

OPPONENT'S REVIEW

Title of the dissertation thesis: The role of ghrelin signalling in the neurobiological mechanisms of rewarding effects of cannabinoids and opioids

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Dissertation thesis of dr. Chrysostomos Charalambous summarizes the results of his experimental work during his study of Addictology. The structure and length of the thesis are standard; the main text consists of approximately 60 pages and 170 references covering both recent and historical scientific literature.

The thesis is well-written, and the structure is easy to follow. The theoretical part explains the public health risks, regulatory principles, and epidemiology of drug abuse. The text further elaborates on the neurobiology of addiction, paying particular attention to cannabinoids and opioids. Finally, ghrelin involvement in cannabinoid and opioid addiction is described in detail, focusing on the therapeutic potential of ghrelin receptor antagonists.

The thesis has a well-supported theoretical background. However, the hypotheses and aims are not differentiated. Therefore, asserting that the thesis fulfilled its aims is not formally possible. The hypotheses are formulated rather as aims and reflect the results' structure. The results are nicely described and easy to follow.

The discussion is balanced, detailed, and well supported by the results and available literature. The conclusion adequately summarizes the results and their significance.

The papers which provide the base for the thesis are numerous and published in excellent Journals. A significant contribution of Chrysostomos to the experimental results is evident - he is the first author in two papers and the second author in another three. Despite his position as a Ph.D. student, he could generate an impressive citation record (currently 76 citations, 56 without self-citations, and an H index of 5).

From the formal point of view, I have a remark regarding the first pages of two papers inserted after the list of thesis-related publications. This annex is not mentioned anywhere, and it is unclear why these two papers were included. Similarly, the graphs used in the Results are likely

those published, and it would be fair to cite the source publications. Chapter 5, "Experimental methods used in preclinical addiction research," mentions only in vivo microdialysis and the LABORAS system. This part either belongs to methods or does not cover the topic described by the title.

The quality of the scientific content in the thesis is undeniable. The experiments were well-designed and revealed new evidence regarding the potential therapeutic effect of JMV2959 in drug addiction.

I have the following questions:

JMV2959 decreased drug intake as well as food intake. Can you comment on the effect on food intake? Should not the effect be specific for drugs independently of food? Is there a dose dependency?

It seems, that GHS-R1A exert a very similar effects in experiments using a variety of drugs of abuse. Do you find any major differences in regard to the potential efficacy for treatment of addiction to different substances?

Can you elaborate on the clinical evidence of the therapeutic effects of GHS-R1A in addiction? What will be the next step in your research on the therapeutic potential of JMV2959 in drug addiction?

PharmDr. Chrysostomos Charalambous showed extensive knowledge of the field of addiction and the ability to perform experimental studies and report their results independently. The scientific content of the thesis is excellent and brings new promising evidence in the field of treatment of drug addiction. Therefore, I do recommend the dissertation thesis for public defense as a basis for the successful termination of the doctoral study and awarding the Ph.D. degree.

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