Chapter

Neurotoxicity and Epileptogenesis

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Abstract

Many neurotoxic substances produce toxic effects on the nervous system. Given the neurotoxic substances found in the human body, certain people have been regarded as having a propensity to epileptic seizures. In many situations, the neurotransmission processes of these toxins are similar to the physiopathology of epilepsy. Epileptic models have been developed to induce seizures in animals, allowing researchers to study convulsive seizure mechanisms. Pentylenetetrazol, kainic acid, pilocarpine, penicillin, aluminum, bicuculline, picrotoxine, 4-aminopyridine, strictine, domoic acid, and other compounds fall under this category. However, there are some drugs used in clinical practice that can cause neurotoxicity as well. In this chapter, the predominant substances and drugs involved in epileptogenesis through neurotoxicity effects are reviewed. Throughout this chapter, we attempt to describe the mechanisms documented in the literature, in which epileptic seizures cause neurotoxicity in the brain by themselves, as shown with excitotoxicity mediated by glutamate and ions involved.

Keywords: Epilepsy, Epileptogenesis, Neurotoxic substances, Seizures

1. Introduction

The concept of toxicity refers to any substance capable of producing harm on livings organism. Hence, this chapter emphasizes on those compounds that harm the nervous system, particularly those capable of generating seizures. Within the pathophysiology of epilepsy, multiple mechanisms favor epileptogenesis, one of which is neurotoxicity. These excitotoxic mechanisms can exert their action through the glutamate receptors N-methyl-D-aspartate (NMDA); α-amino-2-3-dihydro-5-methyl-3-oxo-4-isoxazolepropionic acid (AMPA) and kainate, opening ionic channels permeable to calcium ($Ca2^{+}$), sodium ions (Na^{+}), that participate significantly in the neuronal damage derived from the excitotoxic effects. Though there are spontaneous inducers of epilepsy, different models that replicate seizures have been created to better understand the mechanisms underlying epileptic seizures. These models promote neurotoxicity in the brain and are triggered by certain substances, primarily agonists or antagonists of neurotransmitters involved in epileptic activity. In this review we aim to illustrate the neurotoxic potency of numerous agents administered in the brain with neurotoxic qualities, including medications used in clinical practice that can generate neurotoxicity.

Epileptic seizures, according to the World Health Organization, are defined as a neurological, chronic, recurrent, and repetitive condition of paroxysmal phenomena caused by an excessive abnormal discharge of groups of neurons, which can occur

in different parts of the brain [1]. It is the result of synchronous electrical discharge from a group of hyper-excitable neurons, that when repeated consequently leads to neurotoxicity This hyperexcitability is due to an imbalance between the inhibitory processes given mainly by gamma-aminobutyric acid (GABA) and the excitatory ones of glutamate, which consequently modifies the function of ion channels regulated by Ca^{2+}, Na^{+}, and potassium (K^{+}) mainly, which finally play a crucial role between the timing and propagation of abnormal discharges, contributing to the epileptic process [2]. Glutamate release activates NMDA ionotropic receptors, causing a rapid entry of Na^{+} and a slow entry of Ca^{2+}. In epileptic seizures, with this massive entry of Ca^{2+}, there is an increase of mitochondrial Ca^{2+} producing, among other effects an excitotoxic effect, in addition to free radicals production, proteases activation, and synthesis of nitric oxide which, by acting as a retrograde messenger, enhances the excitotoxic effect on the cell by also increasing glutamate release from the presynaptic terminals [3]. This glutamate release also activates the AMPA receptors associated with non-voltage-dependent channels, responsible for depolarizing currents, due to the Na^{+} input. AMPA receptor antagonists are known to have been shown to markedly reduce or decrease epileptic activity [4].

Kainic acid (KA) glutamate agonist acts on glutamatergic receptors with a high affinity for KA which is associated with a Na^{+} ion channel, this depolarization in turn causes Na^{+} channels opening, which leads to Ca^{2+} channels aperture that further increases neuron excitability. Na^{+} channels' participation in epileptogenesis and their mutations in many epileptic disorders has been long studied. The Na^{+} channels classified as type Nav 1.1 and Nav 1.6 are over-expressed in mice administered NMDA, which leads to hyperexcitability. However, when these animals are given phenytoin Na^{+} channel blocker, electrographic excitability decreases. Ion involvement has been described as vital in seizures [5]. The neurotoxic effect of KA appears to exert its action on non-NMDA receptors, located in the postsynaptic region at the dendrites of neurons level or by acting on presynaptic ionotropic glutamate receptors (NMDA, AMPA, and kainate) [6, 7]. Other glutamate receptors are also activated, predominantly found in the membrane of neurons, performing an excitatory response to the cell that presents them. When acting on the cell, there are even injuries to the cytoplasmic membrane, cytoplasmic vacuolization, and edema in the mitochondria, which finally cause cell death [8]. Kainate Glutamate stimulates postsynaptic AMPA receptors. This depolarization is immediately reduced by the GABA receptor recurrent inhibition [9].

Activation of AMPA receptors, particularly NMDA receptors, triggers intracellular Ca^{2+} cascades. Ca^{2+} permeability studies indicate that there is also a low permeability of this ion through kainate receptors [10, 11]. Excessive Ca^{2+} intake, derived from a pathological condition such as epilepsy, contributes to an excitotoxic effect and subsequent neuronal death [12].

In epileptic seizures, glutamate elevation and GABA release are observed from the presynaptic terminals within the synaptic cleft. Astrocytes recapture these abnormally released neurotransmitters during the seizure, protecting neurons from excitotoxicity and eliminating excess glutamate. It is known that, derived from the epileptic processes, there is hypertrophy and significant changes in the ramifications and volume of the astrocyte soma. These changes undoubtedly impact the reuptake of neurotransmitters such as glutamate, allowing an excess of this in the synaptic space [13, 14].

It is worth noting that epilepsy research is so broad that despite not managing to control the neuropathology, some authors have claimed that studying the disease has allowed neuroscience to investigate more than just seizure disorders, but the brain regions not directly implicated in epilepsy, as well. This chapter, however, will concentrate only on epilepsy-related neurotoxicity.

2. Calcium channels and epilepsy

When Ca^{2+} enters, it produces hyperexcitability in the excitable neuron through voltage-dependent Ca^{2+} channels (VDCCs). Intracellular processes are initiated when Ca^{2+} enters the cell, such as membrane excitability regulation, which permits neurotransmitters to be released. The biophysical and pharmacological properties of six types of Ca^{2+} channels (T, L, N, P, Q, and R) have been characterized. Low-threshold channels have been classed as T-type channels, while the rest have been classified as high-threshold channels. The number of depolarizations required for their activation has led to this classification. All channels have four subunits referred to as I through IV, each of which is made up of six transmembrane segments referred to as S1, S2, S3, S4, S5, and S6. The N, P and Q type channels are particularly crucial in controlling the release of neurotransmitters like glutamate and GABA, which, as previously stated, play a key role in epilepsy. The fact that a decrease in extracellular Ca^{2+} concentration can cause hyperexcitability in neurons is evidence that VDCCs play a major role in the epileptic activity [15]. In epilepsy, this correlates with paroxysmal depolarizations. Which correlates with paroxysmal depolarizations in epilepsy. This phenomenon has been observed in the hippocampus's neurons and dendrites, particularly in the CA1 and CA3 neuroanatomical, critical regions in epileptic seizures. Ca^{2+} currents have been demonstrated to promote the development of epileptic seizures; this is thought to be due to an increase in postsynaptic responses triggered by excessive excitement, which then initiates an epileptic seizure. However, this type of activity also leads to neuronal death.

Epileptic activity can also be triggered by the input of extracellular Ca^{2+} into the neuron, which promotes neuronal membrane depolarization and action potential production, resulting in abnormal discharges and seizures. The rise in intracellular Ca^{2+} in the postsynaptic neuron has been linked to various factors that produce epileptogenesis, including persistent depolarization, inducing neurotoxicity. Animal models in mice (tottering, du-du, or stargazer) in which genes coding for Ca^{2+} channel subunits formation have been altered and made it possible to illustrate the role of Ca^{2+} in epileptogenesis, implying that channelopathies may be part of the substrate for abnormal activity. Because Ca^{2+} plays such a role in abnormal epileptic activity, drugs like ethosuximide have been developed to block T-type Ca^{2+} channels by reducing Ca^{2+} entry. Hence, neurotransmitter release is implicated in neuronal excitability [16–19].

3. Molecular signaling pathways for epileptogenesis

This chapter proposes several molecular signaling pathways that are involved in epileptogenesis. We described the most representative pathways in the epileptogenesis study. Until now, the complicated epileptogenesis pathophysiology and molecular processes that lead to seizures have remained a mystery. However, various anatomical pathways mechanisms, pathological pathways, and molecular interactions are known and have been explored based on the research available. Inhibitory and excitatory neurotransmission abnormalities have a big impact on neuron stability. Neuroinflammation and oxidative stress, for example, encourage the emergence of epileptic seizures and can potentially intensify them [20].

It has been claimed that the inflammatory state, and the elevation of its mediators, including IL-1ß, IL-6, high mobility group box TNF-α8, and cyclooxygenase-2. TNF-α produces endocytosis of GABA receptors through AMPA. Therefore, hyperexcitability in the hippocampus is boosted, resulting in seizures. Several studies have linked neuroinflammation to oxidative stress at the same time. The involvement of oxidative stress as a seizure generator is owing to an imbalance in

the generation of reactive oxygen and nitrogen species, resulting in a deficiency in antioxidant mechanisms. The mitochondria are the body's principal generator of oxygen radicals [21]. Other free radicals, including nicotinamide adenine dinucleotide phosphate oxidase and xanthine oxidase, have been shown to act through glutamate receptors. The activation of the NMDA receptor is linked to epileptic activity [22].

Another pathway described in the study of epileptogenesis is the *Wnt* / β-Catenin pathway. *Wnt*/β-catenin is implicated in temporal lobe epilepsy. This pathway modulates, among other events, neuronal circuit formation and synaptic assemblages. Brain areas involved in epileptogenesis also play a key role in neuronal excitability modulation and neurotransmitter secretion. *Wnt* proteins dock with membrane receptors to initiate one of two major signal pathways: the canonical β-catenin pathway or the non-canonical pathway. β-catenin pathway manages transcriptional activity regulation and gene activation through the T-cell factor/ lymphoid enhancing factor pathway (TCF / LEF), that dictates cell determination, proliferation, and differentiation. *Wnt1*, *Wnt*3a, *Wnt*7a, and *Wnt*8 are most commonly found in β-catenin-dependent signaling. When one of these proteins binds to lipoprotein-related protein receptors, they lead to selective activation of the canonical pathway. Therefore, β-catenin dissociates from the degradation complex composed of axin, adenomatous polyposis coli protein (APC), casein kinase 1 (CK1), and glycogen synthase kinase 3 β (GSK3β). This promotes the accumulation of β-catenin in the cytosol, which is then translocated to the nucleus and associated with transcription factors of the TCF/LEF family to regulate *Wnt*-dependent gene expression. In the absence of the Fzd receptor by *Wnt*, the Axin and APC proteins boost phosphorylation of β-catenin through the kinases CK1 and GSK3-β. These proteins promote the ubiquitination and subsequent degradation of β-catenin by the proteasome [23].

Notoginsenoside R1 (NGR1, was recently discovered to upregulate mRNA levels of the proteins β-catenin, Dvl, and Fzd, as well as promote the proliferation of cultured cortical neurons. NGR1 has also been discovered to reduce persistent K^+ currents in hippocampus neurons, resulting in a reduced peak threshold. Treatment with a Wnt3a ligand, which activates the FZD receptor, caused K^+ channel internalization and enhanced β-catenin expression, according to a recent study. GSK-3β inhibition caused by *Wnt*/β-catenin activation resulted in a lack of phosphorylation of GSK on the surface of K^+ channels, resulting in internalization. This action lowers the current density of K^+ channels, preventing them from acting as hyperexcitability regulators. The non-canonical route refers to pathways that do not rely on β-catenin-TCF/LEF and instead rely on alternative downstream effectors to produce a transcription response. The *Wnt* /PCP (planar cell polarity) pathway, via *Wnt*-cGMP/Ca^{2+}, via *Wnt*/Via Ror, via *Wnt*-RYK, and via *Wnt*-mTOR are some of these pathways. Epileptogenesis has been linked to the mTOR signaling pathway. *Wnt*7a, a *Wnt* family ligand, is expressed in cerebellar granule cells and operates as a particular canonical signaling activator. *Wnt*7a is expressed in the developing hippocampus as well, particularly in the dentate gyrus and CA1 regions, as indicated by an increase in active β-catenin immunofluorescence after recombinant *Wnt*7a was applied. Other studies have shown that *Wnt*7a has a role in synapse formation, with an increase in the number of vesicular glutamate transporters puncta per dendritic area after hippocampal neurons were treated with recombinant *Wnt*7a, resulting in an increase in excitatory neurotransmitter. *Wnt*8a is also involved in synaptic terminal excitability modulation. Additionally, it is also involved in the regulation of synaptic terminal excitability. These findings show that *Wnt* impacts synaptic regions important in excitatory neurotransmitter release control and regulation and

ligand-gated ion channels in the postsynaptic membrane via canonical activation. These physiological changes on the synaptic terminal of hippocampus neurons may play a role in the temporal lobe epilepsy pathophysiological pathway. The aforementioned is attributed to synaptic transmission imbalances between inhibitory and excitatory synapses [24].

In a previous study, a significant increase in β-catenin signaling in the cerebellar cortex of rats after kindling-induced generalized seizures was observed. β-catenin activation induces apoptosis through the expression of cMyc upregulation, a protein that negatively regulates anti-apoptotic proteins such as Bcl-2. This leads to a loss of mitochondria, membrane potential, releasing cytochrome-c and promoting activation of caspases 3 and 9, leading to neuronal death. The *Wnt*/β-catenin pathway participates not only in neuronal synchrony regulation. But also in NMDA receptor modulation, which, as previously described, plays an important role not only in epilepsy but also in epileptogenesis [25, 26].

4. Toxic substances that cause seizures

Exposure to toxins can trigger seizures due to their damaging effect on the nervous system through different mechanisms (**Table 1**). The ability of organophosphate insecticides to induce epileptic seizures is known through the inhibition of acetylcholinesterase due to its chemical structure that contain the groups carbamoyl and thiocarbamoyl, due to its capacity to phosphorylate and inactivate acetylcholinesterase and in addition to stimulating cholinergic receptors, these pesticides include parathion, chlorpyrifos, aldicarb, and carbaryl. Certain toxins present a dual mechanism for epileptic seizures production through the facilitation of the activation and the inhibition of voltage-gated Na^+ channels, how is the case for chemical and biological warfare agents like sarin and soman, as well as toxins such as scorpion venom and ciguatoxin that can lead to seizures by modulating ion flow through Na^+ channels. In other instance, anatoxin is a potent agent that causes seizures by the nicotinic receptor activation. The imbalance in inhibitory and excitatory neurotransmission is one of the mechanisms by which seizures occur. Par excellence GABA is the inhibitory neurotransmitter and glutamate is the excitatory neurotransmitter in the CNS, seizures are triggered by the activation of glutamate receptors by kainic acid and domoic acid, cyanide and azide both display the same process after cellular damage. Interference with the inhibition produced by GABA can trigger epileptic events, GABA receptor inhibition is caused by lindane, picrotoxin, strychnine, and tetramethylenedisulfotetramine [27–29].

Toxic substance	Mechanism
Parathion, chlorpyrifos, aldicarb, and carbaryl	Inhibiting acetylcholinesterase and hyperstimulation of cholinergic receptors
Sarin, soman, scorpion venom and ciguatoxin	Modulating ion flow through voltage-gated sodium channels
Anatoxin	Nicotinic receptor activation
Kainic acid and domoic acid	Activation of glutamate receptors
Lindane, picrotoxin and strychnine	GABA receptor inhibition

Table 1.
Toxic substances that can trigger seizures and their exerting mechanism.

5. Drugs associated with seizures

The administration of different drugs used therapeutically can predispose to epileptic seizures presence either by lowering the epileptogenic threshold, intoxication, or overdose of these. The main groups of antimicrobials that can cause seizures are beta-lactams, anti-tuberculous, and antimalarials. The pro epileptogenic effect of beta-lactams is related to high doses or their toxicity. Seizures related to drugs used to treat tuberculosis are mainly due to vitamin B6 deficiency. Mefloquine and chloroquine are reported antimalarial drugs that can lead to seizures. The proconvulsive effect of methylxanthines is thought to be due to A1 adenosine receptor inhibition. Paradoxically, it is known that carbamazepine can worsen generalized-onset seizures. As well as the withdrawal effect of benzodiazepines, which in some cases can lower the seizure threshold [30–34]. **Table 2** summarizes the main drugs associated with seizures. The following part reviews some of the toxic effects of the main antiepileptic drugs used in clinical practice.

5.1 Valproic acid

Since 1978, valproic acid or Na^+ valproate has been characterized as an antiepileptic drug that suppresses the neuronal excitation of different types of epilepsy, such as partial seizures and generalized seizures [35]. It appears that valproic acid exerts its inhibition by blocking the reuptake of the neurotransmitter GABA, the main inhibitory neurotransmitter. It also lowers glutamate levels and modifies K^+ conductance [36], exerting an inhibition through the voltage-dependent Na^+ channels. In this way, it reduces the excitement caused by epileptic seizures [37]. Once this drug reaches the central nervous system (CNS), it binds to plasma proteins and is distributed throughout the extracellular space [38]. It is metabolized in the liver and discharged through the urine. Although it is also eliminated with expirations in the form of CO2 [39]. However, this drug is known to have frequent toxic effects derived from the therapeutic dose in patients with toxic plasma levels greater than 120 μg/ml [40]. After an overdose, the patient may be lethargic and coma, most likely due

Category	Drugs associated with seizures
Sympathomimetics	Phenylephrine, pseudoephedrine, and anorexiants
Analgesics	Opioids
Anticancer drugs	Interferon alfa, methotrexate, mitoxantrone, nelarabine, platinum-based, cisplatin, vinblastine, vincristine, busulfan, chlorambucil, cytarabine, doxorubicin, etoposide, and fluorouracil
Antimicrobials	Carbapenems, cephalosporins, fluoroquinolones, isoniazid, and penicillin
Hypoglycemics	Any antidiabetic that causes hypoglycemia
Immunosuppressants	Cyclosporine, mycophenolate, tacrolimus, and azathioprine
Psychopharmaceuticals	Monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, serotonin modulators, tricyclic antidepressants, antipsychotics, atomoxetine, bupropion, buspirone, and lithium
Stimulants	Amphetamines and methylphenidate
Xanthine	Aminophylline and theophylline
Antiepileptics	Carbamazepine and benzodiazepines

Table 2.
Main drugs associated with drugs.

to inhibition produced in the CNS [41]. Another adverse situation that derives from the consumption of this antiepileptic drug is cerebral edema, probably caused by the overstimulation of the stimulation of NMDA receptors [42]. Cardiovascular alterations such as hypotension with tachycardia, gastric alterations such as pancreatitis, and hepatotoxicity have manifested with elevated transaminases, jaundice, and abdominal pain with inflammation, among others, may also occur [43].

5.2 Phenobarbital

Phenobarbital belongs to the family of barbiturates. These are characterized by providing the central nervous system with a depressant effect depending on the administered dose [44]. Its anticonvulsant mechanism is based on increasing the inhibitory activity of GABA, binding to the GABA receptor, and facilitating even more inhibitory neurotransmission. This inhibition reduces ATP levels, which causes the opening of Ca^{2+} channels associated with the NMDA receptor, coupled with the fact that a prolonged opening of these Ca^{2+} would lead to excitotoxic neuronal death [45]. The anticonvulsant dose ranges between 10 and 40 μg/ml. The administration of these doses and higher ones generates toxicity that is generally due to the increase in Ca^{2+} entry into the neuron [46]. Mitochondria are an intracellular target of barbiturates since they depolarize the mitochondrial membrane by inhibiting complex one of the electron transports chains and, furthermore, they could have an uncoupling effect on oxidative phosphorylation [47]. Its absorption of phenobarbital is gastric, which generates a decrease in peristaltic tone. Although it is metabolized in the liver and discharged through the kidneys and urine, it has a great fat solubility that crosses cell membranes, producing several alterations [48].

5.3 Carbamazepine

Carbamazepine is a mainly antiepileptic psychotropic drug whose mechanism of action is based on reducing glutamate release, reducing the permeability of neuronal membranes to Na^+ and K^+ ions, stabilizing neuronal membranes, and depressing dopamine and norepinephrine turnover, though an inhibitory effect on muscarinic and nicotinic receptors is also known [49]. When its therapeutic plasma concentrations are higher than 10 μg/ml, it produces toxic effects initially characterized by tachycardia, hypotension and hypertension, lethargy, ataxia, dysarthria, and nystagmus can occur, there are also gastric alterations such as vomiting and nausea. When intoxication is severe, it could even cause a coma [50]. Carbamazepine absorption is digestive, metabolized in the liver where it can cause liver dysfunction and, as its elimination is via the kidneys, adverse effects can also occur in this way [51].

5.4 Phenytoin

Phenytoin has been the most commonly used antiepileptic drug for patients with focal and generalized epilepsies since 1938 [52]. Its mechanism of action is exerted by inactivating voltage-gated Na^+ channels. It also acts by inhibiting the flow of Ca^{2+} through neuronal membranes, such as it is to be expected at the cardiac level, it also inhibits Na^+ channels, which is why it has toxic effects on the myocardium [53]. Phenytoin is bound to plasma proteins, such as albumin, which is metabolized in the liver, so it can cause liver diseases. Toxic effects are present even if the patient has adequate therapeutic levels, like at concentrations lower than 20 mg/Kg [54, 55]. Among the clinical toxic effects, patients may present nystagmus, ataxia, and numbness [56]. With more severe intoxications, in addition to the

above: dysarthria, ataxia, the patient might not be able to walk, and may present hyperreflexia, besides consciousness usually being inhibited [57]. With higher doses, patients may even display a coma [58].

5.5 Lamotrigine

Lamotrigine is an antiepileptic drug principally used for generalized and partial seizures; it is also used in the adjunctive treatment of refractory crises [59]. Its action mechanism at the cellular level is based on blocking excitatory neurotransmitters, especially glutamate, through its NMDA receptors, as well as inhibiting voltage-dependent Na^+ currents [60]. The toxic effects on patients who take this drug above 600 mg are characterized primarily at the CNS level by difficulty in concentration, showing dysarthria, nystagmus, and blurred or double vision. Patients may even present a loss of balance or coordination [61]. Its absorption is intestinal, its elimination in the urine, metabolized in the liver. Thus, there is idiosyncratic hepatotoxicity that commonly requires liver transplantation [62].

5.6 Oxcarbazepine

Oxcarbazepine is a derivative of carbamazepine, approved as an antiepileptic drug in America in 2000 [63]. This drug is used in the treatment of any type of epileptic seizure. The cellular mechanism by which it exerts its antiepileptic effects is based on the fact that it blocks voltage-gated Na^+ channels, modulates the activity of Ca^{2+} channels, and increases K^+ conductance, which consequently produces a stabilization of hyperexcited neuronal membranes for epileptic seizures [64]. Oxcarbazepine is a drug that is metabolized like other antiepileptic drugs by the liver and excreted by the kidney [65]. Toxic effects when daily doses are above 30 mg/kg are basically characterized by gastric alterations: mainly nausea and vomiting. The alterations in the CNS are identified by headache, fatigue, drowsiness, and ataxia. It has also been reported that some patients may have vertigo and hyponatremia [66].

5.7 Ethosuximide

Ethosuximide is an anticonvulsant used to reduce the frequency of absence-type seizures. It exerts its mechanism by reducing Ca^{2+} currents antagonized by the T-type Ca^{2+} channels. Furthermore, linked to this drug, modulation of the function of voltage-activated Na^+ channels and Na^+/K^+ dendritic hyperpolarization-activated cyclic nucleotide-gated channel 1 channels has been suggested. It also reduces neuronal excitability by inhibiting the Na^+/K^+ pump [67]. However, ethosuximide is almost entirely absorbed in the digestive tract and metabolized in the liver, which can cause liver disease. The toxic effects of patients who consume above 25 mg/kg comprise gastric issues, nausea, vomiting, constipation, a state of sedation, headache, decreased alertness, drowsiness, and even comas have been reported at the CNS level [68]. Other adverse effects may include weight loss, as well as leukopenia [69].

5.8 Gabapentin

Gabapentin acts mainly by inhibiting partial and generalized seizures. Its mechanism of action is based on enhancing the inhibitory action of GABA [70]. A dose above 1,500 mg of gabapentin can cause hepatotoxicity, additionally, coupling various toxic effects like headaches, diplopia, nystagmus, diplopia, even involuntary movements have been described at the CNS level [71].

5.9 Topiramate

Topiramate is a drug used as an antiepileptic drug that acts by inhibiting partial and generalized seizures. Its action mechanism is exerted by blocking Na^+ channels. As an AMPA receptor antagonist, it reduces excitatory neurotransmission, in addition to enhancing the inhibitory action of GABA [72]. Topiramate taken at a dose above 50 mg produces toxic effects, including dizziness. At the CNS level, patients have headaches, drowsiness, decreased concentration, and even confusion. Nevertheless, other anomalies have also been reported [73].

6. Experimental models of epilepsy and neurotoxicity

As noted, before the development of epilepsy, experimental models have been crucial in the further research of a neurological disorder affecting approximately 1% of the worldwide population. Some drugs cause structural and metabolic alterations in the nervous system as demonstrated by experimental epileptic models, culminating in seizure generation [74]. Antiepileptic drugs that are conventionally used in clinical practice have been successfully tested in many of these models, even though certain models have neurotoxic consequences, as we will discuss below.

With the aluminum model, focal seizures are studied by directly applying the substance to the cerebral cortex of the animal under study, where it has been observed that this substance generates dendritic loss, gliosis, loss of GABAergic neurons, and a decrease in glutamate decarboxylase [75, 76]. This model has been used to study antiepileptic drugs including diphenylhydantoin and pentobarbital, both of which have shown positive outcomes in reducing epileptic seizures frequency [77].

Focal seizures have been researched using cobalt powder, which has been applied to the research animal's cortex or thalamus for epileptogenesis as part of the model development. This has reported GABA and glutamate decarboxylase enzyme production decreased, whereas neuronal death has been observed in the hippocampus. This cobalt model has also been suggested to interfere with Ca^{2+} signaling at NMDA glutamate receptors [78–80].

Similarly, using Zinc as an epilepsy model has been associated to neuronal death in the hippocampus, interference with $GABA_A$ receptors, and changes in the synapses of mossy fibers when there is a high concentration of this metal. It has also been observed to interfere with the responses of various receptors, including GABA, NMDA, and AMPA [81, 82]. While kainic acid, as an epileptic model, functions similarly to glutamate. The hippocampus is the most sensitive structure to this agent, with the highest number of receptors reported in the CA3 layer. This epilepsy model is used to examine focal seizures, with the hippocampus being the most sensitive structure to this substance. Changes in neuropeptide Y levels, hippocampus mossy fiber formation and a decrease in GABAB receptors are reported [83–85].

Pentylenetetrazol is used as an epileptic model to research generalized seizures. Shifts in the CA3 layer of the hippocampus, increased voltage in voltage-responsive K^+ receptors, and interactions with GABAA and NMDA receptors have all been documented [86, 87]. The model has been shown to be suppressed by phenytoin and pentobarbital [88, 89]. Flurothyl gas, on the other hand, can cause status epilepticus in laboratory animals. Although this gas has long been utilized to investigate generalized seizures, the exact mechanism through which it causes seizures is yet uncertain. However, alterations in the lipidic membranes of hippocampus, amygdala, and cerebral cortex cells have been reported. A decrease in GABA synthesis and activation of the c-Fos gene have also been reported [90–92].

On the other hand, penicillin, like cobalt, has been utilized as a model for focal seizures in epilepsy research, causing myoclonic seizures. The loss of GABAergic neurons, neuronal death, and an increase in mossy fibers in the hippocampus are the key abnormalities seen in this model [93–95]. While bicuculline is classified as a GABA antagonist, it causes generalized seizures when used. Edema has been found in the astrocytes of the cerebral cortex, where it interacts with Ca^{2+} and K^{+} channels [96, 97]. Tetanus toxin has also been employed as a model of epilepsy because of its effect on seizure induction. There are interactions with inhibitory neurotransmission, synapse formation, exocytosis blocking, and a decrease in GABAergic signaling threshold with this substance [98, 99].

Additionally, pilocarpine affects the muscarinic acetylcholine receptors. The increase in activation of these receptors in the hippocampus characterizes its epileptogenic effect. In experimental animals, it can even cause status epilepticus. Significant damage to nervous system structures has been observed, particularly the entorhinal and piriform cortex, olfactory bulb, amygdala, hippocampus, and thalamus, as well as abnormalities in the function of Na^{+}/K^{+} ATPase and NMDA receptors [100–103].

7. Conclusion

The described above has enabled us to identify the excitotoxic effect induced by epileptic seizures, whether clinical or experimental. Likewise, it illustrated some of the toxic effects of antiepileptic drugs. From what has been illustrated, it is necessary to conduct research that allows offering other therapeutic alternatives to reduce the toxic effects of seizures and pharmacological therapy. The proposal of alternative treatments to treat seizures is essential to boost anti-toxic defense mechanisms. It can be suggested to propose therapies that minimize neuronal death or treatments with substances that activate antiepileptic protein activity, such as the extrinsic and intrinsic *Wnt* pathway stimulation, or molecules that interact with the proteins involved in inflammatory and oxidative processes. The above mentioned could overall help reduce the interactions between the epileptic and pharmacological processes that ulteriorly lead to toxic effects on epileptic patients.

Appendices and nomenclature

NMDA	Glutamate receptors N-methyl-D-aspartate
AMPA	α-amino-2-3-dihydro-5-methyl-3-oxo-4-isoxazolepropionic acid
GABA	Gamma-aminobutyric acid
Ca^{2+}	Calcium
Na^{+}	Sodium ions
K^{+}	Potassium
CNS	Central nervous system
TCF/LEF	T-cell factor / lymphoid enhancing factor pathway
APC	Adenomatous polyposis coli protein
CK1	Casein kinase 1
GSK3β	Glycogen synthase kinase 3 β
NGR1	Notoginsenoside R1
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