OPINION

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On dissertation

INFLUENCE OF SUBCHRONICALLY APPLIED LIGANDS OF CANNABINOID RECEPTORS ON LEARNING AND MEMORY PROCESSES IN OLFACTORY BULBECTOMIZED RATS

For the acquisition of the educational and scientific degree „DOCTOR (Ph.D.)"
by Dr. Dobrinka Kalinova Doncheva
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By order № P-109-86 / 23.02.2022 of the Rector of the Medical University of Varna and decision of the Scientific Jury of 25.02.2022 I was appointed to prepare an opinion on the dissertation of Dr. Dobrinka Kalinova Doncheva, for acquisition of the educational scientific degree „DOCTOR (Ph.D.)", professional field 4.3. Biological sciences, scientific speciality "Animal and Human Physiology".

1. **Evaluation of the relevance of the topic**

In her dissertation, Dr. Dobrinka Doncheva studies the participation of cannabinoid receptors in learning and memory processes in rats with a model of depression olfactory bulbectomy (OBX).

The endocannabinoid system (ECS) is a modulatory neurotransmitter system that includes endogenous cannabinoids, enzymes and receptors. It is important for the organization of connections in the brain, but is also involved in the control of many other physiological processes such as locomotor activity, learning, memory, eating behavior, nociception, in the regulation of energy balance and emotional reactions of the body. At the end of the 20th century, two types of cannabinoid receptors were identified - CB1 and CB2, expressed in the CNS and peripheral tissues. This has given new impulse to the studies of the effects of ECS in experimental models and in humans. Very often, data from animal model studies are contradictory. The use of substances that modulate the activity of ECS can both disrupt and improve the processes of memory formation. The results of the role of cannabinoid receptors in behavioral responses in animal models of depression and in terms of cognitive functions are contradictory.

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The study of the mechanisms of action of cannabinoid receptor ligands on learning and memory processes is of great importance for clinical practice. Data in the scientific literature indicate altered ECS activity in a number of socially significant psychiatric (depression, anxiety, schizophrenia) and neurological (Parkinson's disease, Alzheimer's) diseases. It is known that many factors are involved in the etiology of depressive disorders and neurodegenerative diseases in humans, which makes it difficult to establish the pathogenetic mechanisms.

This makes the dissertation of Dr. Dobrinka Doncheva relevant and important not only for the basic sciences but also for the clinical practice. The model of depression that is used - olfactory bulbectomy (OBX), contributes to the relevance of the topic and the comparability with the data accumulated from the scientific research. The analysis of the problem in the detailed literature review enabled the doctoral candidate to formulate the aim and tasks of the research in an argumentative, clear and precise way.

2. Evaluation of results

The results of the study are clearly presented in 20 figures and 2 tables. The number of the experimental animals and the many parameters studied allows the doctoral candidate to make an in-depth analysis of the data. Dr. Dobrinka Doncheva demonstrated the ability to interpret the facts reflecting the influence of different ligands of cannabinoid receptors on the learning and memory processes of olfactory bulbectomized rats. By using two cannabinoid ligands: a CB-agonist and a CB1-antagonist, Dr. Doncheva draws logical conclusions about the involvement of cannabinoid receptors in exploratory behaviour and locomotor activity, learning and memory in rats. It has been shown that subchronically i.c.v. applied, CB-agonist shows an antidepressive-like effect and normalizes the OBX-induced disturbances in exploratory activity and memory, while the 7 day i.c.v application of CB1-selective antagonist aggravates the hypermotility and impairs memory of OBX rats. The time interval and the different route of application of the CB1-antagonist are important for the manifestation of the Rimonabant effects on learning and memory processes in OBX-rats - deterioration with intracerebroventricular and improvement with intragastric application are observed.

The results of the study are significant, informative, critically evaluated and summarized. They are presented in three publications related to the dissertation and five participations in scientific forums, which meet the requirements of the Regulations for the development of the academic staff at MU-Varna.

3. Evaluation of contributions

A comprehensive and original experimental study using cannabinoid receptor ligands was performed. The results obtained by Dr. Dobrinka Doncheva in the OBX model and the conclusions formulated, have an indisputable contribution. It has been confirmed

that cannabinoid receptors are involved in learning and memory processes, as well as in the development of depressive-like state in OBX rats.

An original contribution of the dissertation is the established opposite influence of the ligands of the cannabinoid receptors on the learning and memory in Sham-operated and OBX rats, and the fact that activation of cannabinoid receptors has an antidepressant-like effect in the OBX model. It has been found that intragastric application of CB1-antagonist improves learning and memory processes in the OBX model and that the time interval of application of the CB1-antagonist is important and affects the behavioral deficits in the OBX model. I accept that the results contribute to further elucidation of the role of cannabinoid receptors in learning and memory processes.

In my oppinion, the dissertation contains a scientific and scientific-applied results. The data obtained contribute to the understanding of the role of ECS in the complex processes of learning and memory.

I have no significant critical remarks on the dissertation.

4. Conclusion

The dissertation „INFLUENCE OF SUBCHRONICALLY APPLIED LIGANDS OF CANNABINOID RECEPTORS ON LEARNING AND MEMORY PROCESSES IN OLFACTORY BULBECTOMIZED RATS" by Dr. Dobrinka Kalinova Doncheva is an in-depth experimental study and treats a relevant and poorly studied problem. The obtained results fully correspond to the aim and the scientific tasks.

I give my **positive assessment** and I would like to propose to the esteemed Scientific Jury to award the educational and scientific Degree "DOCTOR (Ph.D.)" to Dr. Dobrinka Kalinova Doncheva in the scientific speciality "Animal and Human Physiology".

17.03.2022
Varna

Assoc. Prof. Irina Pashalieva, MD, Ph.D

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