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UNIVERSITÄT BONN



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To the Senate of the Medical University
of Bialystok

Institut für
Molekulare Psychiatrie

Venusberg-Campus 1, Geb. 76
53127 Bonn
Tel. 0228/6885-317
Fax 0228/6885-301
abilkei@uni-bonn.de

Sekretariat:
Anne Zimmer
Tel. 0228/6885-300
neuro@uni-bonn.de
www.molpsychiatrie.uni-
bonn.de

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**Evaluation of the doctoral dissertation of Mr. Patryk Remiszewski
entitled: "Evaluation of the potential therapeutic significance of
chronically administered cannabinoids in experimental models of
arterial and pulmonary hypertension in rats"**

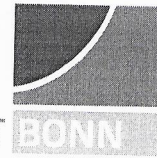
This evaluation follows the invitation of Prof. Dr. Wojciech Miltyk, Dean of the Faculty of Pharmacy of the Medical University of Bialystok to review the doctoral dissertation submitted by Mr. Patryk Remiszewski. I am honored to accept this nomination and present my report here.

The medication of hypertonia and especially pulmonary hypertonia is far from satisfying therefore there is a big need for new therapeutic approaches. In this doctoral thesis Mr. Remiszewski provided an overview and new results about the efficacy and potential therapeutic value of cannabinoids in the treatment of both forms of hypertonia. Although some encouraging results with cannabinoids on isolated organs and in *in vivo* experiments after acute administration was published a clear evidence about the possible application of these compounds in these pathologies was missing. The works of Mr. Remiszewski now made the picture clearer and indicates the direction of further research in this field



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Structure and style



The PhD thesis is based on the summary of 3 published original papers with the first authorship of Mr. Remiszewski: 2 research papers and 1 review. The 3 pages long introduction gives an overview about the most important aspects of the dissertation: arterial and pulmonary hypertension, experimental models of hypertension and cannabinoids. The length of the study aim chapter is a bit more than 1 page followed by the 2 and half pages long, well-illustrated material and methods section. The result section covers 5 pages followed by the conclusions summarized as 3 bullet points. The References chapter is followed by the one and half pages long summaries in English and Polish. The attached publications are integral part of the dissertation because the applicant refers several times in his thesis to the illustrations or tables in these publications.

Goal of the work

The aim of the dissertation is exceptionally well introduced, not just a listing of the relevant information but a clear and nicely illustrated, I would say "digested" interpretation of the relevant literature. I really appreciated the chapter for the discussion and critical presentation of animal models of hypertonia – an important but often neglected topic. The applicant did quite a good job also with the introduction of cannabinoids. This is a notoriously "slippery" field, because under the name cannabinoids are substances which have a similar structure as the bona fide endocannabinoids – arachidonylethanolamid (AEA) and 2-arachidonoylglycerol (2-AG) but do not bind the classical cannabinoid receptor type-1 and type-2 but also compounds – synthetic or with plat origin – which structure largely differs from the structures of 2-AG or AEA but do bind the CB1 or CB2 receptors. Mr. Remiszewski invested a lot to give a concise overview to explain the diversity of cardiovascular effects of this principally heterogenous group. Probably information about the localization of the classical and non-classical cannabinoid receptors in this introduction would help the reader to understand - and to the applicant to explain easier - the variety of cannabinoid effects. Nevertheless, the questions asked were clear and logical. Considering the big need to broaden the pharmacological repertoire against arterial hypertonia to reduce the frequency of therapy-resistant cases and for the effective treatment of pulmonary hypertonia the topic of the dissertation is highly relevant. The actual

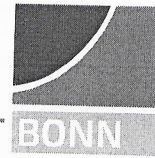
questions as numbered points were rather technical, but they were well supported and incorporated in the context of problematic in the previous parts of this chapter. For the research papers, the author used "gold standard" methods of the field, whereby the treatment design was more advanced as usual. What I most liked is the review paper: it is far above the general level and reflects the deep understanding of the applicant of his field.

Methods

Considering that the cumulative nature of the thesis gives the essence of the methods and not a detailed description of them, this part is exceptionally good. Here, the illustration is a big help to get a direct overview about the study setup and about the administration protocols. The only point I did not understand in the study protocol why positive control was not used – especially in the study with CBD, where no significant effect was found. It was definitely not easy to pick which methods to present here and which could be only referred, but the applicant did a good job although I probably would not send much words to the exact description of anesthesia. Nevertheless, a table or at least a reference to the statements at the end of his thesis (Chapter 13) would be helpful to clarify here which part of the study was technically performed by Mr. Remiszewski and which was done by other contributors. I also checked the case numbers in the study with CBD, where an underpowered study could potentially lead to a false negative effect. This information was not present in the thesis but in the attached publication.

Results and Discussion

This section provides an excellent overview of the most significant findings of his 3 papers. For the research papers, the interpretation of the results show the deep understanding of the applicant of the area, it is refreshingly free from the usual listing of findings. I especially liked the explanation of the applicant about the lack of efficacy of CBD. For sure, there are also alternative explanations but it was also a nice logical one. It would be great to learn what the applicant thinks about the validity of the models used, what he thinks about the possible alternative hypertension models or treatment protocols to answer his questions. The illustrations – as in all other parts of the dissertation – are exceptionally useful



and give a good summary. It is especially true for Figure 4 where quite a complicated study output was visualized and explained in a good way. The discussion of the review paper is a bit short, although it deserved a longer one. A review generally gives only an overview about the relevant findings, but this one provided a new, unexpected information about the importance of target specificity of cannabinoids in the treatment of arterial hypertension and the multitarget effect in the treatment of pulmonary hypertension. To consider the data interpretation I checked also the statistical analysis in the attached publications and the selection of statistical methods - their interpretation was all correct. The final conclusions were also proper, and these were definitely backed by the experimental results. Nevertheless, considering that only one dose, one treatment regime was used, potential alternative interpretations could be also considered. Because this thesis deals with a potential therapeutic use of cannabinoids, their addictive potential should be also mentioned and the lack of this effect in case of the peripherally active JD5037 and CBD emphasized.

The conclusion part is short, but perfect: the points in the aims and as a response the points in the conclusion provide a clear and excellent frame for the whole work.

Literature

Although the review article contained – as expected – an exhaustive list of literature, a proper literature list was added also to the thesis. I appreciated that most of the cited works were quite recent showing that the applicant followed the literature and incorporated in his work the latest findings. I missed from the literature (maybe due to my personal interest) the cannabinoid-related citations, because the citations were restricted to works about the cardiovascular effect of cannabinoids.

Recommendation

The dissertation written by Mr. Patryk Remiszewski is at an exceptionally high level. The applicant showed his ability to perform good science, his knowledge of this particular area and most importantly his logical thinking. He made an excellent overview from his works and perfectly summarized the essence of his

findings also in the mirror of the literature. The points I raised as critics do not diminish the values of this thesis, the quality of the dissertation definitely complies with requirements for a PhD thesis. Therefore, I am happy to recommend the Senate of the Medical University of Bialystok to grant Mr. Patryk Remiszewski a doctoral degree in the field of medical sciences and health sciences in the discipline of pharmacology and pharmacy.

Moreover, considering the quality of the dissertation and the publications of Mr. Remiszewski I recommend to give the doctoral degree with distinction.

Kind regards

Bilkei-Gorzo

Andras Bilkei-Gorzo, PhD, PD