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Repeat Dosing of Novel Selective Inhibitors of $Na_V1.6$ Enhances Efficacy in the Mouse Maximal Electroshock Model

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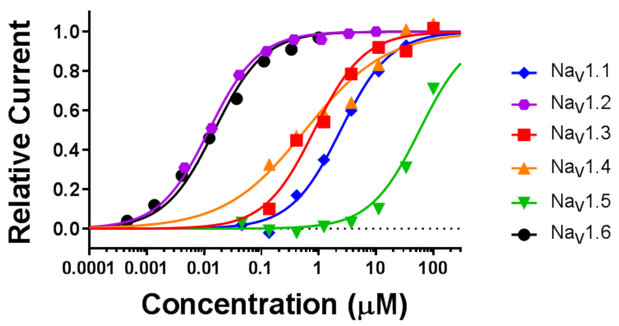
INTRODUCTION

The voltage gated sodium channel $Na_V1.6$ is a critical mediator of CNS excitability. Gain of function mutations in SCN8A, the gene encoding $Na_V1.6$, cause seizure syndromes in humans (EIEE13) and mice. Multiple animal seizure models exhibit upregulation of $Na_V1.6$ channel expression. Non-selective inhibitors of Na_V channels effectively control seizures, but are dose limited by narrow therapeutic indices. We reasoned a more selective $Na_V1.6$ inhibitor would provide an improved safety profile by avoiding block of off-target channels like $Na_V1.5$ (cardiac) and $Na_V1.1$ (inhibitory interneurons).

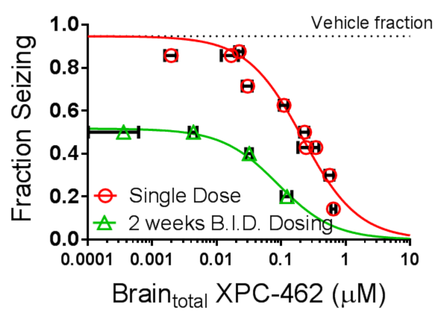
While exploring the efficacy profile of new selective inhibitors we noted that repetitive dosing improved efficacy even though there is no accumulation of compound in the brain.

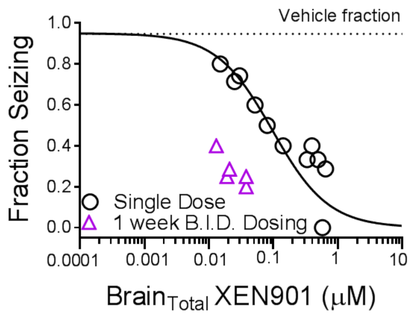
XPC-462 is equipotent on $Na_V1.2$ & $Na_V1.6$ but more than 30 fold selective for all other Na_V isoforms



Repeat dosing improved efficacy

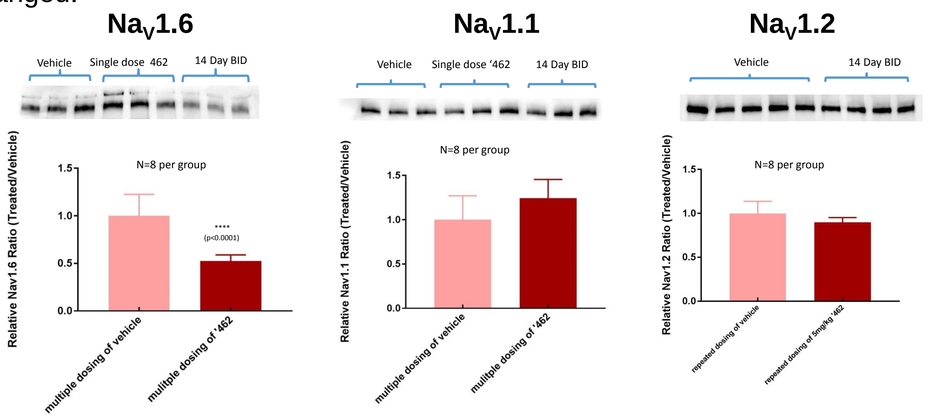
Lower brain (and plasma, not shown) levels were required to provide the same level of seizure protection after chronic exposure. This improved efficacy can not be accounted for by accumulation of the compound in brain tissue. The impact of repeated dosing was seen for both XPC-462 and XEN901 (an $Na_V1.6$ selective compound currently in Phase I clinical trials).



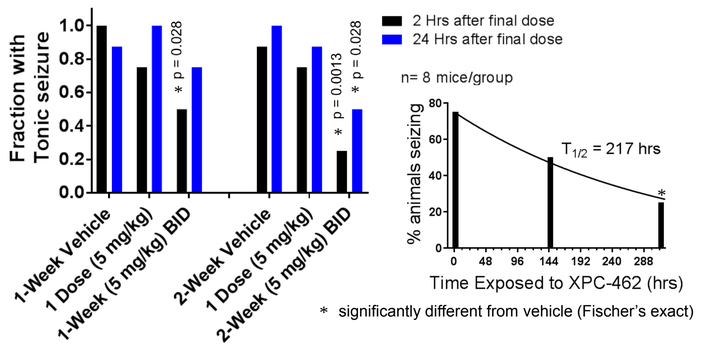


Chronic dosing of XPC-462 selectively reduced $Na_V1.6$ protein levels as assessed by Western blot

Chronic dosing of XPC-462 significantly reduced $Na_V1.6$ protein levels when measured by Western blot. $Na_V1.1$, and $Na_V1.2$ levels were not significantly changed.



Chronic dosing boosted efficacy over time



XPC-462 efficacy improved over time, from 25% protection 2 hours after dosing to 50% after 1 week and 75% after 2 weeks.

24 hours after a single dose there was no apparent efficacy, 50% of animals dosed for 2 weeks were protected from tonic seizure 24 hours after the final dose.

CONCLUSIONS

Repeat dosing increased seizure protection for both XPC-462 and XEN901 at a given brain concentration.

For XPC-462, this effect is coincident with a decrease in membrane $Na_V1.6$ protein levels.

Protein downregulation may provide an alternate mechanism for seizure protection by XPC-462.