Repeat Dosing of Novel Selective Inhibitors of Na\textsubscript{v}1.6 Enhances Efficacy in the Mouse Maximal Electroshock Model

INTRODUCTION

The voltage gated sodium channel Na\textsubscript{v}1.6 is a critical mediator of CNS excitability. Gain of function mutations in SCN8A, the gene encoding Na\textsubscript{v}1.6, cause seizure syndromes in humans (EIEE13) and mice. Multiple animal seizure models exhibit upregulation of Na\textsubscript{v}1.6 channel expression. Non-selective inhibitors of Na\textsubscript{v} channels effectively control seizures, but are dose limited by narrow therapeutic indices. We reasoned a more selective Na\textsubscript{v}1.6 inhibitor would provide an improved safety profile by avoiding block of off-target channels like Na\textsubscript{v}1.5 (cardiac) and Na\textsubscript{v}1.1 (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\textsubscript{v}1.2 & Na\textsubscript{v}1.6 but more than 30 fold selective for all other Na\textsubscript{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\textsubscript{v}1.6 selective compound currently in Phase 1 clinical trials).

Chronic dosing of XPC-462 selectively reduced Na\textsubscript{v}1.6 protein levels as assessed by Western blot

Chronic dosing of XPC-462 significantly reduced Na\textsubscript{v}1.6 protein levels when measured by Western blot. Na\textsubscript{v}1.1, and Na\textsubscript{v}1.2 levels were not significantly changed.

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\textsubscript{v}1.6 protein levels.

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

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