A novel nociceptor excitability protocol to identify abnormal voltage-gated ion channels

- A computational study

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Introduction

Altered excitability of small fibers has been identified in both small fiber neuropathy patients as well as in animal models of neuropathic conditions[1-3]. Since voltage-gated ion channels regulate the excitability of the cell membranes it has been proposed that pathological alterations of voltage-gated ion channels may cause the altered excitability and thereby contribute to the symptom's small fiber neuropathy patients experience. Identifying voltage-gated ion channel abnormalities would not only give insight into the underlying pathological mechanisms but could also give guidance for drug development.

Our research group has previously developed the perception threshold tracking (PTT) technique which can indirectly measure the excitability of cell membranes of nociceptive fibers in humans[4-6]. In the current study, we further improve the PTT technique by developing a novel nociceptor excitability protocol which may be used to estimate abnormal voltage-gated ion channel currents.

Aim

To develop a novel nociceptor excitability protocol to identify abnormal voltage-gated ion channels in small fiber

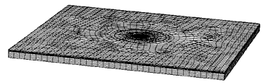
Methods

A two-part computational model

Finite element model (COMSOL version 5.3)
Calculates the electrical field generated by a pin electrode
- The skin model consists of four rectangular skin layers
- Pin electrode (15 pins short circuited, Ø: 0.2 mm)

Detailed multi-compartment model of a nerve fiber (NEURON)
- Aδ axon model
- Ion channels: $Na_v1.7$, $Na_v1.78$and Nav1.9, Kdr, K_M, K_A, and HCN

1. Finite element model



2. Compartmental model

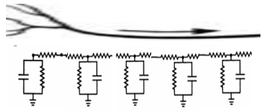


Figure 1. *Computational model design*

Methods (cont.)

Development of the nerve fiber excitability protocol

Three datasets were generated by upregulation and downregulation of the maximum conductance of the four ion channels individually ($Na_v1.7$, $Na_v1.8$, $Na_v1.9$ and HCN). As a result, eight perturbations of the computational model were generated for each dataset.

Dataset 1: Training the classifier
- 50% perturbations of the maximum conductance
- The activation threshold for 31 different pulse shapes from the 8 perturbations was calculated.
- An excitability profile was calculated for each perturbation consisting of the alteration of the activation threshold.

Dataset 2: Identifying the protocol
- 25% perturbations of the maximum conductance
- 31 different pulse shapes
- Normally distributed noise was added (20%)
- The five pulse shapes which could correctly classify the perturbation were identified

Dataset 3: Testing the classifier
- 75% perturbations of the maximum conductance
- Normally distributed noise was added (10%, 20%, 30%, 40%, 50%)

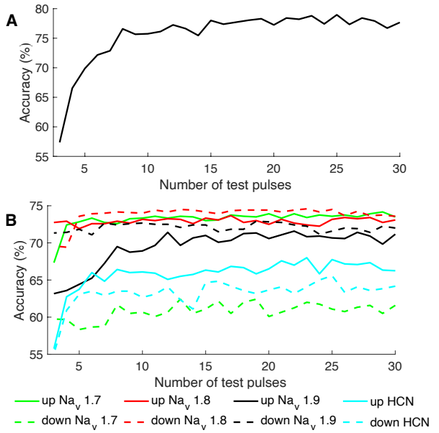


Figure 2. *The development of the novel nerve fiber protocol. A. The mean classification accuracy for all perturbations of ion channels.*
B. The accuracy of the classification of each ion channel perturbation.

Results

A novel nerve fiber excitability protocol has been developed which can be used to predict ion channel alterations.

With the novel protocol, the computational model predicts that individual alterations of the four ion channels can be classified on a population level (n=30) with an accuracy of 99%, 95% 87% 80% and 74%, when the standard deviation of the perception threshold is 10%, 20%, 30%, 40% and 50% respectively.

To predict the correct voltage-gated ion channel on individual level, the standard deviation of the perception threshold needs to be lower than 20%.

Results (cont.)

The nerve fiber excitability protocol

The final protocol consists of five different pulse shapes of the electrical input composed of superpositions of ramp and square pulses preceded by a prepulse.

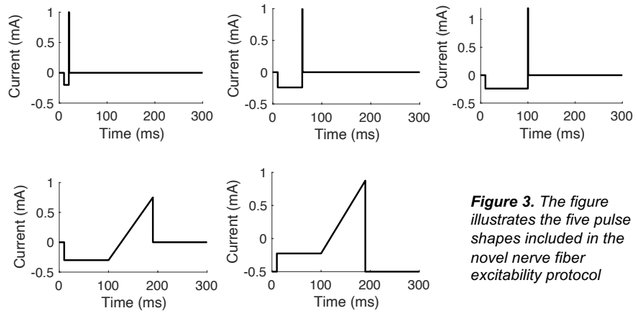


Figure 3. *The figure illustrates the five pulse shapes included in the novel nerve fiber excitability protocol*

Conclusions

A novel protocol to identify abnormal ion channel alterations of the four ion channels ($Na_v1.7$, $Na_v1.8$, $Na_v1.9$ and HCN) has been derived which allow a better understanding of basic mechanisms associated with changes in nerve fiber excitability. Moreover, the perception thresholds of all the five pulse shapes could be developed into a diagnostic tool for small fiber neuropathy.

References

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