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Research Article

Potential Therapeutic Target of Tramadol in Management of Epilepsy

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ABSTRACT
Epilepsy is a neurologic disease that caused by genetic or acquired etiologies. Patients with this disorder usually take pain killer beside antiepileptic agents. Tramadol is an opiate-like analgesic that binds the μ-receptors of opioids and inhibits the re-uptake of monoamines and serotonin in the central nervous system. The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that regulates many physiological functions. Many preclinical and some clinical data have represented that excessive activation of mTOR signaling can be responsible for epilepsy syndromes. Tramadol can inhibit the phosphorylation level of phosphatidylinositol 3' -kinase (PI3K), increase the protein expression level of tumor suppressor gene (PTEN) and also increase c-Jun N-terminal kinase (JNK) phosphorylation. Because of these three different pathways, although acute and high dose consumption of tramadol can cause seizure, but it can inhibit mTOR signaling and be effective in epilepsy treatment in chronic use. In this article we introduced the probable signaling pathways of tramadol in epilepsy treatment and also the reason of causing epileptic seizures.

Keywords: Tramadol; Seizure; Epilepsy; mTOR signaling.

INTRODUCTION

Epilepsy is the second most common neurologic disease with seizure symptoms and caused by genetic or acquired etiologies[1]. Fifty million people in the world suffer from this disease[2]. In epileptic seizures, because of some problems within the brain, a group of neurons begin firing in an abnormal manner[3]. Patients with this disorder usually take pain killer beside antiepileptic drugs. Tramadol is an opiate-like analgesic that has monoaminergic activity. It is used for the treatment of acute and chronic pain. Tramadol binds the μ-receptors of opioids and inhibits the re-uptake of monoamines and serotonin in the central nervous system[4]. The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that regulates many physiological functions. Since 2000, many preclinical and some clinical data have represented that excessive activation of mTOR signaling can be responsible for epilepsy syndromes[1]. The data have shown that tramadol could inhibit the phosphorylation level of phosphatidylinositol 3' -kinase (PI3K), increase the protein expression level of tumor suppressor gene (PTEN)[5] and also increase c-Jun N-terminal kinase (JNK) phosphorylation[6,7]. Because of these three pathways, although acute and high dose consumption of tramadol can cause seizure[8], but it can inhibit mTOR signaling and be effective in epilepsy treatment in the chronic use.

Hypothesis

Our detailed hypothesis is illustrated in Fig. 1. According to this signaling pathway, tramadol binds the μ-receptors and as a result, it increases the protein expression level of tumor suppressor gene (PTEN), increases c-Jun N-terminal kinase (JNK) phosphorylation and also inhibits the phosphorylation level of phosphatidylinositol-3-OH kinase (PI3K). These three pathways cause phosphatidylinositol (PI)-3-kinase generated PI-3,4,5-P3 (PIP3) inhibition and finally from three separated pathways, mTOR signaling is inhibited. In the first pathway, we see that inhibition of PIP3 causes mTOR direct inhibition. In the second pathway, PIP3 inhibition, decreases protein kinase B/Akt (PKB/Akt) level and mTOR signaling, and in the last pathway the figure represents that inhibition of PIP3 causes decreasing in pyruvate dehydrogenase kinase1/2 (PDK1/2) and serine/threonine kinase (Akt) phosphorylation level. These decreasing, increase tuberous sclerosis 1 and 2 (TSC2 and TSC1). After that level of Ras homolog enriched in brain (Rheb) decreases and because of that, we have mTOR signaling inhibition[9]. mTOR inhibitors such as; tramadol, can use in genetic or acquired epilepsy because of their protective effects[1]. Tramadol also has effect on $G_{i/o}$ pathway and because of the role of gamma-aminobutyric acid (GABA) in epileptic phenomena[10]; This pathway can be useful in epileptic studies, too. According to this pathway acute consumption of tramadol can block GABA release. The data have shown that drugs that inhibit GABA release can cause epileptic seizures[11]. But in chronic use of tramadol we have GABA release because of cascade activation of adenylyl cyclase (AC), cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA). Drugs that increase GABA release have the anticonvulsant effect[11]. So we hypothesized that tramadol can be effective in epilepsy treatment from four separated pathways, in chronic use, and also seizure side effect of tramadol relates to acute and overdose[12] drug consumption. Tramadol is an

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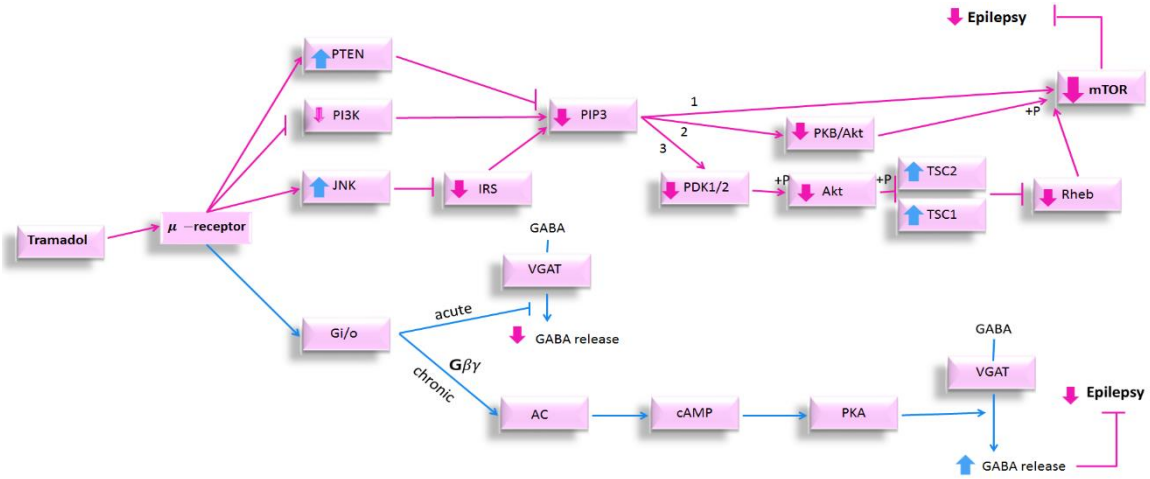

Figure 1: The schematic view of the tramadol signaling pathways related on seizure. PTEN: protein expression level of tumor suppressor gene; PI3K: phosphatidylinositol 3' –kinase; JNK: c-Jun N-terminal kinase; IRS: Insulin receptor substrate; PIP3: phosphatidylinositol (PI)-3-kinase generated PI-3,4,5-P3; PDK1/2: pyruvate dehydrogenase kinase1/2; Akt: serine/threonine kinase; TSC1/2: tuberous sclerosis 1/2; Rheb: Ras homolog enriched in brain; PKB/Akt: protein kinase B/Akt; mTOR: mammalian target of rapamycin; $G_{i/o}$: Gi/o proteins; GABA: gamma-Aminobutyric acid; VGAT: Vesicular GABA Transporter; AC: Adenylyl cyclase; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A.

analgesic drug that is used to relieve pain. It may be taken with anticonvulsant drugs. Chronic use of tramadol with low dose can help in epileptic seizures, but it also may cause epilepsy in acute consumption periods. Ashish et al. and Beyaz et al. believed that at clinically doses, tramadol can suppress severity of seizures. However, at higher doses it induces seizures[4,8].

CONCLUSION

According to our hypothesis, the design of drug delivery systems with controlled and rate programmed drug release can not only reduce seizure side effect, but also in patients taking tramadol reduce risk of epilepsy. In this case, providing new forms of drug delivery systems in addition to be effective on the pharmacokinetic parameters of tramadol, can present new relationship between pharmacokinetics and pharmacodynamics properties of this drug in seizure management[13-17].

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest

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