Chapter 8

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

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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 Aβ 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 Aβ 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.

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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 Aβ 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 membranic 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 Aβ peptide, of the beta-amyloid precursor proteins (beta APPs), whereas Aβ 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 μm in length, was located on the primary dendrite, the second segment, 20–30 μm in length, on the secondary one and the third segment of 40–50 μm, 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 bellow 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.

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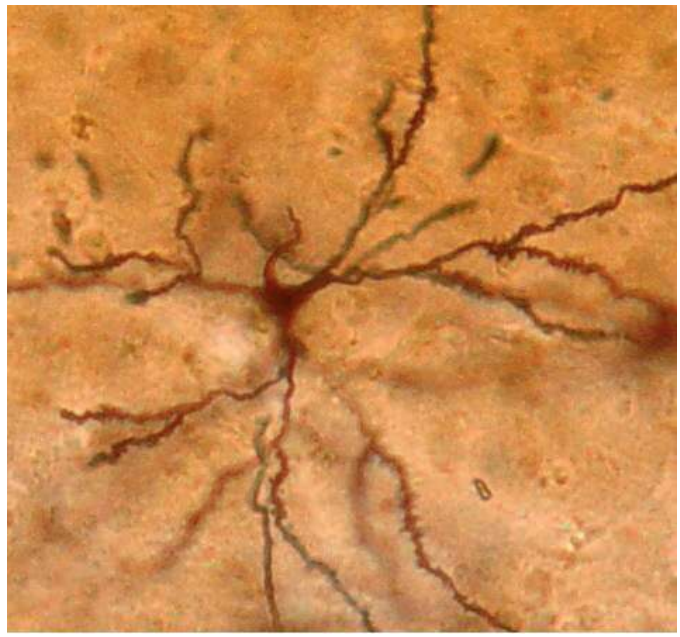

Figure 1. Neuron of the SCN nucleus in AD brain. Golgi staining 1200X.

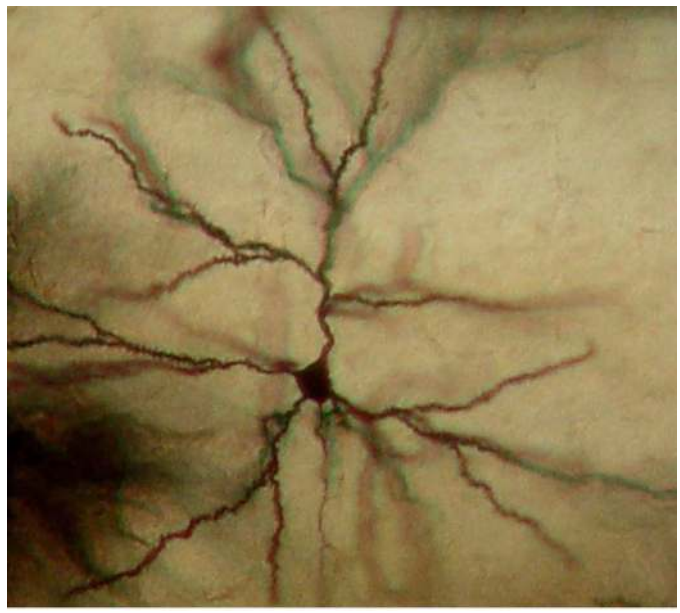

Figure 2. Neuron of SCN of the hypothalamus in a case of AD. The loss of the dendritic branches is obvious. Golgi staining, magnification 1200×.

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

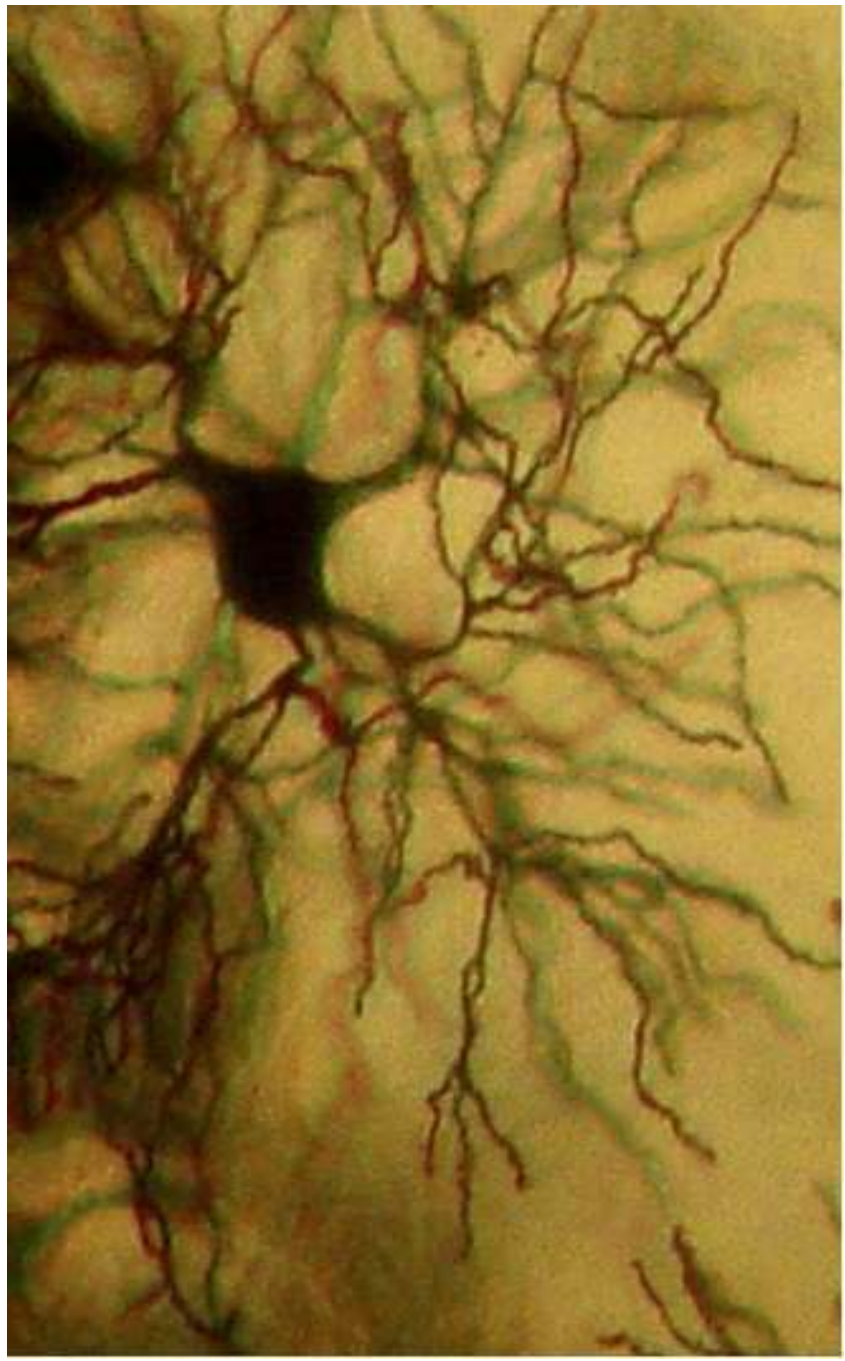

Figure 3. Neuron of the SCN of the hypothalamus of a normal brain aged 75 years.

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

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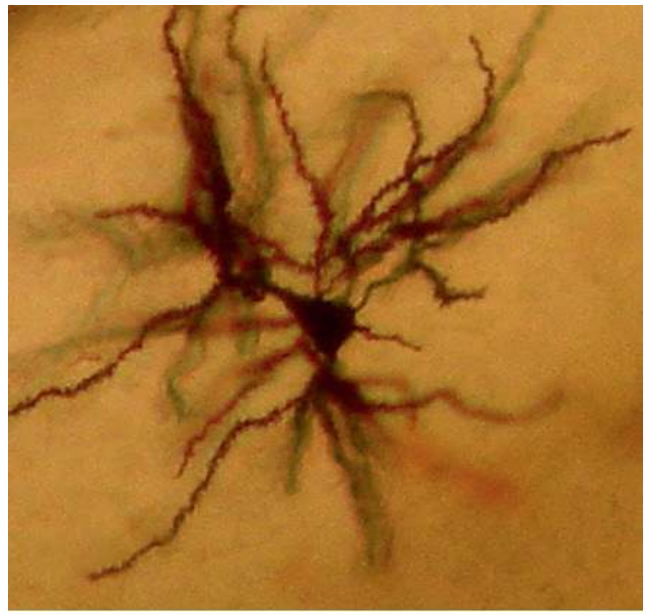

Figure 4. Neuron of the SON of the hypothalamus of a normal brain aged 80 years. The dendritic branches have numerous spines. Golgi staining, magnification 1200×.

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×.

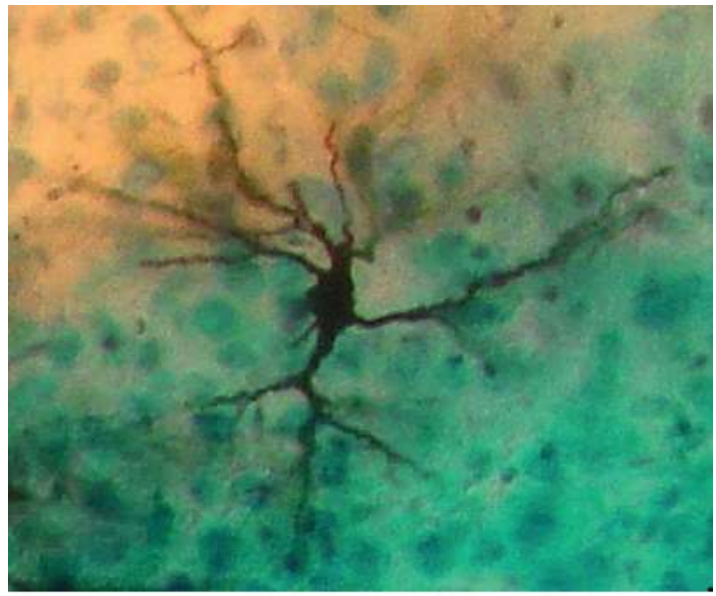

Figure 6. Neuron of the SCN of the hypothalamus of a case of AD. The abbreviation of the dendritic arborization and the poverty of dendritic spines is obvious. Golgi-Nissl staining, magnification 1200×.

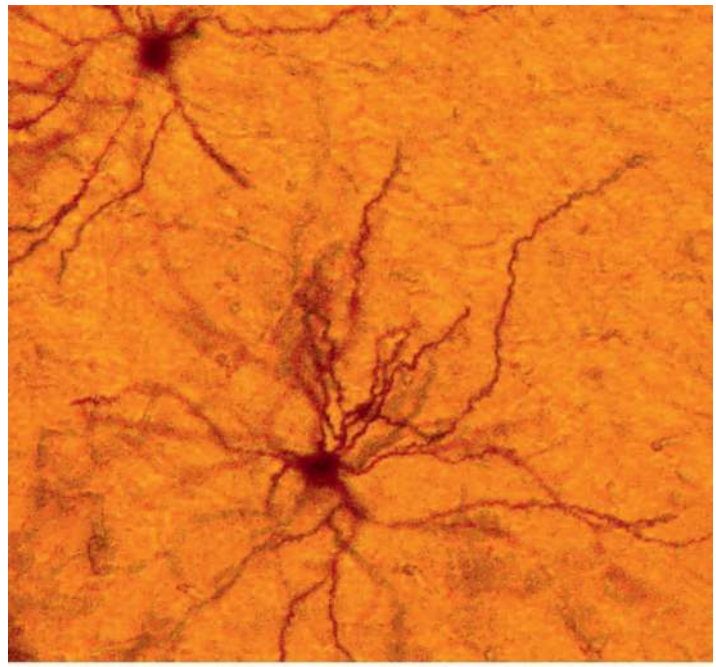

Figure 7. Neuron of the SCN of the hypothalamus of a normal brain 80 years. The dendritic branches are covered by spines. Golgi staining, magnification 1200×.

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

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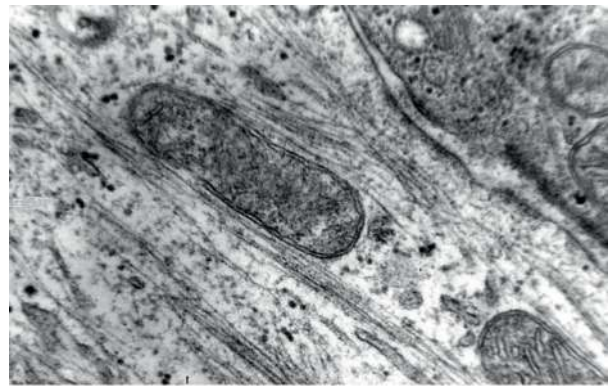

Figure 8. Mitochondrial alterations of a dendritic profile of a neuron of SCN of the hypothalamus of a case of AD. Electron micrograph, magnification 124,000×.

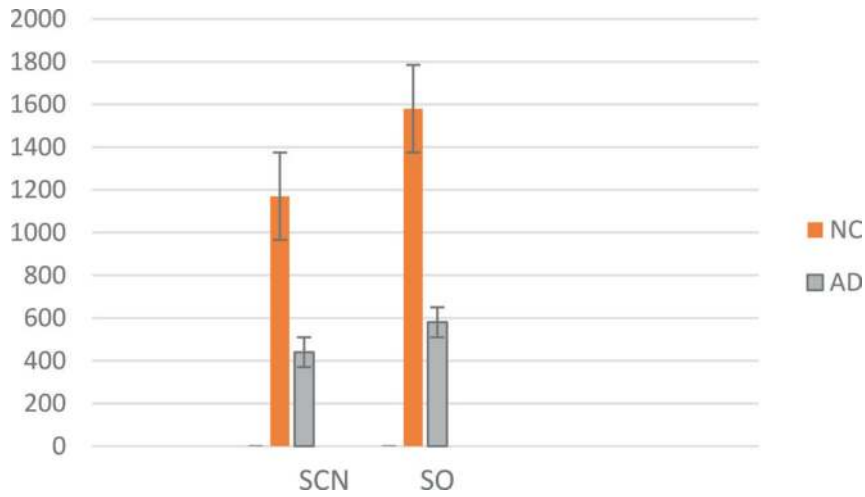

Figure 9. Average dendritic spines per dendritic arbor in SCN and SO neurons, based on measurements of 100 neurons ($p < 0.005$). AD: Alzheimer's disease, NC: normal control, SCN: suprachiasmatic nucleus, SO: supraoptic nucleus.

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.

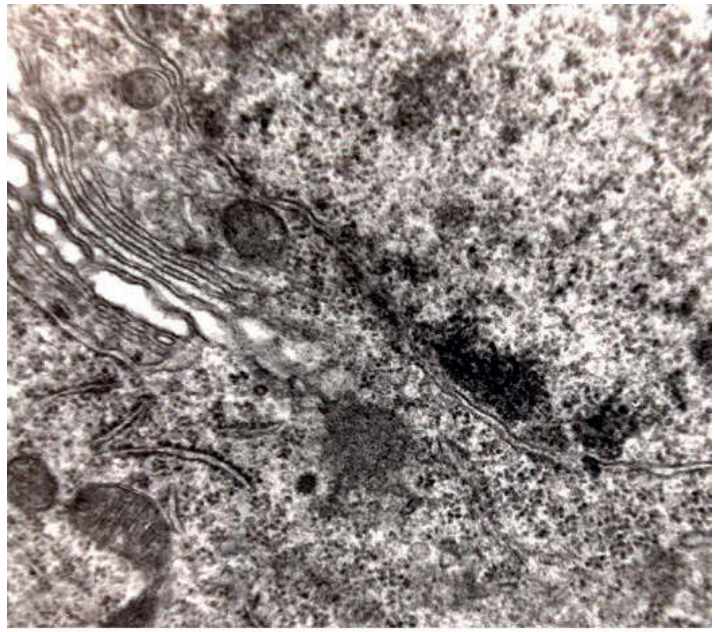

Figure 11. Alteration of Golgi apparatus of a neuron of the SCN nucleus of the hypothalamus of a case of AD. Electron micrograph, magnification 124,000×.

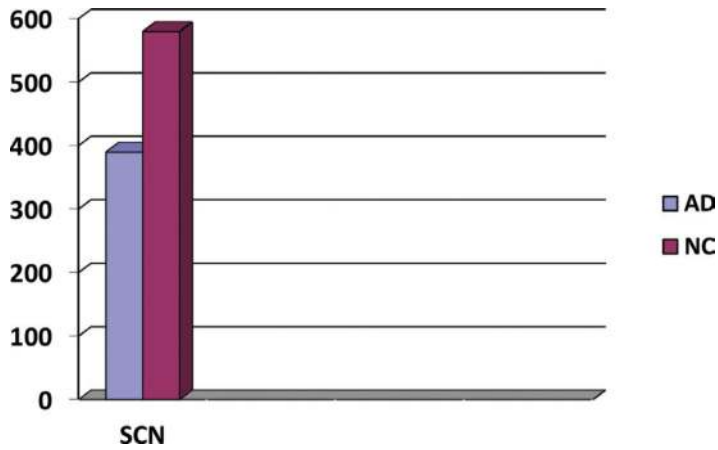

Figure 12. The volume of Golgi apparatus in nm^3. Based on measurements of 100 neurons of SCN ($P < 0.005$). AD, Alzheimer's disease; NC: normal control, SCN, suprachiasmatic nucleus.

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 Aβ 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 Aβ 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 arbores 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 Aβ 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 Mavroudis[1], Demetrios Mitilineos[1], Ioannis S. Baloyannis[1] 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

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