

# Role of Exogenous Neuregulin-1 as a Therapeutic Agent in Focal Epilepsy [Letter]

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## Dear editor

We read with great interest the recently published article “Effects of Anti-Seizure Medication on Neuregulin-1 Gene and Protein in Patients with First-Episode Focal Epilepsy” by Zhao et al.<sup>1</sup> The study helps in understanding the effect of anti-seizure medication (ASM) on the serum levels of Neuregulin-1 (NRG-1) mRNA and protein.

The study compared the serum levels of NRG-1 mRNA and protein among patients with diagnosed focal epilepsy who were never treated with ASM before, to that of control subjects. Results revealed that the levels of NRG-1 mRNA were higher in epileptic patients post treatment with ASM, however remained lower than in healthy controls. Moreover, the levels of NRG-1 protein were found to be higher in epileptic patients both before and after treatment as compared to controls. Spearman correlation analysis demonstrated a negative correlation between the NRG-1 mRNA levels and efficacy of ASM as higher levels were found to be associated with lower frequency of seizures. However, no correlation could be found between the NRG-1 protein levels and the effectiveness of ASM. The study thus concluded that NRG-1 may serve as a therapeutic marker for focal epilepsy, and potential therapeutic targets of ASM may be investigated further.<sup>1</sup>

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy. Chronically elevated glutamate levels are found in patients with refractory TLE. Neuregulin-1, through its activity via epidermal growth factor receptor (ErbB4), has been known to increase glutamate uptake in neurons by upregulating excitatory amino acid transporter 1 (EAAC1).<sup>2</sup> A study examined the role of exogenous NRG-1 treatment at an early phase of epileptogenesis in mice. After the induction of epileptogenesis by intrahippocampal kainic acid (IHKA) injections, mice were either treated with 25 micrograms per kilogram per day of NRG-1 or 0.1% bovine serum albumin intraperitoneal daily for 7 days, followed by euthanasia. The study demonstrated significant results in exhibiting the neuroprotective role of exogenous NRG-1 in early epilepsy mainly via increased uptake of glutamate through EAAC1 as described above, and also through upregulation of glutamine synthetase enzyme which is responsible for glutamate clearance from extracellular space.<sup>3</sup>

In the adult brain, NRG-1/ErbB4 signaling has been observed predominantly in interneurons. Parvalbumin cells belong to a specific class of fast-spiking interneurons that are enriched with ErbB4 receptors, and the dysfunction of these inhibitory interneurons has been linked to the epileptogenesis.<sup>4</sup> A study conducted on mice models showed that the exogenous NRG-1 increased the excitability of Parvalbumin interneurons. This effect was mediated via inhibition of Kv1 voltage gated potassium channels that lead to the shift of action potential towards more hyperpolarized levels. The study also showed that mice with specific deletion of ErbB4 were more prone to seizures after induction and exogenous NRG-1 not only delayed the onset of seizures but also decreased their incidence and stage.<sup>5</sup>

We call for more studies on the role of exogenous NRG-1 as a potential therapeutic agent in epilepsy, and as a novel addition to the current anti-epileptic therapy.

## Disclosure

The authors report no conflicts of interest in this communication.

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<https://doi.org/10.2147/NDT.S477140>