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SCIENTIFIC REVIEW

BASIC MECHANISMS OF ACTION OF THE ANTIEPILEPTIC DRUGS

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Abstract. *Available antiepileptic drugs interact with a variety of different molecular targets. The mechanism of action of most anticonvulsants is most often complex with a number of affected regions. The combination of mechanisms of action of drugs in particular proportions can possibly determine the showcase of its antiepileptic activity. The common factor between the different supposed mechanisms for a number of drugs includes the possibility for modulating the excitatory and inhibitory neurotransmission through effects upon the voltage-gated ion channels, synaptic plasticity, heterogeneous receptors, and metabolism of neurotransmitters. There are controversial data on the extent to which a specific action can be the reason for the wholesome anticonvulsive characteristics of various medications, as well as the relation with the presence of undesired drug effects. The complexity of the action of some antiepileptic drugs creates conditions for optimal choice during therapy. In many cases, the insufficient familiarity with individual genetic differences and the disease related receptor damages can hinder defining a particular drug action. Characterizing the mechanisms of action of the present antiepileptic medications would increase the understanding for the pathophysiological mechanisms of epileptic seizures, as well as the development of new therapeutic strategies. The development of novel antiepileptic drugs and the ongoing research regarding the mechanism of action of established antiepileptic drugs, are continuously increasing the level of complexity in the spectrum of molecular targets relevant for epilepsy therapy. The current state of knowledge as well as the limitations in our understanding should guide future research aiming for a more detailed elucidation of the impact of genetics and pathophysiological mechanisms on interindividual differences in expression and function of antiepileptic drug targets.*

Key words: *antiepileptic drugs, ion channels, molecular targets, neurotransmitters, receptors*

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INTRODUCTION

In the human genome more than 400 genes encode ion channels, which are transmembrane proteins mediating ion fluxes across membranes. Being expressed in all cell types, they are involved in almost all physiological processes, including sense perception, neurotransmission, muscle contraction, secretion, immune response, cell proliferation, and differentiation [1]. Voltage-gated ion channels are important mediators of physiological functions in the central nervous system. The cyclic activation of these channels influences neurotransmitter release, neuron excitability, gene transcription, and plasticity,

providing distinct brain areas with unique physiological and pharmacological response. A growing body of data has implicated ion channels in the susceptibility or pathogenesis of neuropsychiatric disorders [17]. Ion channels are the primary target of only about 5% of the marketed drugs suggesting their potential in drug discovery [1]. There are more than 12 new antiepileptic drugs approved in the last 2 decades. Even with these newer agents, seizure remission is still unachievable in around 30% of patients with epileptic seizures [12]. The antiepileptic drugs interact with various molecular receptors. In order to achieve their anticonvulsant effect, the antiepileptic drugs have two large target categories: damaged specific membrane properties that are usually about abnormal ion permeability (calcium, sodium, potassium) and damaged synaptic functions (increased excitement or insufficient suppression transmission). The majority of the antiepileptic drugs have multiple mechanisms of action that is in effect not only for the new, but for some of the previous antiepileptic drugs, for example valproate, and most of them have additional pharmacological actions, of unclear impact in view of their anticonvulsant effect. It is possible for the combination of mechanisms of action of the drug in certain ratios to define the manifestation of its antiepileptic activity [10]. The preclinical and clinical data confirm the fact that specific mechanisms of action are aimed at the efficiency when it comes to particular types of seizures [29]. The insufficient knowledge of the individual genetic differences and the disease-related damages sustained by the receptors and the particular pathways in many cases does not make it possible to define the particular effect of drugs [29]. The division shared by the various supposable mechanisms for many drugs includes the opportunity to modulate the excitatory and inhibitory neurotransmission via the effects onto the ion channels, receptors and metabolism of neurotransmitters [6].

ACTION OF THE ANTIEPILEPTIC DRUGS ON EXCITATORY MECHANISMS

Sodium flows/channels. Voltage-gated sodium channels (VGSCs) are a family of transmembrane ion channel proteins. VGSCs, which are widely distributed in the excitable cells, are the primary mediators of electrical signal amplification and propagation. The abnormalities of the structures and functions of VGSCs can change the excitability of the cells, resulting in a variety of diseases such as chronic pain and epilepsy [2]. At present, some voltage-gated sodium channel blockers are used for treating those diseases. The voltage-dependent sodium channels take part in generating and disseminating the sodium-dependent action potentials. They make it possible for the extracellular sodium to penetrate the cell which results in neuronal depolarization and excitement. While delaying the reactivation of sodium channels the antiepileptic drugs significantly cut down the frequency of the continuous repetitive discharges and do not impact the normal physiological processes [6]. We have identified numerous sub-types of the sodium channels. First generation sodium channel modulator drugs, despite low inherent subtype selectivity, preferentially act on over-excited cells which reduces undesirable side effects in the clinic. However, the limited therapeutic indices observed with the first generation demanded a new generation of sodium channel inhibitors [2]. The inactivation or closure of sodium channels could happen rapidly, also known as “rapid inactivation” or in more gradual, continuous manner, also known as “slow inactivation” [10]. The slow inactivation is an important mechanism when it comes to regulating and modulating the paroxysmal discharges in neurons and axons [22, 23, 36]. Numerous antiepileptic drugs, including carbamazepine (CBZ) and its derivatives oxcarbazepine (OxCBZ) and eslicarbazepine acetate, phenytoin (PHT), lamotrigine (LTG) and zonisamide act in the capacity of blockers of the voltage-dependent sodium channels according to the mechanism of rapid inactivation, while increasing the number of channels in inactive condition [23, 28, 34]. When it comes to characterizing the abovementioned drugs in their capacity of substances that ensure the rapid inactivation of sodium channels, we should take into consideration the differences in view of their affinity to the functional locations for channels’ connection and in view of their selectivity towards the particular receptor subtypes [36]. The modulation of the additional effect on the continuous sodium flows for valproate (VPA), rufinamide [6] and topiramate (TPM) [11, 24, 36] delays the repolarization and the time for reaching the threshold potential, which is necessary for the occurrence of new action potential. The electrophysiological analyses prove the different mechanism of action of lacosamide (LCM) while accelerating the slow inactivation of the voltage-dependent sodium channels [4] and selective action on the pathologically modified continuous and repetitive neuronal discharges thus ensuring the absence of impact on the normal mechanisms of inactivation [5, 9]. In the recent years, several neurotoxins and a novel cysteine-rich secretory protein (CRBGP) have been designed and modified for targeted drugs of sodium channelopathies in the clinical treatment [2].

Calcium channels. The depolarization of neurons causes the entry of Ca2+ inside the cells through the

presynaptic calcium channels which is related to the release of excitatory neurotransmitters, causing the further Ca2+ influx through the postsynaptic voltage-dependent channels. It is believed that the massive influx of Ca2+ causes discharge activity [6]. The voltage-dependent calcium channels have complex structure since they consist of various substances: α1 subunits making up ion permeable pore with voltage sensitivity and several auxiliary subunits α2δ, β, and γ, which modulate permeability. It was established that the α2δ additional subunits are target of important modulating function [30]. The voltage-dependent calcium channels are classified as high- and low-voltage subtypes in view of their depolarization threshold [6, 7, 29, 36]. The high-voltage calcium channels are additionally classified as: L- (present in the dendrites of the neurons and cellular bodies – via massive calcium influx they activate the enzyme protein kinase, which performs the gene transcription that is necessary for achieving long-term synaptic plasticity in the hippocampus and cerebral cortex); N- (present in the presynaptic endings where they participate in the trigger mechanisms of releasing the neurotransmitter monoamines from the terminals in the GABA-ergic fibres); P/Q- (related to glutamate release in the central nervous system) and R-type calcium channels (related to the exocytosis in numerous areas, including in the hippocampus where they play essential role in the long-term presynaptic activation) [20, 36]. Some antiepileptic drugs of comprehensive and multiple mechanism of action (LTG, felbamate, TPM, levetiracetam (LEV) and phenobarbital (PB)) impact the high-voltage activated calcium channels [19]. We have established the interaction of gabapentin (GBP) and the α2δ auxiliary subunits of the voltage-dependent calcium channels, as well as the functional effects of this connection. The experimental research works show that the connection of the drug to the α2δ in the capacity of ligand decreases the calcium influx inside the cell and the release of neurotransmitters [10, 15, 29]. The T-channels are the type of primary low-voltage calcium channels that are widespread in the central nervous system, including neocortex, hippocampus, thalamus, cerebellum, and nucleus olivary inferior [7, 36]. The T-type calcium channels get activated by the hyperpolarization and play role in implementing the patterns of rhythmic excitatory activity in the thalamic neurons and thalamocortical circles, while appearing during the REM sleep stage, as well as in the case of pathologic conditions such as absence seizures [6, 19, 28]. The selective interaction with the T-type calcium channels predefines the efficiency of ethosuximide (ESM) and zonisamide [7, 19]; the absence of significant effect on other targets of the ESM defines its ineffectiveness when it comes to partial and tonic-clonic seizures [6].

Glutamate receptors. The excitatory processes in the nervous system take place mainly via glutamate, probably via aspartate [29]. Glutamate being the main excitatory neurotransmitter in the central nervous system gets connected to numerous receptor locations that differ in view of their activation and deactivation duration, conductivity and ion permeability. The glutamate receptors are classified as ionotropic and metabotropic types. The ionotropic glutamate receptors are non-selective cation channels that initiate the rapid depolarization [10]. In view of their affinity to certain ligands the glutamate receptors could be additionally classified as follows: N-methyl-D-aspartate (NMDA)-receptors and non-NMDA receptors (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)- and kainic acid- receptors) [29, 35]. The NMDA-receptor is voltage-dependent channel that is highly permeable for calcium. It contains one mandatory NR1 subunit combined with various NR2 and NR3 subunits. In the case of membrane potential at rest, as a result of the voltage-dependent magnesium blockade of the channel pore, NMDA were not activated. The membrane depolarization is related to eliminating the blockade of the ion channel when it comes to magnesium and is prerequisite for the activation of the NMDA receptor. For the activation of the NMDA receptor channel we need glutamate connection to the NR2 subunit and glycine connection in its capacity of co-agonist to the allosteric location onto the NR1 subunit of the receptor complex [13]. If the depolarization has sufficient amplitude and duration (just like in the seizure beginning) the NMDA receptors [6] get activated with follow-up membrane cover by depolarization being the main reason for the tonic-clonic seizure. This way the glutamate-mediated synaptic transmission provides for the synchronization of epileptic activity [6]. NMDA is present in the hippocampus where the epileptic discharges could result in continuous hyper-excitement as a result of the activation of the NMDA receptors and the follow-up activation of NMDA and non-NMDA receptor mechanisms [4, 24]. The density and activity of NMDA receptors are increased in the case of epilepsy of the temporal lobe [13, 29]. The interaction with glutamate receptors is one of the mechanisms of action for numerous antiepileptic drugs with numerous locations for receptor influence and comprehensive action [22, 35]. For example, in view of the type of selective effect onto the subunits of the NMDA receptors felbamate could have inhibiting action [13] TPM is antiepileptic drug with highlighted comprehensive action and pharmacodynamics impact on numerous

molecular targets, including the non-NMDA receptors [10, 28]. The selective interaction of TPM with the kainate receptors significantly predefines the anticonvulsant efficiency of the drug [24]. The activation of the AMPA receptors significantly mediates the normal excitatory neurotransmission in the central nervous system [5], which was discussed about PB [18, 29]. The antagonists of the AMPA receptors with more selective effect (Perampanel) [10, 22, 35] are subjected to research.

ACTION OF THE ANTIEPILEPTIC DRUGS ON THE INHIBITORY MECHANISMS

Gamma aminobutyric acid (GABA). GABA is the main inhibitory neurotransmitter in the central nervous system. The influence of the GABA-ergic neurotransmission is amongst the best known mechanisms of action in the pharmacotherapy of epilepsy [6]. GABA opens up the neurone channels for letting potassium and chlorine ions in thus resulting in hyperpolarization of the neuronal membrane, i.e. in decreased neuronal excitement. It is being synthesized in the GABA-ergic nerve endings via the decarboxylation of glutamate from the enzyme glutamic acid decarboxylase (GAD), and for its activity we need pyridoxal phosphate that is being stored via the vesicular GABA transporter (VGAT). After its release in the synaptic slit, GABA is subjected to decomposition by the enzyme GABA-transaminase (GABA-T) to succinic semialdehyde (SSA), which is metabolized in the mitochondria to α-ketoglutarate (α-KG), being the main substrate for the synthesis of L glutamate.The interim metabolites in the GABA metabolism are homocarnosine and 2-pyrolidinone which also have antiepileptic effect [29]. GABA limits the seizure activity in the amygdala, the area that is believed to be of critical importance to the dissemination of focal seizure activity [21] and substancia nigra reticularis (SNR), where the stimulation of GABA receptors and the GABA increase is related to the anticonvulsant action against broad spectrum of seizures [21]. SNR has indirect control on numerous individual epileptogenic circles through colliculi superiores, including the circles in charge of generating the seizures in the limbic, thalamocortical system and tonic seizures generated in the brainstem [3]. Inside the brain GABA acts onto two different types of postsynaptic GABAA receptors/channels as well as onto the postsynaptic GABAB receptors/channels [24]. The genetic or acquired dysfunction of the GABAA receptor-mediated inhibition is an important pathophysiological mechanism for the increased neural excitement and is described in the case of patients with idiopathic generalized epilepsy and epileptic status [3]. The rapid inhibitory effect of GABA is being mediated by the GABAA receptors that are ligand-connected postsynaptic chlorine channels getting activated when connecting at least two molecules GABA. The neuronal GABAA are pentameric proteins that consist of five subunits (α, β, γ, and δ subunits) located around the central pore. There are several GABAA receptor subtypes whose function varies on the grounds of combinations of α-, β-, γ-, and δ- subunits in the particular receptor. The genes that encode these various subunits are represented in different manners in the various brain regions and they bring about functional differences in the synaptic inhibition, as well as differences in the action of drugs [3, 24]. Tonic GABAA receptors are a subpopulation of receptors that generate long-lasting inhibition and thereby control network excitability. In recent years, these receptors have been implicated in epilepsy as a potential antiepileptic target. Their distinct subunit composition and function, compared to phasic GABAA receptors, opens the possibility to specifically modulate network properties [3, 31]. The antiepileptic drugs could modulate the GABA-ergic activity via various mechanisms: inhibition of the reverse grasp of the GABA by the presynaptic nerve endings [6], suppressing the degradation of GABA via inhibition of the GABA-T receptors, suppressing the GABA-T inside the nerve terminals, increasing the GABA synthesis via activating GAD [10, 21], increasing the GABA concentrations – the interim metabolites homocarnosine and α-pyrolidinone [6], increasing the duration and opportunity for opening the chlorine channels [6, 10]. The GABAB receptor could be found on numerous occasions presynaptically in the axonal endings and is a receptor related to G protein, which increases the conductivity of the potassium channels directed towards the neuron interior and decreases the conductivity of the presynaptic N- and P/Q-calcium channels. The GABAB antagonists significantly reduce the discharges spike-slow wave in the electroencephalography. If it is present in high concentrations, PB could directly activate the GABAA receptors. This explains the higher risk of barbiturates' overdose compared to the other GABAA receptor antagonists [29]. Benzodiazepine (BZD), which remains the first-choice drug in emergencies, gets connected to different location of the GABAA receptor, to certain receptors that contain α1, α2, α3 or α5 subunits in combination with the γ subunit [30]. VPA is related to increasing the general GABA levels inside the brain and potentiating the GABA-ergic activity [6]. In addition to the direct receptor modulation there are numerous opportunities for indirect neurotransmitter influencing [3, 29]: impacting the GABA metabolism or GABA transporters that modulate the reverse grasp by presynaptic neurons or the

GABA uptake by the neighbouring glial cells. Vigabatrin is irreversible inhibitor of the GABA-T enzyme that degrades GABA in the presynaptic neurons and the glial cells [6], thus significantly increasing the GABA concentration in the brain. In this case the vigabatrin rather potentiates tonic inhibition than the synaptic reply mediated by the GABAA-receptor [6, 29]. Tiagabine (TGB) inhibits the reverse grasp in the presynaptic neurons and the neighbouring glial cells via the transporter of GABA – GAT-1 [10, 22] thus potentiating the postsynaptic GABA-ergic potentials, This action has its advantages and less undesirable medicinal effects compared to the direct receptor agonism since it accelerates only the effect of the endogenic GABA, while preserving its physiological specificity. In view of numerous anticonvulsants the impact of the GABA-ergic activity is one of the numerous mechanisms of action, for example TPM, felbamate and zonisamide, which allosterically modulates the GABAA-receptor via the chlorine flows [10, 22].

Inhibition of the carbonic anhydrase. The inhibition of the enzyme carbonic anhydrase increases the concentration of the intercellular hydrogen ions. This results in the shift of potassium ions to the extracellular space and hyperpolarization [6]. Zonisamide and TPM suppress some isoforms of the enzyme carbonic anhydrase that could additionally contribute for their anticonvulsant effect [10, 29].

ACTION OF AEM ONTO OTHER MECHANISMS

SV2A glycoprotein. Inside the neurons SV2A the glycoprotein gets connected to the membrane of the synaptic vesicles [32]. There are various hypotheses on the role and functions of SV2A: connection to the neurotransmitter molecules, decrease of the intravesicular osmotic pressure, change of the vesicular exocytosis in the synapse and regulation of vesicular mobility [32]. Even though there are numerous issues remaining on the precise mechanism [5], according to the experimental data the main mechanism of action of LEV is the interaction with SV2A [22], and its connection to SV2A significantly correlates with the therapeutic effect [10]. The facts about the genetic variations of SV2A make us establish a connection with the different therapeutic reply to LEV [24]. Brivaracetam (BRV), a high-affinity synaptic vesicle protein 2A ligand, is chemically related to LEV and is reported to be 10-30-fold more potent than LEV [12]. BRV and LEV similarly bind to synaptic vesicle protein 2A, while differentiating for other pharmacological effects; in fact, BRV does not inhibit high voltage Ca(2+) channels and AMPA receptors as LEV. Furthermore, BRV apparently exhibits inhibitory activity on neuronal voltage-gated sodium channels playing a role as a partial antagonist [26].

KCNQ/Kv7 potassium channels. The KCNQ genes encode five subunits of the potassium channels (Kv7.1-Kv7.5). Four of them (Kv7.2-Kv7.5) are located in the nervous system. Kv7.2 and Kv7.3 are the main molecular components of the low-voltage-dependent M-channels that regulate the neuronal excitement [29]. The ion flows that get impacted by those channels are designated as “M-flows” meaning that their inhibition is performed by the cholinergic agonist muscarine [6, 27]. The M-flow impacts the action potential that occurs after hyperpolarization and stabilizes the membrane potential which prevents the repetitive neuronal discharge activity. This hypothesis is confirmed by the development of new substances which interact with KCNQ2–5 (Kv7.2–7.5) ion channels, partially with clear interaction with heteromeric channel subtype KCNQ2/3 [4, 29]. Mutations in Kv7.2 (R144Q, R201C, and R201H) and Kv7.3 (R230C) genes, encoding for voltage-gated K(+) channel subunits underlying the neuronal M-current, have been associated with a wide spectrum of early-onset epileptic disorders ranging from benign familial neonatal seizures to severe epileptic encephalopathies [14, 25]. Electrophysiological studies revealed that each of these four mutations stabilized the activated state of the channel, thereby producing gain-of-function effects, which are opposite to the loss-of-function effects produced by previously found mutations [25]. Present results suggest that gain-of-function mutations in Kv7.2/3 currents may cause human epilepsy with a severe clinical course, thus revealing a previously unexplored level of complexity in disease pathogenetic mechanisms [25]. Retigabine shifts the voltage dependence for activation of the heteromeric KV7.2/KV7.3 channel to more negative potentials, thus facilitating activation [8, 14]. In a recent study it was found that low μM retigabine concentrations have ‚off-target‘ effects on KV2.1 channels and inhibit KV2.1 channel function upon prolonged exposure [33].

Hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channels. The ion channels being regulated by the hyperpolarization-activated, cyclic nucleotide (HCN channels) are cation channels that are voltage-dependent and get activated by the hyperpolarization in the case of negative voltage ~ -50 mV [28]. Even though that from structural point of view they resemble the potassium channels, they are less selective for the potassium ions and facilitate the entry of sodium ions [28]. The specific feature of the HCN channels being that their activity increases during hyperpolarization, and their depolarization inacti-

vates the HCN channels [28]. The cyclic nucleotides cAMP and cGMP directly activate the HCN channels. The activation of the HCN channels is an additional mechanism of action for LTG in addition to its main interaction with the voltage-dependent sodium and calcium channels [29].

P2X receptors. P2X receptors are a class of ligand-gated ion channel activated by ATP that contributes to neuro- and glio-transmission. P2X receptors are expressed by both neurons and glia in various brain regions, including the hippocampus. Electrophysiology, pharmacology and genetic studies suggest certain P2X receptors are activated during pathologic brain activity. Expression of several members of the family including P2X2, P2X4, and P2X7 receptors has been reported to be altered in the hippocampus following status epilepticus. Antagonists of the P2X7 receptor modulate neuronal death, microglial responses and neuroinflammatory signaling [16].

The action of many of the antiepileptic drugs onto other receptor types is unclear: monoamine, acetylcholine, adenosine, serotonin, histamine H2 and H3, opiates, glycine, etc. The characterization of the mechanisms of action of the available antiepileptic drugs would improve our understanding of the pathophysiological mechanisms of the epileptic seizures, as well as the development of new therapeutic strategies.

The mechanism of action of the individual drug is comprehensive in many cases, with numerous impact locations. This comprehensiveness of the action of particular antiepileptic drugs creates the prerequisites for making the optimal choice when running the therapy. Mutations in genes encoding ion channel subunits, or their interacting proteins, are responsible for inherited ion channelopathies, resulting from mutations in calcium, sodium, potassium, and chloride ion channels. Developing new and more specific therapeutic approaches is therefore required. Ion channel mutations lead to change in biophysics that can in turn specifically modify the sensitivity to drugs: this opens the way to a pharmacogenetics strategy, allowing the development of a personalized therapy with increased efficacy and reduced side effects. The identification of disease modifiers in ion channelopathies appears an alternative strategy to discover novel druggable targets [1]. The continues research works on the impact of genetic and pathophysiological mechanisms of the individual differences in the action of the antiepileptic drugs cover the strategies for developing figurative techniques for defining molecular receptors and biomarkers' sensitivity to the effect of antiepileptic drugs [29].

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