Modulatory Effects of Fish Liver Oil on Pilocarpine-Model of Epilepsy in Rats Compared to Topirmate as a Common Antiepileptic Drug

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Abstract: Objective: To evaluate the action of fish liver oil and Topirmate in pilocarpine epileptic rats. **Methods:** Six groups of rats were treated daily for 21 days: control; pilocarpine- treated rats (epileptic control) were injected intraperitoneally with 350 mg/kg b. wt pilocarpine; epileptic rats treated with topirmate (100 mg/kg b. wt); epileptic rats was treated with fish liver oil (2.3 mg/kg b. wt); the 5th group was treated with the same previous dose of topirmate and the 6th group was treated with the previously mentioned dose of fish liver oil. **Results:** In epileptic rats a significant increase in hippocampal dopamine, serotonin, glutamate, lipid peroxidation, super oxide dismutase and serum K^+ level was reported. In addition, significant decrease in hippocampal glycine, reduced glutathione content and serum Na^+ level, was recorded. Both fish liver oil and topirmate were found to be able to ameliorate most of the physiologically-altered parameters in epileptic rats. **Conclusion:** Fish liver oil could act as a promising antiepileptic drugs of high efficacy in retarding pathophysiological complications related to the neurophysiological disorders induced by pilocarpine epilepsy in rats.
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1. Introduction:

Epilepsy, as a disease entity, has first been mentioned by the ancient Egyptians who called it *nesejet*, or by the ancient Babylonians who called it the *bennu* disease (Weiergräber *et al.,* 2010). Epilepsy (derived from Greek: "epilambanein", "to seize upon" or "to attack") is one of the oldest known neurological conditions in man (Mannaa *et al*., 2011). It is estimated that approximately 0.8% of the population is affected by some form of epilepsy(Alagpulinsa,2010),characterized by recurrent, unprovoked, paroxysmal episodes of brain dysfunction manifesting as a large number of clinical phenomena, like altered levels of consciousness, involuntary movements, abnormal sensory phenomena, autonomic changes, and transient disturbances of behaviour (Adjel, 2010).

The long lasting seizures can modify the cellular environment through changes of ionic gradient across the cell membrane, alteration of gene expression such as receptors, trophic factors, enzymes, proteins from cytoskeleton, protein from matrix and the phosphorylation of macromolecules, these modifications promote synaptic remodeling which can change the excitability of neurons from temporal structures, leading to the appearance of brain damage and a permanent hyperexcitability (Scorza *et al.,* 2009).

Temporal lobe epilepsy (TLE) is the most common form of symptomatic epilepsy (Nissinen, 2006). It has got its name from the seizures originating from the temporal lobe structures, particularly the hippocampus (Lauren, 2007). The main features of TLE are (1) The localization of seizure foci in the limbic system, particularly in the hippocampus, entrohinal cortex and amygdale (Curia *et al*., 2008). (2) An initial precipitating insult of the brain such as head trauma, status epilepticus, stroke, or brain infarction initiates a cascade of events (epileptogenesis) during which several neurobiological changes occur, including cell death, neurogenesis, gliosis, axonal and dendritic plasticity, and olecular reorganization of cellular membranes and extracellular matrix (Nissinen, 2006). (3) A seizure-free time interval following the precipitating injury known as ″Latent Period″ (Curia *et al*., 2008).

Ideally the research on humans with epilepsy should by carried out on humans with epilepsy, but this not always possible for ethical or practical reasons and therefore experimental models of epilepsy and epileptic seizures in animals are essential (Lauren, 2007). The epileptic model induced by pilocarpine is a useful animal model to study the development and understanding of the neuropathology of human TLE because it reproduces similar behavioral and electroencephalographic alterations (Tejada *et al.,* 2006). The important features of pilocarpine model are: (1) The induction of acute SE more rapidly than with intraperitoneal (i.p.) kainic acid, the other convulsants drug commonly used to reproduce TLE in animals (Curia *et al*., 2008), this acute period built up progressively into a limbic SE and that lasts 24hrs(Scorza *et al*., 2009). (2) The presence of a latent period followed by the appearance of spontaneous recurrent seizures (SRS, chronic phase) and (3) The fact that seizures are poorly controlled by antiepileptic drugs (AEDs)

in patients and pilocarpine-treated epileptic rodents (Curia *et al.,* 2008).

The diagnosis of epilepsy should be confirmed and the type of seizures determined before starting antiepileptic medication (Rattya, 2000). The treatment of epilepsy can be divided into 3 main categories: surgical measures, behavioral treatment and the use of antiepileptic medications (Laud, 2003). Topiramate was effective in status epilepticus by inhibiting both fast and persistent components of Na^+ currents in neocortical cells (Weiergraber *et al.*, 2010). Also increases chloride flux of $GABA_A$ channels by acting on non-benzodiazepine sites, and antagonizes AMPA/kainite evoked inward currents in a concentration dependent way (Francois *et al*., 2006).

The omega-3-fatty acids, eicosapentanoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), are anticonvulsants derived mainly from fish oil (Yuen *et al*., 2005). The proposed mechanism of these anticonvulsant effects of n-3 polyunsaturated fatty acids is through membrane stabilization, which may counteract uncontrolled brain electrical discharges (Lee and Chung, 2010), reduction in oxidative damage and inflammation, and protection against ischemic injury (Bromfield *et al*., 2008).

Thus, our study aims to investigate the effect of fish oil as a natural product against physiological in pilocarpine – epileptic model compared to topiramate as commonly-used antiepileptic drug common use.

2. Materials and Methods:

2.1. Chemicals:

Pilocarpine hydrochloride, a cholinergic agonist (C11H16N2O2.HCl) was purchased from Alexandria CO. for Pharmaceuticals – Alexandria, Egypt. Topiramate, an antiepileptic drug [2, 3: 4, 5 – bis - 0 - (1- ethyl – ethylidene -) - β - D - fructopyranose sulfamate] was purchased from Sabaa International Company for Pharmaceutical and Chemical Industries, Cairo, Egypt. Fish oil was purchased from Jed Co. International Pharmaceutical, Egypt.

2.2. Animals:

Male albino rats (*Rattus norvegicus*) weighing about 110-165 g were obtained from the animal house of the Research Institute of Ophthalmology, El-Giza, Egypt. The chosen animals were housed in plastic cages with good aerated covers at normal atmospheric temperature (25±5°C), humidity 50-60 % and 12 hours daily normal light periods and veterinarian control. Moreover, they were received standard balance diet and water *ad libitum*. All animals received human care in compliance with the guidelines of the Animals Care and Use Committee of National Research Centre, Egypt.

2.3. Induction of epilepsy:

Sustained seizures were induced by a single intraperitoneal administration of pilocarpine hydrochloride (350 mg/kg b.wt.). Methyl-Scopolamine (1mg/kg b.wt.) was injected 30 min prior pilocarpine injection to minimize peripheral cholinergic effects (Turski *et al.,* 1983). One hour after pilocarpine injection, all animals received phenobarbital administration (35 mg/kg, b.wt. i.p) in order to standardize the duration of seizure activity in status epilepticus (SE) animals (Turski *et al*., 1983). The animals were placed in 30cm × 30cm chambers to record behavioral changes during 1 h. Animals were left for 21 days to establish the chronic phase of induced spontaneous recurrent seizures.

2.4. Animal groups:

Rats were divided into six groups of six animals each including three normal groups and three epileptic groups as follows: Group 1, served as normal control; group2 , was considered as epileptic control and lasted without treatment for 21 days; group 3, epileptic rats treated with topiramate (100mg/kg b.wt/day) for 21 days; group 4, epileptic rats received treatment of fish liver oil (2.3ml/kg b.wt/day) for 21 days; group 5, normal animals were treated with toprimate, at dose level of (100mg/kg b.wt/day) for 3 weeks by oral administration; group 6, normal rats given fish oil, at dose levels (2.3 mg/1kg/b.wt/day) for 3 weeks. All the treatments were performed orally and daily between 7.00 and 9.00 a.m.

2.5. Experimental design:

At the end of the experimental period (21 days), rats were sacrificed under diethyl ether anesthesia. Blood samples were collected from each rat, allowed to coagulate at room temperature then centrifuged at 3000 r.p.m. for 20 minutes. The clear, non-hemolysed supernatant sera were quickly removed and kept at -20°C till examined for the detection of glycine and GABA levels and electrolytes measurement. The whole brains were rapidly removed and hippocampus were dissected out, weighed and thoroughly washed with isotonic saline. The hippocampus was obtained as slices. Some were kept on ice and homogenized in 10% (weight/volume) 75% TLC methanol for amino acid and neurotransmitters estimation and the rest slices were homogenized in 0.9% saline for oxidative stress parameters. The homogenate was centrifuged at 20000×g for 10 min at 4°C. The supernatant was collected and preserved at -20°C until used.

a- Behavioural studies: the behavioural changes during the experimental period (21 days) were recorded by naked eyes.

b- Physiological studies: The amino acids were determined by the method of Heinrikson and Meredith (1984) while the neurotransmitters were determined by Pagel *et al*., (2000). Na^+ was measured according to Trinder (1951), potassium concentration was measured by the turbidimetric method according to Sunderman and Sunderman (1958) using (Biodiagnostic) kits. Malondialdehyde (MDA) concentration in

hippocampus brain region was determined according to the method described by Preuss *et al*. (1998). The peroxidase activity was measured according to the modified chemical method of Kar and Mishra (1976). Superoxide dismutase was assayed according to Marklund and Marklin (1974).

2.6. Statistical analysis:

The data were analyzed using the one-way analysis of variance (ANOVA) (PC-STAT, University of Georgia, 1985) followed by LSD test to compare various groups with each other. Results were expressed as mean ± standard error (SE) and values of $P>0.05$ were considered non-significantly different, while those of $P<0.05$ and $P<0.01$ were considered significantly and highly significantly different, respectively.

3.Results:

3.1. Behavioural Changes:

Animals persistently had behavioural changes, including initial akinesia, ataxic lurching, peripheral cholinergic signs (miosis, piloerection, chromodacriorrhea, diarrhea and masticatory automatisms), stereotyped movements (continuous sniffing, paw licking, rearing and wet dog shakes that persist for 10-15 min), and clonic movements of forelimbs, head bobbing and tremors, these behavioural changes progressed to motor limbic seizures as previously described by Turski *et al*., (1983).

3.2. Physiological Variables:

The effects of different treatments on dopamine and serotonin levels in hippocampus of epileptic induced rats are depicted in table (1). Epileptic animals (E) showed a significant increase in brain dopamine and serotonin levels compared with the control animals. The use of antiepileptic drug (Topiramate) showed a significant decrease in serotonin and a non significant decrease in the level of dopamine compared to that in epileptic groups. On other hand, epileptic animals treated with fish oil showed a significant decrease in brain dopamine levels where the value of serotonin showed significant increase in comparison with epileptic rats.

Table (2) illustrates the amino acid concentration in the hippocampus of different groups. A significant increase in the level of glutamate and significant decrease in the level of glycine were detected in the epileptic rats when compared with normal rats. The decrease in hippocampal glutamate was modulated by the oral administration of topiramate or fish oil to epileptic animals. On other hand hippocampal glycine was significantly increased by oral administration of topiramate while the treatment of epileptic rats with fish oil induces significant decrease when compared with normal animals.

The results of oxidative stress′ markers and antioxidant enzymes activities in hippocampus homogenate are illustrated in Table (3). A significant increase in MDA level, peroxidase and superoxide dismutase activities were detected in epileptic animals while a significant decrease in the mean value of MDA level, peroxidase and superoxide dismutase were observed in epileptic animals treated with topiramate or fish oil when compared to the normal animals.

Regarding the electrolytes levels indicated in table (4), potassium concentration was significantly elevated in the epileptic control rats while sodium concentration was significantly decreased when compared with their corresponding control group. The treatment of epileptic rats with toprimate induced a significant slightly decrease in the potassium elevated values and a significantly increase in the sodium concentration in comparison with epileptic rats. The treatment of epileptic rats with fish oil induced a non significant decrease in the potassium concentration as compared with epileptic rats.

Table (1): Changes in neurotransmitter concentrations (Ug/g tissue) in hippocampi of different groups.

	Ng	Eg	ETg	EFg	Tg	Fg	F-Probability	LSD at 5%	LSD at 1%
Dopamine	1.17 ± 0.03^{e}	2.92 ± 0.11^{a}	2.76 ± 0.04^{ab}	2.70 ± 0.03^{b}	2.01 ± 0.05^{d}	2.22 ± 0.06^{c}	*P*<0.001	0.19	0.25
Serotonin	0.61 ± 0.03^{d}	1.22 ± 0.02^{b}	1.09 ± 0.03^{c}	1.29 ± 0.02^{a}	1.27 ± 0.01^{ab}	1.23 ± 0.02^{ab}	*P* <0.001	0.06	0.08

– Ng: Normal control group; Eg: Epileptic control group; ETg: Epileptic rats treated with topiramate; EFg: Epileptic treated with Fish oil; Tg; normal rats treated with topiramate group; Fg: normal rats treated with Fish oil.
– Data are expressed as mean ± standard error.
– Number of animals in each group is six.
– Means, which have the same superscript symbol (s), are not significantly different.

Table (2): Changes in amino acids concentrations (Ug/g tissue) in hippocampi of different groups.

	Ng	Eg	ETg	EFg	Tg	Fg	F-Probability	LSD at 5%	LSD at 1%
Glutamate	11.0 ± 0.09^{d}	15.4 ± 0.15^{a}	12.5 ± 0.15^{b}	11.8 ± 0.13^{c}	10.1 ± 0.22^{c}	2.25 ± 0.07^{f}	*P* <0.001	0.41	0.55
Glycine	2.49 ± 0.03^{b}	1.83 ± 0.03^{d}	3.80 ± 0.17^{a}	1.13 ± 0.19^{f}	2.18 ± 0.08^{c}	1.31 ± 0.08^{f}	*P* <0.001	0.23	0.32

– Ng: Normal control group; Eg: Epileptic control group; ETg: Epileptic rats treated with topiramate; EFg: Epileptic treated with Fish oil; Tg; normal rats treated with topiramate group; Fg: normal rats treated with Fish oil.
– Data are expressed as mean ± standard error.
– Number of animals in each group is six.
– Means, which have the same superscript symbol (s), are not significantly different.

Table (3): Changes in lipid peroxidation concentration (MDA) (nmol/MDA/g tissue/hr) and the activity (U/gm) of Peroxidase and Superoxide dismutase in hippocampi of different groups.

	Ng	Eg	ETg	EFg	Tg	Fg	F-Probability	LSD at 5%	LSD at 1%
MDA	0.44 ± 0.02^{b}	1.22 ± 0.09^{a}	1.02 ± 0.02^{bc}	0.529 ± 0.03^{b}	0.504 ± 0.01^{bc}	0.43 ± 0.00^{c}	*P* <0.001	0.11	0.15
Peroxidase	9.36 ± 1.70^{b}	13.1 ± 1.14^{a}	10.79 ± 0.93^{ab}	11.87 ± 0.46^{ab}	5.74 ± 0.57^{c}	4.93 ± 0.22^{c}	*P* <0.001	2.79	3.75
Super oxide dismutase	10.2 ± 0.65^{b}	13.6 ± 1.27^{a}	10.46 ± 0.59^{b}	11.75 ± 1.46^{ab}	10.16 ± 0.21^{b}	9.10 ± 0.76^{b}	*P* <0.05	2.67	3.59

– Ng: Normal control group; Eg: Epileptic control group; ETg: Epileptic rats treated with topiramate; EFg: Epileptic treated with Fish oil; Tg; normal rats treated with topiramate group; Fg: normal rats treated with Fish oil.
– Data are expressed as mean ± standard error.
– Number of animals in each group is six.
– Means, which have the same superscript symbol (s), are not significantly different.

Table (4): Changes in electrolytes concentrations in serum of different groups.

	Ng	Eg	ETg	EFg	Tg	Fg	F-Probability	LSD at 5%	LSD at 1%
Na^{+} mmol/l	142.6 ± 0.61^{a}	133.7 ± 0.36^{cd}	139 ± 1.96^{b}	132.5 ± 0.31^{d}	133.5 ± 0.97^{d}	135.4 ± 1.66^{bc}	*P* <0.001	3.40	4.58
K^{+} m/Eq/l	4.55 ± 0.26^{c}	6.38 ± 0.23^{a}	5.56 ± 0.21^{b}	6.2 ± 0.21^{a}	4.5 ± 0.06^{c}	4.6 ± 0.08^{c}	*P* <0.001	0.56	0.75

– Ng: Normal control group; Eg: Epileptic control group; ETg: Epileptic rats treated with topiramate; EFg: Epileptic treated with Fish oil; Tg; normal rats treated with topiramate group; Fg: normal rats treated with Fish oil.
– Data are expressed as mean ± standard error.
– Number of animals in each group is six.
– Means, which have the same superscript symbol (s), are not significantly different.

4. Discussion:

Epilepsy is one of the most common neurological problems all over the world, being associated with paroxysmal discharge of cerebral neurons and is characterized by several symptoms including alterations of behaviors and consciousness (Freitas, 2010). Status epilepticus (SE) is one of the most important medical emergencies that result in a significant alteration of neuronal function. SE involves enough seizure activity to induce a

sustained alteration in brain function (Freitas *et al*., 2004).

The pilocarpine model of chronic epilepsy provides a useful animal model for studying mechanisms and therapeutic approaches to temporal lobe epilepsy. In this model, excessive and sustained stimulation of cholinergic receptors can lead to status epilepticus and seizure-related brain damage in rodents (Khongsombat *et al*., 2010). In the hippocampus of pilocarpine treated rats the levels of prostaglandins (PGE_2, PGD_2, $PGF_{2\alpha}$) increased during the acute, silent and chronic periods and the overproduction of these compounds could release O^{2-} and OH^- so the hippocampus of these animals during the acute, silent and chronic periods was more vulnerable to oxidative stress (Bellisimo *et al*., 2011).

The male is more susceptible to the convulsants effects of agents that produce temporal lobe-like seizures, such as kainic acid and pilocarpine due to males presented a higher amount of stronger seizures (full limbic convulsions) than females. In the pilocarpine model, males exhibited full limbic convulsions and status epilepticus (Mejìas-Aponte *et al*., 2002).

The seizures induced by pilocarpine showing the involvement of the cholinergic system in seizures and status epilepticus (Nascimento *et al*., 2005). The activation of muscarinic receptors is the first step for seizure activity, while dopaminergic and other systems (GABAergic, glutamatergic, adenosine and serotonin) appear to mediate seizure propagation and/or maintenance in rodent epilepsy models (Freitas *et al*., 2006). The role of dopamine and serotonin in epilepsy remains controversial, but both had convincingly been implicated in the pathophysiology of seizures (Meurs *et al*., 2008).

In the present study, a significant increase was noticed in dopamine and serotonin of the hippocampus homogenate in epileptic rats. Meurs *et al*., 2008 suggesting that the seizure activity causes dopamine increase. The elevated dopamine mediated by presynaptic muscarinic stimulation (Khan *et al*., 2000) or may accumulate as a result of decreased nor epinephrine formation (Abdel-Reheim *et al*., 2008). On the other hand, the increase in serotonin level in epileptic rats is consistent with the hypothesis of an augmented rate of synthesis of serotonin in hippocampus of epileptic rats because pilocarpine administration induces the synthesis of hippocampal serotonin (Mannaa *et al*., 2011) or may be a result of activation of muscarinic or blockade of $GABA_A$ receptors on serotonergic nerve terminals in the hippocampus (Meurs *et al*., 2008). The brain serotonin is thought now to have an epileptic effect and antidepressant drugs-like selective serotonin re-uptake inhibitors- have proved to be useful in seizure control (Abdel-Reheim *et al*., 2008).

The significant decrease in DA and non significant decrease in 5-HT levels reported here in the hippocampus of epileptic rats treated with topiramate may be attribute to that topiramate is the only drug that possesses the ability to modify excitatory neurotransmission through the kainate and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (Steve-White, 2005), and preventing the mechanism of transmitter release by inhibiting voltage gated calcium channels (VGCC) as preventing calcium influx into cells and thus preventing exocytosis (Abdel-Reheim *et al*., 2009).

The epileptic animals treated with fish oil showed significant decrease in the level of dopamine and non significant change in the level of serotonin. Dietary supply of n-3 poly unsaturated fatty acids could modify aspects of the dopaminergic and serotonergic system and consequently, ccogenitive performance and behaviour (Abdel-Reheim *et al*., 2008), and the docosahexaenoic acid plays a crucial role in membrane fluidity which can influence neurotransmission as well as protection of neural cells from apoptotic death (Mannaa *et al*., 2011).

Secondary generalised seizures generally induced more marked alterations in the amino acids concentrations of excitatory and inhibitory neurotransmitters than partial seizures (Kitgaard, 2003). The effects of pilocarpine - induced hippocampal seizure activity on the extracellular levels of excitatory and inhibitory amino acids were involved in hippocampal transmission (Freitas *et al*., 2010).

The results obtained in the present study, regarding the glutamate and glycine in the hippocampus homogenate of epileptic rats showed a significant increase and a significant decrease in both parameters respectively. The intraperitoneal administration of pilocarpine cause significant increasing in glutamate and the sustained increase in the glutamate level play a key role in the maintenance and spreading of seizures (Freitas *et al*., 2010). The increasing inhibitory amino acid glutamate as an attempt to antagonize the effect of increasing level of glutamate because glycine potentiate glutamate mediated brain injury via the glycine modulation site on the N-methyl aspartate (NMDA receptors) (Khongsombat *et al*., 2010).

The treatment of topiramate induces significant increase in the level of glycine and significant decrease in the level of glutamate. The anticonvulsant effect of topiramate is due, at least in parts, to reduction of abnormally high extracellular level of excitatory amino acids (Kanda *et al*., 1996) by inhibiting glutamate receptors and increasing the frequency of GABA channels opening, which leads to the inhibition of both NMDA/Kainate receptors and finally lead to inhibition of neuronal firing (Abdel-Reheim *et al*., 2008).

Oral administration of fish oil in epileptic animals resulted in significant decrease in the glutamate in the hippocampus. The arachidonic acid is released upon stimulation of NMDA-typed glutamate receptors and inhibits the rate of glutamate

uptake in neuronal synaptic (Abdel-Reheim *et al*., 2008).

The mechanisms of epileptogenesis are not well established. Several studies in the last few years suggested that the body electrolytes, level of some trace elements, and membrane lipid peroxidation due to increase in free radicals or decrease in activities of antioxidant defense mechanisms may be causally involved in some forms of epilepsies and also to increase the recurrence of seizures (Hamed *et al*., 2004). Seizures and status epilepticus can be associated with oxidative stress (Santos *et al*., 2008).

A significant increase in the lipid peroxidation level, the activity of peroxidase and superoxide dismutase reported here in the hippocampus of epileptic rats suggesting that the increasing of thiobarbituric acid reacting substances related to its intermediated free radicals formed during seizures induced by pilocarpine (Freitas, 2010). Epilepsy is characterized by recurrent seizures which increase the content of reactive oxygen species and superoxide generation in brain (Mannaa *et al*., 2011). An increasing in the activities of antioxidants enzymes involved in free radical scavenging showed that the brain cells try to counteract the pilocarpine induced reactive oxygen species over production and the oxidative damage (Freitas *et al*., 2004).

The epileptic animals treated with topiramate showed a significant decrease in lipid peroxidation products and superoxide dismutase activity and a non significant decrease in peroxidase activity. The topiramate may interfere with production of reactive oxygen species due to its inhibitory effect on voltage gated calcium channels (VGCC) or may interfere with exocitoxic process even at their later stage (Kuber *et al*., 2004).

The significant decrease in the level of lipid peroxidation and a non significant decrease in the activity of superoxide dismutase and peroxidase activities were detected in the epileptic rats treated with fish oil. Delattre *et al*., (2010) reported that the possible mechanisms of DHA in decreasing lipid peroxidation as DHA associated with vinyl ether bonds of plasmalogens (glycerophospholipids) in the combat of free radicals.

The body electrolytes play a vital role for seizure conditions to prevail (Hamed and Abdellah, 2004) and routine laboratory estimation of serum Na^+, K^+, Mg^{2+}, and Ca^{2+} is essential for the rational understanding and management of epileptic patients (Uribe-Escamilla *et al*., 2007).

In the present study we found that the decreasing in the concentration of sodium and increasing of potassium concentration in the serum of epileptic rats when compared with normal rats. After seizures, the transmembrane ion gradients have to normalize, a process that is ultimately dependent on the supply of ATP, about of 60% of cerebral ATP consumption is used for operation of the electrogenic Na^+-K^+ pump, which transports 3Na ions out of the cell in exchange for 2K ions (Abdel-Reheim *et al*., 2008). Lowering of potassium concentrations as well as associated neuronal hyperpolarisation reduces the efficacy of the Na^+-K^+ ATPase pump and the inhibition of pump causes intracellular potassium loss, neuronal depolarization, and initially spontaneous discharge (Gorji *et al*., 2001).

The treatment of epileptic rats with toprimate induces a significant increase in serum sodium concentration and significant decrease in serum potassium concentration in comparison with epileptic rats. It is therefore possible that modulation of voltage-gated sodium and calcium channels are the main cause of the observed electrolyte balance by topiramate (Abdel-Rheim *et al*., 2008). One of the mechanism actions of topiramate in treating the epilepsy is voltage-gated sodium channel blockade (McLean *et al*., 2000) and activating potassium currents (Steve-White, 2005). Topiramate interferes with the activity of voltage-gated Na^+ channels in mammalian central neurons as Voltage-gated Na^+-currents which responsible for the generation of fast action potentials and subthreshold depolarizations under normal conditions, and also contribute to the sustained action potential firing that occurs during seizure activity (Zona *et al*., 1997).

The treatment of epileptic rats with fish oil showed non-significant change in the serum concentration of sodium and potassium when compared with epileptic rats. In agreement with our results Mannaa *et al*., (2008) who found the treatment of epileptic rats with fish liver oil plus valproate induce in significant changes in Na^+-K^+ ATPase as the dietary fish liver oil rich in eicosapentanoic and docosahexaenoic fatty acids may prevent the membrane alteration, and by this mechanism prevent the changes in Na^+/K^+-ATPase activity.

5. Conclusion:

The fish oil offered a neuroprotection against pilocarpine induced epileptic model. All the aforementioned effects of fish oil may explain its ameliorative impact on epileptic changes in our study.

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