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Dissertation thesis report

Thesis title: Effects of endogenous NMDA receptor modulators on neuronal morphology and synaptic plasticity

Author of the thesis: Pascal Michel Samir Jorratt Callejas

The thesis, comprising 91 pages (64 pages Abstract, Introduction, Aims, Methods, Results, and Discussion), is based on two original publications. The project had four main objectives:

- (i) To evaluate the morphological changes of excitatory and inhibitory neurons induced by endogenous NMDA receptor modulators.
- (ii) Evaluate the synaptic changes of excitatory/inhibitory neurons induced by endogenous NMDA receptor modulators.
- (iii) Determine the protein expression and activation of the BDNF/TrkB/ERK pathway.
- (iv) Investigate the potential antidepressant-like effect of the most promising endogenous NMDAR modulator in a chronic despair model in mice.

The introductory section of the thesis (25 pages) provides an overview of the structure and pharmacology of NMDA receptors. This section is accessible and provides comprehensive information on channel structure, characterization of subtypes, and their modulation by endogenous modulators with a particular focus on kynurenic acid, neurosteroids, polyamines, and zinc. A portion of the text is dedicated to the role of NMDA receptors in psychiatric disorders. However, this section is relatively brief and only provides a cursory examination of the relationship between NMDAR dysregulation and neuropsychiatric disorders.

The objectives of the study are clearly defined. The methodology section is concise and focuses on the methodological approach used, which encompassed molecular, anatomical, and behavioral aspects. As Mr. Jorratt's results have already been published in seven original publications, two of which were used to prepare his thesis, the results section is brief and includes only the most significant findings. The discussion is divided into six main chapters, each reflecting one of the study's objectives.

I was particularly impressed by the breadth of topics studied, which ranged from the biochemical, morphological, and behavioral effects of endogenous compounds with modulatory action on NMDA receptors. Given thesis's concise format, I will also keep the report to a minimum.

Conclusion: The present dissertation contains results obtained mainly by challenging biochemical, pharmacological, and behavioral methods that have significantly advanced the scientific understanding of the control of NMDA receptors by endogenous compounds. Mr. Jorratt's results also provide information that can be used to develop new strategies for the treatment of neurological diseases. Given that the author has demonstrated his ability to address

experimental questions of basic research at a professional level using modern experimental methods in the submitted dissertation, I recommend that Mr. Pascal Michel Samir Jorratt Callejas be awarded the degree of Doctor of Philosophy.



In Prague 17.5.2024

Prof. Ladislav Vyklický

Questions:

1. In the section titled "Aims of the Study," you hypothesize that inhibition of NMDAR could elicit antidepressant-like effects. Could you please provide a rationale for the use of pregnenolone sulfate (PS), a neurosteroid that has a potentiating effect at NMDARs?
2. Please elucidate the anxiolytic-like effect of PS. Additionally, please describe the effect of NMDAR modulators on the possible anxiolytic/anxiogenic effect. It is curious that PS had only a small behavioral effect. From the perspective of rapid metabolism (Abramova et al., ACS Chem. Neurosci. 2023, 14, 1870–1883), I speculate that PS is metabolized to pregnenolone, or that PS does not penetrate the BBB. Have you conducted a control experiment with the administration of pregnenolone?
3. Are there other arguments, apart from the effect of ketamine, that link depression and NMDARs? What effect does ketamine have in the model of chronic despair model in mice?
4. What neuropsychiatric diseases are directly linked to NMDARs, and by what mechanism?