Title: Alteration of Neuregulin 1/Erbb4 in Absence Epilepsy: Regulatory Effect on TRPV1 Expression

Running title: Regulatory effect on ERbB4 on TRPV1 receptor in absence epilepsy

Authors: Farideh Talebi[1,2], Samira Ghorbani[2], Leila Alizadeh[2], Fatemeh Akhlaghi[3], Sedigheh Sadat Moeeni[4], Fariba Karimzadeh[3*]

1. *Immunoregulation Research Center, Shahed University, Tehran, Iran.*
2. *Shefa Neuroscience Research Center, Khatam Alanbia Hospital, Tehran, Iran.*
3. *Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran.*
4. *Department of Neuroscience and Addiction Studies, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran.*

*** Corresponding Author**: Fariba Karimzadeh, Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran. E-mail: Karimzade.f@iums.ac.ir

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Abstract

The footprint of Neuregulin 1 (NRG1) / ERbB4 in the pathophysiology of some neurological disorders and TRPV1 regulation has been indicated. The alterations of NRG1 and ErbB4 as well as TRPV1 signaling pathway was investigated during development of absence epilepsy in the genetic animal model of absence epilepsy. Male WAG/Rij and Wistar rats were divided into four experimental groups of 2 and 6 months of age. The protein level of NRG1, ERbB4 and TRPV1 were measured in the somatosensory cortex and hippocampus. The cortical protein level of NRG1 and ErbB4 in the 6-month-old WAG/Rij rats was lower than Wistar rats. Protein level of TRPV1 was lower in 2- and 6-month-old WAG/Rij rats compared to age-matched Wistar rats. Hippocampal protein level of NRG1 in 6-month-old WAG/Rij rats was lower than 2-month-old WAG/Rij rats. Low level of ErbB4 protein in 2-month-old and high level in 6-month-old WAG/Rij rats was shown compared to Wistar rats. Protein level of TRPV1 was lower in the 2-month-old and higher in 6-month- old WAG/Rij rats compared to age-matched Wistar rats. Furthermore, high correlation between NRG1/ERbB4 and TRPV1 expressions in the cortex and hippocampus was indicated. The expression of NRG1/ERbB4 and TRPV1 followed a similar pattern during life span of Wistar and WAG/Rij rats. Our findings indicated the potential role of NRG1/ErbB4 pathway as well as TRPV1 in the pathogenesis of absence epilepsy. The regulatory effect of ERbB4 receptor on the TRPV1 expression has been suggested following by the similarity pattern of expression.

Keywords: Absence epilepsy, Epileptogenesis, Cortex, Neuregulin, ERbB4, TRPV1

Introduction

Neuregulin 1 (NRG1) /ErbB4 signaling is one of essential pathways to develop central and peripheral nervous system. The role of this pathway to regulate neuronal migration, myelination, and differentiation, cortical lamination, and synaptic plasticity has been reported in the several studies (Mei & Xiong, 2008; Nave & Salzer, 2006).

This pathway is required for brain development not in the fetal period but in adulthood and its discrepancies is involved in the pathogenesis of some neurodevelopmental disorders (Mei & Xiong, 2008).

In addition, some polymorphism of NRG1 has been contributed to temporal lobe epilepsy and epileptogenesis (Tan et al., 2012; Zhu et al., 2016). It is well understood that deficit in the NRG1/ErbB4 pathway has been associated with schizophrenia in human population and animal models (Mei & Xiong, 2008; Moa & Chen, 2017). In addition, some polymorphism of NRG1 has been contributed to temporal lobe epilepsy and epileptogenesis (Tan et al., 2012; Zhu et al., 2016).

Absence seizures appear during childhood with different clinical manifestation (Maryam Jafarian, Karimzadeh, Kazemi, Divanbeigi, & Gorji, 2013). Spontaneous and synchronous spike-wave discharges (SWDs) are the main characteristics of the electroencephalogram for the absence epilepsy. WAG/Rij rats have been considered the most valid genetic model of absence epilepsy. Absence seizures appear in the adult WAG/Rij rats, mostly after 3 months of age (Karimzadeh et al., 2017). To clarify the developmental alteration of NRG1/ ErbB4 signaling pathway and TRPV1 receptor, two stages of development were assessed. Two- and six-month-old of age have been considered as the early- and late-stage of development.

In addition, imbalances between excitatory and inhibitory receptors have critical role to develop absence epilepsy (Zifkin, Andermann, & Andermann, 2005). NRG1 and its receptor ErbB4 regulated excitatory-inhibitory neurotransmission and sensorimotor gating (Agarwal et al., 2014). NRG1/ERbB4 pathway modulated GABAergic and dopaminergic transmission as well as glutamate in the synapses (Agarwal et al., 2014; Marenco et al., 2011). Over expression of NRG1 disrupted excitatory-inhibitory connections and reduced synaptic plasticity (Barros et al., 2009; Penzes, Cahill, Jones, VanLeeuwen, & Woolfrey, 2011). It has been suggested NRG1/ERbB4 signaling modulated neural excitability as well as long-term potentiation (Pitcher, Beggs, Woo, Mei, & Salter, 2008). Careful regulation of the NRG1/ErbB4 pathway preserved a

critical balance between excitation and inhibition in the nervous system. ErbB4 regulated activity of hippocampal and cortical pyramidal neurons (Buonanno, 2010; Mei & Xiong, 2008), while dysfunction of them perturbed neuronal network activity (Fisahn, Neddens, Yan, & Buonanno, 2009; Nason, Adhikari, Bozinoski, Gordon, & Role, 2011), functional connectivity and synaptic plasticity (Stefan, 2008).

Transient receptor potential vanilloid 1 (TRPV1) with permeability to Ca^{+2} ions modulated neurotransmitter release and synaptic transmission (Saffarzadeh et al., 2016). Involvement of TRPV1 in the pathogenesis of some disorders such as schizophrenia, hyperalgesia and different kind of epilepsy including temporal lobe and tonic-clonic seizures has been indicated (Chahl, 2007; Chizh et al., 2007; Shamsizadeh, Fatehi, Khajehasani, Hassanshahi, & Arababadi, 2016; Sun et al., 2013).

According the role of these pathways in the neuronal development and excitability regulation, this study evaluated alternation of NRG1/ERbB4 and TRPV1 expression during absence seizures development in the WAG/Rij rats.

Further, the regulatory effect of NRG1/ERbB4 pathway on the TRPV1 function has been shown in the sensory neurons (Canetta, Luca, Pertot, Role, & Talmage, 2011). It has been indicated lack of NRG1 level accompanied to TRPV1 deficit (Mei & Nave, 2014). This regulatory effect derived us to evaluate the correlation between NRG1/ERbB4 and TRPV1 expression during rat's life span.

Methods

Animals

Male WAG/Rij and Wistar rats were maintained in the animal lab with free access of food and water and 12 h light and dark cycle for one week and divided into four groups of two- and six-months of age (n = 6 in each group). The protocol of animal ethics had been approved by Shefa neuroscience research center.

Detecting of epileptic rats

Two silver electrodes were implanted on the parietal cortex and the reference electrode was inserted into nasal bone. Electrocortocencephalogram (ECoG) was recorded for six hours under sedated state induced by intraperitoneally (i.p.) injection of 3 μg/kg fentanyl which repeated every 20-30 min (Karimzadeh et al., 2016). Signals were amplified (EXT-02 F; NPI, Germany) and stored in a digital oscilloscope. Signals were analyzed by AxoScope 10 software. Six-month-old WAG/Rij rats were included in the study because of SWDs appearance in their ECoG (Karimzadeh et al., 2013). Two-month-old WAG/Rij rats as well as two- and six-month-old Wistar rats without any SWDs appearance in their ECoG were considered as the non-epileptic rats (M Jafarian et al., 2015).

Western blot analysis

Tissues of somatosensory cortex and hippocampus were manually dissected and homogenized in lysis buffer containing in Tris-HCl (20 mM), EDTA (1 mM), Triton 100X (1 %) and 1 mM of phenylmethylsulfonylfluoride, aprotinin, pepstatin, as well as leupeptin (1 μg/ml). Clear supernatant were gathered and the protein concentrations were measured by Bradford's test.

The same protein concentrations were loaded in 12% SDS-polyacrylamide gel electrophoresis and separated by electro blotted onto polyvinylidene difluoride (PVDF) membranes. Following by blocking, the PVDF membranes were incubated for 3 hours at room temperature with primary antibodies against ErbB4, NRG1, TRPV1 and β actin (1:500, Santa Cruz). PVDF were washed and incubated with secondary antibody (HRP- conjugated goat anti-mouse; 1:1000; Santa Cruz). Immunoreactivity was visible by ECL kit and exposed to X-ray film. The developed films were scanned by Bio-Rad scanner. The images were analysed by the monomeric bands' data with Image J software.

Statistical analysis

All data are given as mean ± S.E.M and were analysed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. The probability values were less than 0.05 was considered as significant difference. The PASW Statistics 20 was used for statistical analysis.

Results

EcoG was monitored for 6 h in all rats. Six-month-old WAG/Rij rats which indicated SWDs in their ECoG, have been considered as the epileptic rats. The mean of SWDs frequency and amplitude were 5-10 Hz and 0.5-1.5 mV, respectively. Two-month-old rats (Wistar and WAG/Rij) as well as six-month-old Wistar rats with no SWDs in their ECoG have criteria to include in the non-epileptic groups (Fig. 1).

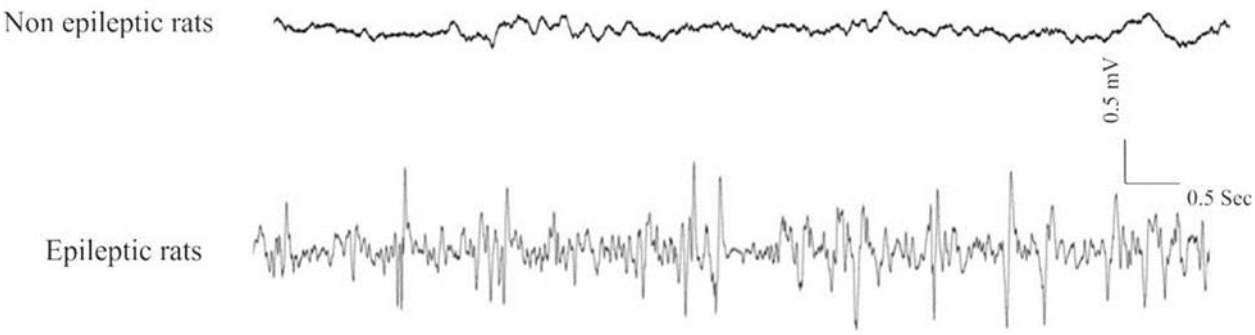

Fig 1. ECoG recording of experiments. ECoG was monitored for 6 h to identify epileptic rats. Six-month-old WAG/Rij rats indicated SWDs in the ECoG and were considered as the epileptic rats.

Cortical protein level

The total protein level of NRG1, ErbB4 and TRPV1 was measured by immunoblotting in the somatosensory cortex (Fig. 2A).

The protein level of NRG1 was significantly lower in the two- and six -month-old WAG/Rij rats compared to the six-month-old Wistar rats ($p < 0.001$, Fig. 2 B).

Furthermore, the NRG1 level of the six-month-old Wistar rats was significantly higher compared to two-month-old Wistar rats ($p < 0.001$, Fig. 2 B).

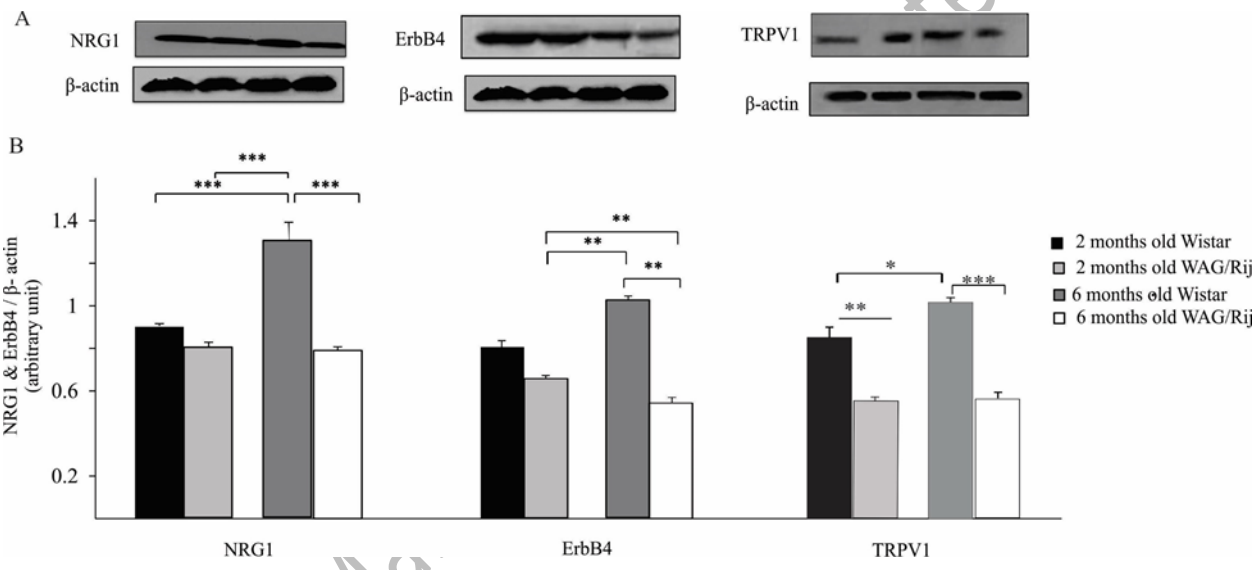

Fig. 2. Immunoblotting analyses of NRG1/ErbB4 and TRPV1 of the somatosensory cortex. A: The representative immunoblot of NRG1/ ErbB4 and TRPV1 of 2- and 6-month-old WAG/ Rij and Wistar rats is shown. B: The bar graphs indicate the quantitative results (mean ± S.E.M) of NRG1/ ErbB4 and TRPV1 protein levels in the cortex. The protein levels of NRG1/ ErbB4 and TRPV1 in two- and six-month-old WAG/Rij rats reduced compared to Wistar rats. *, ** and *** indicate $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively.

The level of NRG1 had no significant difference in two-month-old WAG/Rij rats compared to age-matched Wistar rats.

There was no significant difference in the NRG1 level between two-month-old and six-month-old WAG/Rij rats.

The protein level of ErbB4 was significantly lower in the two- and six-month-old WAG/Rij rats compared to six-month-old Wistar rats ($p < 0.01$, Fig. 2 B). Further, it was significantly lower expressed in the six-month-old WAG/Rij rats compared to two-month-old WAG/Rij rats ($p < 0.01$, Fig. 2 B). The ErbB4 level did not significantly differ between two-month-old Wistar and WAG/Rij rats.

The level of TRPV1 in two- and six-month-old WAG/Rij rats significantly was lower than age-matched Wistar rats ($p < 0.01$, Fig. 2B). TRPV1 highly expressed in 6-month-old Wistar rats compared to two-month-old Wistar rats ($p < 0.05$, Fig. 2B).

Hippocampal protein level

The total protein level of NRG1, ErbB4 and TRPV1 was measured by immunoblotting in the hippocampus (Fig. 3A).

The protein level of NRG1 was significantly lower in the six-month-old WAG/Rij rats compared to two-month-old Wistar and WAG/Rij rats ($p < 0.01$ and $p < 0.05$, respectively). There was no significant difference in six-month-old WAG/Rij rats compared to age-matched- Wistar rats (Fig. 3 B).

The protein level of ErbB4 was significantly lower in the two-month-old WAG/rij rat compared to age-matched Wistar rats ($p < 0.01$, Fig. 3B). The ErbB4 level was significantly higher in six-month-old WAG/Rij rats compared to six-month-old Wistar rats ($p < 0.001$, Fig. 3 B).

In addition, the ErbB4 level was significantly lower in the six-month-old Wistar rats compared to two-month-old Wistar rats ($p < 0.01$, Fig. 3B)

The level of TRPV1 was lower in two-month-old WAG/Rij as well as six-month-old Wistar rats compared to two-month-old Wistar rats ($p < 0.001$ and $p < 0.01$, respectively, Fig. 3B). TRPV1 highly expressed in six-month-old WAG/Rij rats compared to age-matched Wistar rats as well as two-month-old WAG/Rij rats. ($p < 0.01$, Fig. 3B).

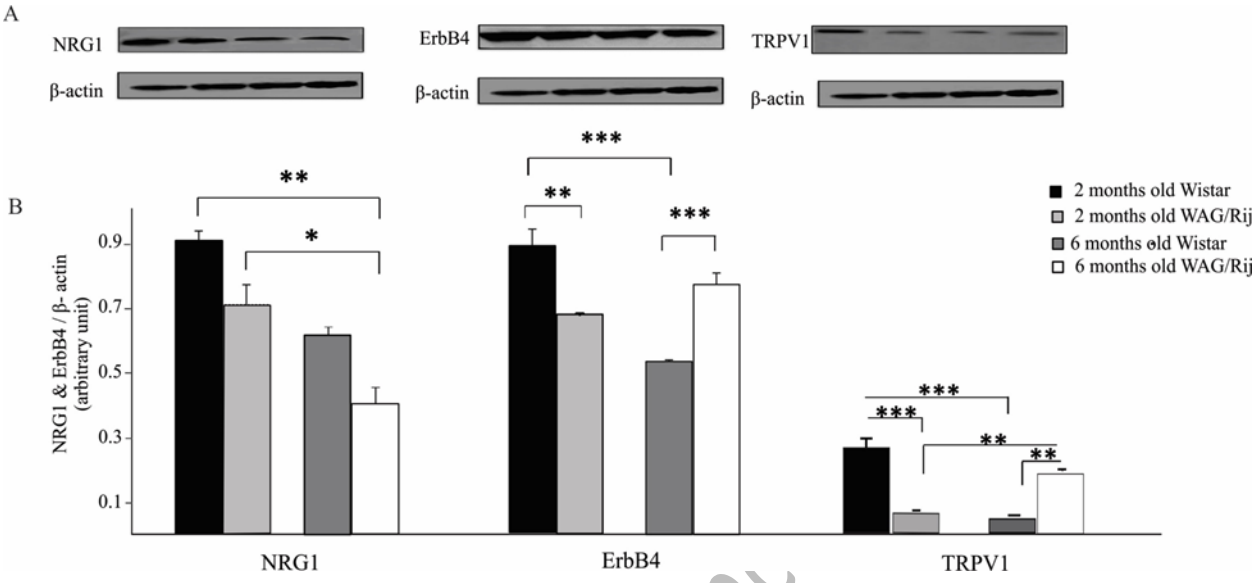

Fig. 3. Immunoblotting analyses of NRG1/ErbB4 and TRPV1 of the hippocampus. A: The representative immunoblot of NRG1/ ErbB4 and TRPV1 of 2- and 6-month-old WAG/Rij and Wistar rats is shown. B: The bar graphs indicate the quantitative results (mean ± S.E.M) of NRG1/ ErbB4 and TRPV1 protein levels in the hippocampus. The protein level of NRG1 in six-month-old WAG/Rij rats decreased but protein level of ERbB4 and TRPV1 increased compared to age-matched Wistar rats. *, ** and *** indicate $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively.

Correlation between expression of NRG1/ERbB4 and TRPV1

The correlation between protein expression of NRG1/ERbB4 and TRPV1 independently to rats' strain was analysed in the somatosensory cortex and hippocampus (Fig. 4). Cortical correlation between protein level of NRG1 and TRPV1 showed that high expression of NRG1 (Fig. 4A; r =0.6) as well as ERbB4 (Fig. 4B; r = 0.8) was accompanied by high level of TRPV1.

Hippocampal correlation between gene and protein level of NRG1/ERbB4 and TRPV1 showed high protein level of ERbB4 was accompanied by an increase in the TRPV1 protein expression (Fig. 4D; r = 0.9). There was no significant correlation between NRG1 and TRPV1 expression (Fig. 4C; r = 0.04).

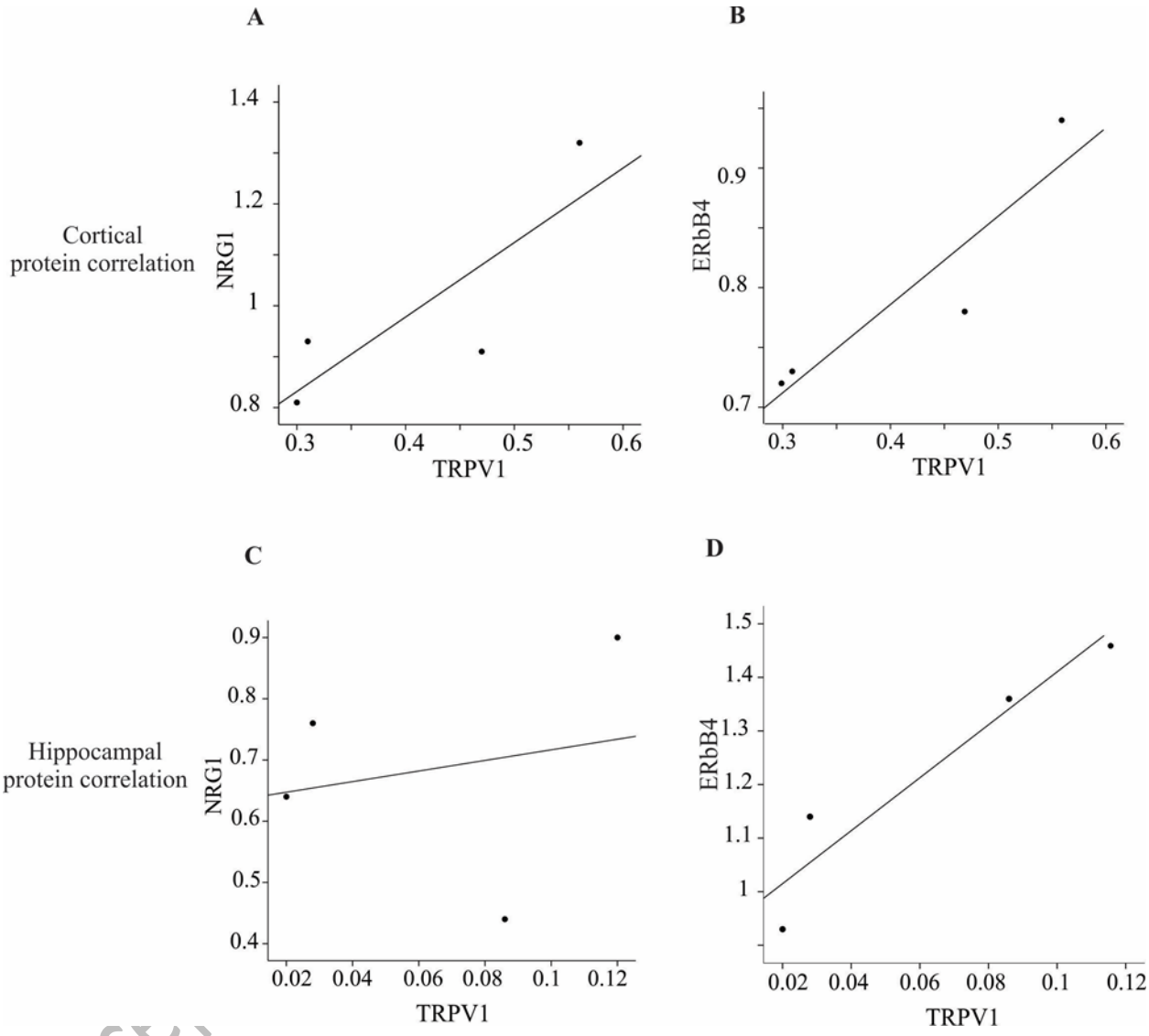

Fig. 4. The correlation between protein expression of NRG1/ERbB4 and TRPV1.

A and B) The scatter plots indicate correlation between expression of NRG1/ERbB4 and TRPV1 in the somatosensory cortex. Strong correlation between protein level of NRG1and TRPV1 as well as ERbB4 and TRPV1 has been indicated in the cortex. C and D) The scatter plots indicate correlation between expression of NRG1/ERbB4 and TRPV1 in the hippocampus. There was significant correlation between protein level of ERbB4 and TRPV1.

Discussion

Cortical expression

Our findings showed the lack of NRG1/ERbB4 as well as TRPV1 expression in the somatosensory cortex of both juvenile and adult WAG/Rij rats compared to Wistar rats.

The critical role of NRG1/ ErBb4 signaling pathway and TRPV1 receptor in the development of brain and cortical lamination has been shown (Rico & Marín, 2011; Storozhuk, Moroz, & Zholos, 2019). During development of the brain, NRG1 through the activation of ErbB2 and ErbB4 helped to radial glia survival and normal neuronal migration in the cerebellum and cerebral cortex (Anton, Marchionni, Lee, & Rakic, 1997). Further, the great role of TRPV1 receptors in the formation of healthy neuro-glial communication is impressive (Ramírez-Barrantes et al., 2016). TRPV1 promoted astrocyte migration in the inflammatory condition and its deficits reduced GFAP (as a specific marker for astrocytes) expression in the cortical and subcortical areas (Wang et al., 2019; Yang et al., 2019).

Multiple studies have insisted on the importance of astrocyte rather than neurons in the pathogenesis of several neurological disorders including epilepsy (Kim, Park, & Choi, 2019; Sidoryk-Wegrzynowicz, Wegrzynowicz, Lee, Bowman, & Aschner, 2011).

In addition, we had shown the lack of GFAP expression in the different cortical layers in the WAG/Rij rats (Karimzadeh et al., 2017).

It seems that disturbances in the cortical expression of NRG1/ERbB4 as well as TRPV1 especially in the early stage of development might be involved in the cortical astrocyte attenuation which has critical role in absence seizure pathogenesis.

In addition, NRG1 has been required to balance of excitatory and inhibitory neurotransmission in the cortex (Agarwal et al., 2014). NRG1 regulated cellular properties associated with GABAergic interneurons and increased excitatory synaptic transmission of GABAergic interneurons in the hippocampal neurons (Longart, Liu, Karavanova, & Buonanno, 2004; Yau, Wang, Lai, & Liu, 2003). NRG1 was also capable to induce the GABAa receptors in the cerebellar granular cell culture (Ozaki, Kishigami, & Yano, 1998; Rieff et al., 1999).

ErbB4 receptor is the main signaling partner of NRG1 signaling pathway (Birchmeier, 2009). The widespread expression of ErbB4 receptor has been shown in the cortical inhibitory interneurons of humans and primates (Neddens & Buonanno, 2011; Rieff et al., 1999; Vullhorst

et al., 2009). Cortical mRNAs of ErbB4 are expressed by dispersed GABAergic neurons (Lai & Lemke, 1991; Woo et al., 2007).

Further, it has been reported TRPV1 modulated GABAergic synapses (Chávez, Hernández, Rodenas-Ruano, Chan, & Castillo, 2014). It has been suggested that TRPV1 could regulate excitatory afferents to GABAergic interneurons (Ferrini, Salio, Vergnano, & Merighi, 2007; Liao, Lee, Ho, & Chiou, 2011).

It seems that cortical decrease of NRG1/ ErbB4 signaling and TRPV1 activity in the epileptic WAG/Rij rats led to deficit in the inhibitory inputs of pyramidal cells and decrease GABA release from cortical interneurons. Deficits in cortical inhibitory transmission and synapses probably trigger SWDs firings in the epileptic WAG/Rij rats.

Hippocampal expression

We showed high expression of hippocampal NRG1 / ErBb4 and TRPV1 at the early stage of Wistar's life span (two months of age) but not in WAG/Rij rats.

The role of NRG1 in synaptic differentiation such as dendritic spine size, modulation of long-term potentiation (LTP) and enhancement of entorhinal-hippocampal synaptic transmission has been reported (Kwon, Longart, Vullhorst, Hoffman, & Buonanno, 2005; B. Li, Woo, Mei, & Malinow, 2007; X.-M. Li et al., 2014; Roysommuti, Carroll, & Wyss, 2003; Shamir et al., 2012). It has been shown NRG1 improved cognitive impairment induced by isoflurane in the aged mice (X.-M. Li et al., 2014). NRG1/ ErbB4 activation compensated the impairment of LTP induced by Aβ1-42 in the hippocampal slices (Min et al., 2011).

In addition, TRPV1 had dramatic role in the regulations of hippocampal synaptic transmission (Hurtado-Zavala et al., 2017). TRPV1 receptors were highly expressed in the molecular layer of the hippocampus. These cells could process inputs/outputs in the hippocampal layers (Anstötz, Lee, & Maccaferri, 2018).

Behavior, emotional and cognitive deficits have been indicated in children who suffer from absence epilepsy and epileptic WAG/Rij rats (Caplan et al., 2008; M Jafarian et al., 2015; Masur et al., 2013). It seems that deficits of NRG1/ERbB4 as well as TRPV1 expression in the early stage of life span of WAG/Rij rats disrupted development of the hippocampus and might impair memory and cognition in the adult WAG/Rij rats.

In addition, hippocampal TRPV1 expression increased in adult (epileptic) WAG/Rij rats but not in adult Wistar rats.

It has been reported TRPV1 receptor increased seizure susceptibility in the chemically induction of seizures (Kong et al., 2014). Hippocampal expression of TRPV1 increased in the patients and animal model with mesial temporal lobe epilepsy (Gonzalez-Reyes, Ladas, Chiang, & Durand, 2013; Sun et al., 2013).

In addition, hippocampal glutamate release enhanced following by endogenous cannabinoid administration (Gonzalez-Reyes et al., 2013). Activation of TRPV1 increased toxicity and cell death in dorsal root ganglions and neocortex (Olah et al., 2001; Shirakawa et al., 2008).

Furthermore, we showed that ERbB4 expression increased in adult epileptic WAG/Rij rats.

It has been reported that down-regulation of ErbB4 in the hippocampal interneurons improved learning and memory in the animals with genetically manipulated of ErbB4 receptors (Tian et al., 2017). Enhancement of LTP in the genetically deficient of hippocampal ErbB4 has been indicated (Pitcher et al., 2008).

In addition, ErbB4 selectively expressed in the hippocampal interneurons and has regulatory effect on glutamatergic synapses on the inhibitory interneurons (Vullhorst et al., 2009). These evidences showed reciprocal role of ERbB4 receptor in neuronal excitability as well as memory encoding in the hippocampus. It seems that decrease of ERbB4 expression is required for adult hippocampal function. High level of hippocampal ERbB4 as well as TRPV1 receptor in the adult WAG/Rij rats probably has developed absence seizures in the WAG/Rij rats.

Signaling correlation between NRG1/ERbB4 and TRPV1

We showed high correlation between NRG1 or ERbB4 and TRPV1 expressions in the neocortex and hippocampus. The expression of NRG1 or ERbB4 and TRPV1 follows a similar pattern during life span of Wistar and WAG/Rij rats. Increase of NRG1 or ERbB4 expression is accompanied by high level of TRPV1 in Wistar rats. Deficit in the NRG1 or ERbB4 expression is accompanied by diminution of TRPV1 in WAG/Rij rats.

It is well understood that interaction between NRG1 and ERbB receptors can facilitate cell-cell communication during development of brain to form healthy functional synapses (Bao, Wolpowitz, Role, & Talmage, 2003; Leimeroth et al., 2002).

Activation of tyrosine kinase domain of ERbB4 receptor leads to phosphorylation of intracellular domain and results in the main signaling cascades downstream of NRG1/ERbB4 pathway. The

mitogen-activated protein kinase (MAPK) pathway as well as phosphoinositide 3-kinase (PI3K) are the main downstream cascades of this signaling (Liu, Tao, Woo, Xiong, & Mei, 2007).

NRG1 modulated the functional TRPV1 in the sensory neurons (Bao et al., 2004). Back signaling of ERbB4 enhanced TRPV1 receptors through the activation of phosphatidylinositol-3-kinase (Bao et al., 2004; Canetta et al., 2011).

It has been suggested that activation of PI3K by NRG1 back signaling, up-regulated TRPV1 receptors. Intra cellular domain of NRG1 is required to activate PI3K and effect on the TRPV1 regulation (Canetta et al., 2011). Furthermore, activation of MAPK in the injured neurons of dorsal roots ganglions hyper synthesized TRPV1 receptors (Chen et al., 2016).

In addition the role of TRPV1 receptors in the epileotpgenesis has been reported. Cortical as well as hippocampal TRPV1 receptors highly expressed in the epileptic people suffering with temporal lobe epilepsy (Sun et al., 2013). Functional discrepancies of TRPV1 receptors altered the seizure susceptibility in the animal model of tonic-clonic epilepsy(Jia et al., 2015). In contrast, epileptogenesis were postponed by administration of TRPV1 agonist in the kainic acid model of epilepsy (Lee et al., 2011).

According our findings, alteration of NRG1/ ERbB4 signaling pathway disturbed TRPV1 expression and might triggered SWDs appearance during development of WAG/Rij rats.

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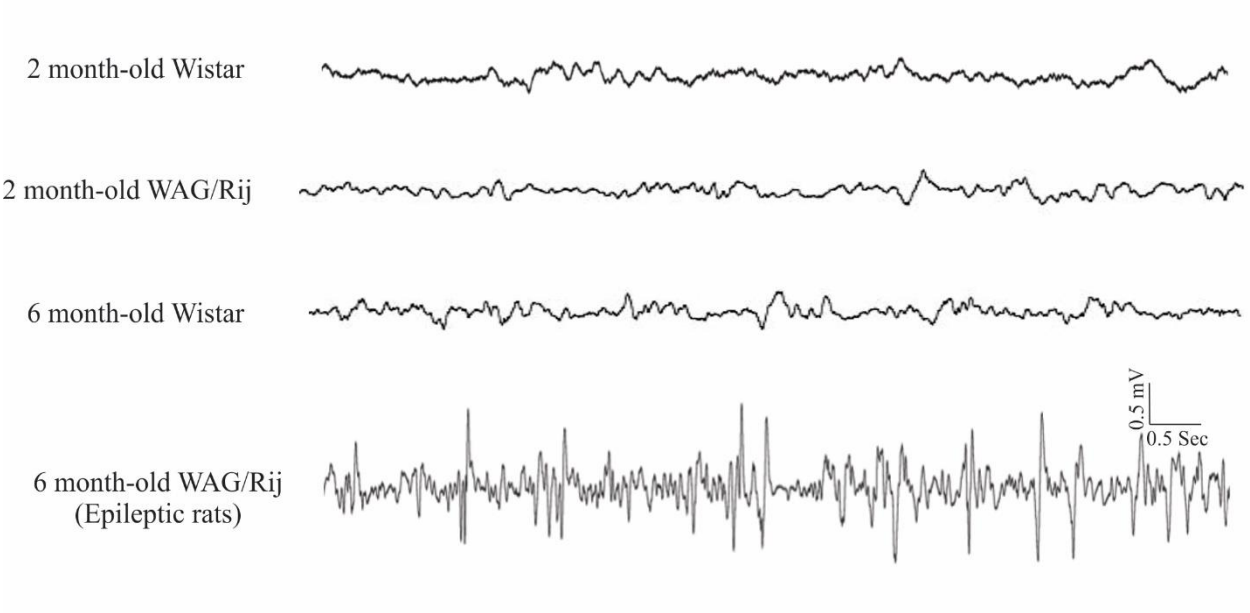
Conflict of interest

All authors declare that they have no conflict of interest.

Legends



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