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**Sex-specific anti-allodynic mechanisms of Cav3.3 T-type calcium channels in trigeminal neuropathic pain**

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Aleyah Goins, Marena Montera, Mitra Afaghpour-Becklund, Sabrina McIlwraith, Karin Westlund-High, and Sascha Alles
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**Background**

T-type Ca2+ channels mediate neuronal excitability in chronic pain states. However, the roles of the Cav3.3 subtype of T-type channel in chronic pain, especially trigeminal neuropathic pain (TG NP) are understudied. Previously, we found that administration of a highly specific TAT-C3P Cav3.3 peptide reverses allodynia in our model of TG NP. The mechanism of action of TAT-C3P involves reducing Cav3.3 expression, hyperpolarizing resting membrane potential, reducing firing frequency and incidence of spontaneous firing in TG neurons. Anti-allodynic effectiveness of Cav3.3 blockade was stronger in females compared to male TG NP mice. These differences in effectiveness may be explained by a stronger reduction of Cav3.3 expression and a significant hyperpolarization of RMP in female TG neurons. Further work is required to elucidate the basis of these sex differences and develop Cav3.3-targeting therapeutics for chronic pain.

**Cellular mechanisms of Cav3.3 in FRICT-ION mice**

**Figure 1.** Model of mouse skull. Blue indicates where a 5mm inserted piece of chronic pain model was used that causes friction against the trigeminal nerve. All mice had chronic pain induced for at least 3 weeks.

**Figure 2.** von Frey behavioral test for mechanical allodynia.

**Figure 3.** Western blot of female and male TG tissue with Cav3.3 blocking peptide TAT-C3P (Control) or TAT-C3P (Treatment). Females showed a greater decrease in signal intensity than males, which may explain why TAT-C3P has greater efficacy in females. Normalized ratio of intensity also showed females had lower levels of Cav3.3 protein than males.

**Figure 4.** Resting Membrane Potential was hyperpolarized under Treated (n=25) compared to Control (n=21) conditions in females only. This indicates a mechanism of increased effectiveness of TAT-C3P in females, as supported by the behavioral data. Current clamp traces are shown for stepwise current injections from -100 to +190 pA.

**Figure 5.** Effect of Cav3.3 blockade on other intrinsic electrophysiological properties of TG neurons in male and female FRICT-ION mice. No significant effects on rheobase, input resistance or AP half-width were observed between treated and control conditions.

**Conclusions**

- Cav3.3 blockade with TAT-C3P reverses allodynia in male and female chronic FRICT-ION mice but appears to be more effective in female mice.
- These effects are partially explained by a greater reduction of Cav3.3 levels in female than male mice and significant hyperpolarization of RMP in TG neurons from female mice, but not male mice.
- AP firing frequency was reduced in TG NP neurons from both male and female mice.
- Incidence of spontaneous activity of TG neurons was reduced by Cav3.3 blockade similarly in both male and female mice.

**Future Directions**

- Further f-I analyses is pending.
- We will be performing further immunohistochemistry studies of TG neurons to determine the role of specific cell types in the periphery.
- We will be using the FASTRAP system to elucidate the central mechanisms in the mediolateral dorsal horn of Cav3.3 blockade in male and female TG NP mice.
- Further work is required to elucidate the basis of these sex differences and develop Cav3.3-targeting therapeutics for chronic pain.

**References**