RESVERATROL attenuates kainic acid-induced epilepsy in male swiss albino mice.

Samy Ali Hussein; Afaf D. Abdel-mageid; Omnia M. Abd-Elhamed and Hassan S . Al-Harthy
Department of Biochemistry, Faculty of Vet. Med. Benha University, Egypt. Corresponding author: Samyaziza@yahoo.com

A B S T R A C T

Epilepsy is a highly prevalent serious brain disorder, and oxidative stress is regarded as a possible mechanism involved in epileptogenesis. The present study was designed to evaluate the potential protective and beneficial effect of resveratrol (RESV) on kainic acid (KA)-induced epilepsy in mice. Twenty four male Swiss Albino mice were divided into four groups. Group I:(Control group) mice received no drugs. Group Π:(epilepsy-induced group): mice administered with a single dose of KA (10 mg/kg b.wt) intraperitoneally (i.p). Group III:(epilepsy+RESV protected group) mice received RESV (10 mg/kg b.wt/day/i.p.) for 7 days before KA administration. Group IV: (epilepsy+RESV treated group): mice first injected with KA(10 mg/kg b.wt/i.p.) then after 15 min. RESV was administered as in group III for 3 consecutive days. Blood samples for serum separation and brain tissue specimens were collected after 12 hours and 3 days from the onset of KA administration for determination of serum sialic acid (SA) and tumor necrosis factor alpha(TNF-α), brain tissue superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), reduced glutathione (GSH), L-Malondialdehyde (L-MDA), nitric oxide (NO), caspase-3 and DNA-fragmentation. The obtained results showed that, KA-induced epilepsy in mice caused significant decrease in serum SA and brain tissue SOD, CAT, GPX activities and GSH concentration. However, serum TNF-α and brain tissue NO, L-MDA level, caspase-3 activity and DNA-fragmentation were significantly increased. Administration of RESV was able to mitigate epilepsy induced by KA through increasing of SA and brain tissue SOD, CAT, GPX activities and GSH in addition to declining NO, L-MDA, caspase-3 and DNA-fragmentation in brain tissue. These results suggest that, resveratrol administration attenuate kainate-induced epileptic seizures in mice and may be potential effectiveness for the prevention and control of seizure development, has anticonvulsant therapies of brain epilepsy by its anti-inflammatory effect, radical scavenging and anti-apoptotic activity, inhibited caspase-3 and regenerating endogenous antioxidant mechanisms in brain tissues.

Keywords: Resveratrol, kainic acid, epilepsy, apoptosis, Oxidative stress.

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1. INTRODUCTION

Epilepsy is a serious neurological disorder while anticonvulsant therapies are limited and unable to control seizures in all patients. The Kainic acid (KA) seizure model is particularly useful for the study of the evolution, propagation, and pathological consequences of epileptic discharge in the limbic system. Activation of the KA subtype of ionotropic gluatamate receptors results in sustained epileptic activity in the hippocampus, followed by a selective pattern of neuropathology that is similar to human TLE (Eun *et al.*, 2013). A relationship between status epilepticus (SE) and oxidative stress has recently begin to be recognized both in animal models. It has been established that blood flow, energy and oxygen are increased during seizure and that SE induces the production of redundant reactive oxygen species (ROS). Compared with other organs, the brain uses the highest amount of oxygen and contains a high concentration of polyunsaturated fatty acids

that are easily peroxidated, which makes it particularly susceptible to oxidative stress. Similarly, increased oxidative stress contributes to seizure-induced brain injury and subsequently results in epilepsy. In turn, ROS may be a contributing factor in the generation of epileptic seizures in animal models and in patients (Martinc *et al.*, 2012). Flavonoids present has a variety of beneficial health effects including regulation of oxidative stress. Resveratrol decreased the frequency of spontaneous seizures and inhibited the epileptiform discharges induced by kainate in rats. Importantly, resveratrol prevented the kainate-induced hippocampal cell death and reduced mossy fiber sprouting, which are thought to be histological markers of epileptogenesis in this model of temporal lobe epilepsy. Studies on mice revealed that, regular exercise and resveratrol administration (40 mg/kg b.wt./day) for 6 weeks inhibited kainate-induced seizure activity, mortality and oxidative stress in those animals. The synergic effect of regular exercise and resveratrol suggests its potential usefulness for the prevention of seizure development. However, in contrast to adult rats, repeated resveratrol administration did not attenuate kainate-induced seizures, and had only modest effect on preventing hippocampal cell death and lipid peroxidation in young rats (Frombaum *et al.*, 2012). Accordingly, the present study was designed to evaluated the beneficial and the potential protective effect of resveratrol against kainic acid-induced epilepsy in Swiss albino mice by determination of serum sialic acid (SA) and tumor necrosis factor alpha(TNF-α), brain tissue superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), reduced glutathione (GSH), L-Malondialdehyde (L-MDA), nitric oxide (NO), caspase-3 and DNA-fragmentation.

2. MATERIALS AND METHOD

2.1. Experimental animals:

Twenty four male Swiss albino mice of 6-8 weeks old and weighting 25-30 gm were used in this study. Mice were housed in separated metal cages and kept at constant environmental and nutritional conditions throughout the period of experiment. The animals were fed on constant ration and water was supplied ad-libitum. The mice were left 14 days for acclimatization before the beginning of the experiment. Resveratrol (purity~99%) was manufactured by Sigma Chemical Co.(St. Louis, Mo, USA) and purchased from Schnelldorf, Germany through the Egyptian International Center for Import Cairo, Egypt. Resveratrol was freshly prepared in normal saline and administered to mice at a dose level of (10 mg/kg b.wt/day i.p) (Karalis *et al.*, 2011).

2.2. Induction of epilepsy:

Epilepsy was induced in mice by a single intraperitoneal injection of kainic acid at a dose of (10 mg/kg body weight). kainic acid has been purchased by Sigma Chemical Co. (St. Louis, Mo, USA) and purchased from Schnelldorf, Germany through the Egyptian International Center for Import Cairo, Egypt. KA was dissolved in normal saline and the PH of KA solution was adjusted to 7.2±0.1. Following administration of KA all mice were observed for behavioral alteration (groom in, rearing, wt dog shakes, jam movement, hind limb scratching, urination, defection, salivation, head nodding, incidence and latency of convulsions and mortality over a period of 4 hours (Gupta *et al.*, 2002).

2.3. Experimental design:

Mice were randomly divided into four main equal groups, 6 animal each, placed in individual cages and classified as follow: Group (1): Control Normal Group: Mice received no drugs, served as untreated control for all experimental groups. Group Π :(epilepsy- induced group): Mice administered with a single dose of KA (10 mg/kg b.wt, intraperitoneally), served as epilepsy non treated group. Group III :(

epilepsy + RESV protected group): Mice received RESV (10 mg/kg b.wt./i.p) daily for 7 successive days prior to KA injection (10 mg/kg b.wt, intraperitoneally). Group IV :(epilepsy + RESV treated group): Mice injected with KA (10 mg/kg b.wt, intraperitoneally) after 15 min. mice were treated with RESV (10 mg/kg b.wt/day, i.p) for three days.

2.4. Sampling:

Blood samples and tissue specimens (brain tissues) were collected after 12 hours and 3 days from the onset of KA administration.

2.4.1. Blood:

Blood samples for serum separation were collected by ocular vein puncture at the end of each experimental period in dry, clean, and screw capped tubes and serum was separated by centrifugation at 2500 r.p.m for 15 minutes. The clean, clear serum was separated by automatic pipette and received in dry sterile samples tube and kept in a deep freeze at -20°C until used for subsequent biochemical analysis. All sera were analyzed for the determination of sialic acid and TNF-alpha

2.4.2. Tissue samples (Brain tissue):

The skull was opened carefully and the brain was quickly removed, cleaned by rinsing with ice-cold isotonic saline, cleared off blood, then blotted between 2 filter papers. The brain tissue samples were quickly frozen in a deep freeze at -20°C for consequent biochemical analysis. Briefly, 0.5 gm from each brain tissues were minced into small pieces, homogenized with ice cold phosphate buffer saline (PBS) (i.e., 50 mM potassium phosphate, PH 7.5, 0.1 mM EDTA) to make 10% homogenates using tissue homogenizer. The homogenates were centrifuged at 6,000 r.p.m. for 15 minute at 4°C. The resulting supernatant was directly used for determination of the following biochemical parameters: SOD, CAT, GPx, GSH, L-MDA, NO, caspase-3, and DNA fragmentation

2.5.Biochemical analysis:

Serum sialic acid and TNF-α were determined using human sialic acid ELISA kit (Cat.No.CSB-E09605h) and Beyaert and Fiers, (1998), respectively. Moreover, brain tissues SOD, CAT, GPx, GSH, L-MDA, NO, caspase-3 and DNA-fragmentation were determined according to the methods described by Kakkar *et al.* (1984), Luck (1974), Gross *et al.* (1967), Moron *et al.* (1979), Mesbah *et al.* (2004), rat caspase-3 ELISA Kit (CUSABIO BIOTECH CO., LTD) Cat.No.CSB-E08857r) and Shi *et al.* (1996), respectively.

2.6.Statistical analysis

The obtained data were analyzed and graphically represented using the statistical package for social science (SPSS, 13.0 software, 2009), for obtaining mean and standard deviation and error. The data were analyzed using one-way ANOVA to determine the statistical significance of differences among groups. Duncan's test was used for making a multiple comparisons among the groups for testing the inter-grouping homogeneity.

3. RESULTS

3.1. Protective and treatment effect of resveratrol on serum sialic acid and TNF-α concentrations and brain tissue SOD, CAT and GPx activities of kainic acid-induced epilepsy in mice:

The obtained data demonstrated in table (1) revealed that, a significant decrease in serum SA level and brain tissue SOD, CAT and GPx activities were observed in KA-induced epilepsy in male mice group. However, serum TNF-α level was significantly increased when compared with normal control group. On the other hand, protection and treatment with resveratrol administration in KA induced epilepsy in mice resulted in a significant increase in serum SA level and brain tissue SOD, CAT and GPx activities with significant decrease

in serum TNF- α level when compared with epilepsy-induced non treated group.

3.2. Protective and treatment effect of resveratrol on brain tissue L-MDA, GSH and NO concentrations, caspase-3 activity and DNA fragmentation percent of kainic acid-induced epilepsy in mice:

The obtained results demonstrated in table (2) revealed that, administration of KA induced epilepsy in mice exhibited a significant decrease in brain tissue GSH level and significantly increased L-MDA, NO, Caspase 3, and DNA fragmentation when compared with normal control group. Meanwhile, protection and treatment with resveratrol administration in epilepsy-induced in mice significantly increased GSH level and markedly decrease and attenuate the increased of NO and L-MDA concentrations, Caspase 3 activity and DNA fragmentation in brain tissues when compared with KA-induced epilepsy non-treated group.

4. DISCUSSION

Epilepsy is a chronic neurological disorder characterized by recurrent unprovoked seizures (Lawrence *et al.*, 2012). In rodents, systemic administration of KA leads to a well-characterized seizure syndrome. One hour after KA administration, the animals start to present with recurrent limbic motor seizures. The limbic seizures then develop into status epilepticus and lasted 1-2 hours (Xiang *et al.*, 2011). The obtained results revealed that, a significant decrease in serum SA concentration was observed after 12 hours and 3 days in KA-induced epilepsy group. Bonfanti (2006) found that, sialic acids play an important role in many neuronal processes including axonal growth plasticity. Moreover, Johnson *et al.* (2004) indicated that the glycosidic linkage of sialic acid is a potential target for superoxide and other related ROS. Charged sialic acid residues have also been proposed to be the moieties responsible for the effects of divalent ions on channel gating behavior. The extracellular membrane surface contains a substantial amount of negatively charged sialic acid residues. Some of the sialic acids are located close to the pore of voltage-gated channel, substantially influencing their gating properties. However, the role of sialylation of the extracellular membrane in modulation of neuronal and network activity remains primarily unknown. The level of sialylation is controlled by neuraminidase (NEU),the key enzyme that cleaves sialic acids. Who showed that, NEU treatment causes a large depolarizing shift of voltage-gated sodium channel activation/inactivation and action potential (AP) threshold without any change in the resting membrane potential of hippocampal CA3 pyramidal neurons. Cleavage of sialic acids by NEU also reduced sensitivity of sodium channel gating and AP threshold to extracellular calcium. At the network level, exogenous NEU exerted powerful anticonvulsive action both in vitro and in acute and chronic in vivo models of epilepsy. In contrast, a NEU blocker (N-acetyl-2,3-dehydro-2-deoxyneuraminicacid) dramatically reduced seizure threshold and aggravated hippocampal seizures. Thus, sialylation appears to be a powerful mechanism to control neuronal and network excitability. Who propose that, decreasing the amount of extracellular sialic acid residues can be a useful approach to reduce neuronal excitability and serve as a novel therapeutic approach in the treatment of seizures (Dmytro *et al.*, 2007). On another hand**,** Ratajczak *et al.* (2011) showed that, inflammation in the CNS results in increased amounts of sialic acids which are key determinants of degenerative processes in the brain. The importance of cell surface glycosylation in the brain, changes in the composition of sugar chains of glycoproteins and glycolipids can be crucial for the processes of repair and regeneration of CNS after injury and exposure to degenerative factors (Wielgat and Braszko, 2012). Protection and treatment with

Table (1): Protective and treatment effect of resveratrol on serum sialic acid and TNF-α concentrations and brain tissue SOD, CAT and GPx activities of kainic acid-induced epilepsy in mice.

Groups	Serum sialic acid(mg/ml)		Serum TNF-α (pg/ml)		Brain SOD(U/g.tissue)		Brain CAT(mmol/g.tissue)		Brain GPx(ng/g.tissue)	
	12 hours	3 days	12 hours	3 days	12 hours	3 days	12 hours	3 days	12 hours	3 days
Control	41.23 ±4.19^{a}	48.36 ±4.01^{a}	33.59 ±3.79^{c}	33.34 ±2.29^{b}	38.31 ±5.06^{a}	25.16 ±2.22^{a}	60.12 ±2.99^{a}	53.44 ±2.10^{a}	46.66 ±1.80^{a}	41.70 ±1.48^{a}
KA (epilepsy)	19.31 ±3.27^{b}	17.75 ±2.14^{c}	57.64 ±2.85^{a}	81.74 ±10.90^{a}	6.81 ±1.99^{c}	9.36 ±0.82^{c}	16.55 ±5.64^{d}	23.60 ±4.27^{c}	10.90 ±2.25^{e}	9.93 ±2.88^{e}
Resveratrol protected	26.87 ±1.73^{b}	22.28 ±0.85^{c}	41.13 ±2.53^{bc}	50.11 ±2.25^{b}	12.84 ±0.29^{c}	10.86 ±1.43^{c}	46.14 ±4.50^{bc}	39.35 ±1.49^{b}	26.25 ±2.17^{d}	26.89 ±0.68^{d}
Resveratrol treated	42.22 ±1.41^{a}	45.64 ±4.17^{a}	46.37 ±2.84^{b}	37.38 ±3.94^{b}	23.57 ±1.35^{b}	19.30 ±3.08^{ab}	52.79 ±3.11^{ab}	52.52 ±0.81^{a}	40.38 ±2.39^{b}	36.58 ±2.29^{ab}

Data are presented as (Mean±S.E) S.E = Standard error.
Mean values with different superscript letters in the same column are significantly different at (P≤0.05).

Table (2): Protective and treatment effect of resveratrol on brain tissue L-MDA, GSH and NO concentrations, caspase-3 activity and DNA fragmentation percent of kainic acid-induced epilepsy in mice.

Groups	Brain L-MDA(mmol/g.tissue)		Brain GSH(ng/g.tissue)		Brain Nitric Oxide(mmol/g.tissue)		Brain Caspase-3(ng/g.tissue)		Brain DNA fragmentation %	
	12 hours	3 days	12 hours	3 days	12 hours	3 days	12 hours	3 days	12 hours	3 days
Control	49.21 ±12.33^{d}	52.14 ±15.59^{c}	4.57 ±0.57^{a}	4.79 ±0.22^{a}	29.63 ±4.35^{c}	32.58 ±6.07^{c}	0.56 ±0.13^{d}	0.46 ±0.21^{e}	235.34 ±80.00^{d}	185.19 ±31.66^{d}
KA (epilepsy)	115.91 ±0.87^{a}	139.39 ±10.02^{a}	1.78 ±0.64^{b}	2.27 ±0.34^{c}	86.03 ±5.59^{a}	100.24 ±5.27^{a}	2.26 ±0.19^{a}	2.36 ±0.15^{a}	1394.42 ±222.26^{a}	1207.50 ±229.71^{a}
Resveratrol protected	81.48 ±4.59^{bc}	98.62 ±2.60^{b}	3.02 ±0.47^{ab}	4.49 ±0.49^{ab}	44.83 ±5.52^{b}	66.90 ±2.75^{b}	1.61 ±0.19^{bc}	1.76 ±0.07^{b}	856.92 ±58.44^{b}	640.00 ±111.38^{bc}
Resveratrol treated	39.85 ±9.10^{d}	51.41 ±10.81^{c}	3.23 ±0.46^{ab}	2.71 ±0.33^{c}	75.47 ±2.45^{a}	99.41 ±3.71^{a}	1.25 ±0.21^{c}	0.98 ±0.25^{de}	208.27 ±37.66^{d}	272.46 ±71.53^{d}

Data are presented as (Mean±S.E) S.E = Standard error.
Mean values with different superscript letters in the same column are significantly different at (P≤0.05).

resveratrol administration in KA induced epilepsy in mice resulted in a significant increase in serum SA level when compared with epilepsy-induced non treated group. Sialic acid (SA) is the generic term given to a family of acetylated derivatives of neuraminic acid, which occur mainly at terminal positions of glycoprotein and glycolipids oligosaccharide side-chains. Several biological functions have been suggested for SA, such as stabilizing the conformation of glycoproteins and cellular membranes, assisting in cell-cell recognition and interaction, contributing to membrane transport, providing binding sites for ligands for the membrane receptor functions, and affecting the function, stability and survival of glycoproteins in blood circulation (Sumangala *et al.*, 1998). In the present study RES may be help in protection of brain tissue from KA-induced epilepsy due to its constructive effect on rising serum sialic acid level in both protecting and treatment periods. A significant increase in serum TNF- α concentration was observed in KA-induced epilepsy in mice. These results are nearly similar to those reported by Mahaveer *et al.* (2011) who reported that, the brain level of TNF-alpha was significantly raised after KA-administration in rats. Also, Kerschensteiner *et al.* (2009) showed that, activated microglia and astrocytes after KA treatment release a large amount of inflammatory mediators such as NO, TNF-alpha, and IL-Iβ**.** Seizures and status epilepticus induced by chemical or electrical means stimulates a massive inflammatory response in the brain that consists of increased levels of cytokines, including IL-1β. In addition, IL-1β inhibits glutamate reuptake by astrocytes and enhances its astrocytic release via tumor necrosis factor-alpha (TNF-α) induction (Bezzi *et al.*, 2001). TNF-alpha is mainly produced by microglia and astrocytes in the CNS. KA-activiated microglia expressed high levels of TNF- α mRNA and protein. As with many other cytokines, TNF-α bears neuroprotective properties in contrast to its well-known deleterious role as a pro-inflammatory cytokine, which implies an intricate biological balance in immune and inflammatory responses mediate by TNF-α (Lu *et al.*, 2008). However, **(**Zhu *et al.*, 2010) suggested that, TNF-alpha derived from KA-activated microglia can increase the excitotoxicity of hippocampal neurons and can induce neuronal apoptosis in vitro and *in vivo*. Pro-inflammatory cytokine TNF-α has been implicated in playing an important role in the neuronal apoptosis caused by a variety of brain insults as well as the neurodegenerative disorders (Chaparro-Huerta *et al.,* 2008). Protection and treatment with resveratrol administration in KA induced epilepsy in mice resulted in significant decrease in serum TNF-alpha level when compared with epilepsy-induced non treated group. Resveratrol was very effective in attenuating NO and TNF-α production from LPS-activated primary microglia cultures. Thus, RESV can potentially suppress pro-inflammatory responses of microglia. considering these, it appears that RESV administration would beneficial for curtailing the inflammatory reaction in neurodegenerative diseases. This is particularly applicable to conditions where significant microglial activation is one of the pathological changes such as after acute seizure. RSV is also able to affect survival pathways like NF-κB and mitogen activated protein kinases (MAPKs) (Holme and Pervaiz, 2007). This protective activity was mediated by the inhibition of tumor necrosis factor-α (TNF-α)- induced activation of NADPH oxidase, thus lowering H_2O_2 formation. Furthermore, RSV attenuated both mRNA and protein expression of TNF-α (Zhang *et al.*, 2009). RSV was very effective in attenuating NO and TNF-α production from LPS-activated primary microglia cultures. This protective effect was characterized by reduced accumulation of reactive oxygen species and a significant increase in cellular glutathione levels (Okawara *et al.*, 2007), and thought to be due to the direct antioxidant and free radical

scavenging properties of this dietary compound (Fukui *et al.*, 2010). Resveratrol acting as an anti-inflammatory dietary phytochemical blocked some catabolic effects of proinflammatory mediators such as IL-1β and TNF-α via the inhibition of NF-κB (Kundu *et al.*, 2006). The obtained data revealed that, a significant decrease in brain tissue enzymatic antioxidants (SOD, CAT and GPx) activities were observed in KA-induced epilepsy in male mice. Similarly, Bechman *et al.* (2002) demonstrated that, KA-induced increased seizure susceptibility is associated with mitochondrial oxidative stress in the hippocampus (increased mitochondrial lipid peroxidation and protein oxidation and mitochondrial loss of glutathione homeostasis), that KA-induced mitochondrial dysfunction is attributable to decreased Mn-SOD protein expression, mitochondrial membrane potential, and uncoupling protein (UCP)-2 mRNA expression, and that KA-induced activation of caspase-3 triggered by cytochrome c release potentiates neuronal degeneration. These findings may indicate that, endogenous mitochondrial antioxidant systems do not respond rapidly enough to oxidative stress. Moreover, Erakovic *et al.* (1997) reported that, an acute decrease in regional brain antioxidant levels was observed following electroconvulsive shock in rats. Who showed reduced SOD and glutathione peroxidase (GPx) activities in the hippocampus and the frontal cortex two hours after a single electroconvulsive shock. In patients with progressive myolonic epilepsy, the activity of the cytosolic superoxide dismutase (SOD1) was reported to be low (Ben-Ari *et al.*, 2000). Mitochondarial manganese superoxide dismutase (SOD2) was found to be down-regulated in the cerebral cortex of patients with epilepsy in contrast to non epileptic subjects (Eun *et al.*, 2013). GPx and CAT levels in neuronal tissue appear too low for the prevention of peroxide-induced lesions. Furthermore, neuronal cell membranes contain high levels of polyunsaturated fatty acids. Studies conducted by modulating the level of SOD in a mouse model of epilepsy have given us insights into the role antioxidant system in the prevenation of oxidative stress and a see mingly causal role of oxidative damage in seizure. It has been shown that over expression of Mn SOD, 0.5-2.0 fold, can attenuate kainite induced seizures, however animals with diminished Mn SOD levels showed an exacerbation of Kainate induced seizure and hippocampal damage, which was attenuated with antioxidant treatment (Patel, 2002).

On the other hand, resveratrol administration in KA induced epilepsy in mice resulted in a significant increase in brain tissue SOD, CAT and GPx activities when compared with epilepsy non treated group. Similarly, Simão *et al.*, (2011) reported that, treatment with RSV markedly reversed the alterations in enzymatic antioxidants status SOD, GPx and CAT brought about by ischemia/reperfusion (I/R). The values were almost restored to near normal levels. Also, resveratrol treatment reversed the decrease of SOD activity and the increase of MDA level caused by spinal cord injury (SCI), suggesting its anti-oxidation role in response to the injury (Changjiang *et al.*, 2011). Administration of KA induced epilepsy in mice significantly increased L-MDA concentration when compared with normal control group. KA exposure can significantly increase the production of malondialdehyde (MDA) and 4-hydroxy-alkenals, suggesting an increase in lipid peroxidation (Liang and Patel, 2006). Whereas lipid peroxidation level increases in brain during epileptic seizures (Sudha *et al.*, 2001). The increase in superoxide production and oxidative DNA damage following KA administration are indications of KA-induced mitochondrial and oxidative damage (Ogata *et al.*, 2001). Similarly, Parihar and Hemnani (2003) demonstrated that, hippocampal neurons are susceptible to oxidative attack by free radicals. A 3-fold increase in lipid

peroxidation were observed after administration of KA. Also, Huang *Et Al.* (2004) reported that, elevation of protein oxidation and lipid peroxidation were observed in the hippocampus at early time points (i.e. 4 and 24 h) post-KA administration. The nervous system is more susceptible to the damaging effect of oxidative stress, due to the high content of polyunsaturated fatty acids that are susceptible to lipid peroxidation. Lipid peroxidation, mediated by ROS, is believed to be an important cause of destruction and damage to cell membranes in accordance with the increases in ROS, the MDA level was also significantly increased, indicating the presence of enhanced lipid peroxidation (Korkmaz and Kolankaya, 2010). Furthermore, MDA was increase 2 h post-pilocarpine-induced status epilepsy(SE) in the cortex (Tejada *et al.*, 2007). Additionally, lipid radicals have been detected in the extracellular space during KA-induced seizure activity using *in vivo* electron spin resonance microdialysis in freely moving rats, suggesting a progression of lipid peroxidation during seizure activity which may lead to neuronal damage in the hippocampus following acute seizure activity (Ueda *et al.*, 1997).

Resveratrol administration in epilepsy-induced in mice markedly decrease and attenuate the increased of L-MDA concentrations in brain tissues when compared with KA group. These results are nearly similar to those reported by Simão *et al.* (2011) who found that, a single dose of RESV (at 40 mg/kg i.p) five- minutes prior to kA treatment (10 mg/kg i.p) increased the latency to convulsions. However, with multiple doses of RESV treatment (i.e. at 5 min prior to KA injection and at 30 and 90 min post-KA injection), the incidence of convulsions was significantly reduced. RESV treatment also inhibited the KA-injury related increases in the level of MDA, suggesting that antioxidant function is one of the mechanisms by which RESV mediates neuroprotection against excitoxic injury and acute seizures. The brain MDA levels were found to be significantly attenuated in the trans-resveratrol-treated groups (multiple doses of 20 and 40 mg/kg b.wt) as compared to the kainic acid alone. The protective effect of trans-resveratrol against kainic acid-induced convulsions and the attenuation of raised MDA level suggest the potential use of antioxidants in the prevention of posttraumatic epilepsy (Gupta *et al.*, 2002). Furthermore, malonyldialdehyde levels were significantly increased in model of epilepsy in rats. Dissimilarity, malonyldialdehyde levels decreased significantly after treatment with resveratrol in the cortex and hippocampus as compared with the model group (Xingrong *et al.*, 2013).

KA-induced epilepsy in mice exhibited a significant decrease in brain tissue GSH level when compared with normal control group. Similarly, Shin *et al.*, (2008) demonstrated that, administration of KA caused a decrease in reduced form of glutathione (GSH) levels in the hippocampus. So that intravenous GSH administration protected against KA-induced neuronal loss in the hippocampus and subsequent development of edema. Therefore, GSH may protect neuronal cells against KA neurotoxicity through a mechanism associated with ROS scavenging (Yoneda *et al.*, 2001). Moreover, Ogata *et al.*, (2001) showed that, prolonged GSH depletion may lead to sensitization of the KA receptor to potentiate AP-1 DNA-binding activity in the murine hippocampus, suggesting that endogenous GSH may be partly involved in the underlying molecular mechanisms of transcription control by KA. Resveratrol treatment in epilepsy-induced in mice significantly increased GSH level in brain tissues when compared with KA non-treated group. Kumar *et al.* (2007) reported that, a significant elevation in brain GSH levels of diabetic rats protected with RSV.In the present study RES, may be help in protection of brain tissue from KA-induced epilepsy due to its helpful effect on

increasing GSH level in both protective and treatment periods.

Administration of KA in mice exhibited a significant increase in brain tissue NO level. The increase concentrations of NO and decreased levels of GSH support the role of oxidative stress in KA mediated epilepsy (Dzhala *et al.*, 2008). Systemic or intracerebral KA injections may result in consistent epileptic activity. During an experiment in which KA was injected directly into the CA3 area of the hippocampus, an increase in NO synthesis was demonstrated, contributing to cell death by apoptosis in the CA3 area of the hippocampus after the induction of an status epilepsy (SE) in the experimental temporal lobe (Zsurka and Kunz, 2010). Also, KA administration increases the generation of ROS and RNS by neuroglia, Microglia can produce large a mounts of soluble factors like NO (Hanisch, 2002). Elevated production of NO by increased activity of iNOS is thought to contribute to KA-induced neuronal damage (Amor *et al.*, 2010). Moreover, Yoshida *et al.* (2002) demonstrate that, injection of kainate into the hippocampus induces seizure activity and NO synthesis in the contra lateral hippocampus and that both responses are attenuated by the specific neuronal NOS inhibitor.

Resveratrol administration in epilepsy-induced mice markedly decrease and attenuate the increased of NO concentration in brain tissues when compared with KA group. Similarly, Simão *et al.*, (2011) reported that, administration of RSV to ischemic rats significantly inhibited the increase of NO content in cortex and hippocampus when compared to vehicle-ischemic group. Flavonoids exerted NO production inhibitory activity in several cell lines and cultures (mouse peritoneal macrophages). This effect was probably caused by flavonoid inhibitory effect on expression of inducible NOS but not by the inhibition of its activity. Flavonoids also possess the ability to directly scavenge molecules of NO (Procházková *et al.*, 2011). The level of NO in the brain was diminished in response to treatment with RSV. Resveratrol is reported to possess significant anti-inflammatory activity in various cells and tissues and is reported to inhibit the production of NO by Kupffer cells in a dose dependent manner that occurred at a post-transcriptional level (Palsamy *et al.*, 2010).

A significant increase in brain tissue Caspase 3 activity and DNA fragmentation were observed in KA-induced epilepsy in mice. Caspases are a family of aspartate-specific cysteine proteases. Caspase-3 is among the most studied regulators of apoptosis in the setting of seizure-induced neuronal death. Induction of caspase-3 mRNA and protein occurs within the hippocampus and extrahippocampal regions after seizures (Akbar *et al.*, 2003). These results are nearly similar to those reported by Henshall *et al.* (2001) who reported that, caspase-3- like protease activity was increased within the ipsilateral hippocampus following seizures. A putatively selective caspase-3 inhibitor significantly improved neuronal survival bilaterally within the hippocampal CA3/CA4 subfields following seizures. Also, Kondratyev *et al.* (2004) found that, caspase-activated DNase, which is activated by caspase-3, is involved in DNA fragmentation and apoptotic neuronal cell death in rhinal cortex and hippocampus following SE. Mouser *et al.* (2006) suggests that, caspase 3 activity is crucial for cellular alterations during epileptogenesis. KA induces different neurodegeneration among CA1, CA3 and the dentate gyrus (DG-hilus) regions which may be due to that the stratum lucidum region of CA3 is highly enriched with high-affinity KA binding sites (Ben-Ari *et al.*, 2000). Narkilahti *et al.* (2003) suggested that, SE-mediated nuclear caspase 3 activation may activate caspase-activated DNase (CAD) results in DNA fragmentation and apoptosis. The express of active caspase 3 in the glial fibrillary acidic protein (GFAP)-positive radial glial cells was increased after KA-injection, suggests

that caspase 3 functions as a regulatory molecule in neurogenesis (Aras *et al.*, 2012). The co-injection of caspase 3 inhibitor prevent KA-mediated increase of radial glial cells, newly born neurons, and activated microglia, but not the astrogliosis, suggesting that astroglial caspase 3 was activated after gross astrogliosis, which then regulate microglial activation and neurogenesis. Microglia has been described to be a mediator of neurogenesis (Kohman *et al.*, 2013). David *et al.* (2000) showed that, caspase-3 is cleaved and becomes active within brain regions exhibiting cell death following seizures induced by intra amygdaloidal KA. These events occurred in a sequential manner over a time course compatible with downstream consequences of caspase-3 activation, such as DNA fragmentation. Further, caspase-3 protein likely translocates to the nucleus where it is localized with fragmented DNA. Selective inhibition of caspase-3 in vivo may confer significant protection against seizure-induced brain injury, and inhibition of caspase-3 may therefore provide a novel neuroprotective approach as an adjunct to anticonvulsant therapy. Furthermore, systemic administration of kainate results in apparent DNA fragmentation in a precise and predictable anatomical distribution that is correlated with seizure severity. DNA fragmentation is a delayed effect of kainate (Wijsman *et al.*, 1993). Additionally, DNA fragmentation occurs within 24 h of KA administration and is maximal by 72 h. In general DNA fragmentation in mice is transitory, disappearing by 1 week after treatment (Schauwecker and Stewart, 1997).

Resveratrol administration in epilepsy-induced mice markedly decrease and attenuate the increased of Caspase 3 activity and DNA fragmentation in brain tissues when compared with KA-induced epilepsy non-treated group. polyphenolic compounds were investigated for their protective effects on oxidative DNA damage in a neuronal cell model, with a particular focus on the mechanisms by which they may be acting. Their antioxidant properties have already been well characterized (Sasaki *et al.*, 2003). In neuronal cells, it is described the cumulative effect of DNA damage in human brain over time (especially in mitochondrial DNA), which is supposed to play a critical role in aging and in the pathogenesis of several neurodegenerative diseases (Fishel *et al.*, 2007). It should be taken into account that the effect of antioxidants on recovery from oxidative DNA damage may be justified by at least two different explanations: 1) by stimulating the activity of repair enzymes or 2) through a direct protection against oxidation (Tomasetti *et al.*, 2001).

***CONCLUSION*:** the present study demonstrated that, RESV. possesses significantly neuroprotection and treatment effects against epilepsy and oxidative damage in brain tissue induced by KA in mice.

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5. REFERENCES

Akbar MT, Lundberg A.M, Liu K, Vidyadaran S, Wells KE, Dolatshad H, *et al.* 2003: The neuroprotective effects of heat shock protein 27 overexpression in transgenic animals against kainate-induced seizures and hippocampal cell death. J. Biol. Chem., 278: 19956–19965.

Amor S, Puentes F, Baker D, Van Der Valk P.2010: Inflammation in neurodegenerative diseases. Immunology., 129(2): 154-169.

Aras, RB, Anna MP, Christian J. 2012: Caspase activation contributes to astrogliosis. 2012-03-01.

Bechman I, Diano S, Warden CH, Bartfai T, Nitsch R, Horvath TL. 2002: Brain

mitochondrial uncoupling protein 2(UCP2): a protective stress signal in neuronal injury. Biochem. Pharmacol., 64: 363–367.

Ben-Ari Y, Cossart R. 2000: Kainate, a double agent that generates seizures: two decades of progress. Trends Neurosci. 23: 580–587.

Beyaert R, Fiers W. (1998): Tumor Necrosis Factor and Lymphotoxin. In Cytokines, A.R.M.-S. a. R. Thorpe, eds. Academic Press, San Diego, p. 335-360.

Bezzi P, Domercq M, Brambilla L, Galli R, Schols DDe, Clercq E, Vescovi A, Bagetta G, Kollias G, Meldolesi J, Volterra A. 2001: CXCR4- activated astrocyte glutamate release via TNF alpha: amplification by microglia triggers neurotoxicity. Nat Neurosci, 4: 702-710.

Bonfanti L. 2006: PSA-NCAM in mammalian structural plasticity and neurogenesis. Prog. Neurobiol. 80: 129–164.

Changjiang L, Zhibin S, Lihong F, Chen Z, Kunzheng W, Bo W. (2011): Resveratrol improves neuron protection and functional recovery in rat model of spinal cord injury: Volume 1374, Pages 100–109.

Chaparro-Huerta V, Flores-Soto M.E, Gudino-Cabrera G, Rivera-Cervantes M.C, Bitzer-Quintero OK, Beas-Zarate C. 2008: Role of p38 MAPK and pro-inflammatory cytokines expression in glutamate-induced neuronal death of neonatal rats. Int. J. Dev. Neurosci., 26: 487–495.

David CH, Jun C, Roger P. 2000: Simon Involvement of Caspase-3-Like Protease in the Mechanism of Cell Death Following Focally Evoked Limbic Seizures J. Neurochem., 74(3):

Dmytro, I., Elena, I., Tatiana, S., Qian, Z., Nicole, CS., Nicholas, WS., Rustem, K, Gregory, LH. 2007: Role of Extracellular Sialic Acid in Regulation of Neuronal and Network Excitability in the Rat Hippocampus. Received July 17, 2006; Revised Aug. 25, accepted Sept. 3.

Dzhala, VI., Brumback, AC, Staley, KJ. 2008: Bumetanide enhances phenobarbital efficacy ina neonatal seizure model. Ann. Neurol., 63(2): 222-35.

Erakovic, V., Zupan, G., Mrsic, J., Simonic, A, Varljen, J. 1997: The influence of nicardipine and ifenprodil on the brain free arachidonic acid level and behavior in hypoxia-exposed rats. Prog Neuropsychopharmacol Biol. Psychiatry., 21(4): 633–47.

Eun, J.S., Ji Hoon, J., Yoon, H.C., Won, KK., Kwang, HK., Jae, HB., Jau, SH., Yukio, Y , Hyoung, CK. 2013: Role of oxidative stress in epileptic seizures Neurochem Int. Author manuscript; Available in PMC Mar., 23.

Fishel, ML., He, Y., Smith, ML, Kelley, MR. 2007: Manipulation of base excision repair to sensitize ovarian cancer cells to alkylating agent temozolomide. Clin. Cancer Res.13: 260–267.

Frombaum, M., Solenn, Le C., Dominique, B, Didier, B. 2012: Antioxidant effects of resveratrol and other stilbene derivatives on oxidative stress and NO bioavailability: Potential benefits to cardiovascular diseases. Biochimie 94: 269-276.

Fukui, M., Choi, HJ, Zhu, BT. 2010: Mechanism for the protective effect ofresveratrol against oxidative stress-induced neuronal death. Free RadicalBiology and Medicine 49: 800–813.

Gross, RT., Bracci, R., Rudolph, N., Schroeder, E, Kochen, JA. 1967: Hydrogen peroxide toxicity and detoxification in the erythrocytes of newborn infants. Blood, 29: 481–493.

Gupta, YK., Briyal, S, Chaudhary, G. 2002. Protective effect of trans-resveratrol against kainic acid-induced seizures and oxidative stress in rats. Pharmacol Biochem Behav., 71(1-2): 245-9.

Hanisch, UK. 2002: Microglia as a source and target of cytokines. GLIA., 40(2): 140–155.

Henshall, DC., Skradski, SL., Lan, JQ., Ren, T, Simon, RP. 2001: Increased Bcl-w expression following focally evoked limbic seizures in the rat. Neurosci Lett., 305: 153-156.

Holme, AL, Pervaiz, S.2007: Resveratrol in cell fate decisions. J. Bioenerg. Biomembr., 39(1): 59-63.

Huang, YC., Chang, AY., Lin, JW., Hsu, SP, Chan, SH. 2004: Mitochondrial dysfunction and ultrastructural damage in the hippocampus during kainic acid-induced status epilepticus in the rat. Epilepsia. 45(10): 1202–1209.

Johnson, CR, Jarvis, WD. 2004: Apoptosis: an international journal on programmed cell Death. 9(4): 423-427.

Kakkar, P., Das, B, Viswanathan, PN. 1984. A modified spectrophotometric assay of superoxide dismutase. Indian J. Biochem. Biophys., 21: 130-132.

Karalis, F., Vassiliki, S., Thomas, G., Christos, TN., Constantina, S. Olympia, G, Evangelia, S. 2011: Resveratrol ameliorates hypoxia/ischemia-induced behavioral deficits and brain injury in the neonatal rat brain. Brain research 1425: 98-110.

Kerschensteiner, D., Morgan, JL., Parker, ED., Lewis, RM, Wong, RO. 2009: Neurotransmission selectively regulates synapse formation in parallel circuits in vivo. Nature, 460: 1016-1020.

Kohman, RA, Rhodes, JS. 2013: Neurogenesis, inflammation and behavior. Brain Behav Immun, 27: 22-32.

Kondratyev, A., Selby, D, Gale K. 2004: Status epilepticus leads to the degradation of the endogenous inhibitor of caspase-activated DNase in rats. Neurosci. Lett., 319: 145–148.

Korkmaz, A, Kolankaya, D. 2010: Effects of Rutin The protective against renal ischemia-reperfusion injury in male rats. Journal of Surgical Research, 164(2): 309-315.

Kumar G, Banu GS., Murugesan, AG, Pandian, MR. 2007: Effect of Helicteres isora Bark Extracts on Brain

Kundu, BS., Nandal, S., Tiwari, M, Tomar, M. 2006: Establishment and influence of phosphate solubilizing bacteria on pearl millet. Indian J. Pl. Physiol., 11(2): 201-205.

Lawrence, M., Stephen, J, Maxine, A. 2012: editors. Current Medical Diagnosis and Treatment, 51st edition. New York. Lange Medical Books.

Liang P, Patel, M. 2006: Seizure-induced changes in mitochondrial redox status. Free Radical Biology and Medicine, 40(2): 316-322.

Lu, MC., Yang, KI., Tung, CH., Huang, KY., Yu, HC., Liu, SQ., et al. 2008: Higher LPS-stimulated TNF-a mRNA lenels in peripheral blood mononuclear cells from Chince ankylosing spondylitis patients with–308 G/A polymorphism in promoter region of tumor necrosis factor: association with distinct A33/B58/Cw 10 haplotypes. Rbeumatol Int , In Peripheral Blood Mono

Luck, H. 1974: Estimation of catalase. In: methods in enzymatic analysis. 2nd edition, Bergmeyer, Academic Press, New York. Pp. 885-890.

Mahaveer, G., Uma, C., Jagriti, B.,Daman, S, Dharamvir, S.2011:ARY A. Biol. Pharm. Bull., 34(3): 360-365.

Martinc, B., Grabnar, I, Vovk, T. 2012: The role of reactive species in epileptogenesis and influence of antiepileptic drug therapy on oxidative stress. Curr. Neuropharmacol., 10(4): 328-343.

Mesbah, L., Soraya, B., Narimane, S,Jean, PF. 2004: protective effect of flavonides against the toxicity of vinblastine cyclophosphamide and paracetamol by inhibition of lipid – peroxydation and increase of liver glutathione. Haematol., 7(1): 59-67.

Moron, M.S., Depierre, JW, Mannervik, B. 1979: Levels of glutathione, glutathione reductase and glutathione S-transferase activities in rat lung and liver. Biochimica et Biophysica ACTA 582: 67-78.

Mouser, PE. Head, E., Ha, KH, Rohn, TT. 2006: Caspase-mediated cleavage of glial fibrillary acidic protein within degenerating astrocytes of the Alzheimer's disease brain. Am. J. Pathol., 168: 936-946.

Narkilahti, S., Pirttila, TJ., Lukasiuk, K., Tuunanen, J., Pitkanen, A., 2003: Expression and activation of caspase 3 following status epilepticus in the rat. Eur. J. Neurosci. 18(6): 1486–1496.

Ogata K, Kitayama T, Okuda H, Yoneda Y. 2001: Effects of glutathione depletion by 2-cyclohexen-1-one on excitatory amino acids-induced enhancement of activator protein-1 DNA binding in murine hippocampus. J. Neurochem., 76: 1905–1915.

Okawara, M., Katsuki, H., Kurimoto, E., Shibata, H., Kume, T, Akaike, A. 2007: Resveratrol protects dopaminergic neurons in midbrain slice culture from multiple insults. Biochem. Pharmacol., 73: 550–560.

Palsamy, P., Sivakumar, S, Subramanian, S. ,2010,: Resveratrol attenuates hyperglycemia-mediated oxidative stress, pro-inflammatory cytokines and protects hepatocytes ultra-structure in streptozotocin–nicotinamide-induced experimental diabetic rats. Chemico-Biological Interactions, 186: 200–210.

Parihar, M.S, Hemnani, T., 2003. Phenolic antioxidants attenuate hippocampal neuronal cell damage against kainic acid induced excito-toxicity. J. Biosci., 28: 121–128

Patel, BN.,Dunn, R.J., Jeong, SY., Zhu, Q., Julien, JP, David, S. 2002: Ceruloplasmin regulates iron levels in the CNS and prevents free radical injury. J. Neurosci., 22: 6578-6586.

Procházková, D., Boušová, I, Wilhelmová, N. 2011: Anti-oxidant and prooxidant properties of flavonoids. Fitoterapia 82: 513-523.

Ratajczak, J., Zuba-Surma, E., Paczkowska, E., Kucia, M., Nowacki, P , Ratajczak, MZ. 2011: Stem cells for neural regeneration - a potential application of very small embryonic-like stem cells. J. Physiol. Pharmacol., 62: 3-12.

Sasaki, N., Toda, T., Kaneko, T., Baba, N, Matsuo, M. ,2003: Protective effects offlavonoidson the cytotoxicity of linoleic acid hydroperoxide toward rat pheochromocytomaPC12 cells. Chem. Biol. Interact. 145: 101–116

Schauwecker, PE, Stewart, O. 1997: Genetic influences on cellular reac-tions to brain injury: activation of microglia in denervated neuropil.. in mice carrying a mutation Wld S that causes delayed Wallerian. degeneration. J. Comparative Neurology, 380: 82–94.

Shi, B., De Girolami, U., He, J., Wang, S., Lorenzo, A., Busciglio, J, Gabuzda, D. 1996: Apoptosis induced by HIV-1 infection of the central nervous system. J Clin Invest 98: 1979 - 1990.

Shin, EJ., Ko, KH.,Kim, WK., Chae, JS., Yen, TP., Kim, HJ, Wie, MB. 2008: Role of glurathione peroxidase in the ontogeny of hippocampal oxidative stress and kainite seizure sensitivity in the genetically epilepsy- prone rats. Neurochem. Int. 52: 1134-1147.

Simão, F., Aline, M., Cristiane, M., Flavia, MSS., Angela, TSW., Carlos, AN, Christianne, GS. 2011: Resveratrol prevents oxidative stress and inhibition of Na^+K^+-ATPase activity induced by transient global cerebral ischemia in rats. Journal of Nutritional Biochemistry 22: 921-928.

Sudha, K., Rao, AV, Rao, A. 2001: Oxidative stress and antioxidants in epilepsy. Clinica Chimica Acta, 303(1-2): 19-24.

Sumangala, PR., Dilip, MK., Shivanand, NB, Sathiamoorthy, SS. 1998: Prostaglandin mediated acid secretion inhibitory effect as a possible

mechanism for the anticulcer effect of angiotension converting enzyme inhibitor (captopril) in pylorus ligated rats, Indian J. Pharmacol., 30: 385-389.

Tejada, S., Sureda, A., Roca, C., Gamundi, A, Esteban, S. 2007: Antioxidant response and oxidative damage in brain cortex after high dose of pilocarpine. Brain Res Bull., 71(4):372–5.

Tomasetti, M., Alleva, R, Collins, AR. 2001: In vivo supplementation with coenzymeQ (10) enhances the recovery of human lymphocytes from oxidative DNA damage.FASEB J. 15: 1425–1451.

Ueda, Y., Yokoyama, H., Niwa, R., Konaka, R., Ohya-Nishiguchi, H, Kamada, H. 1997: Generation of lipid radicals in the hippocampal extracellular space during kainic acid-induced seizures in rats. Epilepsy Res., 26(2): 329–33

Wielgat, P, Braszko, JJ. 2012: Significance of the cell adhesion molecules and sialic acid in neurodegeneration ·Advances in Medical Sciences, 57(1): 23-30

Wijsman, JH., Jonker, RR., Keijzer, R., Van de Velde, CJ., Cornelisse, CJ, Van Dierendonck, JH. 1993: A newmethod to detect apoptosis in paraYn sections:in situ end-labeling of fragmented DNA. J. Histochem. Cytochem., 41: 7–12.

Xiang, YZ., Hong, LZ., Qi, L , Jie, Z. 2011: Kainic acid-induced Neurodegenerative Model: Potentials and Limitations. J. List J. Biomed. Biotechnol., PMC2992819

Xingrong, MA., Zhikun, S., Yanru, L., Yanjie, J., Boai, Z , Jiewen, Z. 2013: Resveratrol improves cognition and reduces oxidative stress in rats with vascular dementia: 8 (22): 2050-2059.

Yoneda, M, Hirota, M., Uchida, M., Uzawa, K., Tanaka, A., Shibata, Y, Morita, M. 2001: Marine radiocarbon reservoir effect in the western North pacific observed in archaeological fauna. Radiocarbon 43(2A): 465-71.

Yoshida, T., Hashimoto, K., Zimmer, A.., Maejima, T., Araishi, K, Kano, M. 2002: The cannabinoid CB1 receptor mediates retrograde signals for depolarization-induced suppression of inhibition in cerebellar Purkinje cells. J Neurosci., 22: 1690-1697.

Zhang, H., Zhang, J., Ungvari, Z, Zhang, C. 2009: Resveratrol improves endothelial function: role of TNF {alpha} and vascular oxidative stress. Arterioscler Thromb. Vasc. Biol., 29: 1164-71.

Zhu, W., Zheng, H., Shao, X., Wang, W., Yao, Q, Li, Z. 2010: Excitotoxicity of TNFα derived from KA activated microglia on hippocampal neurons in vitro and in vivo. J. Neurochemistry, 114(2): 386–396.

Zsurka, G , Kunz, WS. 2010: Mitochondrial dysfunction in neurological disorders with epileptic phenotypes. J. Bioenergetics and Biomembranes, 42(6): 443-448.

الرسيفراترول يحسن الصرع المحدث بحمض الكينيك في ذكور الفئران

سامي علي حسين، عفاف دسوقي عبد المجيد، امنية محمود عبد الحميد، حسن شعبان الحارثي
قسم الكيمياء الحيوية -كلية الطب البيطري بمشتهر-جامعة بنها

الملخص العربي

في هذه الدراسة تم تقييم التأثير الوقائي والعلاجي للرسيفراترول على التغيرات في مستوى حمض السياليك، عامل تنخر الورم الفا ، الإنزيمات المضادة للأكسدة ، تركيز إل-مالون داى ألدهيد، انزيم ،الجلوتاثيون المختزل، مستوى النيترك اوكسيد، الكاسبيس 3 وتفتييت الدى ان ايه في دم وأنسجة الفئران المستحدث فيها الصرع فى المخ بحمض الكينيك. هذا وقد أستخدم لأجراء هذه الدراسة عدد24 من الفئران البيضاء أعمارهم تتراوح من 6-8 أسبوع و أوزانها من 25-30جرام وقد قسمت إلي اربعة مجموعات وتم توزيعها كالآتي: المجموعة الأولى: (المجموعة الضابطة): اشتملت على 6 فأر لم تعطى أي أدوية واستخدمت كمجموعة ضابطة للمجموعات الأخرى. المجموعة الثانية: (المجموعة المحدث بها الصرع): تكونت من 6 فأر تم اعطاؤها جرعة واحدة فقط من حمض الكينيك عن طريق الحقن تحت الجلد بجرعة 10ملى جرام/كيلوجرام (2/1 ملى/فأر). المجموعة الثالثة: (مجموعة الرسيفراترول الوقائية والمحدث بها الصرع): اشتملت على 6 فأر تم حقنها تحت الجلد بجرعة مقدراها (10 مللى جرام/ كيلوجرام من وزن الجسم) لمدة 7 ايام وفى اليوم الثامن تم حقنها بحمض الكينيك تحت الجلد بجرعة 10ملى جرام/كيلوجرام (2/1 ملى/فأر) لاحداث الصرع وتكملة العلاج بالرسيفراترول لمدة 3 ايام. المجموعة الرابعة (مجموعة الرسيفراترول العلاجيه والمحدث بها الصرع): اشتملت على 6 فأر تم حقنها بالرسيفراترول بجرعة مقدراها (10 مللى جرام/كيلوجرام من وزن الجسم) لمدة 3 ايام بعد احداث الصرع. هذا وقد تم تجميع عينات الدم والانسجه فى اليوم الثامن من بداية التجربة بعد 24,12ساعه من من حدوث الصرع والعلاج. وقد أسفرت نتائج التحليل البيوكيميائى عن وجود انخفاض معنوى فى حمض السياليك بالمصل بالاضافة إلى نقص معنوى فى نشاط نشاط سوبر أكسيد ديسميوتيز و الكتاليز وانزيم الجلوتاثايون ريدكتاز والجلوتاثيون فى انسجة المخ مع حدوث زيادة معنوية فى مصل عامل تنخر الورم الفا بالاضافة الى زيادة معنوية فى تركيز إل-مالون داى ألدهيد، النيترك اوكسيد، كاسبيس-3 وتجزئة الحمض النووي دى ان ايه فى المجموعه المحدث بها الصرع. كما أوضحت النتائج أن مجموعتى الفئران المحدث بها الصرع والتي تم وقايتها وعلاجها بالرسيفراترول عن وجود زيادة في مصل حمض السيالك بالدم بالأضافه الى فى نشاط نشاط سوبر أكسيد ديسميوتيز والكتاليز وانزيم الجلوتاثايون ريدكتاز والجلوتاثيون فى انسجة المخ فى حين انخفض مستوى عامل تنخر الورم الفا فى المصل بالاضافة الى وجود نقص معنوى مستوى النيترك اوكسيد وتركيز إل-مالون داى ألدهيد، كاسبيس-3 وتجزئة الحمض النووي دى ان ايه فى انسجة المخ. وأوضحت الدراسة أن استخدام الرسيفراترول كان له دور فعال في حماية وعلاج انسجة وخلايا المخ من الصرع المحدث باستخدام حمض الكينيك وأدى استخدامه كذلك الى الحفاظ على نسب القياسات البيوكيميائية

(مجلة بنها للعلوم الطبية البيطرية: عدد 27(2):241–255, ديسمبر 2014)