Epilepsy Research 151 (2019) 1–6

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Protective effects of lycopene on kainic acid-induced seizures

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ARTICLE INFO

Keywords:
Lycopene
Seizures
Oxidative stress
Kainic acid
GABA receptors

ABSTRACT

Lycopene (LCP) is a carotenoid that protects against many diseases by alleviating oxidative stress. However, the effect of LCP on epileptic seizures has not been examined well in previous studies. In the current work, we employed kainic acid (KA) to induce experimental epileptic seizures in mice, and investigated the function of LCP during this process. We found that the onset and extent of KA-induced seizures were alleviated in LCP-pretreated mice. Nissl staining of hippocampus showed that the granule cell dispersion lesion induced by KA was improved by the LCP treatment. Additionally, we analyzed the oxidative stress levels in mice and found that LCP elevated SOD activity and suppressed MDA level in KA-induced seizures. Moreover, the expression of GABA receptors was influenced by LCP treatment. LCP suppressed the upregulation of gabrb2 and gabrb3 induced by KA, whereas it enhanced the expression of gabrb1. Results suggested that LCP plays a protective function in KA-induced seizures. Hence, it may be a potential functional food alternative for controlling and treating epileptic seizures.

1. Introduction

Epilepsy is a common and disabling neurological disorder that affects approximately 1% of the worldwide population. It is characterized by recurrent seizures that are sudden, unprovoked, and transitory, and recurrent episodes of abnormal hypersynchronous neuronal discharge (Stafstrom and Carmant, 2015). However, its pathological mechanism is not well understood, and no effective treatment is currently available to cure it. Status epilepticus is a severe form of epileptic seizures that is associated with significant morbidity and mortality. Epilepsy comprises numerous syndromes, which vary greatly in terms of clinical features, treatment, and prognosis. Temporal lobe epilepsy (TLE) is the most prominent example of acquired and frequent epilepsy, and the seizure origin of TLE typically involves the hippocampus (Mendez-Armenta et al., 2014). To reveal the pathology of epilepsy and find way to cure it, numerous animal models have been built. Among such models, the kainic acid (KA) model is widely used for TLE (Ben-Ari and Cossart, 2000). KA, which is an excitatory amino acid extracted from seaweeds, is an analog of glutamate. It can act on hippocampal neurons, evoke glutamatergic and GABAergic spontaneous currents, and mimic TLE episodes.

Oxidative stress is an imbalance among the production of reactive oxygen species (ROS), reactive nitrogen oxygen (RNS), and detoxification; it is the most prominent mechanism in the development and progression of epilepsy and other diseases (Roma-Mateo et al., 2015; Waldbaum and Patel, 2010). Sustained neuronal discharge could result in the generation of free radicals in the brain and cause oxidative stress secondary to the unpaired electrons escaping the electron transport chain and reacting with molecular oxygen. The enhanced oxidative stress then damages the neurons which are particularly vulnerable to oxidative imbalances, thereby accelerating the syndrome (Geronzi et al., 2018). Increased ROS generation can lead to prolonged seizures, which may result in mitochondrial dysfunction and cell death in the hippocampus due to subsequent epileptogenesis (Chen et al., 2010; Mendez-Armenta et al., 2014). Therefore, antioxidant treatment could possibly prevent epilepsy.

Lycopene (LCP) is a lipophilic, unsaturated, and biologically active natural product that is abundant in fruits and vegetables, especially tomatoes (Kong et al., 2010). Moreover, LCP is one of the strongest antioxidants found in plants. Its ability to scavenge oxygen radicals is far beyond those of vitamin E and other carotenoids. Consuming LCP or LCP-enriched food is inversely associated to diseases, such as cancers, cardiovascular diseases, and diabetes, among others (Cheng et al., 2017; Mozos et al., 2018; Zhao et al., 2018). The protective function of

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https://doi.org/10.1016/j.eplepsyres.2019.01.010
Received 23 October 2018; Received in revised form 10 January 2019; Accepted 17 January 2019
Available online 17 January 2019
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LCP in neurodegenerative diseases has been studied in vivo and in vitro. Hwang et al. (2017) have reported that LCP is beneficial for preventing oxidative stress-mediated neuronal death by reducing ROS and inhibiting mitochondrial dysfunction and NF-κB-target gene expression. The neuroprotective effects of LCP against MPTP-induced Parkinson's disease in mice have been reported by Prema et al. in, 2015. However, the function of LCP in TLE has not been studied until now. Only few studies have reported the protective effect of LCP on pentylenetetrazol-induced kindling epilepsy model, a model of epileptogenesis, which rarely results in epilepsy (Bhardwaj and Kumar, 2016; Kumar et al., 2016). In the current study, we used KA systematic injection mice model to verify the neuroprotective effect of LCP on the onset and score of seizures, cell damage of neurons, oxidative stress in hippocampus, and expression of GABA receptors.

2. Materials and methods

2.1. Experimental animals

Adult male Kunming mice weighing 20–22 g (about 8 weeks old) were obtained from Jiesijie Laboratory Animal Technology Co. Ltd. (Shanghai, China). They were housed at 24 ± 2 °C under a 12-h light–dark cycle with food and water available ad libitum. Animal experiments were conducted under the regulations of laboratory animal management enforced by the Ministry of Science and Technology of the People's Republic of China [1988] No. 134, which coincides with internationally recognized NIH guidance.

2.2. Drugs administration

LCP was purchased from Hongfan Biotechnology Co. Ltd, and KA was purchased from Santa Cruz. LCP was diluted in olive oil at a concentration of 50 mg/mL. KA was diluted in 0.9% physiological saline at a concentration of 30 mg/mL. A total of 36 animals were randomly divided into three groups: the control group (control), the KA-treated group (KA) and the LCP-pretreated group (LCP–KA). Prior to KA injection, the LCP–KA group mice were pretreated with LCP (50 mg/mL) via intragastric administration once a day for a week. By contrast, the control and the KA mice were given olive oil pre-treatment with the same volume. One hour after the last LCP treatment, the KA and LCP–KA mice were intraperitoneally injected with KA (30 mg/kg), whereas the control mice were injected with 0.9% physiological saline.

2.3. Behavioral assessment of seizures

All animals were evaluated for behavioral progression and scored according to Racine's classification (Racine, 1972): Stage 0, no reaction; Stage 1, stereotypic mounting, eye blinking, and/or mild facial clonus; Stage 2, head nodding and/or multiple facial clonus; Stage 3, myoclonic jerks in the forelimbs; Stage 4, clonic convulsions in the forelimbs with rearing; and Stage 5, generalized clonic convulsions and loss of balance. The animals were scored at 15 min, 30 min, 60 min, 3 h, and 5 h after KA injection.

2.4. Nissl staining

Animals (n = 3 for each group) were employed for drug administration. Seven days after KA injection, the mice were deeply anesthetized with 4% chloral hydrate (0.2 mL/20 g) and perfused with 4% paraformaldehyde. Following perfusion, the brains were isolated and immersed with 4% paraformaldehyde at 4 °C for 4 h. They were then transferred to 30% sucrose (in phosphate buffer) at 4 °C for 2 or 3 days. Their brain sections were then cut at a thickness of 25 μm on a frozen microtome (Leica, Germany). The sections were performed using Nissl-stained sections with 0.1% cresyl violet. In such sections, neurons in hippocampus were observed, and images were captured under a Leica microscope. In the stained sections, granule cell dispersion was determined by measuring the average width of the granule cell layer (GCL) in the mid and medial one-fourth portions of the upper blade of the DG. To maintain consistency across the groups, a settled rectangular frame was centered between the mid and medial one-fourth portions of the GCL. The width of GCL inside the frame on each section was analyzed by using Image J. 5 measurements were taken equidistantly and the average width was calculated per section. At least 6 sections were analyzed for each mouse.

2.5. Measurement of SOD activity, MDA, and GSH concentration

To determine the oxidative stress level in the hippocampus, the control, the KA, and the LCP–KA mice (n = 6 for each group) were sacrificed one hour after KA injection, and their hippocampuses were isolated, homogenized and stored at −80 °C until use. The SOD activity, MDA level, and GSH level were detected using specific detection kits that obtained from Beyotime Co. LTD according the manufacturers' instructions.

2.6. QPCR analysis

One hour after KA injection, the mice in three groups (n = 6) were sacrificed, and their hippocampuses were isolated. After homogenization, the total RNA was prepared using Trizol (Vazyme Biotech Co. LTD) according to manufacturer's instructions. Afterward, cDNA was synthesized via reverse transcription using HiScript 1st Strand cDNA synthesis kit (Vazyme Biotech Co. LTD). The expression levels of GABA receptor subunits GABRB1, GABRB2, and GABRB3, and the pro-inflammatory factor TNF-α were detected via QPCR analysis using AceQ QPCR SYBR green master mix (Vazyme Biotech Co. LTD). The housekeeping gene GAPDH was used as an internal control. The primer sequences were as follows: GAPDH forward- gagaggccctatcccaactc, GAPDH reverse- tcaagagagtagggagggct; GABRB1 forward- gatcacaaccactgcagcat, GABRB1 reverse- tactgctccctctcctccat; GABRB2 forward- tgcctgacacctacttcctg, GABRB2 reverse- ttaggtccatcatgcaggca; GABRB3 forward- cacaacaacccatgaccgtt, GABRB3 reverse- tctagtaaaccggtgcacct; TNF-α forward- gtgcctagttctcagcctct, TNF-α reverse- ctgatgagagggaggccatt.

2.7. Statistical analysis

The results were presented as mean ± standard deviation (SD). Multiple comparisons among groups were performed using *one-way ANOVA*. $P < 0.05$ was considered statistically significant. The statistical analysis between KA group and control group, or LCP–KA group and KA group, was performed by using unpaired *t-test*.

3. Results and discussion

3.1. LCP pretreatment alleviated the seizures induced by KA injection

Seizures are the main symptoms of epilepsy, and the KA injection model has been reported to induce seizures efficiently. In this study, we determined the behaviors of mice according to Racine's classification regulation on seizures onset stages, and verified the effect of LCP on the behaviors of epilepsy mice models. The behaviors of live KA mice and LCP–KA mice were evaluated and recorded every 15 min after KA injection for 5 h. Results showed that approximately 80% of KA group mice showed Stage 1 behaviors 15 min after KA injection, whereas 66.7% of LCP–KA group mice exhibited such conditions (Fig. 1A). After 30 min, 66.7% KA mice showed Stage 2 behavior and 33.3% resident in Stage 1. However, most LCP–KA injected mice (66.7%) showed Stage 1 behavior, and only a small number (16.7%) reached Stage 2 (Fig. 1B). After 60 min, all KA mice showed Stage 2 and 3 behaviors. However, the behaviors of LCP–KA mice were more multiplex than others

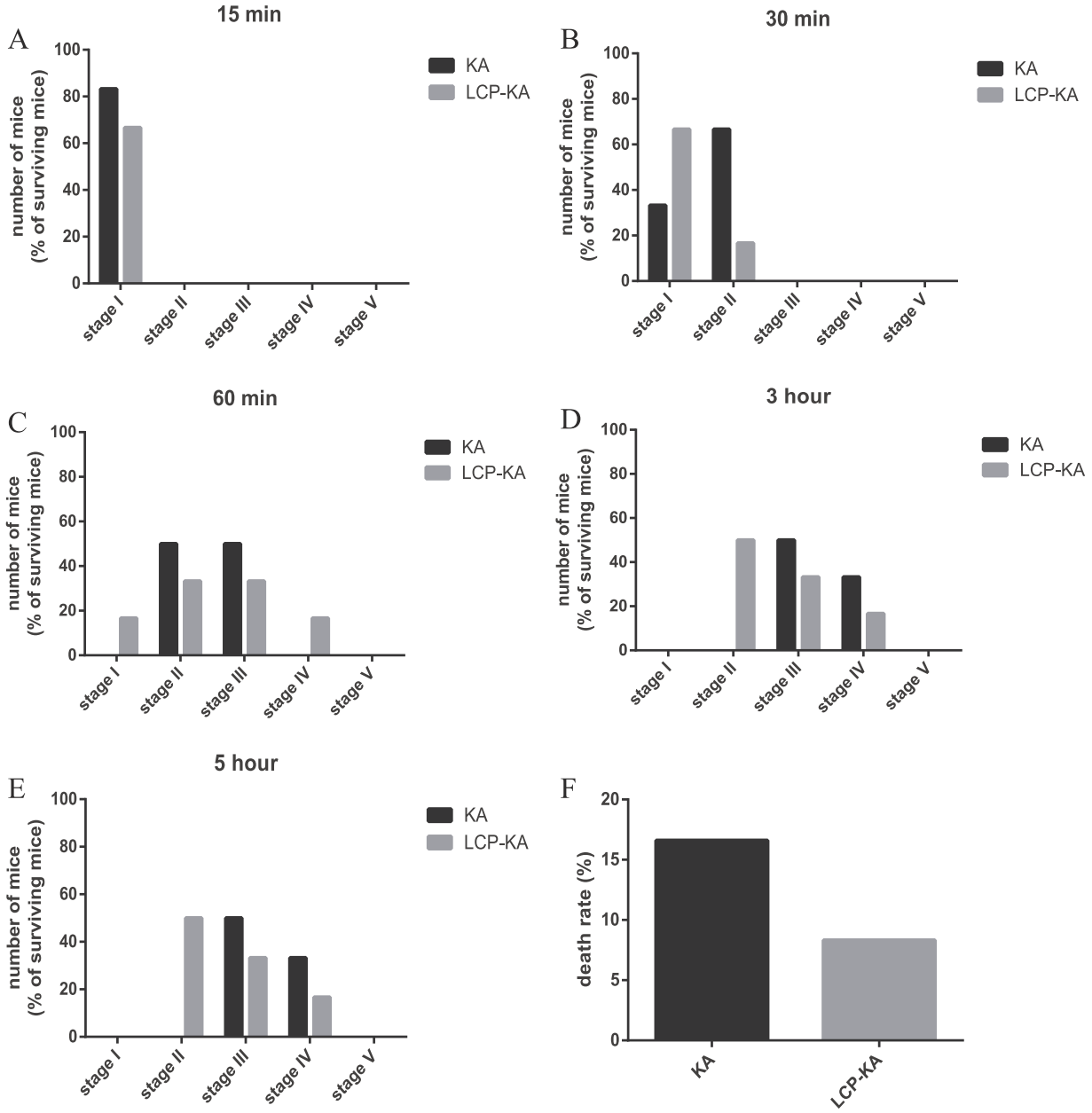
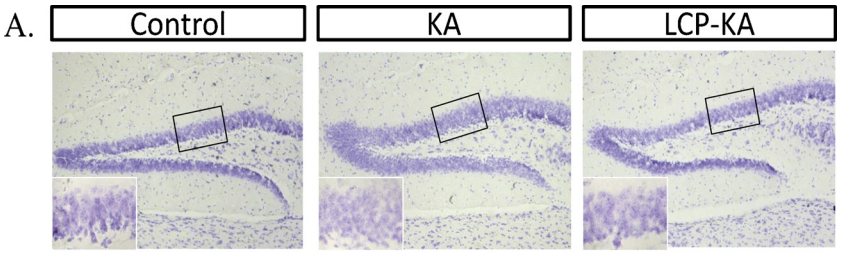


Fig. 1. Effects of LCP on the onset of seizures in KA-induced epileptic mice model. A: Behaviors of mice 15 min after KA injection. B: Behaviors of mice 30 min after KA injection. C: Behaviors of mice 60 min after KA injection. D: Behaviors of mice 3 h after KA injection. E: Behaviors of mice 5 h after KA injection. F: Death rate of LCP pretreated mice and control mice after KA injection.

(Fig. 1C). After 3 h, the behaviors of mice in each group became stable. About 50% KA mice showed Stage 3 behavior, and 33.3% showed Stage 4 behavior. In addition, 50% LCP–KA mice showed Stage 2 behaviors, 33.3% showed Stage 3, and 16.7% showed Stage 4 behaviors (Fig. 1D and E). These results indicated that LCP treatment attenuated the symptoms of seizures. As previously reported, the onset of KA-induced seizures could lead to mice mortality. Hence, we also analyzed the death rates of the KA and LCP–KA groups. The KA group had a 16.7% death rate, which was similar to previous results (Hellier et al., 1998), whereas the death rate in LCP–KA group was 8.3%. Thus, LCP pretreatment could alleviate the behavioral symptoms and death rate induced by KA.

3.2. LCP pretreatment showed protective effects on hippocampus neurons

Hippocampal sclerosis and granule cell dispersion are common structural lesions closely related to frequent seizures in TLE. Previous studies have reported an enlargement of the GCL and abnormalities in KA-induced epileptic mice hippocampal cytoarchitecture (Jang et al., 2016; Jeong et al., 2015). In the current work, we examined the neural morphologies in hippocampus by Nissl staining, which is often used to display neural architectures and neurons. In the control group, the thickness of GCL was normal, and the neurons were stained in blue (Fig. 2A). However, in the KA group, the thickness of GCL became larger and the staining color of neurons was lighter in comparison with the control group (Fig. 2B). The fading of Nissl staining indicates damage of neurons. This result, which is consistent with previous studies (Jang et al., 2016; Jeong et al., 2015), suggested that our mice model was well established, as proven by behavioral observations. In the LCP–KA group, the thickness of GCL and the pigmentation of cell body were between those of the control and KA groups (Fig. 2C), thereby suggesting that LCP could not only attenuate the symptoms of seizures



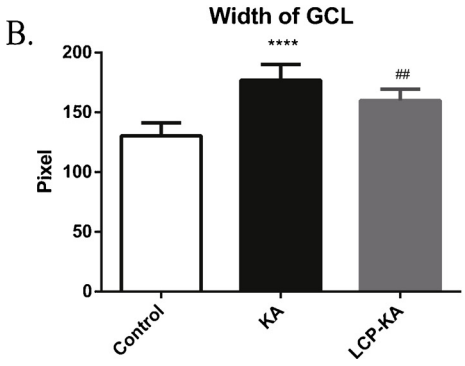


Fig. 2. The Nissl staining of hippocampus after KA and LCP–KA treatment. A: Nissl staining of granule cell layer (GCL). The width of GCL insides the rectangular box was analyzed for statistical analysis. B: statistical analysis of the width of granule cell layer. The significance among the three groups was analyzed with *one-way ANOVA*, and result showed $P < 0.0001$. * represents the significance between the KA and the control groups, and **** means $P < 0.0001$. # represents the significance between the KA and the control groups, and ## means $P < 0.01$. The comparison between each two groups was analyzed with *t-test*.

but also offer protective effects to hippocampal structures and neurons.

3.3. LCP showed antioxidant effect during KA-induced seizures

Oxidative stress in KA-induced seizures has been reported by previous studies. The superoxide dismutase (SOD) activity and malonaldehyde (MDA) and glutathione (GSH) levels are common indexes for evaluating oxidative stress. Si P.P. et al. have found that SOD activity and GSH level decreased, whereas the MDA level increased, 15 min after KA injection (Si et al., 2016). As a powerful antioxidant, LCP can trap singlet oxygen and scavenge free radicals (Pirayesh Islamian and Mehrali, 2015). We verified that LCP administration could suppress the oxidative stress in KA-treated hippocampus. We isolated the hippocampus after LCP pretreatment and KA injection and examined the SOD activity and MDA and GSH levels. The results showed that SOD activity was decreased in KA mice hippocampus but increased in LCP–KA mice (Fig. 3A). Therefore, LCP pretreatment could improve oxidative stress by increasing SOD antioxidant activities. MDA level represents the lipid peroxidation level in the brain. We found that KA treatment could increase MDA level in hippocampus, and LCP pretreatment suppressed this increase to normal criteria (Fig. 3B). This result may due to the free radical scavenging ability of LCP. Hence, free radicals did not attack lipids in the presence of LCP. However, we did not observe any significant alteration on GSH levels among the three groups, and the change was mild in the KA and LCP–KA groups (Fig. 3C). We suspected that the influence of KA injection may have slight influence on GSH levels. Hence, further research needs to be taken. However, based on the SOD and MDA levels, our present study indicated that LCP could suppress KA-induced oxidative stress in the hippocampus.

Oxidative stress is accompanied by inflammation because ROS generated form oxidative stress could evoke the expression of pro-inflammatory factors (Mittal et al., 2014). A lasting inflammation may accelerate neural damage. Numerous studies have reported the inflammatory changes after KA injection, such as the upregulation of pro-inflammatory IL-1β, TNF-α, and IL-21, or the activation of microglia (Sabilallah et al., 2016; Xiong et al., 2016). We analyzed the expression of TNF-α (Fig. 3D) and found that its expression was dramatically increased in the KA group, thereby indicating the occurrence of inflammation. In the LCP–KA group, the expression levels of TNF-α became lower than the KA group but still higher than the control group. Thus, LCP could suppress the upregulation of pro-inflammatory factors in KA-induced seizures. Previous studies have mentioned the role of oxidative stress and inflammation during cell death in neurodegenerative diseases (Mendez-Armenta et al., 2014; Sabilallah et al., 2016). By incorporating this finding with ours, we suspected that LCP may exert neural protective functions by suppressing oxidative stress and pro-inflammatory factor expression.

3.4. LCP pretreatment influence the expression of GABA receptors

Epileptic seizures occur due to the imbalance of excitation and inhibition in the brain, and GABA is the main inhibitory neurotransmitters. Many studies have observed the alteration of GABA receptor expression levels in epilepsy models (Moghbelinejad et al., 2016) and proved that the abnormal receptor level is related to epilepsy (Seo and Leitch, 2014; Sokal and Large, 2001). However, the exact roles of GABA receptors in epilepsy have not been clearly described. To examine the function of LCP on GABA receptors expression, we detected the mRNA level of three $GABA_A$ receptor subunits, namely, GABRB1, GABRB2, and GABRB3, which are distributed throughout the principal cell layers of the hippocampus (Drexel et al., 2013). In this study, all of the three subunits were upregulated in the KA group (Fig. 4), which was consistent with previous studies. However, the expression levels of GABRB2 (Fig. 4B) and GABRB3 (Fig. 4C) was suppressed in the LCP–KA group, whereas the expression of GABRB1 (Fig. 4A) was upregulated. These results suggest that LCP administration could influence the expression of GABA receptors, which may play a role in regulating the onset of KA-induced seizures. However, the underlying mechanisms must be determined further.

4. Conclusion

In conclusion, our findings indicated LCP pretreatment could offer protective effects on KA-induced seizures by alleviating behavioral symptoms and cell damage. In addition, LCP also regulates the

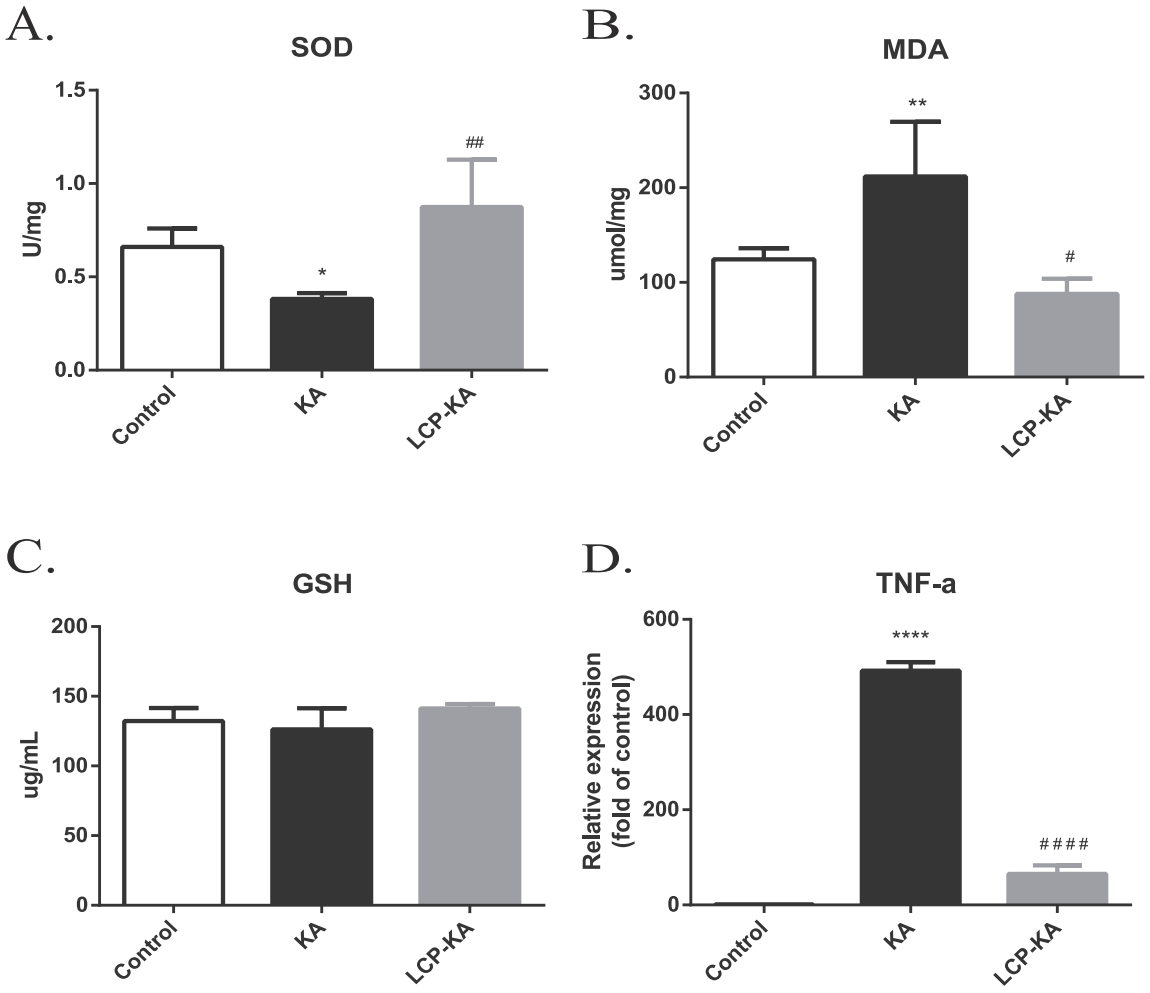


Fig. 3. Oxidative stress in hippocampus after KA and LCP–KA treatment. A: SOD activity in hippocampus. B: MDA level in hippocampus. C: GSH level in hippocampus. D: Relative expression level of TNF-α. The significance among the three groups was analyzed with *one-way ANOVA*. For SOD, $P < 0.05$. For MDA, $P < 0.01$. For TNF-α, $P < 0.0001$. * represents the significance between the KA and the control groups. ** means $P < 0.01$ and **** means $P < 0.0001$. # represents the significance between the KA and the control groups. # #means $P < 0.01$, and #### means $P < 0.0001$. The comparison between each two groups was analyzed with *t-test*.

oxidative stress level and the expression of pro-inflammatory factors and $GABA_A$ receptors. This finding may help illuminate the molecular mechanisms underlying the neural protective function of LCP in epilepsy. Our study indicates that LCP is beneficial for controlling epileptic seizures and a potential functional food alternative in epilepsy treatment.

Conflicts of interest

We do not have conflicts of interest to declare.

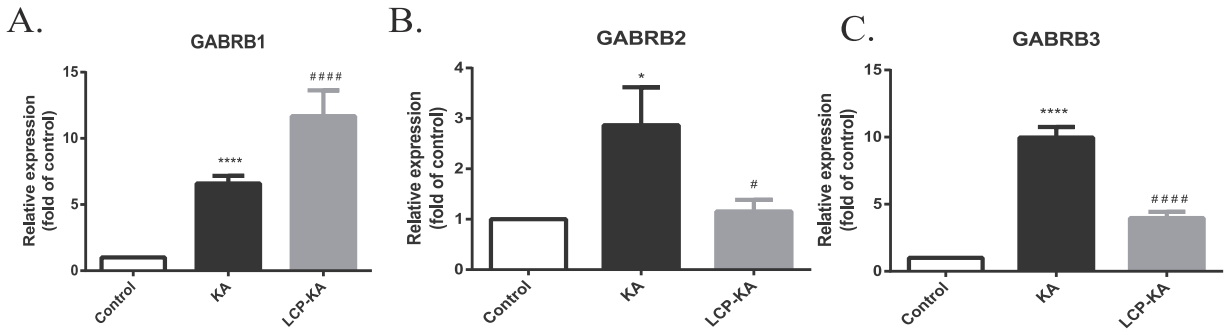


Fig. 4. The expression level of GABA receptors after KA and LCP–KA treatment. A: the relative expression level of GABRB1 in hippocampus. B: the relative expression level of GABRB2 in hippocampus. C: the relative expression level of GABRB3 in hippocampus. The significance among the three groups was analyzed by *one-way ANOVA*. For all GABA receptors, $P < 0.01$. * represents the significance between the KA and the control groups. * means $P < 0.05$, and **** means $P < 0.0001$. # represents the significance between the KA and the control groups. # means $P < 0.05$, and #### means $P < 0.0001$. The comparison between each two groups was analyzed with *t-test*.

Acknowledgements

This work is supported by the college students' innovation and entrepreneurship program of Shanghai University for Science and Technology (No. 10-18-308-301) and Special Fund for Scientific Research in the Grain Public Interest (No. 201513003-8).

References

Ben-Ari, Y., Cossart, R., 2000. Kainate, a double agent that generates seizures: two decades of progress. Trends Neurosci. 23, 580–587.
Bhardwaj, M., Kumar, A., 2016. Neuroprotective effect of lycopene against PTZ-induced kindling seizures in mice: possible behavioural, biochemical and mitochondrial dysfunction. Phytother. Res. 30, 306–313.
Chen, S.D., Chang, A.Y., Chuang, Y.C., 2010. The potential role of mitochondrial dysfunction in seizure-associated cell death in the hippocampus and epileptogenesis. J. Bioenerg. Biomembr. 42, 461–465.
Cheng, H.M., Koutsidis, G., Lodge, J.K., Ashor, A.W., Siervo, M., Lara, J., 2017. Lycopene and tomato and risk of cardiovascular diseases: a systematic review and meta-analysis of epidemiological evidence. Crit. Rev. Food Sci. Nutr. 1–18.
Drexel, M., Kirchmair, E., Sperk, G., 2013. Changes in the expression of GABAA receptor subunit mRNAs in parahippocampal areas after kainic acid induced seizures. Front. Neural Circuits 7, 142.
Geronzi, U., Lotti, F., Grosso, S., 2018. Oxidative stress in epilepsy. Expert Rev. Neurother. 18, 427–434.
Hellier, J.L., Patrylo, P.R., Buckmaster, P.S., Dudek, F.E., 1998. Recurrent spontaneous motor seizures after repeated low-dose systemic treatment with kainate: assessment of a rat model of temporal lobe epilepsy. Epilepsy Res. 31, 73–84.
Hwang, S., Lim, J.W., Kim, H., 2017. Inhibitory effect of lycopene on amyloid-beta-induced apoptosis in neuronal cells. Nutrients 9.
Jang, H., Jeong, K.H., Kim, S.R., 2016. Naringin attenuates granule cell dispersion in the dentate gyrus in a mouse model of temporal lobe epilepsy. Epilepsy Res. 123, 6–10.
Jeong, K.H., Lee, D.S., Kim, S.R., 2015. Effects of eugenol on granule cell dispersion in a mouse model of temporal lobe epilepsy. Epilepsy Res. 115, 73–76.
Kong, K.W., Khoo, H.E., Prasad, K.N., Ismail, A., Tan, C.P., Rajab, N.F., 2010. Revealing the power of the natural red pigment lycopene. Molecules 15, 959–987.
Kumar, V.P., Sharma, S.K.M., Nagarajan, K.P., Dixit, P.K.M., 2016. Effects of lycopene and sodium valproate on pentylenetetrazol-induced kindling in mice. Iran. J. Med. Sci. 41, 430–436.
Mendez-Armenta, M., Nava-Ruiz, C., Juarez-Rebollar, D., Rodriguez-Martinez, E., Gomez, P.Y., 2014. Oxidative stress associated with neuronal apoptosis in experimental models of epilepsy. Oxid. Med. Cell. Longev. 2014, 293689.
Mittal, M., Siddiqui, M.R., Tran, K., Reddy, S.P., Malik, A.B., 2014. Reactive oxygen species in inflammation and tissue injury. Antioxid. Redox Signal. 20, 1126–1167.
Moghbelinejad, S., Rashvand, Z., Khodabandehloo, F., Mohammadi, G., Nassiri-Asl, M., 2016. Modulation of the expression of the GABAA receptor beta1 and beta3 subunits by pretreatment with quercetin in the KA model of epilepsy in mice: -the effect of quercetin on GABAA receptor Beta subunits. J. Pharmacopuncture 19, 163–166.
Mozos, I., Stoian, D., Caraba, A., Malainer, C., Horbanczuk, J.O., Atanasov, A.G., 2018. Lycopene and vascular health. Front. Pharmacol. 9, 521.
Pirayesh Islamian, J., Mehrali, H., 2015. Lycopene as a carotenoid provides radioprotectant and antioxidant effects by quenching radiation-induced free radical singlet oxygen: an overview. Cell J. 16, 386–391.
Prema, A., Janakiraman, U., Manivasagam, T., Thenmozhi, A.J., 2015. Neuroprotective effect of lycopene against MPTP induced experimental Parkinson's disease in mice. Neurosci. Lett. 599, 12–19.
Racine, R.J., 1972. Modification of seizure activity by electrical stimulation. II. Motor seizure. Electroencephalogr. Clin. Neurophysiol. 32, 281–294.
Roma-Mateo, C., Aguado, C., Garcia-Gimenez, J.L., Knecht, E., Sanz, P., Pallardo, F.V., 2015. Oxidative stress, a new hallmark in the pathophysiology of Lafora progressive myoclonus epilepsy. Free Radic. Biol. Med. 88, 30–41.
Sabilallah, M., Fontanaud, P., Linck, N., Boussadia, B., Peyroutou, R., Lasgouzes, T., Rassendren, F.A., Marchi, N., Hirbec, H.E., 2016. Evidence for status epilepticus and pro-inflammatory changes after intranasal kainic acid administration in mice. PLoS One 11, e0150793.
Seo, S., Leitch, B., 2014. Altered thalamic GABAA-receptor subunit expression in the stargazer mouse model of absence epilepsy. Epilepsia 55, 224–232.
Si, P.P., Zhen, J.L., Cai, Y.L., Wang, W.J., Wang, W.P., 2016. Salidroside protects against kainic acid-induced status epilepticus via suppressing oxidative stress. Neurosci. Lett. 618, 19–24.
Sokal, D.M., Large, C.H., 2001. The effects of GABA(B) receptor activation on spontaneous and evoked activity in the dentate gyrus of kainic acid-treated rats. Neuropharmacology 40, 193–202.
Stafstrom, C.E., Carmant, L., 2015. Seizures and epilepsy: an overview for neuroscientists. Cold Spring Harb. Perspect. Med. 5.
Waldbaum, S., Patel, M., 2010. Mitochondria, oxidative stress, and temporal lobe epilepsy. Epilepsy Res. 88, 23–45.
Xiong, X.Y., Wang, T.G., Yang, M.H., Meng, Z.Y., Yang, Q.W., Wang, F.X., 2016. Interleukin-21 expression in hippocampal astrocytes is enhanced following kainic acid-induced seizures. Neurol. Res. 38, 151–157.
Zhao, Y., Xin, Z., Li, N., Chang, S., Chen, Y., Geng, L., Chang, H., Shi, H., Chang, Y.Z., 2018. Nano-liposomes of lycopene reduces ischemic brain damage in rodents by regulating iron metabolism. Free Radic. Biol. Med. 124, 1–11.