

HABILITATION THESIS REVIEWER'S REPORT

Masaryk University	
Faculty	Faculty of Medicine
Procedure field	Medical Pharmacology
Applicant	Mgr. MVDr. Leoš Landa, Ph.D.
Applicant's home unit, institution	Department of Pharmacology – Faculty of Medicine, Masaryk University
Habilitation thesis	The effect of selected psychotropic substances on behavioural sensitization to methamphetamine in animal models
Reviewer	Prof. Dr. rer. nat. Thomas M. Tzschenke
Reviewer's home unit, institution	Grünenthal GmbH, Global Innovation, Zieglerstr. 6, 52078 Aachen, Germany <i>and</i> RWTH Aachen University, Institute of Biology II, Aachen, Germany

Drug abuse and addiction is a major medical and societal problem. Addiction is a complex phenomenon in humans, and consequently, it is difficult to model in animals.

Behavioral sensitization is a relatively simple model, but is considered to have a good degree of construct validity for human addiction (based on the seminal work by Robinson and Berridge, 1993). The selection and exploration of this model for the presented habilitation work is therefore an appropriate one.

Dr. Landa selected a relatively narrow topic (the effect of psychotropic drugs on methamphetamine sensitization), but addressed this topic from different methodological angles to provide an in-depth analysis.

The main part of the work was done using behavioural sensitization as measured by locomotion in an open field. In an additional approach, analysis of agonistic behaviour was also used. These behavioural data are supplemented by *in vitro* analysis of brain cannabinoid and dopamine receptor mRNA expression in drug-treated animals.

Although being one of the psychostimulants with the highest addictive potential, methamphetamine receives less attention in preclinical scientific research as compared to amphetamine or cocaine. Dr. Landa has provided a very comprehensive volume of work addressing the question of how the behavioural effects of methamphetamine can be modulated (and, possibly, eventually ameliorated) by pharmacological means. Treatment of addiction and the attenuation of the acute effects of drugs of abuse is an important issue in the field of medical pharmacology, and as such, the present thesis makes a valuable contribution to this field.

The thesis is made up by a brief introduction on the phenomenon of sensitization, and the compounds and methods used in the studies. The main part of the thesis consists of a collection of 9 published original articles, along with further articles in the appendix.

The research rationale and the aims of the conducted research is well laid out in the respective chapter.

The main findings from the annotated papers are nicely summarized in the Results section, and each of the papers is preceded by a short summary and interpretation. The annotations in toto provide a good overview of the research that has been conducted. However, I would have found it helpful to have an overarching summary and, in particular, discussion of the overall findings presented in this thesis. (This is my personal view. I am not familiar with the general template of habilitation theses at Masaryk University, and maybe a general/overall discussion is not foreseen in the overall layout.) Of course, each paper contains a very appropriate discussion, but an overarching discussion across different, topically related papers would have been easier to digest (e.g. for papers 1,2,3,9, papers 4+5, papers 6+7). Especially the question of how cannabinoids may influence the consumption of other drugs (i.e. to what extend they may act as a gateway drug) is hotly debated, and the relevance of the present findings for this discussion could have been elaborated a bit more. On the other hand, this is also a highly controversial political question, and I appreciate that Dr. Landa offers a conservative, if short, interpretation firmly based on his experimental findings. I therefore refrain from suggesting a respective question for the defence.

One interesting aspect of the presented work is that in the studies addressing the influence of glutamatergic and dopaminergic drugs, compounds are used as tools that are actually in clinical use or have been in clinical use (memantine, felbamate, sertindole). Working with clinically used drugs, rather than with experimental research tools, automatically increases the clinical relevance of the research, as a potential translation from preclinical to clinical situation would be much more straightforward. This is particularly relevant for a work that is evaluated by a medical faculty in the field of medical pharmacology.

The 9 annotated papers as core part of the habilitation thesis appear to have been carefully and reasonably selected from a much longer list of publications of Dr. Landa. The complete publication list shows his scientific proficiency and productivity. I appreciate that he as a trained behavioural pharmacologist, embarked on PCR analysis to complement his behavioural data with receptor (RNA) expression data. Combining methodologically different approaches not only broadens methodological skills but is also at the core of significant scientific advancements.

Taken together, in my opinion the presented habilitation thesis makes a substantial and relevant contribution to the field of Medical Pharmacology and demonstrates that Dr. Landa is a well-established scientist in the field.

Reviewer's questions for the habilitation thesis defence (number of questions up to the reviewer)

- While the thesis focusses on behavioural sensitization to methamphetamine, Dr. Landa has also done some work on MDMA and morphine sensitization. Could he comment on commonalities and differences in sensitization between different psychostimulants (e.g. methamphetamine vs. amphetamine, MDMA vs. cocaine), and between psychostimulants on the one hand, and opioids on the other hand? To what extent could his findings on methamphetamine sensitization be generalized to cocaine or morphine sensitization?
- Does Dr. Landa have any explanations for the observed difference between mouse and rat regarding the cross-sensitization between methamphetamine and cannabinoids?
- Does Dr. Landa have any explanations for the observed difference between the effects of felbamate and memantine on methamphetamine sensitization (both being glutamatergic drugs)?

Conclusion

The habilitation thesis entitled "The effect of selected psychotropic substances on behavioural sensitization to methamphetamine in animal models" by Mgr. MVDr. Leoš Landa, Ph.D. **fulfils** the requirements expected of a habilitation thesis in the field of Medical Pharmacology.

Date:

Signature:

05. 06. 2019