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Investigation of The Effects of Endogenous BDNF on Kainic Acid Induced Seizures

Endojen BDNF'nin Kainik Asit Kaynaklı Nöbetler Üzerindeki Etkilerinin İncelenmesi

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ABSTRACT

Brain derived neurotrophic factor (BDNF), a major mediator of plasticity in the central nervous system. Due to fast synaptic actions of BDNF, it is thought to be a modulator of excitability in neuronal circuitry. There is a two sided relationship between BDNF and epileptic activity. BDNF levels increase following seizure or kainate administration. Additionally, BDNF administration causes hyperexcitability. BDNF deficiency attenuates seizures or epileptiform activity in several epilepsy models. In this study, our aim was to investigate modulatory effects of reduced endogenous BDNF on kainic acid (KA) induced seizures. For this purpose, BDNF heterozygous mice and their wild type littermates were compared. Animals were injected intraperitoneally with either vehicle (0.9% saline) or kainic acid (15 mg/kg). Four groups were formed: vehicle (saline, SA) injected wild type (SA-WT; n=9) and BDNF heterozygous mice (SA-HT; n=9), kainic acid injected wild type (KA-WT, n=10) and BDNF heterozygous mice (KA-HT, n=10). Racine scorings were determined for 5 min epochs from the video recordings. In the hippocampal tissue synaptic markers proteins synaptophysin (SYP), post-synaptic density (PSD-95) and inflammatory markers interleukin-6 (IL-6) and tumor necrosis factor Alpha (TNF-α) were measured. Besides, oxidative stress parameters were evaluated. KA-WT group's score were higher at 20 and 25 min than that of KA-HT group ($p<0.05$). MDA levels were higher in kainic groups ($p<0.05$). Kainic acid did not affect neuroinflammation and synaptic proteins significantly. Our results showed that reduced BDNF temporarily posed a resistance against seizure but intact levels of BDNF failed to protect against oxidative stress in kainic acid model.

Keywords: BDNF, Kainic acid, Epilepsy, Synaptic proteins, Oxidative stress

ÖZET

Beyin kaynaklı nörotrofik faktör (BDNF), merkezi sinir sisteminde plastisitede rol oynayan önemli bir peptittir. BDNF'nin hızlı sinaptik etkileri nedeniyle, nöronal devrede uyarılabilirliği düzenlediği düşünülmektedir. BDNF ile epileptik aktivite arasında iki yönlü bir ilişki vardır. Nöbet veya kainat uygulamasını takiben BDNF seviyeleri yükselir. Bunun yanında, BDNF uygulaması aşırı uyarılabilirliğe neden olur. BDNF eksikliği, birkaç epilepsi modelinde nöbetleri veya epileptiform aktiviteyi azaltır. Bu çalışmada amacımız, azaltılmış endojen BDNF'nin kainik asit (KA) kaynaklı nöbetler üzerindeki modülatör etkilerini araştırmaktı. Bu amaçla BDNF heterozigot fareler ve bunların yabani tip kardeşleri karşılaştırıldı. Hayvanlara %0.9'luk tuzlu su çözeltisi veya kainik asit (15 mg/kg) intraperitoneal olarak verildi. Dört grup oluşturuldu: tuzlu su (saline, SA) enjekte edilen yabani tip fareler (SA-WT; n=9) ve BDNF heterozigot fareler (SA-HT; n=9), kainik asit enjekte edilen yabani tip (KA-WT, n=10) ve BDNF heterozigot fareler (KA-HT, n=10). Video kayıtlarından 5 dakikalık periyotlarla 120 dakika boyunca Racine skorları belirlendi. Hipokampal dokuda, sinaptik proteinler sinaptofizin (SYP) ve PSD-95'in yanında inflamatuar belirteçler interlökin-6 (IL-6) ve tümör nekroz faktörü alfa (TNF-α) ölçüldü. Ayrıca oksidatif stres parametreleri değerlendirildi. KA-WT grubunun skoru 20 ve 25. dakikada KA-HT grubuna göre daha yüksekti ($p<0.05$). MDA düzeyleri kainik gruplarda daha yüksekti ($p<0.05$). Kainik asit, nöroinflamasyonu ve sinaptik proteinleri önemli ölçüde etkilemedi. Sonuçlarımız, azalmış BDNF'nin geçici olarak nöbete karşı bir direnç oluşturduğunu, ancak normal BDNF düzeylerinin kainik asit modelinde oksidatif strese karşı koruma sağlamadığını gösterdi.

Anahtar Kelimeler: BDNF, Kainik asit, Epilepsi, Sinaptik proteinler, Oksidatif stres

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INTRODUCTION

Brain derived neurotrophic factor (BDNF), a member of neurotrophin family is widely distributed in the central nervous system, with the highest expression levels in the hippocampus and cortex which are involved in learning, memory, excitability and plasticity.[1,2] Relevant to its trophic roles, BDNF is required for normal functional development of neuronal structures, maturation and maintenance of synaptic transmission. However, BDNF changes the synaptic transmission within minutes.[3] BDNF exerts its neuronal roles both in presynaptic and postsynaptic functions. Presynaptic actions of BDNF is to increase glutamate release, phosphorylate synapsin, a presynaptic protein that is involved in synaptic transmission[4], and postsynaptically BDNF phosphorylate NMDA receptors.[5] Thus, BDNF may be an endogenous modulator of excitability in adult brain. Studies have shown that the level of BDNF protein increased after kindling[6] and kainate administration.[7] Exposure to exogenous BDNF can lead to hyperexcitability in cultures[8] and in brain.[7] In line with this hypothesis, kindling was prevented in BDNF knockout mice[9]. Besides, BDNF heterozygous mice were slightly more resistant to an experimental focal epilepsy model and reduced Gamma band activity in their Ecog recordings.[10] On the other hand, in transgenic mice overexpressing BDNF, seizures in response to kainic acid were more severe and even spontaneous seizures were observed in some animals.[11] However, the alterations in BDNF levels in response to epileptic insults may be a protective action of BDNF. Indeed, some studies suggest exogenous BDNF has a protective action in epilepsy.[12-14] As can be seen, there are conflicting results in the literature on BDNF and epilepsy. Apart from its roles as a neurotrophic factor and a neuromodulator peptide, BDNF more lately shown to act as a supporting factor of antioxidant systems[15] and contributes to anti-inflammatory mechanisms in the central nervous system.[16] In fact BDNF heterozygous mice have been shown to have higher inflammation and higher oxidative stress in the brain tissues.[17] Systemic administration of kainic acid (KA) induces epileptic seizures and neuroexcitotoxicity in animal models.[18] KA binds to kainate receptors which are ionotropic non-NMDA (N-methyl-D-aspartate) glutamate receptors. KA activates glutamate receptors and this over stimulation of glutamate receptors causes influx of calcium ions, production of superoxide radicals, and mitochondrial dysfunction leading to neuronal apoptosis and necrosis.[19] Administration of kainic acid leads to seizures[20], behavioral changes[21], oxidative stress[22], and inflammatory responses.[23,24] Although these effects of KA are well known, effects on synaptic proteins responsible for synaptic vesicular trafficking are not known. The concentrations of synaptic proteins are directly related to the neuronal function and we wanted to test whether kainic acid induces any changes in synaptic protein levels. In this study, our aim was to define the seizure severity of BDNF heterozygous mice in kainic acid model of epilepsy. Besides, we investigated the possible protective role of BDNF against kainic acid induced inflammation and synaptotoxicity.

METHODS

Animals

The study was approved by Karadeniz Technical University Animal Care and Ethics Committee (approval number: 2017/38). All experimental procedures were performed in Karadeniz Technical University Surgical Application and Research Center. Male BDNF heterozygous and their wild type litter mates were used in this study. In total 38 male mice aging 5-6 months weighing 20-25 g housed 3-4 animals per cage under regulated temperature and humidity in the 12 h light-dark cycle. BDNF heterozygous mouse model used in the present study was established by Korte and coworkers.[25] Heterozygous knockout model is characterized by one missing allele of the BDNF coding region. This allele was replaced by NEO, a neomycine-resistance gene. BDNF heterozygous mice (BDNF (+/−)) are viable and fertile. Mice are produced by crossing a male BDNF (+/-) with a normal wild-type female mouse, BDNF (+/+). The phonotypes of wild-type and heterozygous age matched male mice were compared for the study. To determine the genotype of the mice, the presence of the NEO was verified by polymerase chain reaction (PCR). The tissue for genotyping was collected from tail tissue. Animals were randomly divided into four groups. All animals were injected intraperitoneally (ip) with either vehicle (0.9% saline) or kainic acid at a dose of 15 mg/kg body weight. The groups were vehicle injected wild type (SA-WT) and BDNF heterozygous mice (SA-HT), kainic acid injected wild type (KA-WT) and BDNF heterozygous mice (KA-HT). Injections were made in the morning

between 9:00 and 9:30 as a single dose. After 24 hours from injection, animals were decapitated and brains were removed and dissected to separate right and left cortices and hippocampus. Until the biochemical analysis the tissues were stored at -80 °C.

Behavioral Seizures

Behavioral observations were recorded for 120 min after vehicle or kainic acid injections. Each animal was placed in a plastic cage separately and video recordings were made to verify neurological effects. Onset of seizure latency and seizure incidence were measured offline. Racine scoring[26,27] were used to assess convulsive behavior. Score 0: no abnormal behavior; Score 1: freezing briefly, staying immobile; Score 2: facial and whisker automatism; Score 3: clonic head bobbing; Score 4: forelimb clonus; Score 5: clonic rearing; Score 6: generalized seizures: shivering, falling and jumping. Scores 1–4 were accepted as low-grade or mild seizures. Scores 5–6 are accepted as high-grade or severe seizures. The behavioral experiments were recorded to a personal computer by using a camera. The analysis was made offline. During the analysis and scoring, the researcher was blinded to group or number of the animals.

Enzyme-linked immunosorbent assay (ELISA)

ELISA was used for the determination of cortical concentration of synaptophysin protein (SYP) and postsynaptic density 95 kD (PSD-95) protein and the levels of neuroinflammation markers IL-6 and TNF-α. For ELISA measurement, left cortex of each mouse were separated and processed. Lysis buffer (1 mg/tissue weight) contained: 137 mM NaCl, 2.7 mM KCl, 1.5 mM KH_2PO_4, 7.7 mM Na_2HPO_4, 1% Triton X-100, 5 mg/mL aprotinin, 5 mg/mL leupeptin m, pH 7.4. Then the cortical tissue was homogenized by an ultrasonic cell disrupter (Sonics vibracell, Newtown, CT, USA) and the suspension was centrifuged at 20,000 x g for 20 min. The supernatant was used for ELISA tests. TNF-α, IL-6, SYP and PSD-95 levels were determined by using enzyme-linked immunosorbent assay (ELISA) kits (Elabscience, Catalog No: E-EL-M0049, E-ELM0044, E-EL-M1105 and USCN, Catalog No: SEG168Mu, respectively) according to the manufacturer's guide. Samples and standards absorbance were measured at 450 nm by using tunable microplate reader (VERSA max, Molecular Devices, Sunnyvale, CA, USA). Results were expressed as ng/mL.

Tissue malondialdehyde (MDA) measurement

Right cortex of the mice was used for oxidative stress parameters. Tissue was homogenized in 2 mL ice-cold buffer 1.15% KCl solution containing 0.5 mL/L Triton X-100. MDA concentrations were measured from homogenates according to method by Mihara and Uchiyama.[28] Tetramethoxypropane was used as standard solution. MDA levels were expressed as nmol/ml per gram of wet tissue.

Measurements of tissue antioxidant enzyme activities

For measurement of superoxide dismutase (SOD) and catalase (CAT) activities, tissues were homogenized in 2 ml ice-cold Tris-HCl buffer (50 mmol/L, pH = 7.4). SOD activities were measured by the method of Sun et al.[29] This method essentially is based on reduction of nitroblue tetrazolium by xanthine/xanthine oxidase system. SOD activity was given in U/mg protein. CAT activities were determined by the method of Goth.[30] This method utilizes H_2O_2 and ammonium molybdate stable complex. The yellow complex was measured at 405 nm. CAT activities were expressed as kU/mg protein. For determination of protein concentrations, the tissue lysates were used. Bicinchoninic acid protein assay kit was used (Merck Millipore, Darmstadt, Germany) and results were expressed as mg/mL.

Statistical analysis

5 min Racine scores were compared between KA-WT and KA-HT groups by using paired t test. One way ANOVA was used for the statistical analysis of biochemical data of each group. For multiple comparisons Tukey's post hoc test was used. All the statistical tests were performed by using GraphPad Prism software. Data were presented as means ± SEM. For the significance $p < 0.05$ was accepted.

RESULTS

Behavioral seizure

All mice that injected kainic acid (KA) were observed and video recorded for 2 hours. Racine scorings were determined for 5 min epochs from the video recordings. The wild type or heterozygous mice received saline (SA-WT and SA-HT groups) did not exhibit any seizure like behavior. Hence their scores were 0 for all time epochs. Their scores also removed from the graph. The other two groups received kainic acid injections and developed seizures which were eminent from the behaviors. There were no significant differences in onset of seizure latency between two groups. Racine scores were significantly different between KA-WT and KA-HT group only in two 5 min epoch that are 20 and

25 min ($p<0.05$) (Figure 1). KA-WT group's score were higher at this time points than that of KA-HT group. At these time points, the seizures were more severe in wild type than BDNF heterozygous animals.

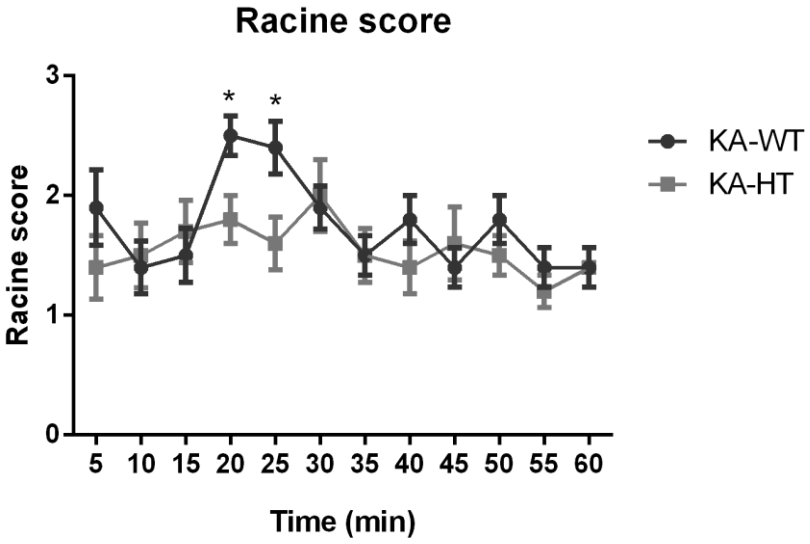

Figure 1. Seizure severity of the mice were evaluated according to Racine Scorings. The mice received kainic adic injections showed epileptic seizures. The seizure of BDNF heterozygous mice (KA-HT) were significantly milder than wild types (KA-WT) after 20 to 25 minutes kainic adic injections (*: $p<0.05$). The control groups for this experiment received saline and did not showed any epileptic behavior. The scores of all the mice in saline groups (SA-WT and SA-HT) were zero and were not included in the graph.

Oxidative Stress Neuroinflammation

To search the effects of KA injection on oxidative stress parameters were measured brain MDA level, SOD and CAT activity. MDA levels were significantly different between groups according to one way ANOVA test ($F(3.34) = 10.82$, $P < 0.0001$). MDA levels were importantly higher in KA-WT and KA-HT compared to SA-WT groups according to Tukey's post hoc test ($p=0.0075$ for KA-WT group and $p=0.0004$ for KA-HT group). MDA levels in the groups that received KA were also significantly higher than that of SA-HT group ($p=0.0082$ for KA-WT group and $p=0.0005$ for KA-HT group). MDA levels of all groups were shown in Figure 2A. One way ANOVA showed no significance in SOD ($F(3.34) = 1.793$, $p> 0.05$) and CAT activities ($F(3.34) = 1.952$, $p>0.05$) between groups (Figures 2B and 2C).

Neuroinflammation

The effects of KA injection to wild type and BDNF heterozygous mice on neuroinflammation were investigated by measuring the levels of cortical levels of interleukins (IL-6β) and tumor necrosis factors (TNF-α). Statistical analysis displayed no significance in IL-6β ($F(3.34=0.766$, $p>0.05$) and TNF- α ($F(3.34)=1.343$, $p>0.05$) differences between the groups (Figure 3A and 3B).

Synaptic Proteins

In this study, KA administration to mice did not affect the synaptophysin protein (SYP) and postsynaptic density 95 kD (PSD-95) protein levels. One way ANOVA revealed no significant differences in synaptic proteins between the groups ($F(3.34)= 0.371$, $p>0.05$ for SYP; $F(3.34)=0.216$, $p>0.05$). The levels of synaptic proteins are shown in Figure 4A and 4B.

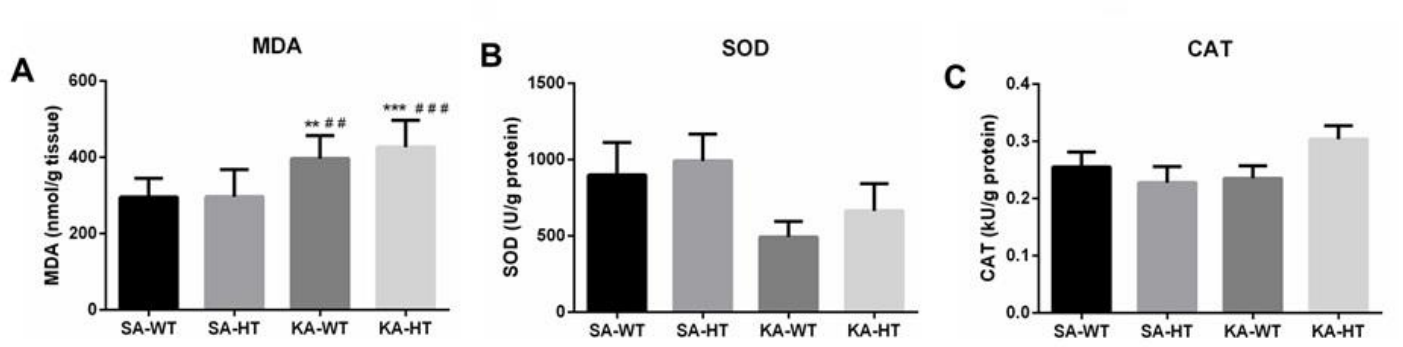

Figure 2. Oxidative stress parameters measured in the hippocampus tissues are shown. BDNF concentration did not affect the oxidative stress parameters. A. Kainic acid significantly increased MDA levels. MDA levels of KA-WT group (##: p< 0.01 , **: p< 0.01) and KA-HT group were higher than the SA-WT and SA-HT groups (###: p<0,001, ***: p< 0.001) B and C show the SOD and CAT activity in the hippocampal tissue homogenates. Antioxidant enzymes were not changed after kainic acid administration.

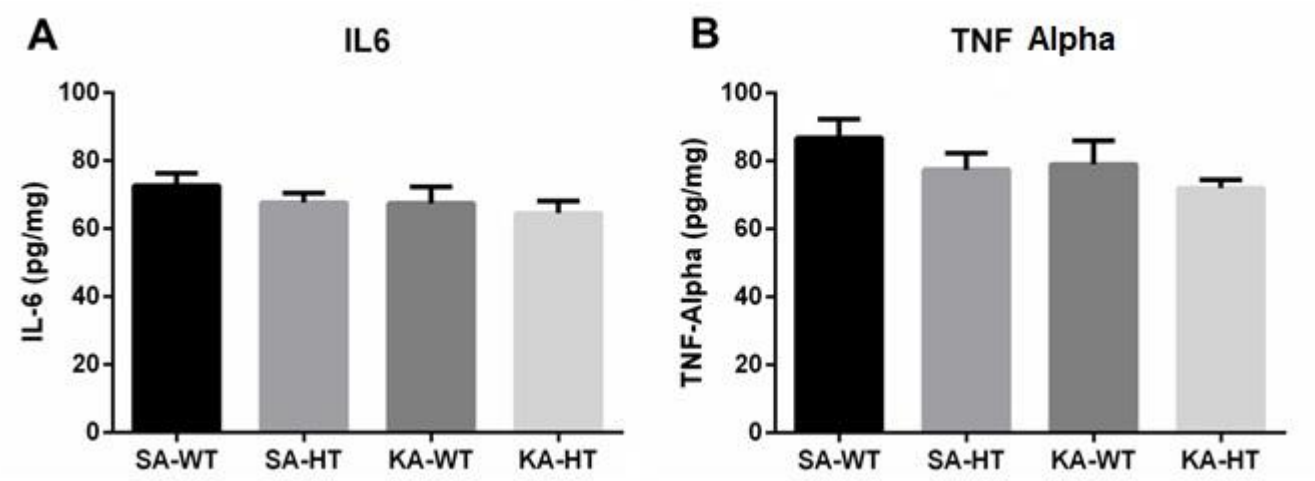

Figure 3. IL-6 and TNF alpha levels were measured in the hippocampus. Inflammation markers showed no change following kainic acid administration. In the hippocampus tissues of BDNF heterozygous mice, inflammation markers were not different than the wild type group.

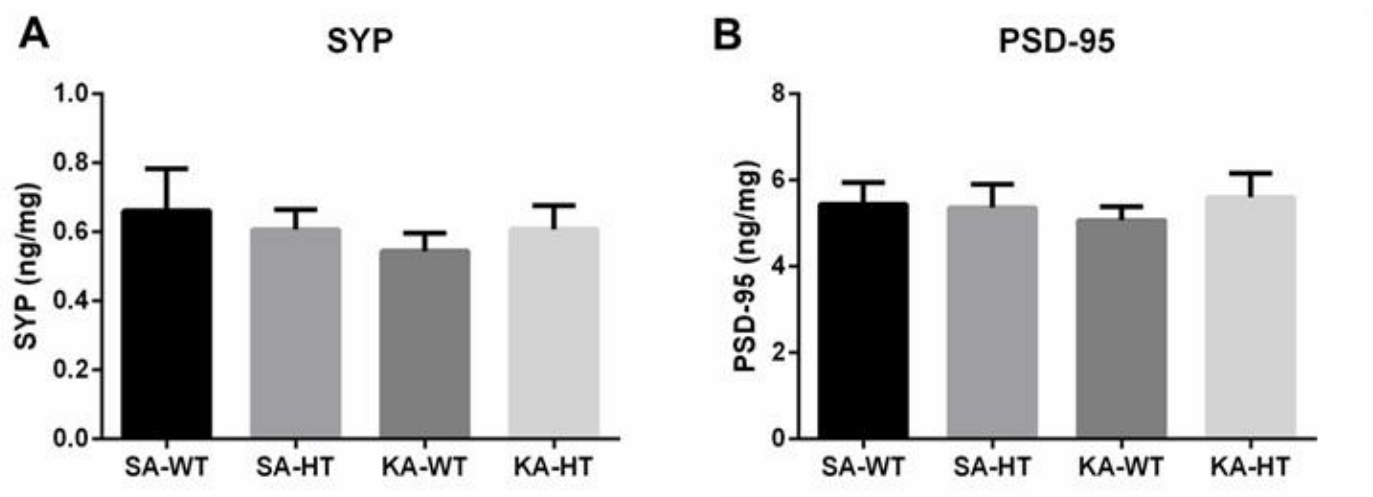

Figure 4. As a biochemical correlate of behavior and possible loss of function, synaptic protein levels measured in the hippocampus tissues. A typical presynaptic protein (synaptophysin (SYP)) and a postsynaptic protein (postsynaptic density 95 kD (PSD-95)) has been chosen and measured by ELISA. SYP and PSD-95 concentrations in the hippocampus tissues were not altered.

DISCUSSION

Since its discovery, BDNF is essentially considered as a neurotropic factor that is pivotal for the adaptive long-term changes in the central nervous system. Yet, it has been proposed that BDNF acts as a neuroprotective, anti-inflammatory and antioxidant properties as well. Kainic acid binds to kainat receptors which are ionotropic glutamate receptors and leads to potent excitatory post synaptic currents. This unusual strong activation of kainat receptors results in unbalanced excitation which in turn triggers seizures. Sustained activity also results in oxidative damage, inflammation and loss of neuronal function.[19,22,23] In the present study, we aimed to reveal the role BDNF on the severity of kainic acid induced seizures. Besides, we investigated whether BDNF poses a protective role against kainic acid induced changes in the hippocampus. Our data showed i) BDNF heterozygous mice slightly more resistant to kainic acid induced seizure. ii) Kainic acid application increased the lipid peroxidation but had no effect of synaptic proteins and inflammation markers. BDNF heterozygous mice lack one BDNF coding alleles in their genome and in the brain these mice express nearly %40-50 lower levels of BDNF.[31] It has been a useful model to study the physiological roles of BDNF since the heterozygous mice did not show abnormal phenotype.[32,33] The epileptic phenotype of BDNF heterozygous mice has been investigated in different experimental models. In a kindling model BDNF heterozygous mice more resistant[9] and in an electrically induced seizure model, BDNF heterozygous mice did not differ from the wild type littermates.[34] In another study, similar to present findings BDNF heterozygous mice showed reduced frequency of electrical discharges in their electro-corticogram activities in a focally induced epilepsy model.[10] Apart from the above mentioned findings, in the present study, for the first time we showed that, in kainic acid model too, BDNF heterozygous mice were slightly more resistant to epileptic seizures. This finding of ours is in line with the previous reports. In general, the BDNF/Trk-B signaling favors the excitation and disrupted Trk-B signaling reduced the excitation.[35,36] In kainic acid model, we can argue that, reduced levels of BDNF in hippocampus led to suppressed levels of excitability which eventually resulted in a less severe epileptic seizure. Epileptic seizures often lead to elevated inflammation and oxidative stress in the brain. In this study, we also tested whether BDNF has an antiinflammation and/or antioxidant role in kainic acid induced seizure model. The relation between BDNF and neuroinflammation in various experimental models of neurological disorders and neurodegenerative diseases are well documented.[37] Studies showed that BDNF had anti-inflammatory effects both in vitro and in vivo[38]. In BDNF heterozygous mice, upon LPS administration, higher inflammation levels were measured compared to wild type.[39] In our study, the kainic acid administration did not lead to increased levels of measured inflammation markers. Hence, we could not evaluate whether BDNF posed a protection against inflammation. We have used the lowest dose of kainic acid (15 mg/kg) to be able to reveal the difference between heterozygous and wild type animals. Higher doses would create a stronger effect in both groups and the hypothesized differences would be lost. Unlike the neuroinflammation markers, lipid peroxidation levels were increased in kainic acid groups. Kainic acid administration increased the MDA levels in hippocampus. BDNF was shown to support the antioxidant systems in various studies.[15,17] However, in the present work, wild type and heterozygous mouse exhibited similar MDA levels, indicating that the reduced BDNF levels did not further exacerbate the lipid peroxidation. This result contradicts with the literature. The model used in this study was different than the other reports. The pathway that kainic acid induced lipid peroxidation might be independent of the BDNF-Trk-B pathway. Neurons are strong cells that are resistant to many challenging conditions. We thought that, following kainic acid administration, there may not be a neuronal loss. However, in such mild to moderately harmful conditions, number of synaptic contacts is lost between the neurons which in turn reduce the performance. The number of functionally active synapses is directly correlated to synaptic proteins. In our study we measured two synaptic proteins: a major presynaptic protein synaptophysin protein (SYP) and a postsynaptic protein postsynaptic density 95 kD (PSD-95). To our knowledge, there is only one study to investigate the effects of KA on synaptic proteins. However, in that study, they investigated the effects of administration of KA to 7 days old (P7) rat on synaptic markers in adulthood (P100). They observed a decrease in two synaptic markers, SNAP-25 and syntaxin.[40] Similar to inflammatory markers, we did not observe any changes in the levels of synaptic proteins. Kainic acid

administration did not result in reduced number of synapses. Higher doses of kainic acid probably could have triggered a stronger seizure and led to loss of synapses.

CONCLUSION

In kainic acid induced seizure model, weakened BDNF signaling led to milder seizures. Slight and transient seizures are associated with increased lipid peroxidation but did not result in increased neuroinflammation. Similarly, synaptic proteins were not affected.

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Authorship contribution statement

Consept and desing: SAA, İA

Acquisition of data: HK, ES.

Analysis and interpretation of data: SAA, İA and AA.

Drafting of the manuscript: SAA, İA.

Critical revision of the manuscript for important intellectual content: İA.

Statistical analysis: SAA.

Supervision: SAA.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

This study was approved by the Local Animal Research Ethics Committee of Karadeniz Technical University.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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