

Documents

Zulkifli, N.A.^a, Sirajudeen, K.N.S.^b, Mustapha, M.^a, Zin, A.A.M.^c, Hasim, H.^d, Tang, S.P.^e

Effects of Tualang Honey Pre-Treatment on Cerebellar and Striatal Neuronal Changes and Excitatory Amino Acid Transporter-2 (EAAT2) Expression Following Kainic Acid Exposure in Rats

(2024) *Tropical Journal of Natural Product Research*, 8 (1), pp. 5861-5868.

DOI: 10.26538/tjnpr/v8i1.22

^a Department of Neurosciences, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Malaysia

^b Department of Basic Medical Sciences, Kulliyah of Medicine, International Islamic University, Malaysia

^c Department of Pathology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Malaysia

^d Department of Chemical Pathology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Malaysia

^e Department of Pharmacology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Malaysia

Abstract

Excitatory amino acid transporter-2 (EAAT2) is the predominant glutamate transporter that helps in maintaining low extracellular glutamate levels in the brain. Defect in EAAT2 causes impaired clearance and accumulation of this excitatory neurotransmitter, leading to excitotoxicity and neuronal cell death. The cerebellum and striatum play an important role in motor functions. This study aimed to evaluate the effects of Tualang honey (TH) on cerebellar and striatal neuronal changes as well as EAAT2 expression following kainic acid (KA) exposure in rats. Male Sprague-Dawley rats (n=48) were divided into four groups depending on the respective treatment. Each group was further divided into two subgroups based on time-point of sacrifice at 24-hour or at 5-days after KA injection. The rats were initially treated orally with distilled water, TH (1.0 g/kg) or topiramate (40 mg/kg), 12-hourly for five times. Then, the rats were injected with saline or KA (15 mg/kg) 30 minutes after the fifth oral dose. Before the rats were sacrificed, an open field test was conducted. Locomotor activity significantly increased in all KA-injected groups 5 days after KA administration. TH pre-treatment significantly reduced cerebellar neuronal death 5 days after KA injection. TH pre-treatment also showed to reduce KA-induced loss of striatal neurons 24 hours after KA injection as well as increases EAAT2 expression in 24 hours and 5 days groups. These results imply that pre-treatment with TH may mitigate the KA-induced excitotoxicity in the cerebellum and striatum partly via modulation of EAAT2 expression. © 2024 Zulkifli et al.

Author Keywords

cerebellum; EAAT2 expression; kainic acid; striatum; Tualang honey

Funding details

Central Research Laboratory/CRL

Universiti Sains Malaysia/USM1001/PPSP/8012249

This work was supported by the Universiti Sains Malaysia under the Research University (Individual) Grant (Grant number: 1001/PPSP/8012249). The authors also wish to acknowledge staff from the Animal Research and Service Centre (ARASC), Central Research Laboratory (CRL) and Pharmacology Laboratory, Universiti Sains Malaysia, Health Campus for their technical support for this research work.

References

- Moujalled, D, Strasser, A, Liddell, JR.
Molecular mechanisms of cell death in neurological diseases
(2021) *Cell Death Differ*, 28 (7), pp. 2029-2044.
- Andreone, BJ, Larhammar, M, Lewcock, JW.
Cell death and neurodegeneration
(2020) *Cold Spring Harb Perspect Biol*, 12 (2), p. a036434.
- Todd, AC, Hardingham, GE.
The Regulation of Astrocytic Glutamate Transporters in Health and Neurodegenerative Diseases
(2020) *Int J Mol Sci*, 21 (24), p. 9607.
- Green, JL, dos Santos, WF, Fontana, ACK.
Role of glutamate excitotoxicity and glutamate transporter EAAT2 in epilepsy:

Opportunities for novel therapeutics development

(2021) *Biochem Pharmacol*, 193, p. 114786.

- Malik, AR, Willnow, TE.
Excitatory Amino Acid Transporters in Physiology and Disorders of the Central Nervous System
(2019) *Int J Mol Sci*, 20 (22), p. 5671.
- Hotz, AL, Jamali, A, Rieser, NN, Niklaus, S, Aydin, E, Myren-Svelstad, S, Lalla, L, Neuhauss, SCF.
Loss of glutamate transporter eaat2a leads to aberrant neuronal excitability, recurrent epileptic seizures, and basal hypoactivity
(2022) *Glia*, 70 (1), pp. 196-214.
- Qu, Q, Zhang, W, Wang, J, Mai, D, Ren, S, Qu, S, Zhang, Y.
Functional investigation of SLC1A2 variants associated with epilepsy
(2022) *Cell Death Dis*, 13 (12), p. 1063.
- Ramandi, D, Salmani, ME, Moghimi, A, Lashkarbolouki, T, Fereidoni, M.
Pharmacological upregulation of GLT-1 alleviates the cognitive impairments in the animal model of temporal lobe epilepsy
(2021) *PLoS One*, 16 (1), p. e0246068.
- Sha, L, Li, G, Zhang, X, Lin, Y, Qiu, Y, Deng, Y, Zhu, W, Xu, Q.
Pharmacological induction of AMFR increases functional EAAT2 oligomer levels and reduces epileptic seizures in mice
(2022) *JCI Insight*, 7 (15), p. e160247.
- Rusina, E, Bernard, C, Williamson, A.
The Kainic Acid Models of Temporal Lobe Epilepsy
(2021) *eNeuro*, 8 (2).
ENEURO.0337-20.2021
- Riljak, V, Marešová, D, Pokorný, J, Jandová, K.
Subconvulsive dose of kainic acid transiently increases the locomotor activity of adult Wistar rats
(2015) *Physiol Res*, 64 (2), pp. 263-267.
- Zheng, X-Y, Zhang, H-L, Luo, Q, Zhu, J.
Kainic Acid-Induced Neurodegenerative Model: Potentials and Limitations
(2011) *J Biomed Biotechnol*, 2011, p. 457079.
- Kandashvili, M, Gamkrelidze, G, Tsverava, L, Lordkipanidze, T, Lepsveridze, E, Lagani, V, Burjanadze, M, Solomonias, R.
Myo-Inositol Limits Kainic Acid- Induced Epileptogenesis in Rats
(2022) *Int J Mol Sci*, 23 (3), p. 1198.
- Lintunen, M, Sallmen, T, Karlstedt, K, Panula, P.
Transient changes in the limbic histaminergic system after systemic kainic acid-induced seizures
(2005) *Neurobiol Dis*, 20 (1), pp. 155-169.
- Sperk, G, Wieser, R, Widmann, R, Singer, EA.
Kainic acid induced seizures: Changes in somatostatin, substance P and neurotensin
(1986) *Neuroscience*, 17 (4), pp. 1117-1126.
- Guevara, BH, Torrico, F, Hoffmann, IS, Cubeddu, LX.
Lesion of caudate-putamen interneurons with kainic acid alters dopamine and serotonin metabolism in the olfactory tubercle of the rat
(2002) *Cell Mol Neurobiol*, 22 (5-6), pp. 835-844.

- Bostan, AC, Strick, PL.
The basal ganglia and the cerebellum: nodes in an integrated network
(2018) *Nat Rev Neurosci*, 19 (6), pp. 338-350.
- Centonze, D, Rossi, S, De Bartolo, P, De Chiara, V, Foti, F, Musella, A, Mataluni, G, Petrosini, L.
Adaptations of glutamatergic synapses in the striatum contribute to recovery from cerebellar damage
(2008) *Eur J Neurosci*, 27 (8), pp. 2188-2196.
- El-Seedi, HR, Khalifa, SAM, El-Wahed, AA, Gao, R, Guo, Z, Tahir, HE, Zhao, C, Abbas, G.
Honeybee products: An updated review of neurological actions
(2020) *Trends Food Sci Technol*, 101, pp. 17-27.
- Weis, WA, Ripari, N, Conte, FL, Honorio M da, S, Sartori, AA, Matucci, RH, Sforcin, JM.
An overview about apitherapy and its clinical applications
(2022) *Phytomedicine Plus*, 2 (2), p. 100239.
- Azman, KF, Aziz, CB, Zakaria, R, Ahmad, AH, Shafin, N, Ismail, CA.
Tualang Honey: A Decade of Neurological Research
(2021) *Molecules*, 26 (17), p. 5424.
- Mohd Sairazi, NS, .N.S. S, K, Asari, MA, Mummedy, S, Muzaimi, M, Sulaiman, SA.
Effect of tualang honey against KA-induced oxidative stress and neurodegeneration in the cortex of rats
(2017) *BMC Complement Altern Med*, 17 (1), p. 31.
- Mohd Sairazi, NS, .N.S. S, K, Muzaimi, M, Swamy, M, Sulaiman, SA.
Tualang honey attenuates kainic acid-induced oxidative stress in rat cerebellum and brainstem
(2017) *Int J Pharm Pharm Sci*, 9, p. 155.
- Mohd Sairazi, NS, Sirajudeen, KNS, Muzaimi, M, Mummedy, S, Asari, MA, Sulaiman, SA.
Tualang Honey Reduced Neuroinflammation and Caspase-3 Activity in Rat Brain after Kainic Acid-Induced Status Epilepticus
(2018) *Evid Based Complement Alternat Med*, 2018, p. 7287820.
- Obernier, JA, Baldwin, RL.
Establishing an appropriate period of acclimatization following transportation of laboratory animals
(2006) *ILAR J*, 47 (4), pp. 364-369.
- Gage, GJ, Kipke, DR, Shain, W.
Whole animal perfusion fixation for rodents
(2012) *J Vis Exp*, (65), p. e3564.
- Paxinos, G, Watson, C.
(2006) *The rat brain in stereotaxic coordinates: hard cover edition*, Elsevier
- Feldman, AT, Wolfe, D.
Tissue processing and hematoxylin and eosin staining
(2014) *Methods Mol Biol*, 1180, pp. 31-43.
- Garman, RH.
Histology of the central nervous system
(2011) *Toxicol Pathol*, 39 (1), pp. 22-35.
- Mahale, A, Fikri, F, Al Hati, K, Al Shahwan, S, Al Jadaan, I, Al Katan, H, Khandekar, R, Edward, DP.
Histopathologic and immunohistochemical features of capsular tissue around failed

- Ahmed glaucoma valves**
(2017) *PLoS One*, 12 (11), p. e0187506.
- Mustafa, HN, El Awdan, SA, Hegazy, GA, Abdel Jaleel, GA.
Prophylactic role of coenzyme Q10 and Cynara scolymus L on doxorubicin-induced toxicity in rats: Biochemical and immunohistochemical study
(2015) *Indian J Pharmacol*, 47 (6), pp. 649-656.
 - Mattson, MP.
Chapter 11-Excitotoxicity
(2019) *Stress: Physiology, Biochemistry, and Pathology*, pp. 125-134.
Fink G (Ed). Academic Press
 - Verma, M, Lizama, BN, Chu, CT.
Excitotoxicity, calcium and mitochondria: a triad in synaptic neurodegeneration
(2022) *Transl Neurodegener*, 11 (1), p. 3.
 - Löscher, W, Stafstrom, CE.
Epilepsy and its neurobehavioral comorbidities: Insights gained from animal models
(2023) *Epilepsia*, 64 (1), pp. 54-91.
 - Georgescu Margarint, EL, Georgescu, IA, Zahiu, CDM, Tirlea, SA, Ștepoaie, AR, Zăgrean, L, Popa, D, Zăgrean, AM.
Reduced Interhemispheric Coherence in Cerebellar Kainic Acid-Induced Lateralized Dystonia
(2020) *Front Neurol*, 11, p. 580540.
 - Nam, HY, Na, EJ, Lee, E, Kwon, Y, Kim, H-J.
Antiepileptic and Neuroprotective Effects of Oleamide in Rat Striatum on Kainate-Induced Behavioral Seizure and Excitotoxic Damage via Calpain Inhibition
(2017) *Front Pharmacol*, 8, p. 817.
 - Pisa, M, Sanberg, PR, Fibiger, HC.
Locomotor activity, exploration and spatial alternation learning in rats with striatal injections of kainic acid
(1980) *Physiol Behav*, 24 (1), pp. 11-19.
 - Zhang, P, Duan, L, Ou, Y, Ling, Q, Cao, L, Qian, H, Zhang, J, Yuan, X.
The cerebellum and cognitive neural networks
(2023) *Front Hum Neurosci*, 17, p. 1197459.
 - Streng, ML, Krook-Magnuson, E.
The cerebellum and epilepsy
(2021) *Epilepsy Behav*, 121, p. 106909.
 - Lee, M, Cheng, MM, Lin, C-Y, Louis, ED, Faust, PL, Kuo, S-H.
Decreased EAAT2 protein expression in the essential tremor cerebellar cortex
(2014) *Acta Neuropathol Commun*, 2, p. 157.
 - Rabenstein, M, Peter, F, Rolfs, A, Frech, MJ.
Impact of Reduced Cerebellar EAAT Expression on Purkinje Cell Firing Pattern of NPC1-deficient Mice
(2018) *Sci Rep*, 8 (1), p. 3318.
 - Yoo, SY, Kim, JH, Do, SH, Zuo, Z.
Inhibition of the activity of excitatory amino acid transporter 4 expressed in xenopus oocytes after chronic exposure to ethanol
(2008) *Alcohol Clin Exp Res*, 32 (7), pp. 1292-1298.

- Perkins, EM, Clarkson, YL, Suminaite, D, Lyndon, AR, Tanaka, K, Rothstein, JD, Skehel, PA, Jackson, M.
Loss of cerebellar glutamate transporters EAAT4 and GLAST differentially affects the spontaneous firing pattern and survival of Purkinje cells
(2018) *Hum Mol Genet*, 27 (15), pp. 2614-2627.
- Wadiche, JI, Jahr, CE.
Patterned expression of Purkinje cell glutamate transporters controls synaptic plasticity
(2005) *Nat Neurosci*, 8 (10), pp. 1329-1334.
- Mancini, A, Ghiglieri, V, Parnetti, L, Calabresi, P, Di Filippo, M.
Neuro-Immune Cross-Talk in the Striatum: From Basal Ganglia Physiology to Circuit Dysfunction
(2021) *Front Immunol*, 12, p. 644294.
- Brodovskaya, A, Shiono, S, Kapur, J.
Activation of the basal ganglia and indirect pathway neurons during frontal lobe seizures
(2021) *Brain*, 144 (7), pp. 2074-2091.
- Planas-Fontánez, TM, Dreyfus, CF, Saitta, KS.
Reactive Astrocytes as Therapeutic Targets for Brain Degenerative Diseases: Roles Played by Metabotropic Glutamate Receptors
(2020) *Neurochem Res*, 45 (3), pp. 541-550.
- Umpierre, AD, West, PJ, White, JA, Wilcox, KS.
Conditional knock-out of mGluR5 from astrocytes during epilepsy development impairs high-frequency glutamate uptake
(2019) *J Neurosci*, 39 (4), pp. 727-742.
- Obeid, M, Frank, J, Medina, M, Finckbone, V, Bliss, R, Bista, B, Majmudar, S, Strahlendorf, J.
Neuroprotective effects of leptin following kainic acid-induced status epilepticus
(2010) *Epilepsy Behav*, 19 (3), pp. 278-283.
- Drexel, M, Preidt, AP, Sperk, G.
Sequel of spontaneous seizures after kainic acid-induced status epilepticus and associated neuropathological changes in the subiculum and entorhinal cortex
(2012) *Neuropharmacology*, 63 (5), pp. 806-817.
- Matias, I, Morgado, J, Gomes, FCA.
Astrocyte Heterogeneity: Impact to Brain Aging and Disease
(2019) *Front Aging Neurosci*, 11, p. 59.
- Silva, RFM, Pogačnik, L.
Polyphenols from food and natural products: Neuroprotection and safety
(2020) *Antioxidants*, 9 (1), p. 61.
- Grabska-Kobyłecka, I, Szpakowski, P, Król, A, Książek-Winiarek, D, Kobyłecki, A, Głąbiński, A, Nowak, D.
Polyphenols and Their Impact on the Prevention of Neurodegenerative Diseases and Development
(2023) *Nutrients*, 15 (15), p. 3454.
- Tang, SP, Wan Yusuf, WN, Abd Aziz, CB, Mustafa, M, Mohamed, M.
Effects of six-month tualang honey supplementation on physiological and biochemical profiles in asymptomatic, treatment-naïve HIV-infected patients
(2020) *Trop J Nat Prod Res*, 4 (12), pp. 1116-1123.

- Lin, TY, Lu, CW, Wang, SJ.
Luteolin protects the hippocampus against neuron impairments induced by kainic acid in rats
(2016) *Neurotoxicology*, 55, pp. 48-57.
- Maya, S, Prakash, T, Madhu, K.
Assessment of neuroprotective effects of Gallic acid against glutamate-induced neurotoxicity in primary rat cortex neuronal culture
(2018) *Neurochem Int*, 121, pp. 50-58.

Correspondence Address

K.N.S. S.; Department of Basic Medical Sciences, Malaysia; email: knssiraj@iiium.edu.my
Tang S.P.; Department of Pharmacology, Malaysia; email: sukpeng@usm.my

Publisher: Faculty of Pharmacy, University of Benin

ISSN: 26160684

Language of Original Document: English

Abbreviated Source Title: Trop. J. Nat. Prod. Res.

2-s2.0-85184692292

Document Type: Article

Publication Stage: Final

Source: Scopus

ELSEVIER

Copyright © 2024 Elsevier B.V. All rights reserved. Scopus® is a registered trademark of Elsevier B.V.

 RELX Group™