**:478-487
- [55] 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
- [56] Braak H, Braak EV. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiology of Aging*. 1995;**16**:271-278
- [57] Leonard C. Silver degeneration methods. In: Johnson JE Jr, editor. *Current Trends in Morphological Techniques*. Boca Raton, Florida: CRC Press; 1981. pp. 93-140
- [58] 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
- [59] Baloyannis SJ. Staining neurons with Golgi techniques in degenerative diseases of the brain. *Neural Regeneration Research*. 2015;**10**:693-695
- [60] Baloyannis SJ. Staining of dead neurons by the Golgi method in autopsy material. *Methods in Molecular Biology*. 2015;**1254**:167-179
- [61] Cavalieri B. *Geometria Indivisibilibus Continuorum*. Bononiae: Typis Clementis Ferronij; 1635. (Reprinted 1966 as *Geometria Degli Indivisibili*. Unione Tipografico-Editrice Torinese, Torino)
- [62] Gundersen HJ, Jensen EB. The efficiency of systematic sampling in stereology and its prediction. *Journal of Microscopy*. 1987;**147**(Pt. 3):229-263
- [63] Abercrombie M. Estimation of nuclear population from microtome sections. *The Anatomical Record*. 1946;**94**:239-247
- [64] 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
- [65] 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, MA: MIT Press; 1990. pp. 35-76

- [66] Sholl DA. Dendritic organization in the neurons of the visual and motor cortices of the cat. *Journal of Anatomy*. 1953;**87**(4):387-406
- [67] 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
- [68] West MJ. Estimating volume in biological structures. *Cold Spring Harbor Protocols*. 2012;**2012**(11):1129-1139
- [69] West MJ. Counting and measuring ultrastructural features of biological samples. *Cold Spring Harbor Protocols*. 2013;**2013**:593-605
- [70] West MJ. Estimating surface area in biological structures. *Cold Spring Harbor Protocols*. 2013;**2013**:77-82
- [71] West MJ. The precision of estimates in stereological analyses. *Cold Spring Harbor Protocols*. 2012;**2012**:937-949
- [72] Sterio DC. The unbiased estimation of number and sizes of arbitrary particles using the disector. *Journal of Microscopy*. 1984;**134**:127-136
- [73] 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**(12):805-881
- [74] Fiala JC, Harris KM. Cylindrical diameters method for calibrating section thickness in serial electron microscopy. *Journal of Microscopy*. 2001;**202**(Pt. 3):468-472
- [75] Feuerwerker 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
- [76] 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
- [77] 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
- [78] 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
- [79] Liguori C, Chiaravalloti A, Nuccetelli M, Izzi F, Sancesario G, Cimini A, Bernardini S, Schillaci O, Mercuri NB, Fabio P. Hypothalamic dysfunction is related to sleep impairment and CSF biomarkers in Alzheimer's disease. *Journal of Neurology*. 2017;**12**:1-9
- [80] Baloyannis SJ. Dendritic pathology in Alzheimer's disease. *Journal of the Neurological Sciences*. 2009;**283**:153-157

- [81] 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
- [82] 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
- [83] Baloyannis SJ. The mossy fibres of the cerebellar cortex in Alzheimer's disease. An electron microscopy study. *Neuroscience*. 1997;**2**:160-161
- [84] Coogan AN, Schutová B, Husung S, Furczyk K, Baune BT, Kropp P, Häßler F, Thome J. The circadian system in Alzheimer's disease: disturbances, mechanisms, and opportunities. *Biological Psychiatry*. 2013;**74**:333-339
- [85] Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, Ensrud KE, Cauley JA, Redline S, Hillier TA, Cummings SR, Yaffe K, SOF Research Group. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. *Annals of Neurology*. 2011;**70**:722-732
- [86] Klein DC, Moore RY. *Suprachiasmatic Nucleus: The Mind's Clock*. New York: Oxford University Press; 1991
- [87] 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
- [88] 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**:765-771
- [89] Van Someren EJW, Hagebeuk EEO, Lijzenga C, Scheltens P, De Rooij SEA, Jonker G, Pot AM, Mirmiran M, Swaab DF. Circadian rest-activity rhythm disturbances in Alzheimer's disease. *Biological Psychiatry*. 1996;**40**:259-270
- [90] Chen HF, Chang-Quan H, You C, Wang ZR, Hui W, Liu QX, Si-Qing H. The circadian rhythm of arterial blood pressure in Alzheimer disease (AD) patients without hypertension. *Blood Pressure*. 2013;**22**:101-105
- [91] Waterhouse J. Circadian rhythms and cognition. *Progress in Brain Research*. 2010;**185**: 131-153
- [92] 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- ϵ 4/4 genotype. *The Journal of Clinical Endocrinology and Metabolism*. 1999;**84**:323-327
- [93] Wu YH, Swaab DF. The human pineal gland and melatonin in aging and Alzheimer's disease. *Journal of Pineal Research*. 2005;**38**:145-152

- [94] 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
- [95] 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
- [96] 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
- [97] Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. *Biochimica et Biophysica Acta*. 1998;**1366**:211-223
- [98] Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature*. 2006;**443**:787-795
- [99] Sorrentino V, Romani M, Mouchiroud L, Beck JS, Zhang H, D'Amico D, Moullan N, Potenza F, Schmid AW, Rietsch S, Counts SE, Auwerx J. Enhancing mitochondrial proteostasis reduces amyloid- β proteotoxicity. *Nature*. 2017;**552**:187-193
- [100] 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
- [101] 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**:2538-2547
- [102] 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
- [103] Sheng B, Wang X, Su B, Lee HG, Casadesus G, Perry G, Zhu X. Impaired mitochondrial biogenesis contributes to mitochondrial dysfunction in Alzheimer's disease. *Journal of Neurochemistry*. 2012;**120**:419-429
- [104] Brown MR, Sullivan PG, Geddes JW. Synaptic mitochondria are more susceptible to Ca^{2+} overload than nonsynaptic mitochondria. *The Journal of Biological Chemistry*. 2006;**281**:11658-11668
- [105] Baloyannis SJ. Alterations of mitochondria and Golgi apparatus are related to synaptic pathology in Alzheimer's disease. In: Kishore U, editor. *Neurodegenerative Diseases*. Rijeka, Croatia: InTech Publishers; 2013. pp. 101-123
- [106] Chang PK-Y, Boridy S, RA MK, Maysinger D. Letrozole potentiates mitochondrial and dendritic spine impairments induced by β amyloid. *Journal of Aging Research*. 2013;**2013**:538979. pp. 1-11

- [107] Baloyannis SJ. Mitochondria are related to synaptic pathology in Alzheimer's disease. *International Journal of Alzheimer's Disease*. 2011;**2011**:305393. pp.1-7
- [108] 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
- [109] 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
- [110] Kirkwood CM, Ciuchta J, Ikonovic MD, Fish KN, Abrahamson EE, Murray PS, Klunk WE, Sweet RA. 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
- [111] Budd SL, Nicholls DG. Mitochondria in the life and death of neurons. *Essays in Biochemistry*. 2017;**33**:43-52
- [112] 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**:347-357
- [113] Elmquist JK, Elias CF, Saper CB. From lesions to leptin: Hypothalamic control of food intake and body weight. *Neuron*. 1999;**22**:221-232
- [114] Grossberg AJ, Scarlett JM, Marks DL. Hypothalamic mechanisms in cachexia. *Physiology & Behavior*. 2010;**100**:478-489
- [115] 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
- [116] Pascualy M, Petrie EC, Brodtkin 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
- [117] 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**
- [118] Brureau A, Zussy C, Delaira B, Ogiera C, Ixarta G, Mauricea T, Givaloisa L. Deregulation of hypothalamic-pituitary-adrenal axis functions in an Alzheimer's disease rat model. *Neurobiology of Aging*. 2013;**34**:1426-1439
- [119] 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**:1532-1540
- [120] Piguet O, Petersen A, Ka Lam BY, Gabery S, Murphy K, Hodges JR, Halliday GM. Eating and hypothalamus changes in behavioral-variant frontotemporal dementia. *Annals of Neurology*. 2011;**69**:312-319

