Advancing insights into central nervous system disorders: behavioral, metabolic and histological studies in experimental rat models

Habilitation Thesis

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Summary

This thesis presents in a compact and transparent manner the most important scientific research activity performed since obtaining PhD degree by its author. The focus was put on the central nervous system (CNS) disorders linked to neurodegeneration, neuroinflammation, network hyperexcitability, and stress. These processes were demonstrated to be involved in the pathophysiology of Alzheimer's disease, epilepsy, depression, and cognitive decline. Many studies support the implication of abnormal reorganization of the neuronal networks due to accelerated apoptosis or necrosis of certain cell types. Thus, the adaptive and compensatory mechanisms which could be engaged in the development of disorders affecting the central nervous system can only be studied using in vivo animal models. This habilitation thesis supports the utility of experimental models and presents the potential benefits in fundamental and translational research. It is structured in three chapters, the first describing the most interesting and remarkable results obtained in the last 9 years, since obtaining PhD title by the author of this thesis, while the second presenting the future research directions and perspectives for professional and personal development. The third chapter contains the scientific references cited in the first and second chapters.

The first chapter is divided into five sections, each presenting one of the complex interdisciplinary approaches to study CNS disorders. Specifically, behavioral assays that focus on anxiety, depression, and cognition are presented along with molecular and histological evaluation of brain tissue samples. Each section presents the scientific background supporting the tested hypotheses, the animal models that were used to elucidate features of the studied condition, and the pharmacological interventions performed to better understand the role of drug therapy in disease progression. For each experimental animal model, specific interventions such as surgical techniques, intracerebral or systemic injections of chemical agents were performed personally by the author of this thesis. All animal models were tested for the characteristic behavioral alterations that demonstrate their construct validity. Subsequently, the following pharmacological agents and natural compounds were studied for presumed disease modifying actions: cannabidiol, melatonin, cholecalciferol, lacosamide, and levetiracetam. At the end of each study biological samples were collected to determine the studied drug's concentration along with specific serum and neuronal tissue markers. For drug level monitoring highly specific and sensitive liquid-chromatography-mass spectrometric methods were developed and applied. Tissue markers were investigated

either by mRNA quantification or by protein labeling using triple fluorescent immunohistochemistry.

The research activity summarized here was primarily conducted at the George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș. Due to the interdisciplinary nature of the projects, collaborations were established with Semmelweis University and the Sapientia Hungarian University of Transylvania. Funding was secured by applying for and accessing national and local research grants. The obtained results were published in high impact journals, the list of representative publications containing 7 articles published in Q1 journals and 3 articles in Q2 journals.

The second chapter of this habilitation thesis describes the author's development plan regarding his professional, scientific and academic career. The main research directions are already being defined by the acquired skills and knowledge, specifically the study of CNS disorders using experimental models. However, several complementary techniques such as microdialysis or in situ hybridization, are expected to be employed to better understand the impact of environmental factors and drug therapy on the CNS. In this context, the main objectives of the proposed studies represent the elucidation of the roles that environmental factors—such as physical activity, diet, and food supplements—and therapeutic interventions, both pharmacologic and non-pharmacologic, might play in disease progression or alleviation.

My perspectives in the evolution and development of professional and academic careers include expanding my teaching skills and enhancing my expertise in data science. A particular point is the use of student-centered teaching methods and the facilitation of the learning process through various techniques that involve the active participation of students. Looking ahead, I see great value in fostering international collaboration in doctoral education, particularly in the joint supervision of PhD students. Establishing co-supervised PhD programs or cotutelle agreements with respected academic institutions abroad can significantly enhance the academic and scientific development of doctoral candidates. I plan to seize the opportunity to further develop my previous partnerships focused on scientific research with Semmelweis Univeristy, HUN-REN Institute of Experimental Medicine, and Sapientia Transilvanian University to create opportunities for future doctoral candidates. Such partnerships could offer students the unique opportunity to engage in interdisciplinary and cross-cultural research environments, access complementary expertise and advanced infrastructure, and participate in international mobility and networking activities.