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Topiramate mitigates 3-nitropropionic acid-induced striatal neurotoxicity via modulation of AMPA receptors

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ABSTRACT

Prevalence of glutamate receptor subunit 2 (GluR2)-lacking alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors is a hallmark of excitotoxicity-related neurodegenerative diseases. Topiramate (TPM) is a structurally novel anticonvulsant with a well-known modulatory effects on AMPA/kainate subtypes of glutamate receptors. The present study aimed at investigating the neuroprotective potential of TPM on 3-nitropropionic acid (3-NP)-induced striatal neurodegeneration and Huntington's disease-like symptoms. Rats were injected with 3-NP (10 mg/kg/i.p.) for 14 days. TPM (50 mg/kg/p.o.) was given once a day, 1 h before 3-NP. TPM amended 3-NP induced changes in neurobehavioral performance, striatal neurotransmitters levels and histopathological injury. 3-NP control rats showed a significant ablation in the mRNA expression of Ca^{2+}-impermeable Glu2R subunit along with an elevation in its regulatory protein (protein interacting with C kinase-1) PICK1, an effect that was largely reversed by TPM. TPM in addition, enhanced the phosphorylation of the protein kinase B/glycogen synthase kinase-3β/cAMP response element binding protein (Akt/GSK-3β/CREB) cue. Moreover, improvement in oxidative status, suppression of caspase-3 activity and restoration of striatal BDNF were noticed following treatment with TPM. The current study revealed that TPM boosted the neuroprotective (Akt/GSK-3β/CREB) pathway by its negative modulatory effect on AMPA glutamate receptors as well as its direct antioxidant property.

1. Introduction

Huntington's disease (HD) is an incurable progressive neurodegenerative disease characterized by cognitive, moto rand psychiatric disturbances (Colle et al., 2012; Jamwal and Kumar, 2017) HD harmfully affects gamma-amino butyric acid (GABA)-ergic medium spiny neurons in the striatum with a noticeable loss in both dopamine (DA) receptors and content (Colle et al., 2012; Jamwal and Kumar, 2017; 2016; Mahdy et al., 2014).

3-nitroproponic acid (3-NP) is a natural fungal toxin which crosses BBB causing neurotoxicity resembling the progressive nature of HD symptoms in human (Dhadde et al., 2016). It substantially suppresses complex II succinate dehydrogenase (SDH) irreversibly, a key enzyme in Krebs's cycle instigating impairment in mitochondrial activity, decrease in ATP production, energy depletion and excitotoxicity (Colle et al., 2012; Kumar et al., 2011; Lucas and Ortega, 2011).

Several neurodegenerative diseases as Alzheimer's disease, Parkinson's disease, Huntington's,encephalopathy, epilepsy, schizophrenia, and dementia entail uncontrolled glutamate-induced neuronal injury (Dong et al., 2009). During excitotoxicity, activated ionotropic glutamate receptors, N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), permit influx of Ca2+, while the metabotropic glutamate receptors cause intracellular Ca2+ release from the endoplasmic reticulum (Lodge, 2009).The mounting fall in ATP synthesis reduces the energy available to maintain Ca2+ homeostasis (Khadrawyb and Ezza, 2014). Consequently, a state of robust oxidative stress is evoked hasting neuronal death (Dhadde et al., 2016; Mahdy et al., 2014). The neuroprotective concept of NMDA receptor blockers was previously tackled (Sauer et al., 1995). However, the possible adverse effects of the latter drugs, such as learning impairment, psychotomimetic action, and vacuolization of cerebrocortical neurons, may impede their use (Kawasaki-Yatsugi et al., 1997). It was previously reported that the efficacy of AMPA receptor antagonists in curbing neuronal death following severe global ischemia, Parkinsonism and epilepsy is more than that of NMDA receptor antagonists (Jayakar and Dikshit, 2004). Moreover, AMPA receptor activation is a prerequisite for the stimulation of NMDA receptors, providing dual protection from glutamate-induced excitotoxicity without the aforementioned side effects (Jayakar and Dikshit, 2004; Weiser, 2005).So, modulating AMPA receptors activity could be an attractive approach to

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hamper glutamate induced-excitotoxicity.

Topiramate (TPM) is an anti-epileptic drug with various pharmacological effects (Edmonds et al., 2001; Jiang et al., 2014).It exerts its action by negative modulatory effect on AMPA subtype of glutamate receptors, attenuation of voltage gated Na^+ currents, and inhibition of some carbonic anhydrase isozymes (Kudin et al., 2004). It also hinders aspartate and glutamate release from the neuronal terminals, enhances GABA-A mediated neurotransmission and blocks neuronal L-type high voltage-activated Ca^{2+} channels as well as K^+ channel (Chrościńska-krawczyk et al., 2014).

The neuroprotective effect of TPM has been previously established against neuronal injury following focal and global cerebral ischemia in experimental animals (Mao et al., 2015), induction of status epilepticus in rats (Edmonds et al., 2001) as well as in experimental models of Alzheimer's disease (Cheng and Li, 2014; Shi et al., 2013).

Therefore, the aim of the present investigation was to shed light on the possible role of Ca^{2+} −impermeable AMPA receptor subunit 2 (GluR2) alteration in the progression of 3-NP-induced neurotoxicity. It was also extended to explore the neuroprotective potential of TPM on neurobehavioral and neurochemical changes associated with 3-NP induced striatal neurodegeneration in rats.

2. Material and methods

2.1. Animals

Male Wistar rats, weighing 200–250 g, were obtained from the animal facility of Faculty of Pharmacy, Cairo University. Rats were housed under the suitable conditions of controlled humidity, temperature and constant light cycle and permitted for free access to a standard rodent chow diet and water. The investigation fulfills the *Guide for Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 85–23, revised 2011) and was approved by the Ethics Committee for Animal Experimentation at Faculty of Pharmacy, Cairo University (Permit Number: PT 1597).

2.2. Chemicals

3-NP was obtained from Sigma Chemicals, USA, whereas, TPM was purchased from Sabaa Pharmaceutical Company, Egypt.

2.3. Experimental design

Rats were randomly allocated into four groups, 22 rats each, and treated for 14 days as follows: Group I received saline. (normal group), group II received TPM (50 mg/kg/p.o./day) (Yilmaz et al., 2011), group III was i.p. injected with 3- NP (10 mg/kg/day) (Kumar et al., 2011)and group IV received TPM (50 mg/kg, p.o.) 1 h before 3-NP injection for 14 days (Menze et al., 2012).

2.4. Behavioral studies

After 14th days, animals were subjected to the following behavioral tests with at least 30-min gap between each test.

2.4.1. Open field test

Open field was performed to evaluate behavioral responses such as locomotor activity, and hyperactivity of rats. The apparatus is made of wood with 40-cm-high white walls covered with water-resistant Formica. Its white floor (100 cm × 100 cm) is divided by black lines into 16 squares (25 cm × 25 cm). The test was performed in a quiet room under white light. The rats were gently placed in the center of the ground and left to be observed for 3 min. The following parameters were recorded during surveillance period (Ávila et al., 2010).

(i) *Latency time*: time passed until the animal decides to move from the central area. It was measured in seconds.
(ii) *Ambulation frequency*: number of squares intersected by the animal.
(iii) *Rearing frequency*: number of times the animal stood, stretched on its hind limbs with or without forelimb support.

2.4.2. Rotarod activity

Rotarod is extensively used to assess motor coordination by testing the ability of rat to stay on a rotating rod.Concisely, the apparatus comprises of a rod (120 cm long and3 cm in diameter) which is divided into four partitions by disks 24 cm in diameter to allow testing four rats at the same time. The rod rotates at a constant speed of 25 rpm. Each rat was given training session to be acclimatized on the rotating rod (Kumar and Kumar, 2009).Three separate trials were given to each rat at 5 min intervals. The results were recorded as average time of fall (Vis et al., 1999).

2.4.3. String test for grip strength

The length of time to hold the grip on a wire is considered an indirect measure of grip strength. The rat was allowed to hold with the forepaws a steel wire (2 mm in diameter and 35 cm in length), stretched horizontally at a height of 50 cm over a cushion support. The length of time for which the rat was able to hold the wire was recorded (Khan et al., 2010).

2.5. Tissue sampling

At the end of behavioral tests, animals were sacrificed by decapitation under light anesthesia. Brains were rapidly isolated, rinsed in ice cold saline. The brains of 4 rats from each group were used for the histopathological assessment. Striata of the remaining rats were isolated and kept at − 80 °C for further analyses. The striata of 12 rats from each group were homogenized in ice-cold saline using a homogenizer (HeidolphDiax 900, Germany) to prepare 10% homogenate. The right striata of 6 animals were used for determination of phosphorylated protein kinase B (*p*S473 Akt-1) and protein interacting with C-kinase-1 (PICK1) by western blot technique. While, the left striata of the same animals were used for determination of AMPA GluR2 using quantitative real-time polymerase chain reaction.

2.6. Estimation of striatal damage

Brain were separated, rinsed in ice-cold saline, and immediately fixed in 10% formalin for 24 h. Specimens were processed for paraffin embedding, and 3-μm sections were prepared. Sections were stained using hematoxylin and eosin (H&E) and examined microscopically by light microscope (magnification × 400). Images were captured and processed using Adobe Photoshop (version 8.0). Four point numerical scoring system was used to express the degree of severity of histological lesions (Arsad, 2014). Each rat was assigned a damage score between 0 and 3 for each of five parameters namely, necrosis of neurons, neurophagia, neuronal edema, focal glosis, and congestion of blood vessels where, 0 indicates no change, 1,2 and 3 indicate mild, moderate and severe change, respectively. Total histology scores, being maximally 15, were calculated by summing the five parameters for each rat. An experienced observer unaware of the identity of the samples performed all histopathological processing and assessment to avoid any prejudice.

2.7. Biochemical measurements

2.7.1. Enzyme linked immunosorbent assay

GABA, Glutamate and DA levels in striatum were estimated by ELISA assay kits (EIAab, China), (CUSABIO and CusAb, US) and (MyBiosource, USA), respectively. Likewise, Brain-derived neurotrophic factor (BDNF), phosphorylated-cAMP response element-binding protein (*p*S133-CREB) were determined by specific ELISA kits according to the manufacturer's instructions (Chongqing Biospes Co., Ltd, China).

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