Therapeutic to mitigate epilepsy and autism development in newborn seizure patients

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Technology description

Neonatal brains are at high risk for seizures due to heightened electrical activity corresponding to neural development. Though anticonvulsant drugs exist to treat the seizures immediately, certain synaptic receptors (CP-AMPARs) become highly expressed, increasing the likelihood of developing epilepsy and autism-spectrum disorders. The inventors have therefore proposed using CP-AMPAR blockers such as IEM-1460 to curb CP-AMPAR activity and prevent development of epilepsy and other neurological disorders.

Neonatal brains are constantly in a state of electrical excitation due to the heightened neural activity required during development. They are therefore prone to hypoxic seizures, which can lead to long term synaptic development issues. AMPA receptors (AMPARs) are involved in the synaptic transmission of neurotransmitters in the central nervous system and one subset of these AMPARs are calcium-permeable (CP-AMPARs) because they lack the GluR2 subunit. In infants experiencing hypoxic seizures, these CP-AMPARs are upregulated and simultaneously, MeCP2, a transcription factor linked to autism spectrum disorder (ASD) becomes phosphorylated. MeCP2 is involved with synapse and dendrite development and neuronal maturation and thus, disruptions in its expression can lead to ASDs or epilepsy. AMPAR blockers have been considered as antiepileptogenetic drug candidates though they are not specific enough to target only CP-AMPARs.

The inventors have therefore proposed using CP-AMPAR blockers such as IEM-1460 to inhibit CP-AMPAR activity and reduce MeCP2 phosphorylation. These CP-AMPAR blockers prevent the permeation of calcium into the neurons and as a result, the MeCP2 phosphorylation is inhibited.

Surface GluA2 expression decreases 48 h post-HS. A, B) Immunohistochemistry of surface GluA2 (green) and synapsin (red) in (A) control and (B) post-HS inCA1 S. radiatum of the hippocampus of P12 Long-Evans rats 48 h post-HS. Circles highlight colocalization; Bar=2 μm. C) Quantification shows a significant decrease in surface GluA2/Synapsin colocalization in post-HS rats compared to controls overmultiple thresholds represented as a percentage of the control at each threshold; post-HS n=11 fields from 6 rats; control=8 fields from5 rats; $p = 0.04$ by t-test of control vs. HS at each threshold. D) Averaged traces of AMPAR eEPSCs at−60 and +40 mV while blocking NMDARs and GABARs show that rectification increases post-HS. E) Summary of AMPAR eEPSC ratio at−60 mV to +40 mV; n= 5 control and 6 post-HS, $p = 0.014$ by t-test. Data are represented as mean ± SE.

CP-AMPAR antagonists reduce MeCP2 phosphorylation
AMPARs and LT-VGCCs mediate hypoxic seizure (HS)-induced MeCP2 S421 phosphorylation in vivo in P10 rats. Increased MeCP2 S421 phosphorylation 3h. post-HS (HS+V: n=17 vs. C+V n=14, p=0.0003) can be attenuated by in vivo pre-treatment with the AMPAR antagonist NBQX (20mg/kg, i.p.) (HS+NBQX: n=9, vs. HS+V, p<0.0001), the CP-AMPAR blocker IEM-1460 (20mg/kg, i.p.) (HS+IEM-1460: n=9, vs. HS+V p=0.0099), or the LT-VGCC antagonist nimodipine (10mg/kg, i.p.) (HS+NIMO: n=9, vs. HS+V
p=0.0051).

Application area

- An age-specific therapeutic to be used in patients who have suffered from neonatal seizures
- Could be part of a drug cocktail along with other AMPAR blockers to effectively block epileptogenesis

Advantages

- Highly specific therapeutic that can be dose-adjusted for the patient’ s age
- Effectively reduces calcium influx into the neuron to inhibit MeCP2 phosphorylation
- Prevents synaptic development disruption that can lead to epilepsy and autism-spectrum disorders

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