

Prague, May 4, 2021

Review of the Ph.D. dissertation of Michaela Dvořáková, MSc.

The doctoral dissertation of Michaela Dvořáková, MSc., entitled “Molecular mechanism of Cannabinoid receptor 1 regulation by SGIP1” has been submitted at the Second Faculty of Medicine of Charles University, to the doctoral committee of the Biochemistry and Pathobiochemistry in 2021. This review has been written for the doctoral committee for the defense of this Ph.D. thesis. Hereby, I declare that I have written the review based on my best expertise and conscience and I do not have any financial or other interest in the result of the procedure.

The thesis has a form of “full dissertation”, i.e., a self-standing document (as opposed to a “compact form”). It consists of two peer-reviewed papers published in very renowned international journals with impact factor, co-authored by the applicant (the required first-authorship paper has been published in 2021). It consists of an introduction of approximately 20 pages, an overview of theoretic background and state of the art, followed by the specification of the aims of the dissertation. After the statement of the goals, a methods used in the thesis are comprehensively provided, allowing for possible replication of the studies. The results section clearly describes the findings obtained by the applicant, supervisor, and their team. A discussion section critically evaluates the findings obtained in the context of current literature and knowledge and conclusions follow. The thesis is closed by the list of papers related to this thesis and other published papers of the candidate and a list of more than 193 cited references, with the original reports prevailing over reviews. The thesis is accompanied by four already published papers in very sound journals, namely British Journal of Pharmacology (first authorship paper; IF = 7.7), Neuropharmacology (co-authorship paper; IF = 5.0), and two papers (not directly related to the thesis) in the Molecular Pharmacology (IF = 3.9) and Neuropharmacology. The total impact factor of all published papers is 21.7, which I evaluate as excellent. Most of the journals are in the Q1 of the IF and AIS.

In detail, the Introduction section clearly presents the knowledge on cellular signaling via G-protein-coupled receptors (GPCR), G-proteins, discusses the processes of GPCR desensitization and internalization, and the concept of biased signaling. Subsequently the Introduction presents previous results on the role of endocannabinoid-mediated regulation of synaptic communication, especially those mediated by cannabinoid 1 type receptor (CB1R), and effects on synaptic plasticity phenomena such as depolarization-induced suppression of neurotransmission, metabotropic suppression

neurotransmission to long-term potentiation (LTP) and long-term depression (LTD)?

5. Do you think that your findings could stimulate the applied research with aim to use SGIP1 as critical modulator of CB1R function as drugs target in e.g. potentiating antinociceptive effects or CBR ligands or treating cannabis dependence treating? What do you think about the controversial issue of therapeutic use of cannabis in general?

Due to all assets and qualities of the present work, I recommend its evaluation in the council's defense of a Ph.D. degree, and I support awarding Ms. Michalea Dvořáková with a Ph.D. degree, with a high level of enthusiasm.

Ales Stučhlik, PhD, DSc.

Full Professor of Animal Physiology

Institute of Physiology of the Czech Academy of Sciences, Prague