Inhibition of Voltage-Gated $Ca_V2.2$ Calcium Channels in Peripheral Nociceptor Nerve Endings Prevents Neurogenic Hyperalgesia in Mice

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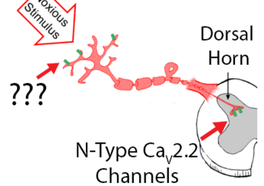
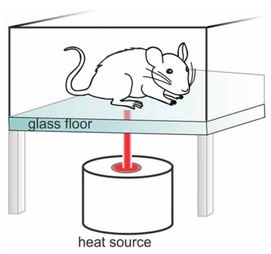
INTRODUCTION

- Chronic pain is a condition that lacks effective treatment. Nerve injury and inflammation can lead to chronic unrelenting pain in a significant number of individuals. New, non-additive, non-opioid therapies are needed.
- Voltage gated $Ca_V2.2$ calcium channels are essential for mediating noxious signals that are perceived as pain, and they also contribute to pathological pain.
- Inhibitors of $Ca_V2.2$ calcium channels are effective analgesics but their use in the clinic has so far been limited to intrathecal application.
- Here we assess the function of $Ca_V2.2$ channels at nociceptor nerve endings in skin. We ask if peripheral $Ca_V2.2$ channels have a role in **neurogenic hyperalgesia.**



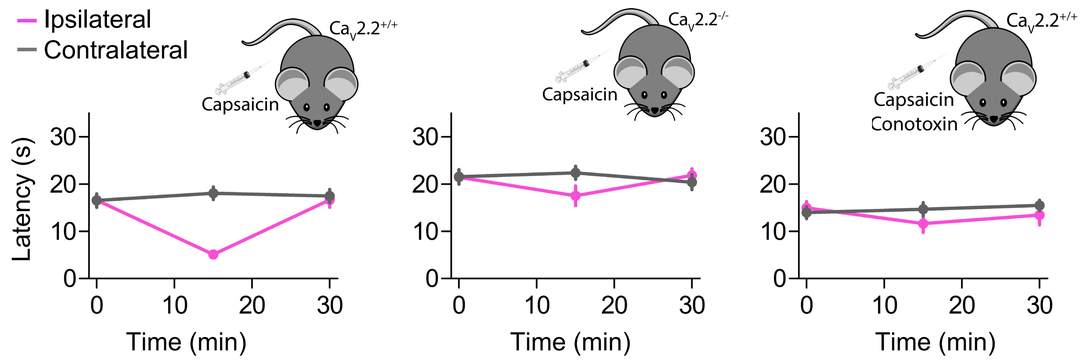
METHODS

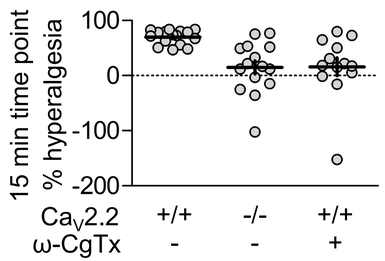
- We use male and female 3-4 month old wildtype ($Ca_V2.2^{+/+}$) and $Ca_V2.2$ null ($Ca_V2.2^{-/-}$) mice. Experimenter was blinded to genotype.
- Paw withdrawal latencies to noxious thermal stimuli, were measured using the Hargreaves method.
- Sensitivity to thermal stimuli applied to hindpaw, measured after injection of saline (control), or capsaicin in the absence and presence of the $Ca_V2.2$ toxin (ω-CgTx MVIIA).



RESULTS

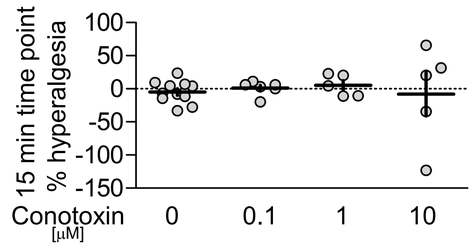
$Ca_V2.2$ in nerve endings are essential for capsaicin-induced hyperalgesia in mice





- $Ca_V2.2^{+/+}$ and $Ca_V2.2^{-/-}$ mice injected with 20 μL of 0.1% capsaicin into hindpaws, with or without 1 μM ω-conotoxin MVIIA. Injections were given immediately following baseline measurements (0 mins). Paw withdrawal latencies to focal noxious heat were measured in contra (gray) and ipsilateral (pink) paws at indicated time points.
- Baseline responses were longer, and capsaicin-induced hyperalgesia was attenuated in $Ca_V2.2^{-/-}$ mice compared to wildtype $Ca_V2.2^{+/+}$.

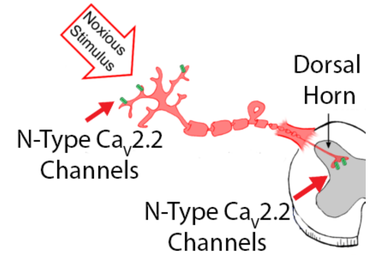
Central, not peripheral $Ca_V2.2$ channels contribute to basal nociception



- $Ca_V2.2^{+/+}$ mice were injected with increasing concentrations of ω-conotoxin MVIIA (20 μL volume).
- Averaged and individual paw withdrawal latencies at 15 min time point are also shown, normalized to baseline (0 min).

CONCLUSIONS

- $Ca_V2.2^{-/-}$ mice lack peripheral and central $Ca_V2.2$ channels and have impaired baseline responses and hyperalgesia following capsaicin injection.
- Local inhibition of peripheral $Ca_V2.2$ channels in wild-type mice by ω-CgTx MVIIA occludes capsaicin-induced hyperalgesia without affecting basal withdrawal latencies.
- We conclude that $Ca_V2.2$ channels in peripheral termini of nociceptors are ***essential*** for capsaicin-induced neurogenic inflammatory response.



FUTURE DIRECTIONS

- Develop a method to visualize Ca^{2+} influx in nociceptor endings in skin of anaesthetized mice directly, by 2-photon imaging.
- Investigate the efficacy of peripheral application of $Ca_V2.2$ channel inhibitors to attenuate chronic pain induced by neurogenic inflammation

ACKNOWLEDGMENTS

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