

## Treatment for Hyperammonemic Encephalopathy and Seizures

A treatment for hyperammonemic encephalopathy and seizures.

### Problem Solved by This Technology

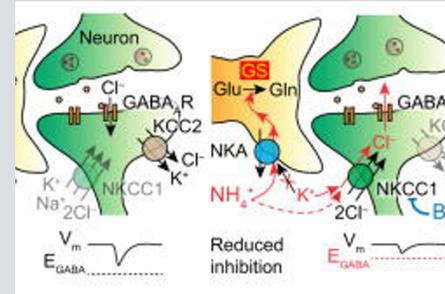
Existing treatments for generalized seizures resulted from hyperammonemia are standard antiepileptic drugs. These medications have significant side effect because they are not mechanistic specific for hyperammonemia. Hyperammonemic seizures are thus usually resistant to these treatments. Treatments that directly target the brain impairment caused by excess ammonia are still eagerly sought.

### Applications

URMC researchers have unveiled the mechanisms that underlie the ammonia toxicity in the brain. Ammonia accumulation increases the activity of the Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter isoform 1 (NKCC1) and depolarizes the neuronal GABA reversal potential, impairing brain function and leading to seizures and encephalopathy. The researchers also discovered that Bumetanide, an FDA approved NKCC1 inhibitor, suppressed the seizures induced by hyperammonemia in an awake mouse model. Bumetanide, has immediate applications for acute treatment of children or adults with generalized seizures when suffering from acute hyperammonemia due to congenital urea cycle deficiencies, metabolic disturbances, or acute liver failure. This approach can also be used for acute treatment of encephalopathy due to hyperammonemia. Further, they may provide prophylactic treatment for patients suffering from chronic hyperammonemia (e.g. congenital enzyme deficiencies) or hepatic encephalopathy (e.g. alcohol related liver failure) to improve cognitive and motor impairment.

Compounds that inhibit NKCC1 activity directly target hyperammonemia-induced brain impairment and thus have fewer side effects than the existing treatments. These compounds can not only provide acute treatment for seizures and encephalopathy caused by acute hyperammonemia, but also offer preventive treatment for patient suffering from chronic hyperammonemia or hepatic encephalopathy. Additionally, FDA approved NKCC1 inhibitors are available, thus the hurdle for future clinical trials for brain impairment is low.

URV Reference Number  
6-2101



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### Publication

Nedergaard M, et al. Ammonia triggers neuronal disinhibition and seizures by impairing astrocyte potassium buffering. *Nat Med.* 2013 Dec;19(12): 1643-8.

### Intellectual Property Status

Patent applications pending in the United States and Europe.

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