The Hypothalamus in Alzheimer's Disease

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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 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 A β peptide in the brain may induce inflammatory reactions, in which activated microglial cells are mostly involved [24]. It is important that the aggregation of A β 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 homeostatic 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 A β peptide, of the beta-amyloid precursor proteins (beta APPs), whereas A β 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 arbors 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 dendritic 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

Figure 1. Neuron of the SCN in AD brain. Golgi staining, 1200 $\times$.

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 $\times$.

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×.

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 $\times$.

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 are obvious. Golgi-Nissl staining. Mag. 1200 $\times$.

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 $\times$.

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 $\times$.

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

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 nm³ 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 A β 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 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 [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 A β peptide deposition, it was revealed that nonfibrillar A β 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

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