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Morphological Characteristics of Neural Tissue During Physiological Aging, Apoptotic and Cellular Contribution

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Abstract

A growing body of evidence suggests that the brain changes as we age. There is loss of both white and grey matter, degeneration of neurons and synapses, as well as oxidative, inflammatory and biochemical changes. The aforementioned age-related characteristics are linked to autophagy and mitochondria. As a result, we sought to identify the most unusual morphological features of brain nervous tissue as well as characterise the expression of autophagy and mitochondrial immunohistochemical biomarkers in neurons from various human brain zones as they aged.

Keywords: Anesthesia • Neurodevelopment • Neurodegeneration • Nonlethal caspase

Introduction

A growing body of evidence suggests that the brain changes as we age. There is loss of both white and grey matter, degeneration of neurons and synapses, as well as oxidative, inflammatory and biochemical changes. The aforementioned age-related characteristics are linked to autophagy and mitochondria. As a result, we sought to identify the most unusual morphological features of brain nervous tissue as well as characterise the expression of autophagy and mitochondrial immunohistochemical biomarkers in neurons from various human brain zones as they aged.

FFPE samples of human prefrontal cortex, corpus striatum and hippocampus were immunohistochemically stained for Microtubule-associated proteins 1A/1B light chain 3B (LC3B), Heat shock protein 70 (HSP70), Lysosome-associated membrane protein type 2A (LAMP2A), Alpha subunit of ATP synthase (ATP5A) and Parkinson disease protein 7 (DJ1). Statistical analysis revealed that the elderly group lost more neurons than the young group. When the expression of macroautophagy (LC3B), chaperon-mediated autophagy (HSP70, LAMP2A) and mitochondrial respiratory chain complex V (ATP5A) markers for the young and elderly groups was compared, the latter had a significantly higher rate of optical density, while DJ1 expression had no significance [1].

Description

These preliminary findings suggest that autophagy and mitochondria are involved in neuronal maintenance during ageing and may play a role in adaptive mechanisms that occur during ageing. Data suggests that the brain changes during ageing, which is a major risk factor for many neurodegenerative disorders. Weight and volume decrease due to loss of both white and grey matter, neurons and degeneration of myelin fibres, neurites and synapses are among the changes mentioned above. Many changes that occur during ageing and neurodegeneration have similar morphology and may differ primarily in quantitative terms.

Over the years, it has become clear that brain ageing is closely related to oxidative stress, bioenergetic deficiency, the accumulation of damaged ultrastructural components and aggregated neurotoxic proteins at the cellular level. These characteristics may contribute to age-related neurodegenerative diseases; thus, maintaining a functional pool of neurons is dependent on mitochondria and autophagy; thus, research into the latter is important in the development of new biomarkers for neurodegenerative target therapy [2].

Various types of autophagy may be used to maintain neuronal cytoplasm and eliminate cytotoxic proteins in non-dividing cell types such as neurons. The primary autophagy pathway is macroautophagy, which is a protective mechanism that allows cells to function in the face of stressors such as energy deprivation, hypoxia, a lack of growth factors, reactive oxygen species and DNA damage. Macroautophagy eliminates dysfunctional proteins, while its disruption can impair axonal movement, dendrite and axon remodelling, and, as a result, nervous tissue plasticity. Chaperone-mediated autophagy (CMA), a type of selective autophagy, is also important in neuron function and survival during ageing. It is distinguished by the following features: proteins containing the KFERQ motif are recognised and then bind to the cytosolic heat shock protein 70 (HSP70).

The cargo is then translocated into the lysosome by this complex's interaction with the lysosome-associated membrane protein type 2A (LAMP2A). Chaperone-mediated autophagy dysfunction causes a reduction in the degradation of misfolded neurotoxic proteins such as tau proteins, amyloid in Alzheimer's disease, synuclein in Parkinson's disease, the mutant protein polyQ huntingtin in Huntington's chorea and the TDP-43 protein in frontotemporal dementia. Furthermore, CMA is involved in mitochondrial quality control indirectly by removing the dysfunctional protein DJ-1 (PARK7) with the KFERQ amino acid sequence. Both autophagy and mitochondria have been shown to play critical roles in coordinating metabolic processes and cell homeostasis [3]. Damaged organelles, in turn, may contribute to ageing and age-related neurodegenerative disorders through decreased oxidative phosphorylation and increased reactive oxygen species, as well as through proapoptotic signalling, inflammasome activation and disrupted synaptic transmission.

Both mitochondria and autophagy appear to be fundamental signalling platforms that regulate various processes and allow the cell to function as a whole. While cell compartmentalization does exist, their interaction coordinates various processes in cells and defects in one or both systems contribute to ageing and age-related diseases. As a result, we sought to identify the most unusual morphological features of senile neurons, as well as to characterise the expression of immunohistochemical biomarkers for macroautophagy (LC3B), chaperon-mediated autophagy (HSP70, LAMP2A), mitochondrial respiratory chain complex V (ATP5A) and mitochondrial quality control (DJ1) in neurons

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from various human brain zones during ageing. Large neurons are lost with age in brain areas such as the precentral gyrus, hippocampus, corpus striatum and substantia nigra. However, it should be noted that some studies found only a slight decrease in the number of neurons in different brain areas during ageing. This disparity in results can be explained by a number of factors.

The neuronal reduction observed in this study could be attributed to cerebrovascular insufficiency caused by cerebral angiopathy to some extent. This is supported by the focal change lesions we discovered in a number of cases as a result of previously suffered small, deep infarcts, the development of which is associated with hypertension. In turn, the presence of cardiosclerosis as the primary cause of death lends support to the cardioembolic aetiology caused by previously suffered small superficial infarcts. It should be noted that the inability to completely exclude comorbid and age-related diseases adds to the difficulty of studying morphological changes caused solely by senile manifestations. Differences in morphometric methodological approaches could also contribute to the data discrepancy. Thus, stereological analysis was used to evaluate the results in the aforementioned studies, allowing for a three-dimensional reconstruction of the studied structures.

Despite the large amount of data on the functions and mechanisms of this selective type of autophagy, the current literature on the expression levels of its markers in human brain nerve tissue is scant and contradictory. For example, Ye et al. [30] discovered increased levels of various heat shock proteins in the brain during ageing. Found the opposite our findings show an increase in the expression of CMA immunohistochemical markers in neurons from elderly people, which is partially consistent with the other data. A number of studies have shown an increased level of expression of various heat shock proteins in both brain tissue and myocardium, liver and skeletal muscle tissue over the last few years; however, most studies have been performed in laboratory vertebrate models, with only a few studies on CMA performed on biopsy and autopsy material. This could be explained by the difficulty of studying changes caused solely by senile features, as well as the inability to rule out comorbid and age-related diseases [4].

The increased levels of CMA markers found in elderly samples could be attributed to the following factors. This type of selective autophagy is known to be a regulator of cell homeostasis. As a result, its expression level can be stress-induced in response to an increased amount of misfolded proteins and reactive oxygen species accumulated over time, as a result of inflammation or hypoxia, for example. The higher optical density of HSP70 detected in elderly brain samples compared to LAMP2A was most likely caused by a dissociation between substrate binding and lysosome translocation.

As a result, we can assume that nonfunctional proteins bind to HSP70 and co-chaperones faster than they move into the lysosome lumen via LAMP2A. The latter's inadequacy most likely underpins the dissociation mechanism described above, but this hypothesis requires further investigation. Furthermore, heat shock proteins have a broader spectrum of functional activity and are involved not only in CMA but also in signalling pathways to maintain cellular homeostasis. There is little information in the literature about macroautophagy and its role in the ageing of human brain nervous tissue. In addition to the study of chaperone-mediated autophagy, the majority of the data obtained came from laboratory animal experimental models [5]. The marker LC3B, which was used in this study to determine the level of macroautophagy, was found on the inner and outer layers of the phagophore membrane. It was removed from the outer surface of. autophagosomes during maturation but remained on the inner surface; thus, its level may correlate with the number of autophagosomes [5].

Conclusion

However, interpreting the measurement results for this protein can be difficult because an increase in its level may be associated with both the activation of macroautophagy and a decrease in autophagosome-lysosome fusion. In turn, mitochondrial dysfunction, defined by decreased activity in respiratory chain complex enzymes and impaired oxidative phosphorylation function, can result in a decrease in ATP production and, as a result, a bioenergetic deficit. Because neurons are vulnerable to ATP depletion and most of their functions rely directly on energy obtained during mitochondrial metabolism, the latter has a significant impact on their functional pool.

Furthermore, mitochondrial quality control is one of the mechanisms of interaction between mitochondria and chaperone-mediated autophagy, which uses proteins with the KFERQ motif. The DJ-1 protein (PARK7), which protects mitochondria from damage during oxidative stress, is one of the proteins containing the KFERQ amino acid sequence. A slight decrease in the optical density of DJ-1 combined with an increase in the level of HSP70 in the elderly group may be due to the increased utilisation of its damaged forms by the mechanism of chaperone-mediated autophagy, which indirectly confirms the development of oxidative stress in brain neurons during ageing.

Acknowledgement

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Conflict of Interest

There are no conflicts of interest by author.

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