Select Potentiation of Inhibitory Networks Prevents Seizures in a Mouse Model of Dravet Syndrome


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BACKGROUND

• Loss-of-function variants of Scn1a cause Dravet Syndrome (SMEI or EIEE6) and generalized epilepsy with febrile seizures plus (GEFS+), by decreasing Na,1.1 expression or conductance in inhibitory interneurons. The resulting hyper-excitability of interneurons reduces inhibitory input on excitatory neurons and leads to epilepsy and developmental delays.

• A precision medicine therapy for Dravet Syndrome should restore Na,1.1 activity specifically without impacting other neuronal proteins or conductances.

• We are pursuing brain penetrant small molecule enhancers of Na,1.1 currents to allow oral dosing and titration of the Na,1.1 current levels.

• We believe that such activators can directly address the underlying cause of Dravet Syndrome vs. Wildtype (WT) mice.

RESULTS

Potency, Selectivity and Mechanism of Action (MOA) of XPC-8770

• XPC-8770 selectively potentiates hNa,1.1 channels and spares neuronal channels Na,1.2 and Na,1.6 and cardiac channel Na,1.5. XPC-8770 acts on Na,1.1 by impairing inactivation of the channel.

• For subsequent neuronal experiments we used a saturating concentration of 1 µM to target the Na,1.1 channels as well as a concentration of 150 nM to look for a concentration response of XPC.

METHODS

• Voltage clamp electrophysiology was used to assess the potency and selectivity of XPC-8770 using the Sophion Cube-384. Potency was measured by determining the increase in charge carried over 10 ms.

• Animals. Scn1a+/- mice were generated as described previously.1

• Brain Slice Preparation. 400 µm parasagittal cortical brain slices were prepared from >P21 mice using standard procedures.2

• Electrophysiological Recordings in Brain Slices. Whole-cell current-clamp recordings were made in cortical layer 5 (20-22ºC). Fast-spiking interneurons were identified by their characteristic fast-spiking pattern and confirmed post hoc by single-cell RT-PCR.

• Scn1a-/- 6 Hz seizure model. Seizures were induced in 20-22 days-old Scn1a-/- mice by a 6 Hz stimulus for 3 seconds delivered through corneal electrodes and the CC57 was determined. Mice were stimulated at this current and placed in a plethysmograph chamber to monitor for the presence of a seizure characterized by jaw clonus, forelimb clonus, Straub tail and loss of balance. An animal was considered “protected” if none of these 4 behaviors occurred. A mouse is considered seizing if at least one of these behaviors was observed.

CONCLUSIONS

• XPC-8770 is a highly selective small molecule potentiator of Na,1.1.

• Compound binding impairs fast inactivation and increases Na+, flux and cellular excitability.

• Selectively potentiating Na,1.1, the dominant sodium channel isoform expressed in inhibitory interneurons, restores the capability of mouse Scn1a-/- interneurons to fire action potentials at high frequency.

• The compound showed efficacy in a Scn1a-/- 6 Hz seizure model, providing in vivo proof of concept for this mechanism of action.

• This profile provides a new, mechanistically differentiated, class of voltage-gated sodium channel potentiators with the potential to provide an improved therapeutic profile for the treatment of Dravet Syndrome.


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