Selective antagonists of Na\textsubscript{\text{v}} 1.6 prevent electrically induced seizures in a mouse model of EIEE13


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Introduction

Na\textsubscript{\text{v}} inhibitors are useful antiepileptics, but currently available drugs are nonselective. Inhibition of Na\textsubscript{\text{v}}1.1 likely limits their efficacy due to its’ important role in inhibitory interneurons. Inhibition of Na\textsubscript{\text{v}}1.5 introduces risk of cardiac adverse events. We set out to create new drugs that block Na\textsubscript{\text{v}}1.6 but spare Na\textsubscript{\text{v}}1.1 and Na\textsubscript{\text{v}}1.5

Mouse model of EIEE13 (Na\textsubscript{\text{v}}1.6 gain of function)

- N1768D mutation in Na\textsubscript{\text{v}}1.6
- Mutation identified by Veeramah et al. (2012)
- Mouse model created by Wagnon et al. (2015)
- Mice in our colony behave as described by Meisler
- Seizures begin ~ p70 to p90
- Only about 60% become epileptic

6-Hz psychomotor seizure induction assay

- 6Hz, 12 mA, transcorneal stimulus
- WT mice are resistant to stimulus
  - 50% show no seizure behavior,
  - 50% have brief clonic seizure
- N1768D mice are much more sensitive
  - All vehicle treated mice have a tonic clonic seizure after stimulus, some have multiple seizures

Seizures Assessed by 2 endpoints

1. % of animals seizing
2. Modified Racine Score

Responses of individual animals are “binary”

Individual animal behavior vs brain concentration

- An animal usually has a strong response or no response
- Improving efficacy results from recruiting more protected individuals

Summary

Novel, selective, inhibitors of Na\textsubscript{\text{v}}1.6 prevented induced seizures in a modified 6Hz psychomotor assay using the N1768D Na\textsubscript{\text{v}}1.6 mouse model of EIEE13 developed by Wagnon et al. at the Univ. of Michigan.

1. Efficacy was well predicted by in vitro potency and brain exposure.
2. Non-selective, or less selective Na\textsubscript{\text{v}} inhibitors had similar efficacy as selective inhibitors
3. The N1768D mouse 6Hz assay appears to be a good measure of on target efficacy for Na\textsubscript{\text{v}}1.6 inhibitors.

We expect that novel, selective Na\textsubscript{\text{v}}1.6 inhibitors will provide the basis for new antiepileptic drugs with an improved efficacy and safety profile