Chemical biological dissection of Ca2+ entry through Ca2+ channels

https://www.neurodegenerationresearch.eu/survey/chemical-biological-dissection-of-ca2-entry-through-ca2-channels/

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USA

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Chemical biological dissection of Ca2+ entry through Ca2+ channels

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NIH (NINDS)

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01/08/2016

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1

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract

DESCRIPTION (provided by applicant): One type of voltage-activated Ca2+-permeable ion channel, known as CaV1.3, is emerging as a preeminent Ca2+ entry pathway into neurons residing at the epicenter of brain rhythmicity and neurodegenerative disease. The lower transmembrane voltages required to open CaV1.3 allow these channels to contribute importantly to pacemaking and subthreshold voltage fluctuations. CaV1.3 channels thus

constitute a dominant Ca2+ entry module into many neurons undergoing oscillatory and subthreshold activity. Nowhere is this Ca2+ entry function more salient than in substantia nigral neurons, where CaV1.3 channels furnish the lion’s share of Ca2+ entry, while driving rapid pacemaking essential for movement control. Notably, degeneration of substantia nigral neurons is central to Parkinson’s disease (PD), and intracellular Ca2+ dysregulation and overload are crucial to PD pathogenesis. Accordingly, a highly promising avenue for novel PD therapeutics involves the burgeoning search for small molecules that selectively inhibit the opening of CaV1.3 channels. Yet, comparatively little is known about the mechanisms controlling the open probability PO of CaV1.3 channels. Ongoing small-molecule screens thereby rely on rank empiricism, largely bereft of known channel interfaces to which drug binding would likely alter opening. Multiplying the challenge is the recent discovery that CaV1.3 channels are not monolithic, but comprised of numerous RNA-edited and splice variants, each with potentially distinct effects on the open probability PO of channels. The mechanism underlying variant-related PO modulation is currently obscure. Additionally, GPCR-mediated changes in the plasmalemmal lipid PIP2 powerfully regulates PO, but it is unknown how this occurs, and how it relates to edited/splice variation. Together, the mechanistic void relating to these two systems precludes quantitative understanding of how Ca2+ entry through these channels contributes to pathogenesis, and obscures the path to rational small-molecule screens for CaV1.3 modulators. Yet, forward progress has proven difficult by traditional means alone. This project thus proposes to clarify CaV1.3 PO modulation by melding electrophysiology with novel chemical-biological and live-cell FRET tools. Overall, this proposal promises elegant clarification, simplification, an unification of seemingly diverse mechanisms of CaV1.3 PO modulation; identification of channel interfaces that could be targeted for discovery of small-molecule PO modulators; and new chemical-biological and FRET-based tools of wide applicability.

Lay Summary
PUBLIC HEALTH RELEVANCE: CaV1.3 calcium channels are emerging as a preeminent Ca2+ entry pathway into neurons residing at the epicenter of brain rhythmicity and neurodegenerative disease. Accordingly, understanding how the opening of these channels is modulated, and discovering small molecules that selectively inhibit such opening, both present as crucial dimensions for novel therapeutics. Here, we will devise chemical-biological and live-cell FRET-based tools to clarify the sought-after modulatory mechanisms and identify channel interfaces that could be targeted for small-molecule drug discovery.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

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