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Original Article

Pharmacological inhibition of ictal and interictal epileptiform discharges

Inibizione farmacologica dell'attività epilettiforme critica e intercritica

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Key words: epilepsy; EEG; antiepileptic drugs; VOC/ROC channel.

ABSTRACT

Background: epilepsy is a brain disorder characterized by an enduring predisposition to generate epileptic seizures. Seizures are a transient occurrence of signs and/or symptoms due to abnormal excessive and synchronous neuronal activity in the brain. Electroencephalogram (EEG), a non-invasive instrumental test, has an important role in the diagnosis of epilepsy, as well as in monitoring the results and long-term treatment because it can detect interictal and ictal discharges that are crucial for confirmation and classification of seizures. Antiepileptic drugs are the first treatment option in patients with epilepsy, although the effectiveness of such drugs is limited only to symptom control and requires a regular intaking by the patient. These drugs exploit the cell membrane channels, modifying their permeability, allowing either an increase in the inhibitory neurotransmission or the reduction in the excitatory one, by hyperpolarizing neurons and avoiding the recurrence of the epileptic seizures without reversing or stopping the underlying mechanism of epileptogenesis.

Materials and Methods: the internship took place in the Neurophysiopathology department of the Antonio, Biagio and Cesare Arrigo's hospital in Alessandria, from October 2022 to March 2023. During this period, it was possible to attend the emergency treatment of prolonged and recurrent epileptic seizures during EEGrafic recording and the consequential amendments of the ictal discharges induced by the administration of antiepileptic drugs. Follow up EEG was also performed to investigate the modifications of interictal activity after a period of treatment with antiepileptic drugs. The patient who has been analyzed in this paper, underwent EEG recordings obtained by using bridge electrodes placed on the scalp according to the international 10-20 system.

Objectives: the aim of this study is to analyze the mechanisms of action of the main antiepileptic drugs, in relation to the physiological cellular mechanisms regulating the neuronal excitability and their effect on the ictal and interictal epileptiform discharges in the EEG recordings.

L'epilessia è un disturbo neurologico caratterizzato dalla persistente predisposizione a sviluppare crisi epilettiche. La crisi epilettica è un evento parossistico provocato da una scarica ipersincrona di cluster di neuroni ipereccitabili del sistema nervoso centrale. L'elettroencefalogramma (EEG), indagine strumentale non invasiva, ricopre un ruolo cardine per quanto riguarda la diagnosi di epilessia, nonché nel monitoraggio dei risultati e nel trattamento, poiché in grado di rilevare anomalie epilettiformi critiche e intercritiche, fondamentali per la conferma e la classificazione delle crisi epilettiche. I farmaci antiepilettici rappresentano il primo approccio terapeutico, sebbene l'efficacia di tali farmaci sia limitata al solo controllo dei sintomi e richieda un'assunzione regolare da parte del paziente. Questi farmaci sfruttano i canali della membrana cellulare, modificandone la permeabilità e consentendo sia un aumento della neurotrasmissione inibitoria, sia la riduzione di quella eccitatoria, iperpolarizzando i neuroni e sopprimendo così la crisi epilettica. Lo scopo di questo elaborato è di approfondire il meccanismo d'azione dei principali farmaci antiepilettici, in relazione ai meccanismi fisiologici cellulari che regolano l'eccitabilità neuronale e il loro effetto a livello delle alterazioni epilettiformi nel tracciato EEG.

INTRODUCTION

Epilepsy is a brain disorder characterized by an enduring predisposition to generate epileptic seizures. Seizures are a transient occurrence of signs and/or symptoms due to abnormal excessive and synchronous neuronal activity in the brain.[1]

Electroencephalogram (EEG), a non-invasive instrumental test, has an important role in the diagnosis of epilepsy, as well as in monitoring the results and long-term treatment because it can detect interictal and ictal discharges that are crucial for confirmation and classification of seizures.[2]

Antiepileptic drugs are the first treatment option in patients with epilepsy, although the effectiveness of such drugs is limited only to symptom control and requires a regular intaking by the patient. These drugs exploit the cell membrane channels, modifying their permeability, allowing either an increase in the inhibitory neurotransmission or the reduction in the excitatory one, by hyperpolarizing neurons and avoiding the recurrence of the epileptic seizures without reversing or stopping the underlying mechanism of epileptogenesis.

Neurotransmitters (NT) are molecules of various nature, which at the synaptic level perform a transformation of the signal from

electrical to chemical, in so doing causing a sequence of events; each neurotransmitter needs, on the postsynaptic terminal, specific receptors, so as to fulfil its function. Two types of neurotransmitters, peptides or with a small molecule, can be distinguished by their molecular nature.[3]

A peptide neurotransmitter needs several organelles for its synthesis; therefore, vesicles are necessarily produced at the level of the neuronal soma, where cellular organelles are located. The vesicles are then transferred by an anterograde axonal transport activity to the presynaptic terminal.

A small molecule neurotransmitter, such as γ-aminobutyric acid (GABA) and glutamate, is synthesized and packaged directly in the synaptic terminal, unlike the previous ones; the precursors are transported at the level of the presynaptic complex, where the packing takes place in vesicles as well, by means of an active secondary protons-neurotransmitters transport.

The synthesis of these neurotransmitters occurs in two separate sites, either neurons or astrocytes. Once released from the presynaptic terminal, the neurotransmitter will be absorbed by astrocytes, which by enzymatic processes will convert it into glutamine, which will then be released from the astrocyte and internalized by the neuron. Depending on the synapse, whether glutamic or GABAergic, glutamine will be converted into glutamate by a Phosphate-Activated Glutaminase (PAG), or into GABA by the action of a glutamine earlier and a Glutamate Decarboxylase (GAD) later.[4] Catabolism, on the other hand, occurs at the level of the glial cells, in the aim of capturing the excess neurotransmitter coming from the synaptic activity, so that any further stimulation may be avoided (Figure 1).[5]

Glutamate

Glutamate is the main excitatory neurotransmitter, involved in the processes of storage and synaptic plasticity. Among its receptors we can find AMPA and kainate receptors, although the main one is represented by the NMDA receptor (N-methyl-D-aspartate), Receptor Operated Channel (ROC) ionotropic receptor, which after binding with Glu allows the entry of cations into the postsynaptic neuron, triggering a depolarization. In both cases the mechanism of action is similar because the two receptors allow the passage, once the ligand has bound, of Na^+ and K^+ ions so that cell depolarizing should be possible (Figure 2).[6]

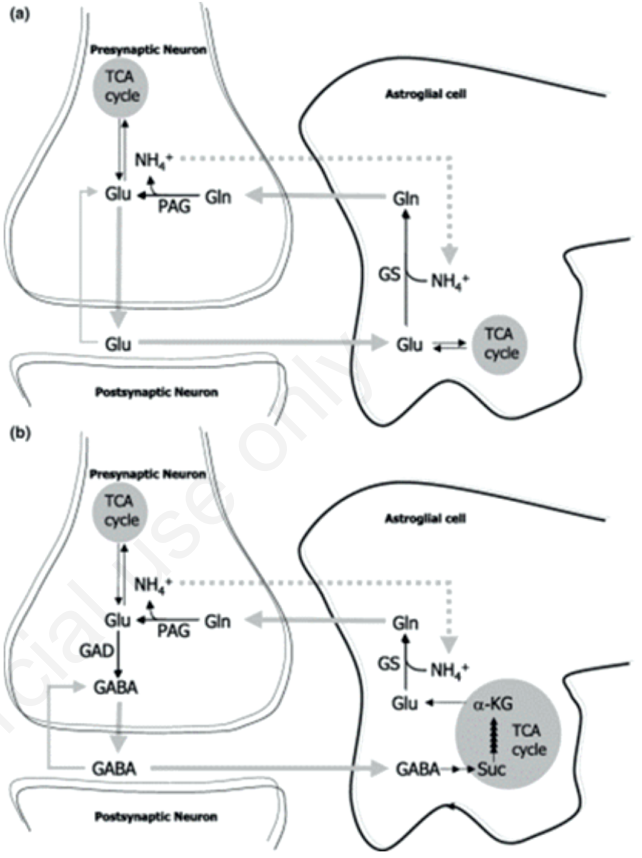

Figure 1. A schematic representation delineating the glutamate-glutamine cycle in a glutamatergic synapse (a) and the GABA-glutamine cycle in a GABAergic synapse (b).

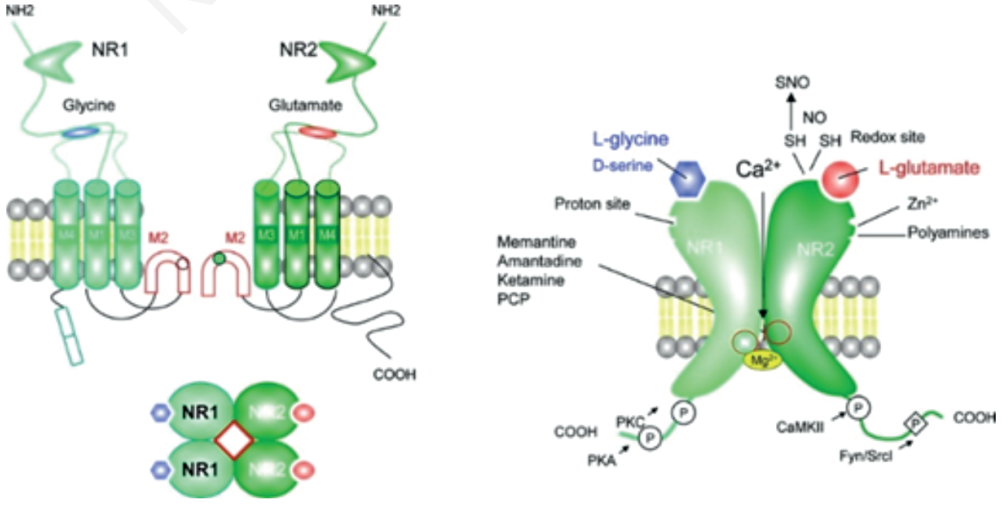

Figure 2. NMDA receptor molecular structure.

The above-mentioned channels become pharmacological targets in altered physiological situations that result in epileptic events.

γ-aminobutyric acid

GABA, or γ-aminobutyric acid, is the main inhibitory neurotransmitter of the central nervous system, as it reduces the ability of a nerve cell to send or receive signals. Its main mechanism of action, once the receptor has been intercepted, is the induction of potential postsynaptic IPSP inhibitors at the level of presynaptic neurons.

After release from the presynaptic terminal, GABA can bind to three different membrane receptors: GABA A, GABA B or GABA C.

GABA A receptors are ligand-dependent chloride channels, composed of five subunits, each consisting of four alpha-helix transmembrane domains. The GABA A receptor has several isoforms, among which the one in most cases represented is the GABA A α 1, β 2 and γ 2 as an isoform. In this particular isoform, the five subunits are grouped around a central ion pore that, following the bond, allows the entrance of chloride ions.[7] The subunits offer attack sites for endogenous and exogenous modulators on allosteric sites such as GABA, benzodiazepines, barbiturates, ethanol, and a number of other molecules that will determine, once the binding process has occurred, a conformational change. Moreover, a channel opening is also possible (Figure 3).[8]

The GABA B receptor is a seven-domain TM metabotropic receptor consisting of two subunits, called GABA B1 and GABA B2. The activation of these receptors inhibits the activity of the enzyme adenylate cyclase, causing a decrease in the conduction of calcium and an increase in the conductance linked to the potassium channels in neuronal cells, thus generating a hyperpolarizing effect at the cellular level.[9]

The GABA C receptors, present at the level of the retina, are ionotropic channels and consist of homo-oligomeric subunits, which, after activation, allow an input of chlorine from the extracellular to the intracellular side, in so doing hyperpolarizing the cell.[10]

Ionic channels of membrane

The channels represent the way of choice for the passage of molecules, which normally could not spread freely inside the phospholipidic double layer.

Voltage Channel Modulators (VOC), or voltage dependent, open in response to membrane depolarization, so making certain ions flow; an example of what above said is represented by sodium VOC channels, present in large numbers on the axonic hillock, which as soon as they reach the activation threshold, open, and allow the entry of Na^+ ions resulting in cell depolarization.

ROC channels, or ligand-dependent, require interaction with a determined molecule to activate: these channels are characterized by the presence of glycoproteins on the surface. These latter work as membrane receptors, with a glycosylated portion that constitutes the receptor site, facing the extracellular environment.

Electrical potential of membrane

The opening of the sodium VOC channels determines the genesis of the action potential, and their regulation mechanism will determine all the stages of the cycle.

Sodium voltage-dependent channels play a key role in generating action potentials and propagating them in neurons and other excitable cells, such as myocytes and endocrine cells (Figure 4).[11]

Pharmacological treatment of epilepsy

Over the years, several treatments have been developed, from pharmacological to surgical, with a fair percentage of success, which allows those who are affected by epileptic disease to have a life almost without any major limitations.

The first therapeutic approach consists in using antiepileptic

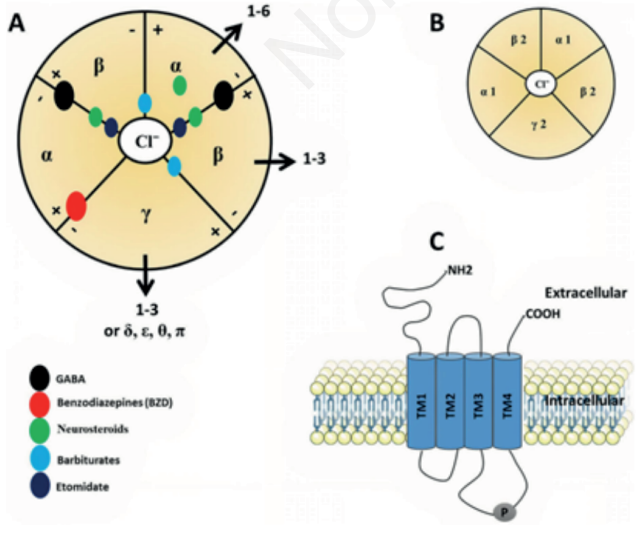

Figure 3. Molecular structure of the GABA A receptor, with its subunits.

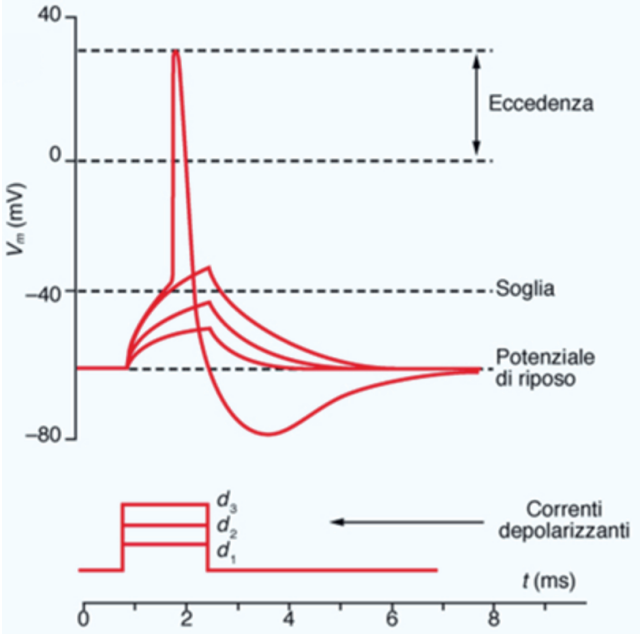

Figure 4. Graphical representation of action potential.

drugs, usually prescribed after at least two seizures, although each case is evaluated individually. Treatment is indicated in relation to the patient's state of health, then on individual traits, and according to the severity and characteristics of the crisis. Once defined, it's modulated according to the minimum dose necessary to ensure a clinical response in the absence of side effects, along with the principle of risk benefits.

The primary objective of drug treatment is the complete control of seizures, although it is a purely symptomatic therapy, not affecting the causal factor. If the drug treatment does not provide the expected results, there may be a problem related to the patient's pharmacoresistance.

Drug treatment is the first therapeutic approach administered to the patient, intervening directly on the cellular substrate at the base of the abnormal neuronal discharge, with efficient inhibition of epileptic seizures, without a direct action on the triggering cause. The target is represented by those epileptic neurons that discharge at high frequency, affecting one or more brain areas. In particular, the effect of antiepileptic drugs is mediated either by increasing the inhibitory activity on GABAergic synapses or by prolonging the inactivation period of sodium and potassium voltage dependent channels, thereby reducing the risk of cations entering.

The pharmacological inhibition then acts rebalancing the physiological periods of depolarization, as well as the frequency of discharge, so blocking the burst of neuronal discharge and causing the disappearance or the reduction of epileptiform discharges, if present, in the EEG recording.

1st subdivision: GABA stimulators

γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter of the cerebral cortex that, by binding to its receptors, regulates neuronal excitability in relation to excitatory excitability. The study of the structure of GABA receptors has made it possible to create several drugs. It was found[12] that deficiencies or abnormalities in the synthesis of this neurotransmitter may lead to the development of seizures. The main drugs belonging to this category are benzodiazepines and barbiturates.

Benzodiazepines (BDZ) have been widely used since the 1960s and are still the first-choice therapies in the treatment of seizures. The benefits result in rapid action, high efficiency, and minimal toxicity; however, their use is limited to sporadic episodes, since prescription for extended periods of time can induce drug resistance in the patient.[13] BDZs share similar characteristics with one another, such as muscle relaxation, reduction of anxiety and sedative abilities. Benzodiazepines bind to the GABA A receptor, thus opening the chlorine channels and generating an entrance of negative charges hyperpolarizing the cell. GABA A is a five-subunit ionotropic receptor, and BDZ possess high affinity particularly for the gamma subunit, responsible for increasing GABAergic inhibition. BDZ bind allosterically to the receptor in a different position respect to GABA, which avoids competing with it. They increase the conductance of chlorine channels by augmenting the opening frequency of such channels, any case without replacing the inhibitory neurotransmitter. The lower toxicity of this class of drugs derives from the fact that they do not increase the amount of GABA in circulation, but only amplify its effect: as evidence of that, the BDZ themselves, without GABA, are not sufficient to open the channel.

Barbiturates are a class of drugs with pharmacological aspects like those of BDZ, as hypnotics, muscle relaxants, anxiolytics, anticonvulsants: however, they have been replaced for their greater toxicity as GABA-agonists. At low concentrations, barbiturates enhance the effects mediated by the present GABA. Anyway, at high concentrations, barbiturates compete for the allosteric site of GABA on the GABA A receptor, so mimicking its effects and becoming sufficient, at channel opening, even without the presence of GABA.[14] Here is a substantial difference compared with BDZ, which cannot activate any channels without the intervention of GABA. Barbiturates reduce the excitability of the neuronal membrane by blocking the genesis of action potentials in nerve fibers.[15] They reduce repetitive spike discharges by hyperpolarizing the neuronal membrane.

2nd subdivision: GABA T inhibitors

GABA transaminase (GABA T) is one of the main enzymes involved in the catabolism of GABA, which is recovered from the synaptic space, by a deamination reaction. The action of this class of drugs aims at reducing the degradation of GABA by inhibiting the enzyme GABA-T. The inhibition of such an enzyme leads to an increase of GABA in cerebral levels, and consequently, to increased inhibitory activity.

Vigabatrin is a drug that resumes the above said mechanism, which produces its own antiepileptic effect by irreversibly inhibiting the enzyme GABA transaminase, resulting in increasing GABA in the brain, so inhibiting the excitatory processes that can induce the epileptic activity. Vigabatrin is indicated as an additional therapy for adult patients with refractory partial seizures, who have inadequately responded to several alternative treatments. At the same time, it is used as a unique monotherapy for pediatric patients with an age comprised between one month's and two years' life, with childhood spasms. Despite the short half-life of only five hours, and the relatively low concentration within the cerebrospinal fluid, vigabatrin increases GABA levels in the brain for several days after a single administration. It is rapidly absorbed and immediately becomes bioavailable and excreted by the kidney.[16]

Valproate (VPA) is among the most used antiepileptic drug due to its efficacy against many types of seizures, as a suppressor of generalized epileptic seizures, for which it represents the first-choice drug for treatments. VPA increases GABAergic transmission through several mechanisms that positively affect GABA metabolism. It increases GABA levels by irreversibly inhibiting GABA-T transaminase, that would degrade it, but which thus persists longer in the circulation.

This drug also reduces the release and effects of excitatory NTs such as glutamate, as well as neuronal depolarization events, by blocking VOC sodium and calcium channels, furthermore modulating serotonin and dopamine transmission. Among the most relevant adverse reactions is liver toxicity, indeed an excessive and prolonged use of this drug can alter the functionality of the organ, up to compromising its morpho-functional integrity.[17]

3rd subdivision: GABA reuptake inhibitors

The GABA, after performing its function at the level of the postsynaptic terminal, is recovered from the glial cells, so as to remove it from the cerebral circle. The GAT-1 transporter (GABA Transporter) has the physiological role of recovering GABA from neurons and in particular astrocytes at the intrasynaptic space once it has performed its function at the postsynaptic terminal. In

particular, the recapture occurs by coupling the recovery to the cotransport, according to gradient, of two sodium ions and one chlorine ion.

Tiagabine is a drug that inhibits GABA reuptake on the part of neuronal and glial cells, after selectively binding to a single class of linking sites involved in GABA recovery, as does the above-mentioned GAT-1: in this way reuptake does not happen and the GABA remains for a longer time inside the synaptic fissure, where it keeps on exercising its inhibitory action. Metabolism occurs mainly in the liver, while excretion proceeds through the urinary tract.[18]

4th subdivision: dependent voltage channel modulators (VOC)

Ion channels are integral membrane proteins that allow the passage of specific ions following a stimulus, of an electrical or chemical nature. Ion channels are implicated in the modulation of neuronal excitability; alterations in the functionality of these structures, such as genetic mutations, are involved in the genesis of epileptic seizures. The main ones we will analyze are the sodium and calcium channels.

VOC sodium channels are integral membrane proteins, regulated by voltage and fundamental for the generation of action potentials in excitable cells, such as neurons. At a condition of rest, the channel is closed, but when the cell membrane is depolarized, the channel opens and starts the phase of rise of the action potential. Once the peak of potential has been reached, the channel undergoes inactivation, so as not to exceed high values excessively. The inactivation period, also referred to as absolute refractory period, when the neuron is not available at the entrance of new sodium ions, is exploited by some drugs in the aim of reducing the entrance of sodium ions.

Phenytoin is an antiepileptic drug used to treat tonic-clonic seizures and partial seizures. It acts by binding to sodium channels: in particular, it has a high affinity with their inactivated states, to prolong the refractory period and cause a lower sodium input, which would depolarize the cell. This drug, therefore, is an inhibitor of sodium VOC channels, since it reduces the probability of triggering an action potential and thus the genesis of abnormal epileptic discharges.[19] This drug is characterized by hepatic metabolism, while excretion occurs mainly by the kidney through urine.

VOC calcium channels are a family of membrane proteins that open in response to membrane depolarization, to allow the inflow of Ca^{2+} along with its electrochemical gradient. Being implicated in changes in membrane potential, they become a key therapeutic target to interrupt seizures.

Gabapentin is a drug indicated as an additional antiepileptic for the treatment of focal seizures with loss of consciousness, with or without generalization. Such a drug adopts an unknown mechanism of action, apparently unlike other antiepileptic agents. The drug is not bound to the proteins; at the same time, it is not metabolized by the hepatic system and does not induce liver enzymes, thus decreasing the probability of drug interactions with other antiepileptic agents. Although gabapentin is a structural analogue of the GABA, which does not cross the blood-brain barrier, it enters the central nervous system, and its activity is apparently distinct from GABA-related effects.[20] The mechanism of action of that drug results in inhibiting the calcium VOC channels, hence consequently reducing the release of excitatory neurotransmitters.

5th subdivision: excitatory neurotransmission inhibitors

Excitatory neurotransmission is characterized by the increased probability of triggering an action potential: it is mainly mediated by the excitatory neurotransmitter by excellence, namely glutamate. A marked excitatory activity can lead to the development of epileptic events; therefore, a modulation of this activity plays a fundamental role in the purposes of pharmacological control.

The main drugs inhibiting the excitatory activity have their main target in the channels for the glutamate, as well as secondarily some ion channels, to decrease the entrance of cations inside the cell.

Perampanel is a non-competitive antagonist drug selective for AMPA receptors, implicated in the treatment of focal seizures, with or without a generalization, in patients over twelve years of age. Perampanel acts through a new mechanism of action, since it has been developed specifically to target AMPA receptors, which play a key role in the fast excitatory synaptic transmission. The binding of the drug to the AMPA receptor leads to a reduction in neuronal stimulation and a decrease in seizure effects, as well as inhibiting the generation and the spread of seizures.[21] Perampanel is rapidly and completely absorbed by the gastrointestinal tract after oral administration, after which it is metabolically oxidated in the liver into several pharmacologically inactive metabolites, while excretion occurs through urine.

6th subdivision: other mechanisms of action

Disfunctions of the release of synaptic neurotransmitters are closely involved in the pathogenesis of a number of diseases of the central nervous system. Synaptic Vesicle Glycoprotein 2A (SV2A) is a membrane protein specifically expressed in synaptic vesicles: it modulates the release of neurotransmitters dependent on cortical action potentials.[22] SV2A has been proven involved in the traffic of vesicles and exocytosis, which are crucial processes for the neurotransmission.

The antiepileptic drug levetiracetam was the first ligand to target SV2A and shows a wide spectrum of antiepileptic activity in a lot of preclinical models, confirming as a first-choice drug in the treatment of seizures, thanks to its marked effectiveness and tolerability towards the patient. This drug did not show any classical actions, as it did not have any effects on voltage-dependent Na^+ channels, GABAergic transmission, or affinity for GABAergic or glutamatergic receptors. It works along with a unique mechanism of action that differentiates it from other conventional anticonvulsant drugs. The mechanism of action of this drug has not yet been fully understood. Its main effects are at the level of SV2 proteins and calcium. For its aspects related to the low probability of incurring into drug resistance despite a daily intake, for the minor side effects and minimal drug interactions, levetiracetam is believed to be a first-choice drug in the treatment of epilepsy chronically.[23]

MATERIALS AND METHODS

The internship took place in the Neurophysiopathology department of the Antonio, Biagio and Cesare Arrigo's hospital in Alessandria, from October 2022 to March 2023. During this period, it was possible to attend the emergency treatment of prolonged and recurrent epileptic seizures during EEGraphic recording and the consequential amendments of the ictal discharges induced by the administration of antiepileptic drugs. Follow up EEG was also

performed to investigate the modifications of interictal activity after a period of treatment with antiepileptic drugs. The patient who has been analyzed in this paper, underwent EEG recordings obtained by using bridge electrodes placed on the scalp according to the international 10-20 system (Figure 5).[24]

RESULTS

The reported clinical case deals with an 83-year-old man with an history of potus, diabetes, mild chronic renal insufficiency, hyperuricemia and hyperkalemia, cirrhosis. The patient did not show a prior history for epilepsy. The first nocturnal episode was reported by his relative, and was characterized by groan, staring, clenched jaw and bavage. A few hours later, he witnessed at least three episodes of loss of consciousness with jerking motion of arms and legs and subsequent slow recovery of consciousness, which could be interpreted as generalized epileptic seizure with motor symptoms. The patient was treated by paramedical staff with diazepam, and in comatose state, was transported to the ER where he underwent an EEG that showed a widespread theta and bilateral delta activity.

After a few minutes of EEGraphic recording, an epileptic seizure with secondary generalization and motor symptoms was observed. The EEG recorded during the event detected a polyspike-wave activity and spike-waves (with an over-inscribed rapid activity) with origin in the left frontal lobe and diffuse projection. The patient was treated with lorazepam, with rapid improvement of the clinical and instrumental picture after only ninety seconds, with a reduction of the ictal epileptiform discharges and the disappearance of motor symptoms. Four minutes after the infusion, the epileptic discharges disappeared completely, replaced by high-voltage delta activity. After the prescription of treatment with levetiracetam 2000 mg/day, the patient was seizure-free, and the EEG showed a global slowdown of brain's electrical activity and neither critical events nor epileptiform abnormalities.

The last check of the clinical and instrumental picture showed a huge improvement, therefore pharmacological treatment played a key-role in the control of epileptic seizures both in emergency and in chronic.

DISCUSSION

Epilepsy is a neurological disorder characterized by the enduring predisposition to generate epileptic seizures. A seizure is a paroxysmal event caused by a hypersynchronous discharge of clusters of hyperexcitable neurons of the central nervous system. The etiology can be genetic, due to trauma or due to metabolic, infectious, or inflammatory factors. Epilepsy and its clinical manifestations are the expression of alterations in neuronal membranes, defects in the permeability of ion channels and changes in the balance of excitatory and inhibitory mechanisms.[25]

The EEG plays a fundamental role in the diagnosis of epilepsy: it is a method of investigating spontaneous cerebral electrical activity that allows the detection of specific abnormalities, called epileptiforms. Moreover, the EEG allows both to monitor the outcome of the treatment administered in emergency, and to verify the effectiveness of the prescribed therapy in the medium/long term.

The first therapeutic approach consists in using antiepileptic drugs, whose composition and dosage vary according to the patient's health status and the type of seizures, following the principle of risk-benefit. The main goal of drug treatment is the complete control of the seizures, although it is a purely symptomatic therapy, which does not affect the underlying mechanism of epileptogenesis and which makes necessary the chronic use of antiepileptic drug. Pharmacological treatment is essential in emergency, in those patients who have prolonged or incoming seizures, to sedate as soon as possible the epileptiform discharges that can be detected both clinically and on EEGraphic live recording. The antiepileptic drugs act on the cellular physiology of the neurons, suppressing the excitatory activity triggering the seizure. Some of the antiepileptic drugs that have been on the market for a long time have a wide spectrum of action, while the most recent have been synthesized specifically to interact with a specific target cell.

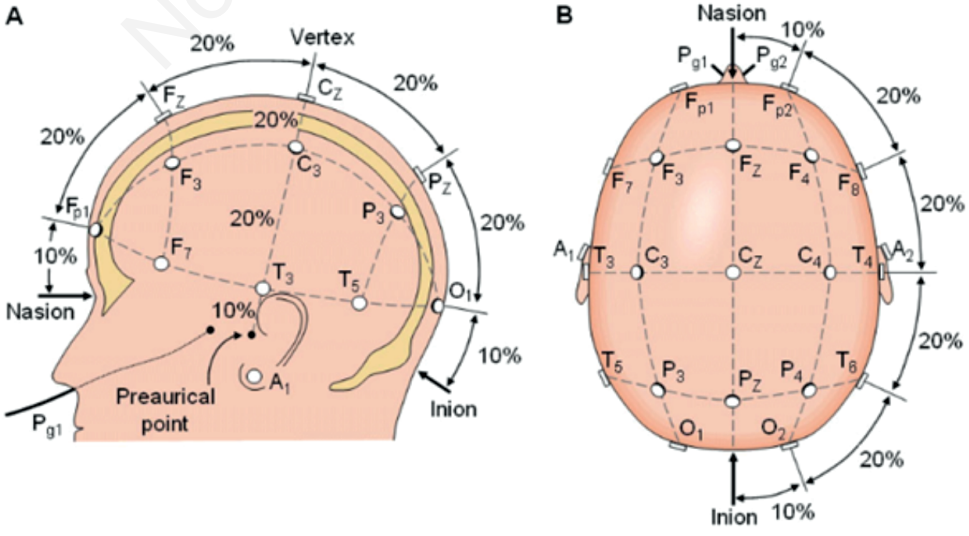

Figure 5. Electrode placement diagram according to Configuration 10-20.

CONCLUSIONS

The clinical cases under examination demonstrate the expected results: emergency EEG recording during pharmacological infusion shows the reduction or disappearance of ictal epileptiform discharges and, if present, also the simultaneous reduction or the complete disappearance of motor manifestations while follow-up EEG during chronic antiepileptic drug therapy proves the disappearance of interictal epileptiform discharges.

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