

„GEORGE EMIL PALADE” UNIVERSITY OF MEDICINE,
PHARMACY, SCIENCE AND TECHNOLOGY OF TÂRGU MUREŞ

DOCTORAL SCHOOL

SUMMARY OF THE DOCTORAL THESIS

Clusterin, a Novel Therapeutic Target for Improving Vascular Amyloid Clearance in Alzheimer’s Disease

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INTRODUCTION

Alzheimer's disease is the most common form of dementia and is a neurodegenerative disorder. This pathology represents a major health problem among elderly individuals, particularly in developed countries. One of the main pathophysiological features involved in Alzheimer's disease is the extracellular deposition of amyloid beta at the level of cerebral blood vessels, most frequently in the leptomeningeal arteries or cortical arterioles. Excess amyloid beta results from an imbalance between its production and impaired elimination. Amyloid beta clearance is ensured by several complex systems, the main pathway being its transport into the bloodstream across the blood brain barrier, while a smaller fraction is eliminated through the flow of interstitial fluid. The absorption of cerebrospinal fluid into the circulatory and lymphatic systems also contributes to this clearance process.

RATIONALE OF THE STUDY

The choice of this topic is determined by the need for an integrated approach between biomechanics, sports medicine, and orthopedics, fields that are frequently analyzed separately in the specialized literature. Interest in this research direction is also supported by the author's multidisciplinary professional experience, which combines the perspective of a performance athlete and coach with medical practice in orthopedics and traumatology. The development of modern methods for functional and biomechanical assessment enables the correlation of data regarding neuromuscular performance, recovery after trauma, and the progression of degenerative joint diseases, thereby facilitating the integrated analysis of these processes in the context of sports medicine and musculoskeletal pathology.

The aim of this thesis is to investigate the role of clusterin in the mechanisms of intramural periarterial drainage of amyloid beta, with emphasis on how this molecule may influence the elimination of A β from the cerebral vascular compartment. The study aims to demonstrate that CLU acts as an important modulator of amyloid beta clearance, contributing to the maintenance of the functionality of intramural periarterial drainage pathways and, implicitly, to limiting vascular A β deposition. By using an in vivo experimental model, complemented by modern stereotaxic injection techniques, confocal microscopy, and digital image analysis, this research seeks to clarify the relationship between the presence of clusterin and the early dynamics of amyloid deposition at the level of cerebral vessels.

The research hypothesis of this research is that the absence of clusterin leads to an impairment of intramural periarterial drainage of amyloid beta, thereby promoting the accumulation and aggregation of A β within the walls of cerebral blood vessels. In this context, it is hypothesized that the administration of human recombinant clusterin may facilitate the elimination of A β through intramural periarterial drainage pathways and may reduce the tendency of the peptide to form intramural aggregates. Thus, CLU could exert a protective effect on the cerebral

vascular compartment, contributing to the delay or prevention of cerebral amyloid angiopathy and of the pathological changes associated with Alzheimer's disease.

The first study, entitled "The Impact of Human Recombinant Clusterin on the Reduction of Amyloid- β Aggregates in Cerebral Arterioles of Clusterin Knockout Mice", analyzes the role of clusterin in modulating vascular amyloid beta deposition in the brain. The research investigates the relationship between A β , the arteriolar wall, and intramural periarterial drainage mechanisms, using an experimental clusterin knockout mouse model.

The second study, entitled "Acquisition, Implementation, and Standardization of the Intrahippocampal Injection Technique in Mice within an Experimental Model of Alzheimer's Disease", analyzes the process of acquiring and applying a high-precision experimental method used for the controlled administration of substances into the hippocampus. The research focuses on the technical steps required to perform stereotaxic intrahippocampal injection, including animal positioning, identification of anatomical landmarks, establishment of stereotaxic coordinates, control of the injected volume, and standardization of the administration rate.

The results of the research show that the administration of human recombinant clusterin did not significantly modify the total vascular surface area occupied by A β at the level of cerebral arterioles and capillaries. In contrast, CLU was associated with a reduction in the size of intramural A β aggregates within the walls of cerebral arterioles. This effect was not observed in the tissue located outside the arterioles, suggesting a predominantly vascular/perivascular action of clusterin. Through advanced imaging and statistical analysis, the thesis demonstrated that CLU mainly influences the aggregation state of A β rather than the total amount deposited. In addition, the intrahippocampal injection technique in mice was implemented and standardized, which was essential for obtaining reproducible experimental data.

The originality of the thesis derives from the integrative approach to an insufficiently explored issue in the pathology of Alzheimer's disease, namely the role of CLU in regulating vascular A β deposition and modulating IPAD mechanisms. In a context in which most previous studies have focused predominantly on parenchymal A β deposits or on classical transgenic models of Alzheimer's disease, the present thesis proposes a perspective specifically oriented toward the cerebral vascular compartment, which is now considered an essential element in the pathophysiology of the disease.