

Responsibility of peroxisome proliferator activated receptor- α (PPAR- α) in epilepsy.

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Epilepsy is a brain disorder characterized by uncontrolled repeated seizure which may be secondary to organic brain disorders or primary due to mutation in the neuronal ion channels. Seizure occurs due to increases in the excitatory neurotransmitters or reduction in the inhibitory neurotransmitters [1].

Moreover, neuro-inflammation that is initiated by microglia is responsible for refractory epilepsy which is not controlled by traditional anti-epileptic agents thus; many studies were conducted into the research for many neuronal pathways and mediators that may play a role in the epileptogenesis [2].

PPAR have been regarded as a drug target for control of epilepsy through lift elevation of seizure threshold thus; PPAR- α agonist is of value in control of seizure frequency [3].

PPAR- α is a nuclear receptor encoded by PPAR-A gene, it was discovered by Stephen Green in 1990 when it regarded as potent proliferators of rodent peroxisomes thus it classified as class of hepato-carcinogens [4]. PPAR- α is necessary for ketogenesis during fasting and energy deprivation since; activation of PPAR- α increases mitochondrial fatty acid β -oxidation. Endogenous activators of PPAR- α are arachidonic acid, poly-unsaturated fatty acids and linoleic acid whereas exogenous activators are fibrate, herbicides and insecticides. Moreover, PPAR- α is highly expressed in tissues that oxidized fatty acids such as liver, kidney and small intestine [5].

Additionally, PPAR- α is regarded as a receptor for fibrates so; PPAR- α agonists have a role in the treatment of coronary heart disease, non-alcoholic fatty liver disease and play a role in prevention of epileptogenesis [6].

Indeed, PPAR- α is also expressed in many brain regions which play an important role in prevention of nicotinic induced-dopaminergic neuron excitations ,since there is a significant interaction between PPAR- α and neuronal nicotinic receptors [7].

Many studies showed that PPAR- α agonist reduced seizure frequency that was induced by nicotinic receptor activations at pyramidal neurons due to modulation of tyrosin-kinase and phosphatase enzymes which are involved in the neuronal currents. So, PPAR- α agonist like fenofibrate may be of value in control of refractory epilepsy. Animal model

study illustrated that fenofibrate prevents pentylentetrazole-induced convulsion due to modulation of presynaptic GABA neurotransmissions [8,9].

Therefore, chronic stimulation of PPAR- α by polyunsaturated fatty acids protect the cerebral neurons and prevent progressions of abnormal neuronal discharge which may explain the anti-seizure effect of ketogenic diets [10].

Additionally, PPAR- α agonist potentate the anti-epileptic effect of carbamazepine and lomatrixine at neuronal cholinergic nicotinic receptors via prevention of neuronal excitability and stabilization of neuronal membranes [11].

The potential mechanism of PPAR- α agonists may be through modulation of neuronal neurotransmitters gene expression, reduction of neuro-inflammation, inhibition of neuronal oxidative stress, improvement of neuronal fatty acid oxidation and equiponderate of excitatory and inhibitory neurotransmitters [12].

Morimoto et al., study showed that free radicals have been concerned in the development and progression of seizure due to lipid peroxidation that prevent the binding of polyunsaturated fatty acids to PPAR- α receptors thus; anti-oxidants like vitamin E possess a potential anti-convulsive effect in pilocarpin-induced seizure. Therefore, oxidative mediator like MDA is elevated while anti-oxidant potential is decreased following seizure which gives an idea about the implication of free radical in pathogenesis of epilepsy; these events are inhibited during bezafibrate therapy [13]. Consequently, bezafibrate add on valproate therapy prevent refractory epilepsy and progression of neurodegenerative disorders through maintaining neuronal basement membrane.

Moreover, PPAR- α agonist reduce neuronal specific enolase which is a specific biomarker of neuronal damage during seizure and cerebral stroke hence; PPAR- α agonists are regarded as neuro-protective agents [14].

Further studies are recommended to explore the precise mechanism of PPAR- α agonists in prevention of epileptogenesis and also to illustrate drug specific effect of PPAR- α agonists in seizure control.

Therefore, PPAR- α agonists should be selected in epileptic patients that have dyslipidemia as add on therapy.

References

1. Aronica E, Mühlebner A. Neuropathology of epilepsy. *Handb Clin Neurol*. 2017;145:193-216.
2. Barker-Haliski ML, Löscher W, White HS, et al. Neuroinflammation in epileptogenesis: Insights and translational perspectives from new models of epilepsy. *Epilepsia*. 2017;58:39-47.
3. Saha L, Bhandari S, Bhatia A, et al. Anti-kindling effect of bezafibrate, a peroxisome proliferator-activated receptors alpha agonist, in pentylenetetrazole induced kindling seizure model. *J Epilepsy Res*. 2014;4(2):45-54.
4. Issemann I, Green S. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature*. 1990;347(6294):645-50.
5. Grabacka M, Pierzchalska M, Dean M, et al. Regulation of ketone body metabolism and the role of PPAR α . *Int J Mol Sci*. 2016;17(12):E2093.
6. Puligheddu M, Pillolla G, Melis M, et al. PPAR-alpha agonists as novel antiepileptic drugs: Preclinical findings. *PLoS ONE*. 2013;8(5):e64541.
7. Ghosh A, Jana M, Modi K, et al. Activation of peroxisome proliferator-activated receptor α induces lysosomal biogenesis in brain cells: Implications for lysosomal storage disorders. *J Biol Chem*. 2015;290(16):10309-24.
8. Citraro R, Russo E, Scicchitano F, et al. Antiepileptic action of N-palmitoylethanolamine through CB1 and PPAR- α receptor activation in a genetic model of absence epilepsy. *Neuropharmacology*. 2013;69:115-26.
9. Porta N, Vallée L, Lecoq C, et al. Fenofibrate, a peroxisome proliferator-activated receptor-alpha agonist, exerts anticonvulsive properties. *Epilepsia*. 2009;50(4):943-8.
10. Viggiano A, Stoddard M, Pisano S, et al. Ketogenic diet prevents neuronal firing increase within the substantia nigra during pentylenetetrazole-induced seizure in rats. *Brain Res Bull*. 2016;125:168-72.
11. Citraro R, Russo E, Leo A, et al. Pharmacokinetic-pharmacodynamic influence of N-palmitoylethanolamine, arachidonyl-2'-chloroethylamide and WIN 55,212-2 on the anticonvulsant activity of antiepileptic drugs against audiogenic seizures in DBA/2 mice. *Eur J Pharmacol*. 2016;791:523-534.
12. Moran EP, Ma JX. Therapeutic effects of PPAR α on neuronal death and microvascular impairment. *PPAR Res*. 2015;2015:595426.
13. Morimoto M, Satomura S, Hashimoto T, et al. A study of oxidative stress and the newer antiepileptic drugs in epilepsy associated with severe motor and intellectual disabilities. *J Chin Med Assoc*. 2017;80(1):19-28.
14. DeGiorgio CM, Gott PS, Rabinowicz AL, et al. Neuron specific enolase, a marker of acute neuronal injury, is increased in complex partial status epilepticus. *Epilepsia*. 1996;37:606-9.

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