Therapeutic potential of selective serotonin reuptake inhibitor and anti-inflammatory COX-2 inhibitors drugs for epilepsy

Potencial terapêutico de fármacos inibidores seletivos da recaptação de serotonina e anti-inflamatórios inibidores da COX-2 para epilepsia

Potencial terapéutico de los fármacos inhibidores selectivos de la recaptación de serotonina y los antiinflamatorios inhibidores de la COX-2 para la epilepsia

Abstract
Epilepsy is a neurological disease caused by disturbances in the electrical propagation between neurons, which causes great damage to patients' lives, and can even lead to death. There are several proposals to understand its biochemical functioning, so current pharmacological treatments are based on the interruption of electrical conduction or modulation of neurotransmitters, such as phenobarbital and phenytoin. Thus, the present work aims to analyze the therapeutic potential of drugs such as COX-2 inhibitors and selective serotonin reuptake inhibitors (SSRIs) in the control of epilepsy. Thus, a narrative review of the literature was carried out using the “PubMed” database in order to find the theoretical bases and experimental works that demonstrate the mechanism of such drugs. The work concludes that SSRIs and COX-2 inhibitors have several mechanisms that can theoretically treat epilepsy, this is due to the establishment of a higher concentration of the neurotransmitter serotonin, as well as a reduction in the formation of quinolinic acid, which is a potential neurotoxic agent, which contributes to epileptogenesis.

Keywords: Epilepsy; Anti-inflammatory; Selective serotonin reuptake inhibitors; Serotonin; Kynurenine.

Resumo
A epilepsia é uma doença neurológica causada por distúrbios na propagação elétrica entre os neurônios, e que cursa com grandes prejuízos na vida dos pacientes, podendo até mesmo levar à morte. Há diversas propostas para entender seu funcionamento bioquímico, de modo que os tratamentos farmacológicos atuais se baseiam na interrupção da condução elétrica ou modulação de neurotransmissores, como o fenobarbital e a fenitoína. Desse modo, o presente trabalho objetiva analisar o potencial terapêutico que medicamentos como os anti-inflamatórios inibidores de COX-2 e os inibidores seletivos da recaptação de serotonina (ISRS) no controle da epilepsia. Assim, foi realizada uma revisão narrativa da literatura usando a base de dados “PubMed” a fim de encontrar as bases teóricas e trabalhos experimentais que demonstram o mecanismo de tais medicamentos. O trabalho conclui que os ISRSs e inibidores da COX-2 possuem diversos mecanismos que teoricamente podem tratar a epilepsia, isso se deve ao estabelecimento de maior concentração do neurotransmissor serotoninina, bem como redução da formação do ácido quinolínico, o qual é um potencial agente neurotóxico que contribui para a epileptogênese.

Palavras-chave: Epilepsia; Anti-inflamatório; Inibidor seletivo da recaptação da serotoninina; Serotonina; Quinurenina.

Resumen
La epilepsia es una enfermedad neurológica causada por alteraciones en la propagación eléctrica entre las neuronas, lo que provoca grandes daños en la vida de los pacientes, pudiendo llegar incluso a la muerte. Existen varias propuestas para entender su funcionamiento bioquímico, por lo que los tratamientos farmacológicos actuales se basan en la interrupción de la conducción eléctrica o la modulación de neurotransmisores, como el fenobarbital y la fenitoína. Así, el presente trabajo tiene como objetivo analizar el potencial terapéutico de fármacos como los inhibidores de la COX-2
y los inhibidores selectivos de la recaptación de serotonina (ISRS) en el control de la epilepsia. Así, se realizó una revisión narrativa de la literatura utilizando la base de datos “PubMed” con el fin de encontrar las bases teóricas y trabajos experimentales que demuestren el mecanismo de tales fármacos. El trabajo concluye que los ISRS y los inhibidores de la COX-2 tienen varios mecanismos que teóricamente pueden tratar la epilepsia, esto se debe al establecimiento de una mayor concentración del neurotransmisor serotonina, así como a una reducción en la formación de ácido quinolínico, que es un potencial agente neurotóxico que contribuye a la epileptogénesis.

Palabras clave: Epilepsia; Antiinflamatório; Inhibidor selectivo de la recaptación de serotonina; Serotonina; Quinuirenina.

1. Introduction

There are a number of diseases which are involved in the spectrum of neuroinflammation. Diseases such as epilepsy that, according to the World Health Organization, affect around 50 million people in the world, makes it a significant pathology in the field of neurological disorders, in addition to predisposing the patient to greater risk of death. This finding becomes even more worrying when taking into account, for example, that in the USA from 1999 to 2017 there was a 98.8% increase in the mortality rate from epilepsy (DeGiorgio et al., 2020; WHO, 2022).

Epilepsies, scientifically, are neural disorders that affect the coordinated circuit of brain neurons, so that there is neuronal hyperexcitability and release of discharges in a disorganized way. Etiology itself is quite diverse, it may be due to a genetic susceptibility or an acquired cause such as encephalitis or a stroke (Shneker & Fountain, 2003).

Although the causes of such diseases are not yet fully understood, the drugs that exist to treat such conditions are based on the diverse circuits that have influences on such diseases. Neurodegeneration involves, for example, activation of the sympathetic system and glucocorticoid release in the face of psychological stress, which increases the secretion of pro-inflammatory cytokines, causes astrocytic degeneration and upregulation of the IDO enzyme (indoleamine 2,3 dioxygenase) in the microglia, responsible for neurotoxicity and changes in the production of monoaminergic neurotransmitters such as serotonin (Afridi & Suk, 2021).

Such neuroinflammatory findings are present in epilepsy, as well as evidence of serotonin alterations with epileptic manifestations, when also considering that depolarization and hyperpolarization of serotonergic receptors have been shown to reduce neuronal excitability caused by the disease (Bagdy et al., 2007; Kanner, 2016).

Given its clinical importance, a series of treatments have emerged as a way to control epilepsies. There is no cure for the disease, however, there are several alternative forms of treatment to at least control such crises. Many of them occur through the use of drugs, such as phenobarbital, which acts by modulating the concentration of GABA, in order to increase hyperpolarity and also block the action of the excitatory neurotransmitter glutamate, in order to prevent uncoordinated synaptic discharges. Others, such as phenytoin, act by interfering with the sodium transport of neurons, thus controlling the propagation of the electrical impulse. Also worth mentioning is the valproic acid, which acts both by blocking sodium channels and increasing the availability of GABA (Silva & Cabral, 2008; Maranhão et al., 2011).

Other studies have also brought the perspective of the use of fluoxetine, which acts as a selective serotonin reuptake inhibitor (SSRI), as a promising treatment, given that there were associations of increased serotonin in the extracellular space and a reduction of seizures in rats compared to methods such as the use of phenobarbital (Hernandez et al., 2002).

Furthermore, the use of anti-inflammatory drugs is also associated with a possible treatment for neuroinflammatory diseases, such as depression and epilepsy. Celecoxib, for example, acts by inhibiting the formation of COX-2, an enzyme that’s responsible for the production of pro-inflammatory factors, and whose concentration is increased during epilepsy crises. Due to its inflammatory action, COX-2 induces the IDO enzyme that is involved in the synthesis of quinolinic acid, a substance involved in the neurogenesis of such diseases (Singh & Goel, 2017). For all the above, this study aims to analyze the potential therapeutic
effects of SSRI drugs, such as fluoxetine, and anti-inflammatory drugs, such as celecoxib on the neuroinflammatory processes involved in epilepsy.

2. Methodology

The present study is a narrative review carried out (Pereira et al., 2018), with a descriptive character about the studies that verified the use of anti-inflammatory COX-2 inhibitors drugs and selective serotonin reuptake inhibitors for neurological diseases with underlying neuronal inflammatory changes, such as epilepsy. The review included scientific articles, monographs, theses and dissertations published and available in PubMed database, without restricting the publication date, that demonstrated practical applications of these drugs, as well as those that brought theoretical foundations to justify the results found. Articles that did not present an abstract or title according to the theme, as well as those with deficient methodology, letters to the editor and opinion articles were excluded.

3. Results and Discussion

Serotonin

Serotonin (5-HT) is one of the most abundant neurotransmitters in the central nervous system (CNS), with numerous functions. It is primarily responsible for stimulating the serotonergic system, which is a network of neurons that spans different locations in the brain, mainly regulating hunger, mood, sleep, memory and learning. Other important functions of serotonin are the endocrine regulation, hematopoiesis and muscle contractions, mainly in the gastrointestinal tract (Deurwaerdère & Giovanni, 2020). So far, 14 different subtypes of serotonin receptors have been discovered, in different parts of the CNS and PNS (Deidda et al., 2021). Being a neurotransmitter comprehensive in functions, changes in the serotonergic system are related to several CNS pathologies such as anxiety, schizophrenia, obsessive-compulsive disorder, parkinson's disease, depression and epilepsy (Deurwaerdère & Giovanni, 2021).

Serotonin and Epilepsy

The role of the serotonergic system was first suggested in 1957, but it has only recently been taking a prominent position as a possible modulatory mechanism of convulsive epilepsy. The mechanisms of serotonin interaction are still being studied, the main one being the interaction between receptors of serotonin and the release of the inhibitory neurotransmitter GABA during seizures when there is neuronal hyperexcitation (Bonnycastle et al., 1957; Deidda et al., 2021). Being a neurotransmitter comprehensive in functions, changes in the serotonergic system are related to several CNS pathologies such as anxiety, schizophrenia, obsessive-compulsive disorder, parkinson's disease, depression and epilepsy (Deurwaerdère & Giovanni, 2021).

As an example, in a study with mice, it was identified that serotonin 5-HT1A receptors have an antiepileptic activity when excited, and are expressed both in excitatory neurons and in GABAergic neurons. Conventional antiepileptics act by promoting the action of GABA, either by stimulating its release in the matrix, stimulating production, acting as transporters or acting as receptor agonists. Therefore, the interaction between serotonin and GABAergic neurons is a potential novel mechanism for the treatment of convulsive epilepsy (Rodríguez et al., 2011; Sills & Rogawski, 2020; Deidda et al., 2021).

Patients diagnosed with Temporal Lobe Epilepsy (TLE) have fewer binding sites on 5-HT1a serotonin receptors in the temporal lobe, as well as a lower density of these receptors (Merlet et al., 2004; Meschaks et al., 2005). Other studies have also indicated that receptors of the 5-HT2a type, when stimulated, reduce seizures and body tremors induced by tryptamine. 5-HT2a
and 5-HT2c receptor antagonists (ketanserin and ritanserin) were responsible in one study for lowering the seizure threshold. Receptors of types 5-HT1a and 5-HT1b, when stimulated by agonists, caused an increase in the seizure threshold in rats after electroshock induction, indicating antiepileptic properties (Przegalinski et al., 1994; Oekelen et al., 2003; Stean et al., 2005).

During another study with mice, serotonin receptor proteins were identified in areas of the brain involved with focal epilepsy, such as the hippocampus and amygdala; and also in areas involved with absence seizures, such as the basal thalamus and the thalamic ventricular nucleus (Li et al., 2003; Bombardi, 2012). Other studies have also identified that the presence of serotonin in the extracellular matrix of areas related to epilepsy is directly related to both a lower intensity of the crises, as well as with the increase of the patient's seizure threshold. (Yan et al., 1994).

Still, there are other antiepileptic drugs currently used that have effects on the action of serotonin. Lamotrigine, an anticonvulsant, acts as an unconventional serotonin reuptake inhibitor, while carbamazepine causes an increase in CNS serotonin release. (Yan et al., 1994; Southam et al., 1998).

In a study conducted by Kommajosyula & Faingold (2019) with mice that were administered the SSRI drug fluoxetine and then subjected to audiogenic seizures, there was a lower susceptibility to respiratory arrest and sudden death compared to the control group. A significant increase in neuronal activity in the periaqueductal gray was also observed in mice that received fluoxetine in the study compared to control, indicating that it may be one of the critical areas for the prevention of sudden death from epilepsy.

Experiments carried out with fenfluramine (Tupal & Faingold, 2019), another SSRI, showed a similar reduction in the incidence of respiratory arrest in mice, as well as a decrease in the frequency and severity of seizures after acoustic stimuli. Finally, in another large study (Faingold et al, 2014) that analyzed the effect of multiple serotonergic drugs (fluvoxamine, paroxetine, venlafaxine and AS-19) favorable results were found for the prevention of respiratory arrest in seizure-induced mice.

**Kynurenine Pathway**

Tryptophan is an essential amino acid that follows distinct metabolic pathways. By the action of the tryptophan hydroxylase enzyme, this amino acid is converted into serotonin, generally less than 5% of the amino acid undergoes this change. The 95% are metabolized via the kynurenine pathway, through dioxygenase enzymes (IDO and TDO). This conversion is stimulated by pro-inflammatory cytokines such as IL-6, IL-1 and TNF (Deng et al., 2021).

Kynurenine crosses the blood-brain barrier where it will be processed by CNS (Central Nervous System) cells. Astrocytes usually have the enzyme KAT (kynurenine aminotransferase) responsible for converting kynurenine into kynurenic acid (KYN), which performs neuroprotective effects via antagonism of NMDA receptors and inducing the formation of neprilysin (NEP) (Klein et al., 2013).

On the other hand, kynurenine is metabolized by microglia by the action of KMO enzymes (kynurenine monooxygenase) into quinolinic acid (QUIN). Such acid has the property of stimulating NMDA receptors (N-methyl D-aspartate), and causing neurotoxic effects, involving oxidative stress, neurodegeneration and clinical aspects such as depression. It is known that the NMDA receptor is activated following the binding of glutamate on AMPA receptors, which favor postsynaptic depolarization and calcium influx through the NMDA receptor. Such a mechanism is important for neuroprotection and neuroplasticity, however the high excitability and greater influx of calcium is involved in the formation of reactive oxygen species and cell death, with strong excitotoxicity, as occurs in the stimulation by QUIN. In addition, inflammatory states lead to death of astrocytes, which end up not capturing glutamate in the cleft, thus increasing the availability of this neurotransmitter, with subsequent greater neural excitability and harmful toxicity (Wang & Reddy, 2018; Mattson, 2019; Afridi & Suk, 2021).

In particular, QUIN binding occurs on NMDA receptors of NR2A and NR2B subtypes, and the distribution of these receptors throughout the nervous system will influence the sites of greatest neuronal damage, such as the hippocampus and
striatum. In addition, QUIN also stimulates greater glutamate release and inhibits its reuptake, which causes greater calcium influx and neurodegeneration (Lugo-Huitrón et al, 2013).

In addition, pro-inflammatory cytokines, such as IL-1 and TNF, favor the action of IDO's and TDO's with greater formation of kynurenine, and promote inflammatory states with the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) causing even more nerve damage. TDO, although present in liver tissue, is responsible for converting tryptophan into kynurenine, which will cross the blood-brain barrier and favor the formation of more oxidative stress in the central nervous system (Singh & Goel, 2017).

Epilepsy

In epileptic states, there is a tendency to alter the hypothalamic-pituitary axis in order to increase the production of glucocorticoids, which will stimulate the TDO enzyme in the liver and thus generate even more neuroinflammation. In addition, inflammatory cytokines are also increased, which on the other hand elevates the action of IDO. This joint action of IDO and TDO ends up reducing the amount of tryptophan available for the formation of serotonin, a neurotransmitter that is essential for regulating neural excitability and controlling epilepsy (Singh & Goel, 2017).

Besides that, cyclooxygenases (COX) as mediators of inflammation, by acting on the production of prostaglandins, are also relevant in the pathophysiology of epilepsies. These are subdivided into COX-1 (physiological) and COX-2 (induced in pathological and pro-inflammatory situations). The level of COX-2 expression in the brain increases during and after epileptic seizures, which leads to greater cytokine release and greater IDO activity. Thus, it is theorized that the application of COX-2 inhibitors such as celecoxib may reduce the inflammatory response, as well as increase serotonin production by reducing the conversion of tryptophan to kynurenine, and thus better control of epilepsy (Singh & Goel, 2017).

Experimental research in mice, for example, shows positive results for such treatments. Song et al. (2016) in a study with pilocarpine-induced status epilepticus model rats, found that long-term use of the selective COX-2 inhibitor celecoxib reduced damage to hippocampal neurons. The authors therefore believe that COX-2 inhibitors can prevent epilepsy and nerve damage after brain trauma, have neuroprotective effects, and have an advantage over other drugs, due to the fact that they have fewer gastrointestinal side effects and do not increase the incidence of cardiovascular events.

Alsaegh et al. (2021) did a study with pilocarpine-induced rats and divided into groups that received celecoxib, and another that received celecoxib together with valproic acid (VPA) (classic anticonvulsant). In this study, treatment with celecoxib alone or in combination with VPA significantly reduced the Racine score (a scale used to assess the degree of epileptic seizure) and delayed the latency to onset of generalized tonic-clonic seizures with a significant decrease in hippocampal inflammation and oxidative stress markers compared to the exclusive administration of VPA.

4. Final Considerations

It is concluded that SSRIs and COX-2 inhibitor anti-inflammatory drugs have strong potential for the treatment of epilepsy, considering that both act by increasing the concentration and availability of serotonin, which has the function of increasing GABA and preventing neuronal excitability. Furthermore, COX-2 inhibitors act by reducing the conversion of tryptophan into kynurenine, and consequently preventing the formation of quinolinic acid, which is associated with a strong neurotoxic effect. Furthermore, studies with rats show increasingly promising results, with improvements in the Racine scale and a reduction in both the frequency and intensity of epileptic seizures.

Therefore, it is expected that from this present study, new researches may be developed, in order to prove the theory, in which serotonin and SSRI act in a better control of neuroinflammation through the kynurenine pathway. Above all, more
experimental researches is necessary to support the efficacy of such drugs, and for in the future, they may be used as well-established interventions in the treatment of epilepsy.

References


