Brain Disorders & Therapy
ISSN: 2168-975X

Zeiler, Brain Disord Ther 2015, 4:5
DOI: 10.4172/2168-975X.1000195

Short Communication Open Access

NMDA Receptor Antagonism in Refractory Status Epilepticus: Right Idea, Wrong Target?

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Description

Antagonism of the upregulated NMDA receptors has been a focus of recent literature on refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE), with ketamine at the forefront. Recent systematic review of ketamine use in SE/RSE displayed 23 articles on the subject, with 110 adult and 52 pediatric patients treated with ketamine for refractory seizures [1]. The review documented a 56·5% and 63·5% seizure response (greater than 50% reduction in electrographic seizures) with ketamine administration in adult and pediatric populations respectively. Complications related to ketamine therapy were sparse. The final recommendations by the authors were an Oxford level 4, GRADE C evidence for the use of ketamine in refractory seizures, with further prospective evaluation recommended [1].

The concept of utilizing NMDA receptor antagonists in RSE/SRSE makes sense mechanistically. However, how come the results of the systematic review displayed only a 50 to 60% efficacy for ketamine in refractory seizures? Maybe it was related to the complex nature of these patients' critical illness? Secondary to numerous AED interactions? Or maybe it was just an example of the refractory nature of their illness? Or perhaps the idea of NMDA mediated potentiation of seizure in RSE/SRSE is sound, but targeting the NMDA receptor is wrong? Is this success rate with NMDA receptor antagonists acceptable in such refractory and difficult cases? Our goal with NMDA receptor antagonists in the management of refractory seizures is really to reduce the downstream effect of calcium uptake into the neuron that leads to excitoxicity. Most NMDA receptor antagonists utilized are non-selective towards individual NMDA receptor subtypes. Furthermore, it is known that the GluN2B NMDA receptor subtype is primarily responsible the adverse calcium mediated damage seen with glutamate mediate NMDA receptor stimulation, and has been implicated in a variety of neuropathological processes [2,3]. We currently do not have selective NMDA Glu2B receptor antagonists available for clinical use [2].

Interestingly, it has been demonstrated in recent literature that this NMDA regulated calcium influx is mediated in large part by transmembrane transporters called transient receptor potential cation transporters (TRP), in particular the M2 subtype (TRPM2) [4]. The TRPM with highest expression in the brain is TRPM2 and it is believe to be a key player in the calcium mediated damage seen in a variety of neuropathological processes [5]. It is TRPM2 that has garnered a lot of attention recently as a potential therapeutic target for neurodegenerative processes [4,5], such as Alzheimer's disease. Therefore, if TRPM2 is the cause of the calcium influx leading to the excitotoxic damage seen with NMDA receptor upregulation and glutamate stimulation in refractory seizures, then we should seriously evaluate targeting it in the setting or RSE and SRSE. To date, fenamates, catalase, dimethythiourea, mannitol, and clotrimazol/econazole have demonstrated anti-TRPM2 activity [6]. Further research into TRPM2 inhibition is active and ongoing with recent literature displaying compounds superior to those non-selective inhibitors previously mentioned [7,8]. Shifting the focus from NMDA receptor antagonists to TRPM2 inhibition in RSE/SRSE provides a novel therapeutic target to reduce glutamate mediated excitoxicity and potentially lead to seizure control/cessation. To date there has never been an attempt to target TRPM2 in the setting of epilepsy or SE/RSE/SRSE. A single case documenting a link between juvenile myoclonic epilepsy and TRPM2 expression is the only reference of this transporter in relation to human seizures [9]. Thus, TRPM2 is an exciting potential target for RSE/SRSE and future study into this is paramount.

Declaration of Interest

The author has no conflict of interest.

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Received Octobe 25, 2015; **Accepted** November 18, 2015; **Published** November 24, 2015

Citation: Zeiler FA (2015) NMDA Receptor Antagonism in Refractory Status Epilepticus: Right Idea, Wrong Target?. Brain Disord Ther 4:195. doi:10.4172/2168-975X.1000195