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T-type calcium channels in neurological disorders

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Abstract

This thesis provides a comprehensive exploration of Voltage-gated Calcium Channels (VGCCs), with a particular focus on T-type channels and their role in cellular physiology. It delves into the crucial function of VGCCs in controlling calcium ion influx during membrane depolarization, highlighting their importance in neurons. VGCCs are classified into two different subtypes, including T-type (low voltage activated) and high voltage activated channels (N-, L-, R-, P/Q-type), each with distinct functions and roles. One focus of this thesis was on the regulation of T-type channel expression, examining the impact of post-translational modifications and trafficking proteins, notably non-canonical N-glycosylation sites and SCAMP2, on channel trafficking and surface expression. In the context of neurological disorders, the research links T-type channels to conditions such as ALS, DEE, PDN, and TN, investigating the functional effects of *CACNA1H* gene variants, including ALS-associated loss-of-function and TN-associated gain-of-function variants in $Ca_v3.2$ channels. The final part of the thesis is dedicated to the development of new drugs targeting T-type channels, with a spotlight on S13, a novel quinolone-based VGCC blocker, demonstrating its efficacy in preclinical models of neuropathic pain. Overall, the thesis provides a detailed understanding of T-type channels, their regulatory mechanisms, involvement in diseases, and potential as therapeutic targets, underscoring their importance in various physiological systems and roles in neurological disorders.

Keywords: Ion channel, Calcium channel, T-type channel, Glycosylation, SCAMP2, Trafficking, Diabetes, Amyotrophic lateral sclerosis, Epilepsy, Encephalopathy, Trigeminal neuralgia, Pain, Mutation, Channelopathy, Quinoline, Neurons, Biophysics

1 Background

1.1 Voltage-gated Calcium Channels

Voltage-gated Calcium Channels (VGCCs) are essential modulators in cellular physiology, controlling the influx of calcium ions in response to membrane depolarization (Catterall 2011). This influx is a pivotal in a variety of cellular activities, particularly in excitable cells like neurons and muscle cells. In muscle cells (cardiac, skeletal, and smooth), VGCCs facilitate the crucial process of excitation-contraction coupling (Cooper, Soeller, and Cannell 2010). They translate electrical signals into mechanical muscle contractions. In neurons, VGCCs play a pivotal role at presynaptic terminals, enabling rapid neurotransmitter release, which is fundamental for neural communication (Reid et al. 2004; Cao et al. 2004). They also contribute to synaptic plasticity by activating gene expression, a process crucial for learning and memory (Dolmetsch et al. 2001). In endocrine cells, VGCCs trigger hormone secretion and activate various calcium-dependent enzymes, influencing metabolic and physiological processes (Comunanza et al. 2010).

VGCCs are classified into several types based on their response to voltage changes and pharmacological properties. These include T-type (low voltage activated), and high voltage activated channels such as N-, L-, R-, and P/Q-types (Catterall et al. 2005). Each type possesses distinct physiological functions and is involved in different cellular processes. T-type channels are especially important in regulating cellular excitability due to their activation near resting membrane potentials (Bean 1985).

High Voltage Activated (HVA) calcium channels consist of complex structures with multiple subunits. The central pore-forming subunit $Ca_v\alpha1$, along with auxiliary subunits $Ca_v\alpha2\delta$, $Ca_v\beta$, and $Ca_v\gamma$, forms the functional HVA channel (Curtis and Catterall 1984; 1986). The $Ca_v\alpha1$ subunit is particularly significant,

composed of four homologous domains and six transmembrane helices. This subunit plays a major role in defining the channel's specific properties and is crucial in determining the subtype of calcium channel(Catterall et al. 2005; Catterall 2000). In total, there are ten known calcium channel α1 subunits, classified into three families: Ca_v1, Ca_v2, and Ca_v3 (Perez-Reyes 2003; Catterall et al. 2005). These families are associated with different cellular functions and are finely regulated by various mechanisms, which impact their biophysical properties and their expression on the plasma membrane (Arikkath and Campbell 2003).

1.1.1 HVA Distribution and Function

HVA channels constitute the majority of VGCCs and are integral to numerous physiological processes. The Ca_v1 family channels, for example, are involved in linking depolarization of the plasma membrane to cellular responses such as muscle contraction, neurotransmitter release, and hormone secretion (Armstrong, Bezanilla, and Horowicz 1972; Numa et al. 1990; Coetzee 1988; Bers 2002; Kollmar et al. 1997; Braun et al. 2009; Vandael, Marcantoni, and Carbone 2015; Barnes and Kelly 2002). These channels are thus crucial in mediating the physiological response of cells to electrical stimuli. The $Ca_v2.1$ channels, abundant in the nervous system, are essential for neurotransmitter release, influencing synaptic efficiency and neural communication (Sutton et al. 1999; Hoxha et al. 2018; Folacci et al. 2023; Alehabib et al. 2021). $Ca_v2.2$ channels, localized primarily in neuronal tissues, mediate the release of neurotransmitters and the transmission of sensory information, playing a significant role in the sensory processing and pain perception (Nowycky, Fox, and Tsien 1985; Weber et al. 2010; Bourinet et al. 2014). $Ca_v2.3$ channels, predominantly found in the central nervous system, are involved in various functions such as synaptic plasticity, pain modulation, and motor coordination (Metz et al. 2005; Tai, Kuzmiski, and MacVicar 2006; Dietrich et al. 2003; Osanai et al. 2006; Saegusa et al. 2000; Breustedt et al. 2003).

1.1.2 T-type calcium channels

T-type calcium channels are a unique subset of VGCCs, characterized by their activation at relatively lower voltage thresholds compared to other VGCCs (Hagiwara, Ozawa, and Sand 1975). They are widely expressed throughout the body, including in nervous tissues, heart, kidneys, smooth muscle, reproductive cells, and glands (Perez-Reyes and Schneider 1994; Perez-Reyes 2006; Talley et al. 1999). These channels are particularly important in regulating the dynamics of neuronal networks, contributing to various neuronal activities such as pacemaking and the propagation of subthreshold synaptic potentials (Mesirca, Torrente, and Mangoni 2014; Perez-Reyes and Schneider 1994).

1.1.2.1 Molecular Structure and Biophysical Properties

T-type channels are encoded by individual genes that give rise to $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$ channels (Cribbs et al. 1998). Each type exhibits unique inactivation speeds and activation thresholds, contributing to their specific roles in cellular physiology (Edward Perez-Reyes and Schneider 1994). Structurally, T-type channels resemble other VGCC family members but function independently without auxiliary subunits (Perez-Reyes 2006). Their activation in response to small depolarizations makes them active at more negative membrane potentials, influencing neuronal activity, and contributing to the generation and propagation of electrical impulses within the nervous system (Chemin et al. 2002).

1.1.2.2 Tissue Distribution and Physiological Functions

T-type channels are integral in both the central and peripheral nervous systems (Talley et al. 1999). They enhance subthreshold excitatory potentials in neurons, regulate the timing and generation of action potentials, and contribute to neuronal oscillations, particularly during sleep rhythms (Crandall, Govindaiah, and Cox 2010; Kim et al. 2001; Hughes et al. 2002). Their presence in cardiac tissues

influences cardiac pacemaking and in vascular smooth muscles, they play a role in controlling vascular tone (Mesirca, Torrente, and Mangoni 2014; Cazade et al. 2017). Additionally, T-type channels are involved in hormone secretion and immune cell functions, demonstrating their broad physiological significance (Mahapatra et al. 2012).

1.1.2.3 Regulation of T-type channels

T-type channels are intricately regulated by various interacting proteins and post-translational modifications, which influence their expression levels, gating properties, and cellular functions (Weiss and Zamponi 2023). Key regulatory proteins include KLHL1, Spectrin α/β, Ankyrin B, STAC1, RACK1, SNARE, Calnexin, CACHD1, Caveolins, Calmodulin, G-protein β2γ2, WWP1/2, and USP5 (Weiss and Zamponi 2023). These proteins interact with T-type channels in different ways, affecting their trafficking to the plasma membrane, gating kinetics, and sensitivity to physiological signals (Weiss and Zamponi 2023).

1.1.2.4 Channelopathies Involving T-type Channels

T-type channels are implicated in a variety of diseases. Mutations in genes encoding these channels (CACNA1H, CACNA1G, CACNA1I) have been linked to conditions such as primary aldosteronism, epilepsy, chronic pain, autism spectrum disorder, neuromuscular disorders, schizophrenia, cerebellar ataxia, and essential tremor (Weiss and Zamponi 2020). Abnormalities in the expression or function of T-type channels can lead to a range of neurological and psychiatric disorders, underscoring their critical role in brain function and cognition.

1.1.2.5 T-type Channel Drugs

A range of drugs targeting T-type channels are used to treat disorders like epilepsy, hypertension, depression, schizophrenia, and cardiovascular diseases (Melgari et al. 2022; Nam 2018). These drugs modulate cellular activities and physiological

responses by inhibiting calcium entry through T-type channels. The development of drugs targeting T-type channels is a growing field, with ongoing research exploring their potential in treating various disorders.

2 Objectives

This thesis comprehensively explores T-type channels, emphasizing their crucial role in various physiological systems, including neuron activity, heart rate regulation, cancer cell proliferation, and embryonic development. The research underscores the importance of studying T-type channels to address neurological and other disorders.

The thesis is structured into three main parts:

1. **Regulation of T-type Channel Expression**:
    - It discusses the post-translational modifications of T-type channels, which affect their expression and function at the cell membrane. The study investigates the role of non-canonical N-glycosylation and the involvement of trafficking proteins like Secretory carrier-associated membrane proteins (SCAMPs), especially SCAMP2, in regulating T-type channel expression.
2. **T-type Channelopathies Associated with Neurological Disorders**:
    - This section links T-type channels to neurological disorders. It examines the role of *CACNA1H* gene variants or regulatory proteins in these diseases. The thesis explores the functional effects of these variants, particularly their association with amyotrophic lateral sclerosis (ALS), developmental and epileptic encephalopathy (DEE), peripheral diabetic neuropathy (PDN) and trigeminal neuralgia (TN).
3. **Drugs Targeting T-type channels**:
    - The final part highlights the urgent need for new drugs targeting T-type channels, given their association with various disorders. It proposes research aims to explore the effects of surfen derivatives on VGCC activity.

Specific objectives include determining the roles of non-canonical N-glycosylation sites and SCAMP2 in T-type channel expression, ascertaining the functional effects of *CACNA1H* variants in various neurological conditions, and evaluating new potential drug treatments. The thesis positions T-type channels as a pivotal research area for developing treatments for a range of disorders.

3 Methods

1. **Biophysical Characterization (Studies 1-7)**:
    - These studies used patch-clamp recordings in tsA-201 cells expressing $Ca_v3.2$ channel variants and regulatory proteins. The focus was on analyzing the voltage dependence of activation, conductance, and steady-state inactivation, as well as recovery from inactivation, using various mutations and regulatory proteins.
2. **Biotinylation Studies (Study 1)**:
    - This study involved isolating biotinylated proteins from cell lysates using Neutravidin beads, followed by SDS-PAGE and Western blot analysis to detect and analyze the presence of $Ca_v3.2$ and other proteins.
3. **Co-Immunoprecipitation (Study 2)**:
    - This method was used to study the interaction between $Ca_v3.2$-HA and SCAMP2-Myc in tsA-201 cells, employing specific antibodies and magnetic protein G beads.
4. **Western Blot (Study 2)**:
    - This involved separating immunoprecipitation samples and total cell lysates using SDS-PAGE and analyzing them with specific antibodies.
5. **Transcriptomic Analysis (Study 3)**:
    - This study analyzed glycan-modifying enzymes in the dorsal root ganglia of mice, focusing on key genes encoding enzymes for processing various sugars.
6. **Computational Modeling (Study 6)**:
    - The study simulated the firing of thalamic reticular neurons using the NEURON simulation environment, incorporating electrophysiological properties of $Ca_v3.2$ channels.
7. **Cell Toxicity Assay (Study 7)**:

- This assay measured the cytotoxicity of compounds on various human cancer cell lines using the CellTiter-Glo® 2.0 Cell Viability Assay.

8. **Molecular Docking (Study 7)**:
    - The study involved docking simulations using the Schrödinger Docking Suite to analyze ligand-receptor interactions.
9. **Preclinical Efficacy (Study 7)**:
    - This study assessed mechanical allodynia in rats using von Frey filaments, determining the paw withdrawal threshold as an indicator of allodynia.

4 Results

The thesis comprises seven studies, each contributing to the understanding of T-type channels in different contexts. These studies are divided into three parts, focusing on channel regulation and expression, channelopathies associated with neurological disorders, and drug targeting of T-type channels.

Part 1: Regulation of T-type Channel Expression

1. **Study 1: Non-Canonical Glycosylation Motifs in $Ca_v3.2$**
    - Biophysical characterization revealed crucial roles for the N345 and N1780 motifs in $Ca_v3.2$ membrane trafficking, confirmed by reduced channel conductance and surface expression in mutated channels.
    - Biotinylation studies indicated that the reduced current in mutated channels was due to decreased surface expression, not channel dysfunction.
2. **Study 2: Regulatory Properties of SCAMP2 on T-type Channels**
    - Co-immunoprecipitation confirmed a physical interaction between SCAMP2 and $Ca_v3.2$.
    - Electrophysiological analysis showed significant reduction in channel conductance when co-expressed with SCAMP2, implicating SCAMP2 in channel regulation.
    - Western blot analysis suggested a non-significant increase in total $Ca_v3.2$ expression, hinting at a possible role in preventing channel degradation.
    - Intramembrane charge movement measurement indicated changes in channel surface expression and gating regulation due to SCAMP2.

Part 2: T-type Channelopathies Associated with Neurological Disorders

3. **Study 3: Glycan-Processing Genes in Diabetic Mice**
    - Transcriptomic analysis in diabetic conditions showed upregulation of genes encoding glycosyltransferases and sialic acid-modifying enzymes.
    - Functional analysis revealed an unexpected loss of channel function when these enzymes were applied to recombinant $Ca_v3.2$ channels.
4. **Study 4: *CACNA1H* Variants Linked to ALS Patients**
    - Whole genome sequencing identified two heterozygous CACNA1H variants in ALS patients.
    - Electrophysiological analysis of these variants showed a complete loss of function and a dominant-negative effect on the wild-type channel in one variant, and a mild reduction in channel activity in the other.
5. **Study 5: *SCN8A* and *CACNA1H* Variants Associated with DEE**
    - Whole exome sequencing identified variants in *SCN8A* and *CACNA1H*.
    - Patch clamp electrophysiology showed a gain-of-function for the *SCN8A* variant and a loss-of-function for the *CACNA1H* variant.
6. **Study 6: *CACNA1H* Variants Associated with TN**
    - Electrophysiological analysis of several variants revealed gain-of-function changes that could enhance neuronal excitability, potentially contributing to TN.
    - Computational modeling supported these findings, suggesting enhanced neuronal excitability due to these variants.

Part 3: Drugs Targeting T-type Channels

7. **Study 7: Quinolone-Based Calcium Channel Blockers**
    - Patch clamp electrophysiology identified S13 as an effective blocker of VGCC subtypes, including $Ca_v2.2$ and $Ca_v3.2$.

- Cell toxicity assay showed improved cell tolerance for S13.
- Molecular docking analysis predicted direct binding of S13 to $Ca_v2.2$ and $Ca_v3.2$ channels.
- Preclinical efficacy demonstrated significant antinociceptive effects in a rat model.

5 Discussion

The comprehensive research presented in this thesis addresses three critical areas related to T-type channels: their regulation, involvement in neurological disorders, and the development of novel drugs targeting these channels. Each part contributes to a deeper understanding of T-type channels and their potential as therapeutic targets.

Part 1: Regulation of T-type Channel Expression

1. **Non-Canonical Glycosylation in $Ca_v3.2$ Channels**:
    - This study revealed a novel aspect of T-type channel regulation through non-canonical glycosylation sites in $Ca_v3.2$, highlighting their role in the channel's trafficking and expression. The mutations at these sites led to a reduced presence of channels at the cell surface, emphasizing the importance of glycosylation in channel modulation.
2. **Role of SCAMP2 in T-type Channel Regulation**:
    - The discovery of SCAMP2 as a novel regulator of T-type channels underscores its role in cellular processes like membrane trafficking and signal transduction. This study enhances our understanding of T-type channel modulation and points to the importance of SCAMP2 in various physiological and pathological contexts.

Part 2: T-type Channelopathies Associated with Neurological Disorders

3. **Glycosylation and Diabetes**:
    - The study on glycosylation in the context of diabetes and its impact on T-type channels highlighted the complex interplay of glycosylation processes in channel trafficking. The contradictory findings between upregulated glycan-processing genes and reduced $Ca_v3.2$ surface

expression in recombinant systems suggest a need for further investigation in more native conditions.

4. ***CACNA1H* Variants in ALS**:
    - Investigating rare genetic variants in ALS patients revealed varying degrees of loss-of-function in $Ca_v3.2$ channel variants, suggesting the potential impact of these variants on disease pathology. Further research in more native conditions, such as motor neurons, could elucidate the role of $Ca_v3.2$ in neuronal degeneration associated with ALS.
5. ***CACNA1H* and *SCM8A* Variants in DEE**:
    - The study on a child with DEE carrying variants in *SCN8A* and *CACNA1H* provided new insights into the complex genetic underpinnings of the disorder. The contrasting gain-of-function in *SCN8A* and loss-of-function in *CACNA1H* warrant further exploration in neuronal models to understand their combined effects on DEE pathogenesis.
6. ***CACNA1H* Variants in Trigeminal Neuralgia**:
    - The functional analysis of $Ca_v3.2$ variants in TN patients revealed a pattern of gain-of-function, suggesting their potential role in trigeminal pathway sensitization. Further studies on the specific effects of these variants in relevant neuronal populations could provide deeper insights into TN pathology.

Part 3: Drugs Targeting T-type Channels

7. **Development of S13 as a Novel VGCC Blocker**:
    - S13, a novel quinolone-based compound, showed promising results as a broad-spectrum VGCC blocker with significant analgesic potential in a rat model of neuropathic pain. Its efficacy and gender-

independent effects underscore its potential as a novel therapeutic agent for neuropathic pain.

Overall, the thesis presents a multidimensional exploration of T-type channels, from basic regulatory mechanisms to clinical implications in neurological disorders and drug development. This holistic approach not only deepens the understanding of T-type channels but also opens new avenues for therapeutic interventions in diseases associated with these channels.

6 Conclusion

This thesis was focused on three aspects of T-type channels. It includes basic research on the modulation of T-type channel expression with two studies. This is followed by four papers on channelopathies of T-type channels. Finally, focusing on the development of novel compounds for targeting disorders associated with T-type channel dysfunction. What we found was the following:

- We discovered two key non-canonical glycosylation sites required for correct expression of $Ca_v3.2$ to the surface. We also found that two other potential non-canonical glycosylation sites were unnecessary.
- SCAMP2 is a key regulatory protein in the trafficking of T-type channels to the surface, and overexpression of SCAMP2 in a recombinant system displays a varied reduction of channel expression to the surface, dependent on channel subtype.
- Diabetes impacts the glycosylation of $Ca_v3.2$, but we could not find definitive evidence of how this takes place. This was due to the unexpected differences between recombinant expression of glycan-enzymes and phenotypic data in diabetic mice. Further studies in more native conditions would need to be carried out to elucidate the impact of diabetes on glycosylation.
- We identified a LoF in *CACNA1H* variants associated with ALS. This increases the evidence for characterising *CACNA1H* as a susceptible gene in the development of ALS.
- We discovered a GoF in *SCN8A*, consistent with previous studies. We also identified a LoF in *CACNA1H* associated with DEE. A gene that has not been previously linked to DEE. It is unknown what the significance of this variant is to the development of DEE, especially

considering LoF in *CACNA1H* is usually associated with developmental disorders such as autism.

- We discovered seven *CACNA1H* variants associated with TN had a GoF. This is indicative of an increase in excitability, which coincides with an increase in pain as previously documented. Interestingly, there was a correlation between TN patients with idiopathic TN with concomitant continuous pain and GoF *CACNA1H* variants. Whereas there was no dysfunction of the channel in patients with congenital TN and concomitant pain.
- Finally, we identified and characterised a group of broad-spectrum VGCC blockers and their use as pain therapeutics. Suggesting the importance of using broad-spectrum VGCC blockers over selective VGCC blockers in treating some disorders.

7 Summary

This comprehensive thesis offers a deep exploration of the crucial role played by T-type voltage-gated calcium channels (VGCCs) in numerous physiological functions, emphasizing their importance in the cardiovascular, neuroendocrine, and nervous systems. It is divided into three primary research areas.

The first area of focus is the regulation of T-type channels. It includes studies that provide new insights into the mechanisms controlling these channels. The first study highlights the identification of non-canonical N-glycosylation sites on T-type channels, a discovery that sheds light on how these sites affect channel trafficking and surface expression. This finding points to a significant regulatory role for glycosylation in channel function, though the exact mechanisms remain to be fully understood. The second study introduces the protein SCAMP2 as a novel modulator of T-type channels, linking its dysfunction to a range of diseases, including neurodegenerative disorders and cancer. This suggests a broader impact of T-type channel regulation in various pathophysiological conditions, underlining the need for more in-depth research in this area.

The second area of research delves into T-type channelopathies and their association with neurological disorders. This segment of the thesis is composed of multiple studies, each examining a different aspect of channelopathy. The third study investigates the role of glycosylation in T-type channels in the context of diabetes, yielding contradictory results regarding $Ca_v3.2$ expression. This inconsistency highlights the complexity of channel regulation in disease states and the need for further study in primary neurons to better understand the implications for diabetic neuropathy. The fourth study analyses *CACNA1H* variants in amyotrophic lateral sclerosis (ALS) patients, uncovering varying degrees of channel dysfunction, which deepens the understanding of ALS pathology and

suggests new avenues for research. The fifth study reports on a child with developmental and epileptic encephalopathy (DEE), possessing a mutation in *SCN8A* and a variant in *CACNA1H*, offering insights into the complex interplay of channel functions and interactions. The sixth study examines $Ca_v3.2$ variants in patients with trigeminal neuralgia, finding a predominance of gain-of-function effects, which could contribute to pain pathway sensitization.

Lastly, the thesis also ventures into the development of novel VGCC blockers, aiming to find more effective treatments for conditions exhibiting a gain-of-function in these channels. This includes the exploration of broad-spectrum VGCC blockers for treating neuropathic pain, a significant step towards new therapeutic approaches.

Overall, the thesis underscores the critical importance of T-type VGCCs in health and disease, highlighting the intricate regulation of these channels and their impact on various neurological disorders. It sets the stage for future research and drug development, targeting these channels to alleviate the symptoms of associated diseases.

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9 Publication record

1. Functional identification of potential non-canonical N-glycosylation sites within Cav3.2 T-type calcium channels

Ficelova, Vendula, Ivana A. Souza, Leos Cmarko, Maria A. Gandini, Robin N. Stringer, Gerald W. Zamponi, and Norbert Weiss. 2020. 'Functional Identification of Potential Non-Canonical N-Glycosylation Sites within Cav3.2 T-Type Calcium Channels'. Molecular Brain 13 (1): 149. https://doi.org/10.1186/s13041-020-00697-z.

Impact factor: 4.399

2. Secretory carrier-associated membrane protein 2 (SCAMP2) regulates cell surface expression of T-type calcium channels

Cmarko, Leos, Robin N. Stringer, Bohumila Jurkovicova-Tarabova, Tomas Vacik, Lubica Lacinova, and Norbert Weiss. 2022. 'Secretory Carrier-Associated Membrane Protein 2 (SCAMP2) Regulates Cell Surface Expression of T-Type Calcium Channels'. Molecular Brain 15 (1): 1. https://doi.org/10.1186/s13041-021-00891-7.

Impact factor: 4.399

3. Transcriptomic analysis of glycan-processing genes in the dorsal root ganglia of diabetic mice and functional characterization on Cav3.2 channels

Stringer, Robin N., Joanna Lazniewska, and Norbert Weiss. 2020. 'Transcriptomic Analysis of Glycan-Processing Genes in the Dorsal Root Ganglia of Diabetic Mice and Functional Characterization on Ca v 3.2 Channels'. Channels 14 (1): 132–40. https://doi.org/10.1080/19336950.2020.1745406.

Impact factor: 3.493

4. A rare CACNA1H variant associated with amyotrophic lateral sclerosis causes complete loss of Cav3.2 T-type channel activity

Stringer, Robin N., Bohumila Jurkovicova-Tarabova, Sun Huang, Omid Haji-Ghassemi, Romane Idoux, Anna Liashenko, Ivana A. Souza, et al. 2020. 'A Rare CACNA1H Variant Associated with Amyotrophic Lateral Sclerosis Causes Complete Loss of Cav3.2 T-Type Channel Activity'. Molecular Brain 13 (1): 33. https://doi.org/10.1186/s13041-020-00577-6.

Impact factor: 4.399

5. De novo SCN8A and inherited rare CACNA1H variants associated with severe developmental and epileptic encephalopathy

Stringer, Robin N., Bohumila Jurkovicova-Tarabova, Ivana A. Souza, Judy Ibrahim, Tomas Vacik, Waseem Mahmoud Fathalla, Jozef Hertecant, Gerald W. Zamponi, Lubica Lacinova, and Norbert Weiss. 2021. 'De Novo SCN8A and Inherited Rare CACNA1H Variants Associated with Severe Developmental and Epileptic Encephalopathy'. Molecular Brain 14 (1): 126. https://doi.org/10.1186/s13041-021-00838-y.

Impact factor: 4.399

6. Electrophysiological and computational analysis of Cav3.2 channel variants associated with familial trigeminal neuralgia

Mustafá, Emilio R., Eder Gambeta, Robin N. Stringer, Ivana A. Souza, Gerald W. Zamponi, and Norbert Weiss. 2022. 'Electrophysiological and Computational Analysis of Cav3.2 Channel Variants Associated with Familial Trigeminal Neuralgia'. Molecular Brain 15 (1): 91. https://doi.org/10.1186/s13041-022-00978-9.

Impact factor: 4.399

7. Synthesis and pharmacological evaluation of quinolone-based calcium channel blockers with analgesic properties (Unpublished)

Leoš Cmarko, Mikhail Klychnikov, Kimberly Gomez, Robin N. Stringer, Samantha Perez-Miller, Miroslav Hájek, Michel De Waard, Rajesh Khanna, Ullrich Jahn, Norbert Weiss