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ORIGINAL RESEARCH

Effects of Anti-Seizure Medication on Neuregulin-1 Gene and Protein in Patients with First-Episode Focal Epilepsy

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Introduction: Neuregulin-1 (NRG-1) appears to play a role in the pathogenesis of several neuropsychiatric disorders, including epilepsy. We conducted a study to investigate the effect of anti-seizure medication on NRG-1 mRNA and NRG-1 protein levels in patients with first-episode focal epilepsy.

Methods: The levels of NRG-1 mRNA isoforms (type I, II, III, and IV) in peripheral blood mononuclear cells (PBMCs) of 39 healthy controls, 39 first-episode focal epilepsy patients before anti-seizure medication (ASM) therapy and four weeks after administration of ASM were measured by RT-qPCR, and the levels of NRG-1 protein in the serum of samples of each group were determined using ELISA. In addition the relationship between efficacy, NRG-1 mRNA expression, and NRG-1 protein expression was analyzed.

Results: The levels of NRG-1 mRNA progressively increased in patients with first-episode focal epilepsy treated with ASM and were distinctly different from those before medication, but remained lower than in healthy controls (all $P < 0.001$). Before and after drug administration, NRG-1 protein levels were substantially higher in epileptic patients than in healthy controls, and no significant changes were detected with prolonged follow-up ($P < 0.001$). Patients with epilepsy who utilized ASM were able to control seizures with an overall efficacy of 97.4%. There was a negative correlation between NRG-1 mRNA levels and efficacy: as NRG-1 mRNA levels increased, seizures reduced (all $P < 0.05$).

Conclusion: Our research indicated that NRG-1 may play a role in the pathophysiology of epilepsy. NRG-1 mRNA may provide ideas for the discovery of novel epilepsy therapeutic markers and therapeutic targets for novel ASM.

Keywords: neuregulin-1, focal epilepsy, drug treatment, pathophysiology

Introduction

Epilepsy is a severe, chronic neurological disorder that affects approximately 50 million individuals worldwide.[1,2] There are several manifestations of epilepsy,[3] of which focal epilepsy represents 60%. The pathogenesis of epilepsy is not yet completely elucidated. The imbalance of neural excitation and inhibition, which is the imbalance of glutamate (Glu) and γ-aminobutyric acid (GABA) neurotransmission, is one of the hypotheses for the pathogenesis of epilepsy.[4] The role of genetic factors as endogenous factors in the pathogenesis of epilepsy is gaining increasing attention.[5] Exploration of genes associated with epilepsy may be instrumental in elucidating the pathogenesis of epilepsy.

Seizures seriously damaged the physical and mental health of patients, diminishing their quality of life and placing tremendous stress on epilepsy patients' families.[3,6] Although a variety of anti-seizure medication (ASM) is available, many have similar efficacy and it is not possible to predict which drug is best for a given patient. Furthermore, only a few biomarkers can reliably forecast treatment response or the risk of epilepsy drug resistance.[7] Effective prevention and

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treatment of epilepsy is therefore a current clinical priority, and it is essential to seek potential therapeutic markers, identify therapeutic targets for novel ASM, and develop novel drug candidates.

Neuregulin (NRG) is a family of growth factors that transmits signals via ErbB family receptors. Neuregulin-1 (NRG-1) is located on chromosome 8p and is the most extensively researched member of its family.[8] Notably, chromosome 8 has been one of the more problematic chromosomes in terms of rearrangements and translocations,[9] which may be one cause for its association with certain diseases. NRG-1 is divided into six isoforms (I–VI), with types III and II being the most prevalent in humans, followed by type I. In the brain, types I, II, and III are mainly expressed by neurons, and astrocytes also express type I, but not type IV, V, or VI.[10] Type IV is more abundantly expressed in the fetal brain and may play an important role during early development.[11] This gene produced numerous isoforms closely associated with synaptic plasticity, neuronal migration, regeneration, and repair.[12–14] The receptor for NRG-1 is the ErbB tyrosine kinase receptor. There are four types of ErbB receptors: ErbB1, ErbB2, ErbB3, and ErbB4. NRG-1-mediated signaling is mainly via ErbB2, ErbB3, and ErbB4. NRG-1 has been found to activate signaling pathways by binding to ErbB2/ErbB3, ErbB2/ErbB4 heterodimers, and ErbB4 /ErbB4 homodimers.[15,16]

NRG-1 and ErbB4 have been identified as risk alleles for psychiatric disorders such as depression and schizophrenia, with type I and type IV NRG-1 possibly being especially associated with schizophrenia.[17,18] Recent research demonstrates that NRG-1 rs35753505 is closely associated with temporal lobe epilepsy.[19] Additionally, studies suggested that NRG-1/ErbB4 signaling was likely an endogenous inhibitor of epileptogenesis.[20] Current ASM exerts its effects primarily through Glutamatergic or GABAergic neurotransmitters.[21] In addition to inhibiting the glutamate receptor N-methyl-D-aspartic acid, NRG-1/ErbB4 signaling also increases GABA release, which inhibits neuronal excitability.[22–24] To determine whether the NRG-1/ErbB4 signaling could be a viable therapeutic target for ASM, however, additional research is required.

Considering the potential role of NRG-1 in the pathogenesis of epilepsy and its therapeutic implications, we conducted a study to analyze the levels of NRG-1 mRNA and NRG-1 protein in the peripheral blood of epilepsy patients and healthy controls.

Materials and Methods

Participants

This research included 39 people with focal first-episode epilepsy. Between December 2021 and May 2022, all patients were seen at the First Affiliated Hospital of Kunming Medical University. A neurologist or pediatrician diagnosed a patient with focal epilepsy based on the patient's medical history, MRI scan results, and EEG, in accordance with the 2017 International League Against Epilepsy classification criteria. Two eligibility requirements were a confirmed diagnosis of focal epilepsy and a lack of prior ASM use. Exclusion criteria included patients with any form of epilepsy other than focal epilepsy, other neurological disorders, psychiatric diseases, a history of positive hepatitis B, hepatitis C, HIV antibody/antigen testing, and MRI lesions. In addition, we recruited 39 healthy controls from the health administration center of the First Affiliated Hospital of Kunming Medical University who did not have epilepsy or other neurological disorders, psychiatric diseases, or an infectious disease history. Our study complied with the Declaration of Helsinki. The Ethics Committee of the First Affiliated Hospital of Kunming Medical University granted approval for this study. All participants or their legal guardians signed a form indicating their informed consent. Patients with epilepsy were sampled twice: once before the ASM therapy and again on day 28, which marked the conclusion of the fourth week of treatment. Samples from healthy controls were collected only once. All samples were stored in the biobank of the First Affiliated Hospital of Kunming Medical University.

Measurement of NRG-1 mRNA Levels

Blood samples were collected in heparin-coated collection tubes and centrifuged at 1000g for 15 minutes. Blood cell samples were taken in a separate centrifuge tube and peripheral blood mononuclear cells (PBMCs) were selected by Lymphocyte Separation Medium (Solarbio, Beijing, China). PBMCs samples were stored at −80°C for backup. Total RNA was extracted from PBMCs using the Total RNA Extraction Kit (Solarbio, Beijing, China), and the RNA concentration and purity were measured by ultra-micro UV-Vis spectrophotometer (BioTeke, Beijing, China), followed

by cDNA synthesis using the PrimeScript RT reagent Kit (TaKaRa, Tokyo, Japan). Quantitative real-time polymerase chain reaction (RT-qPCR) was performed using TB Green® Premix Ex Taq™ II Kit (TaKaRa, Tokyo, Japan) based on the manufacturer's recommended protocol. Gene expression was carried out on a LiKang CG-05. The sequences of the primers are shown in Table 1. GAPDH was used as an internal control to standardize gene expression. The relative expression of each gene was calculated using the $2^{\wedge-\Delta\Delta Ct}$ method.

Measurement of NRG-1 Protein Levels

Blood samples are collected in additive-free collection tubes and centrifuged at 1000g for 15 minutes. Serum samples were stored at −80°C for backup. Using the Human NRG-1 ELISA Kit (MeiMian, Jiangsu, China) according to the manufacturer's instructions, serum NRG-1 protein levels were measured. In brief, three microplate wells were filled with standards or samples. The detection range of the ELISA assay is 0.3 pg/mL to 12 pg/mL. At 450 nm, absorbance was measured using a microplate reader (PerkinElmer VICTOR Nivo). Based on the concentration and absorbance of the standards, the linear regression equation of the standard curve was calculated, and the absorbance of the samples was used to determine the concentration of NRG-1 in the serum samples.

Drug Efficacy Assessment

A total of 39 patients with first-episode focal epilepsy were treated with ASM and observed on day 28, the conclusion of the fourth week of medication administration. The duration of drug administration, the amount administered, the number of seizures, and the EEG results were recorded. The treatment's efficacy was classified into four groups: control, significantly effective, effective, and ineffective. On the basis of the patient's frequency of seizures every 28 days, the overall efficacy of the treatment was determined, with control denoting a 100% reduction in seizures, significantly effective denoting a 75% or greater reduction in seizures, effective denoting a 50% or greater reduction in seizures, and ineffective denoting a reduction of less than 50%. The relationship between efficacy, NRG-1 mRNA expression, and NRG-1 protein expression was analyzed.

Statistical Analysis

Statistical analysis was performed using IBM SPSS statistical software (IBM, version 26.0, Armonk, NY, USA). Each measurement was expressed as the mean ± standard deviation. Chi-square tests were used to analyze gender differences, while Student's *t*-tests were used to compare age differences. One-way ANOVA was used to compare NRG-1 levels in patients before and after medication with healthy controls, and LSD post hoc tests were used to analyze experiments with two variables. We also examined the potential correlation between NRG-1 levels and efficacy in patients using Spearman correlation coefficient. A p-value of less than 0.05 was deemed statistically significant.

Results

Levels of NRG-1 mRNA and Protein

Epilepsy patients and healthy controls were matched for age ($P = 0.896$) and sex ($P = 0.820$) (Table 2).

Among the four NRG-1 mRNA isoforms, type IV NRG-1 was not detected, therefore, this isoform will be excluded from further analysis. One-way ANOVA analysis revealed that type I NRG-1 ($F = 26.045$, $P < 0.001$), type II NRG-1 (F

Table 1 Sequences of the Primers Used for RT-qPCR

Primers	Forward Primer (5'→3')	Reverse Primer (5'→3')
GAPDH	GGAGTCCACTGGCGTCTTCA	GTCATGAGTCCTTCCACGATACC
NRG-1-I	GCCAATATCACCATCGTGGAA	CCTTCAGTTGAGGCTGGCATA
NRG-1-II	GAATCAAACGCTACATCTACATCCA	CCTTCTCCGCACATTTTACAAGA
NRG-1-III	GCAGTTGCGTCCAGAGAAAT	GCTCCGGCAGCAGCAT
NRG-1-IV	GCTCCGGCAGCAGCAT	GAACCTGCAGCCGATTCCT

Table 2 Demographic Characteristics of All Participants

Characteristic	Epilepsy patients (n=39)	Healthy controls (n=39)	χ2/t value	*P* value
Males	17(43.6)	18(46.2)	0.052	0.820[a]
Females	22(56.4)	21(53.8)		
Age	27 ± 15	28 ± 15	−0.131	0.896[b]

Notes:[a]Chi-square test; [b]Student's *t*-tests.

= 15.307, $P < 0.001$), and type III NRG-1 (F = 13.570, $P < 0.001$) mRNA levels were higher in epilepsy patients administered ASM than before medication, but still lower than in healthy controls. (Figure 1).

In contrast to the reduced levels of NRG-1 mRNA in first-episode epilepsy patients, we found that NRG-1 protein levels were higher in patients with epilepsy before and after treatment with ASM than in healthy controls (F = 17.728, $P < 0.001$), and there was no statistical difference in NRG-1 protein levels after four weeks of medication compared to before ($P = 0.681$) (Figure 2).

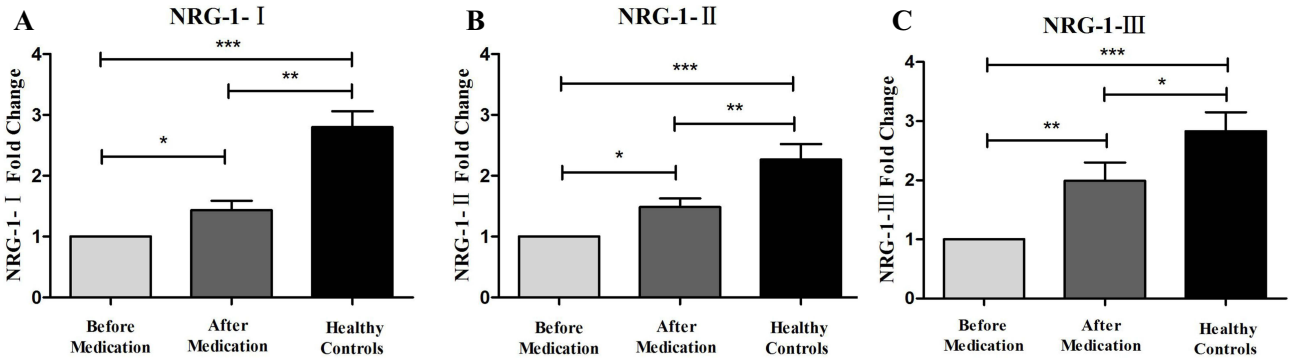

Figure 1 Levels of NRG-1 (type I, II, III) mRNA in first-episode focal epilepsy patients and healthy controls. Before treatment with ASM, type I, II, III NRG-1 mRNA levels (**A**–**C**) were lower in patients with first-episode focal epilepsy than in healthy controls. Type I, II, III NRG-1 mRNA levels (**A**–**C**) increased to some extent after drug administration, but remained lower than in healthy controls. (*: P < 0.05;**: P < 0.01;***: P < 0.001).

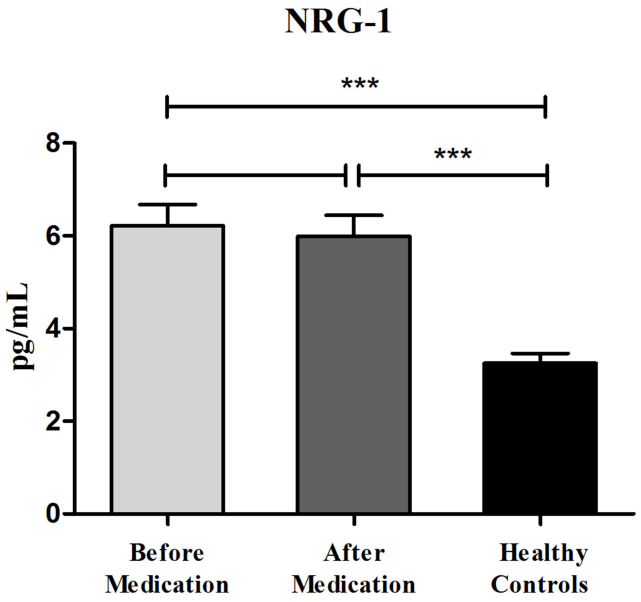

Figure 2 Levels of NRG-1 protein in first-episode focal epilepsy patients and healthy controls. Patients with first-episode focal epilepsy had higher NRG-1 protein levels before and after treatment with ASM than healthy controls, and there was no statistical difference between NRG-1 protein levels before and after dosing. (***: $P < 0.001$).

Table 3 Medication Use in 39 Patients with Focal Epilepsy

Medication	Number of cases	Duration of medication	Dose of medication
Levetiracetam	17	4 weeks	0.25–0.75g Bid
Oxcarbazepine	9		0.3–0.45g Bid
Lamotrigine	5		50mg Bid
Lacosamide	4		50–150mg Bid
Perampanel	2		2–4mg Bid
Zonisamide	1		100mg Bid
Topiramate	1		50mg Bid

Table 4 Efficacy Evaluation After Four Weeks of Medication in 39 Patients with Focal Epilepsy

	Control	Significantly effective	Effective	Ineffective	Total effective
Number of cases	28	6	4	1	38
Percentage	71.8%	15.4%	10.2%	2.6%	97.4%

Relationship Between NRG-1 and Efficacy of ASM

After four weeks of continuous treatment with ASM in 39 patients with first-episode focal epilepsy (The medications used are listed in Table 3), with NRG-1 mRNA levels increased, seizures were effectively controlled and relieved, with an overall efficacy rate of 97.4% (Table 4). In addition, all patients showed varying degrees of EEG improvement (Figure 3). Spearman correlation analysis revealed that type I ($r_s = -0.46$, $P = 0.003$), type II ($r_s = -0.563$, $P < 0.001$), and type III ($r_s = -0.36$, $P = 0.034$) NRG-1 mRNA were negatively correlated with the efficacy of ASM: as NRG-1 mRNA levels increased, the frequency of seizures decreased (Table 5). We found no correlation between NRG-1 protein and the effectiveness of ASM ($r_s = -0.234$, $P = 0.157$).

Discussion

In this study, we evaluated the levels of NRG-1 in the peripheral blood of patients with first-episode focal epilepsy before and after ASM treatment. We discovered that NRG-1 levels differed between epilepsy patients and healthy controls and that ASM increased NRG-1 mRNA levels. These findings indicate that NRG-1 may play a role in the onset and progression of focal epilepsy.

Of the four NRG-1 mRNA isoforms we measured (I, II, III, and IV), type IV NRG-1 mRNA was not detected between epilepsy patients and healthy controls, consistent with a study conducted in schizophrenic patients that failed to detect this isoform in PBMCs.[25] In the human brain, all six types of NRG-1 are detectable, but the abundance of each form varies greatly,[26] with NRG-1-III being the most abundantly expressed,[10] and unlike the other isoforms, NRG-1-IV is only expressed in the brain,[11] which may be one of the reasons why we did not detect this isoform in peripheral blood. In addition, we attempted to detect ErbB4 mRNA expression, but it was not detected in almost all samples. This may be because ErbB4 is specifically expressed in GABAergic neurons in cortical and subcortical regions, but not in PBMCs.[27,28] Furthermore, these probes and primers have been used successfully in other studies involving human brain tissue, but to our knowledge, they are rarely used in blood research. Future studies using blood samples should consider alternative probes and primers for type IV NRG-1 and ErbB4. Since NRG-1 activates multiple ErbB receptors, whether NRG-1 can cause changes in the expression of other ErbB receptors needs further investigation.

We first found that the levels of NRG-1 mRNA were lower in PBMCs in first-episode focal epilepsy patients than in healthy controls. After 4 weeks of drug administration, the levels of NRG-1 (type I, II, III) mRNA increased progressively and were distinctly different compared to before drug administration, but they remained lower than in healthy controls. Several studies have demonstrated a gradual increase in NRG-1 mRNA expression in epilepsy model mice treated with a ketogenic diet.[29] Moreover, our findings are comparable to those of a study that found a progressive increase in NRG-1 mRNA expression in patients with first-episode schizophrenia treated with antipsychotic

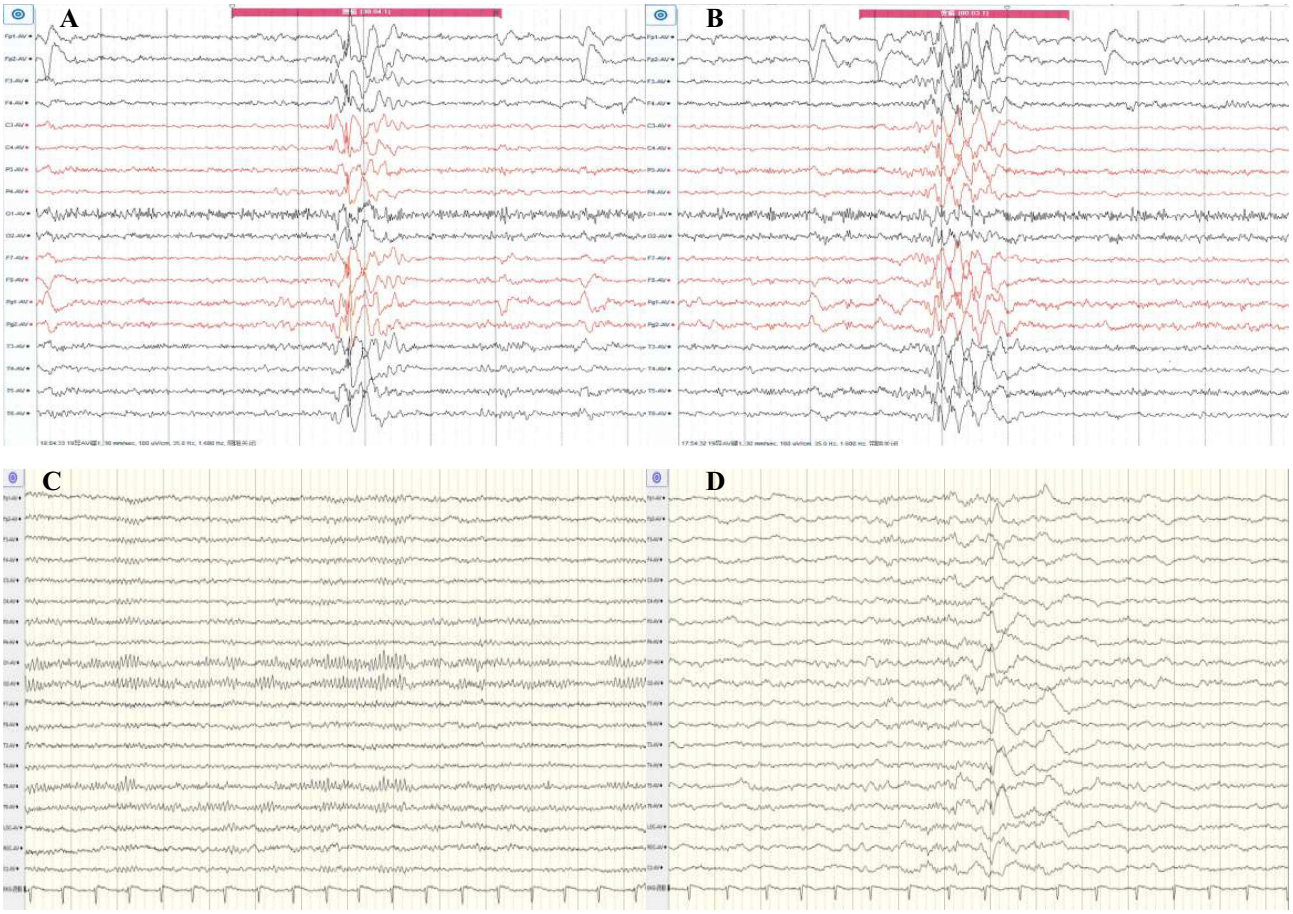

Figure 3 EEG results of epilepsy patients before and following ASM treatment. (**A** and **B**) Before treatment with ASM, the patient's VEEG revealed frequently synchronized paroxysm of short-range spike and wave complex, polyspike wave complex in both frontal regions, apparent in the right frontal area, which could spread to the adjacent leads. (**C** and **D**) After treatment with ASM, the patient's AEEG revealed spike and wave complex in the right middle and posterior temporal areas during sleep.

medication.[30] NRG-1 mRNA expression was higher in schizophrenic patients than in healthy controls, according to a separate study.[25] The schizophrenic patients included in this study were already on medication, and we hypothesize that the long-term effects of the medication may cause an increase in NRG-1 mRNA expression. Some evidence suggests that NRG-1 signaling needs to be within a certain range to function, and that exceeding this range may lead to disease-related consequences.[31] NRG-1 signaling may function as a homeostatic regulator by maintaining NRG-1 mRNA levels within an optimal range, thereby protecting the brain from seizure discharges.[32]

In contrast to the decreased levels of NRG-1 mRNA in patients with first-episode focal epilepsy, we observed higher NRG-1 protein levels in epilepsy patients both before and after drug administration than in healthy controls. Over the longer follow-up time, there were no discernible differences in NRG-1 protein levels. One study revealed that unmedicated patients with autism spectrum disorders had higher NRG-1 protein levels than healthy controls.[33] Additionally, another study on schizophrenia showed that NRG-1 mRNA and protein exhibited opposite alterations.[25] This study suggested that smoking may be one of the factors influencing NRG-1 protein levels. We hypothesize that other factors may influence NRG-1 protein levels in epilepsy patients. Symptoms such as anxiety are common in epilepsy

Table 5 Relationship Between NRG-1 mRNA and Efficacy

	Correlation coefficient	*P* value
NRG-1-I	−0.46	0.003
NRG-1-II	−0.563	0.001
NRG-1-III	−0.36	0.034

patients, and it remains to be determined whether these factors influence NRG-1 expression. In addition, mRNA and protein levels may differ due to the complexity of NRG-1 splicing and the influence of multiple post-transcriptional regulatory processes, such as protein stability and degradation, on protein levels. Moreover, weak correlations between transcripts and proteins are common in brain tissue. Since current NRG-1 antibodies cannot discriminate between isoforms, it is very difficult to compare transcripts and proteins from distinct isoforms.[34]

The majority of studies did not address the function of ASM. Our findings imply that ASM positively regulates NRG-1 mRNA levels. With the use of ASM, NRG-1 mRNA levels gradually increased, and seizures were reduced and controlled. Although long-term follow-up was not performed, transcriptional abnormalities of NRG-1 may be involved in the onset and progression of epilepsy.

Because the forms of seizures are complicated, only focal seizure patients were included in our study, which is not a large enough sample size. To determine whether other types of epilepsy also cause changes in NRG-1 mRNA and protein levels, additional sample expansion and strict subtype typing are required for more in-depth studies. Current ASM primarily acts on Glutamatergic or GABAergic neurotransmitters that directly target neurons.[30] Glutamatergic and GABAergic neurotransmission imbalances may also be relevant to the pathophysiology and treatment of epilepsy.[35] By interacting with the Glutamatergic or GABAergic transmitter system, NRG-1 may be involved in the pathophysiology of diseases such as epilepsy.[36] A discussion of the combined action of NRG-1 with Glu or GABA may be more relevant to investigate new ASM mechanisms and drug targets. Since our study did not limit the categories of ASM, further research is required to determine which medications have the most pronounced effect on NRG-1. In addition, this study is a single-center study, so further validation in other regions is required.

Conclusions

The current study is the first to comprehensively investigate NRG-1 mRNA and protein expression in the peripheral blood of epilepsy patients treated with ASM. Our findings imply that NRG-1 transcription is dysregulated in focal epilepsy and that ASM can modulate it to some extent. NRG-1 may serve as a therapeutic marker for focal epilepsy and provide ideas for identifying therapeutic targets for novel ASM.

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Disclosure

The authors declare that they have no known competing interests that could affect the work reported in this paper.

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