

БЪЛГАРСКА АКАДЕМИЯ НА НАУКИТЕ
И-Т ПО ЕКСПЕРИМЕНТАЛНА МОРФОЛОГИЯ,
ПАТОЛОГИЯ И АНТРОПОЛОГИЯ С МУЗЕЙ
Вх. № 131
..... 20.05 2021 г.
СОФИЯ

OPINION

By Prof. Svetlozara Lyubomirova Petkova - Institute of Experimental Morphology, Pathology and Anthropology with Museum (IEMPAM) - BAS, member of the Scientific Jury, appointed by order RD-15-27.

Subject: dissertation for obtaining the scientific degree "Doctor of Sciences" in the specialty "Biochemistry" (01.06.10) from the Professional field 4.3 "Biological sciences" on the topic: **"Biochemical bases of Alzheimer's disease" author Prof. Ludmil Penov Kirazov.**

The documents submitted at the competition are completed correctly and precisely prepared. They are in accordance with the requirements of Academic Staff Development Act and the regulations for opening a procedure for defense of a dissertation for the award of the academic degree "Doctor of Sciences".

Prof. Ludmil Kirazov graduated from the University of Leipzig with a degree in Biochemistry and defended his dissertation in the field of neurobiochemistry at the Paul Flexig Institute for Brain Research, Leipzig. In 1988 he defended his doctoral dissertation at the Paul Flexig Institute for Brain Research, Leipzig. The author's biographical report presents his consistent scientific career in the field of neurobiology and biochemistry with many specializations in Germany and collaborations with research teams. In 2016 he was elected Professor of Biochemistry at IEMPAM-BAS.

Prof. Kirazov's dissertation is structured correctly, is presented on 280 pages and is illustrated with 86 figures and 9 tables. The reference presented by Prof. Kirazov with the requirements for acquiring the scientific degree "Doctor of Sciences" from the Regulations of IEMPAM for application of Academic Staff Development Act shows 652 points with a required minimum of 350 points.

The topic of the dissertation is specific and concerns a problem of exceptional social and health significance, such as Alzheimer's disease. The literature review is well structured and gives a comprehensive view of the problem. The data from 700 sources were used, which shows the seriousness of the problem and the ability of Prof. Kirazov to specify and present the information. The clearly stated goal - to establish basic biochemical approaches for scientific screening of the etiology and pathogenesis of Alzheimer's disease follows the course of development. It is supported by logically following and building on the topic of research and contributes to the presentation of a completed dissertation contribution to science. A wide range of different methods is applied: morphological, histological, immunohistochemical, biochemical, statistical, in situ hybridization, cell culture. The results are a consequence of the experiments made and follow the overall logic of the scientific work and achievements of Prof. Kirazov. 12 conclusions were made based on the obtained results, which accurately and correctly summarize the work. The contributions with original character are 10 and two with scientific-applied character. The author's scientific activity on the topic is presented and illustrated in 45 scientific papers in forums and 31 scientific papers. The citations related to the dissertation are over 400.

I will highlight some of the results obtained from the work and I will emphasize that most of them are of a contributory nature.

Amyloid β -peptide ($A\beta$) has been shown to rapidly, reversibly, and reversibly affect the electrical activity of neuronal cells. The different isoforms of $A\beta$ and the biologically active fragment $A\beta_{25-35}$ have different effects. The effect is not due to oxidative stress, but is most likely due to the activation of inhibitory receptors.

The secreted amyloid precursor protein (sAPP) has been shown to undergo additional physiological, Ca^{2+} -dependent degradation in brain tissue. It has also been shown that there is no feedback between sAPP and APP secretion, which is important in different study models. It has been shown for the first time that vascular endothelial growth factor can affect APP metabolism by modulating the activity of α - and β -secretases, and thus amyloidogenesis. Using the cholinergic immunotoxin saporin, models have been developed that have demonstrated for the first time in vivo the role of cholinergic innervation in APP processing. Studies of changes in APP expression in brain homogenate, isolated growth cones, and synaptosomes from embryonic developmental stages to adult animals (rats) were performed. At the same stages of development, the expression of the mRNA isoforms APP695, APP751 and APP770 was studied. The results confirm the role of APP in synaptogenesis. It has also been found that the APP695 isoform plays a major role in the differentiation of nerve cells not only in the central but also in the peripheral nervous system. A method for studying the secretion of APP from native brain sections has been developed and original results have been obtained for stimulating the secretion of APP from the neurotransmitter glutamate and for the modulating role of different subtypes of glutamate receptors. For the first time, a comparative study of the transcriptome in the synaptosomal fraction of young and adult mice was performed and a number of undescribed long intervening non-coding RNAs in adult synaptosomes were identified. These results provide a wide field for studying the significance of this transcriptional regulation. Original results were obtained for the effect of lead on APP secretion and a hypothesis was formulated for the mechanism of the toxic effect of lead on nerve cells. An in-depth comparison of the most widely used methods for determining protein - Lowry's and Bradford's - is of scientific and practical significance. A model for the study of APP processing using synaptosomes has been proposed. This model is particularly suitable for studying the role of various neurotransmitters and their receptors. It should be noted the active project activity of Prof. Kirazov. He has conducted several specializations in Germany, and in the last five years has actively participated in various commissions of the Research Fund of the Ministry of Education and Science. He is a member of the Supervisory Board of IEMPAM and is Chairman of the General Assembly of Scientists at the Institute. The abstract reflects fully and accurately the content of the dissertation.

Conclusion: The dissertation of Prof. Ludmil Kirazov is an in-depth and precise study with a contribution to the knowledge of the biochemical mechanisms of the pathogenesis of Alzheimer's disease. Prof. Kirazov's scientometric indicators fully comply with the requirements of Academic Staff Development Act and its regulations. I am convinced of my positive assessment and I recommend to the Scientific Jury to award the scientific degree "Doctor of Sciences" to Prof. Dr. Ludmil Kirazov in the specialty "Biochemistry" (01.06.10) from Professional direction 4.3 "Biological Sciences".

19. 05.2021

Prepared the opinion:

