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Dissertation thesis report

Thesis title: T-type calcium channels in neurological disorders


Author of the thesis: Robin Stringer

The thesis of 120 pages (69 pages Abstract, Introduction, Aims, Methods, Results, and Discussion), is based on 7 original publications. The project focused on three main objectives: (i.) regulation of T-type channel expression, (ii.) T-type channelopathies associated with neurological disorders, and (iii.) drugs targeting T-type channels.

The introductory part of the thesis (35 pages) summarizes information about voltage-gated calcium channels. This section is easy to read and gives detailed information on channel structure, characterization of subtypes, their distribution in organs, molecular structure and regulation. An important section is devoted to channelopathies. The aims of the work are well defined. The methods section is condensed and focuses on the methodological approach used in each publication. As Mr. Stringer's results have already been published in 7 original publications, he has decided to present the thesis in an abbreviated form. Therefore, the results section is concise and includes only the most important results for each paper. The discussion is divided into three main chapters reflecting the three objectives (defined above).

I was really impressed by the breadth of topics studied, ranging from the biophysical study of the potential role of glycosylation sites, the role of regulatory proteins, channelopathies associated with certain neurological disorders, and the characterization of compounds targeting T-type channels. Since the thesis is presented in an abbreviated form, I will also keep the report to a minimum. Congratulations, I really enjoyed reading it.

Conclusion: The present dissertation contains results obtained mainly by challenging biophysical and molecular biology methods that have significantly advanced the scientific understanding of voltage-gated calcium channels and the role these channels play in neurological disorders. Mr. Stringer's results also provide information that can be used to develop new strategies for the treatment of neurological diseases. Since in the submitted dissertation the author has demonstrated that he can address experimental questions of basic research at a professional level using modern experimental methods, I recommend that Mr. Robin Stringer be awarded the degree of Doctor of Philosophy.



In Prague 28.2.2024

Prof. Ladislav Vyklický

Questions:

1. Patch clamp data obtained when studying missense variants of voltage-gated calcium channels could be used to determine regional intolerance to the mutation. This or the opposite “missense tolerance ratio”, can be used as an indicator of the ability of the polypeptide chain to tolerate changes without compromising protein function in a way that affects human health. Do such maps of tolerated/intolerable 3D structure exist for voltage-gated calcium channels? Are there common structural features?
2. For some ion channels missense (complete loss of function) and nonsense variants have shown to have quite different behavioral consequences. This raises the question of possible compensatory changes. Are there compensatory changes in the case of missense/nonsense variants of voltage-gated calcium channels?
3. Is there a genetic approach that could correct for some voltage-gated calcium channel variants?