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PATHOPHYSIOLOGICAL OR EMPIRICAL APPROACH TO THE PHARMACOTHERAPY OF EPILEPSY?

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The knowledge of etiopathogenesis of epilepsy and the therapeutic treatment of this disease has evolved from the mechanistic approach to the time when a lot is known about the pathophisyological basis of this disease, the mechanisms of epileptogenesis and the propagation of seizures.

The aim of this review article is to point to some analyses about the ways the understanding of the mechanisms of action of antiepileptic drugs (AEDs) can help with the prediction of the clinical response to AEDs, and, therefore, ultimately improve the treatment of epilepsy.

In contrast to other therapeutic areas, epilepsy is still an area where therapeutic algorithms cannot be designed through pathophysiological mechanistic approach. It is very unlikely that in the near future doctors will be advised to treat the given epileptic syndrome with a "sodium channel blocker", "AMPA receptor antagonist", "GABA transmission blocker", or the "combination of sodium channel blocker and P glycoprotein inhibitor".

Preliminary evidence suggest that, when it comes to patients with refractory epilepsy, the cause can be a disorder at the level of ionic channels which are insensible to the effects of the medication used, or the genetically determined abnormality of a receptor subunit. According to this evidence, dysfunctional ionic channels may be the new target of antiepileptic treatments. *Acta Medica Medianae 2012; 51(1):59-65.*

Key words: *epilepsy, epileptogenesis, antiepileptic therapy*

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Introduction

The understanding of epilepsy and the therapeutic treatment of epilepsy have evolved from the purely mechanistic approach to the time when a lot is known about the pathophisyological basis of this disease, the mechanisms of epileptogenesis and the propagation of seizures.

Nowadays, it is known that epilepsy is the intermittent, paroxysmal, sudden, transitory, and debilitating modification of motoric activity, sensibility, sensorium, behavior, emotions, consciousness, or autonomic functions, which is caused by the abnormal hypersynchronous electrochemical hyperactivity of a group of neurons (1).

A number of effective antiepileptic drugs (AEDs) has been introduced into clinical practice, and their mechanisms of action have been intensely examined.

The aim of this paper is to point to some analyses about the ways the understanding of the mechanisms of action of antiepileptic drugs (AEDs) can help with the prediction of the clinical response to AEDs, and, therefore, ultimately improve the treatment of epilepsy.

Mechanism of action of AEDs

One of the problems which arises when trying to connect the effect of the drug and the clinical response in relation to epilepsies is the fact that the mechanism of action of the majority of AEDs is still not entirely known. This refers not only to the new generation of drugs, but also to the standard AEDs which have been in use over a number of years. The reason for this may be the fact that the large number of AEDs has more than one mechanism of action (Table 1). The primary mechanism of antiepileptic action of a drug used to treat a specific type of seizure may be different from the mechanism of its antiepileptic action when used to treat another type of seizure; i.e. lamotrigine (LTG) prevents partial seizures mainly by blocking sodium channels. However, according to current knowledge, this mechanism cannot explain the effectiveness of this drug in treating absence seizures combined with childhood absence epilepsy (1). On the other hand, after almost four decades of clinical use, there are still controversies about whether the sodium channel blocking contributes to the activity of valproates (VPA) (2).

Voltage-dependent sodium channels are the primary locus of action of the majority of AEDs, since they are crucial in generating and propagating of the action potential (3). These channels have

transmembrane domains with multiple passages, α subunits complexed with at least one ß subunit. In the mammalian organisms, there are 9 sodium channel isoforms, even 7 of which are highly expressed in the nervous system (4). Antiepileptic drugs (phenytoin, carbamazepine, oxcarbazepine, and lamotrigine) bind to sodium channels and stabilize them in their inactivated form, thus preventing changes in the membrane potential when at rest (5).

Ca channels also represent one of the target loci of action of AEDs, given that they are involved in the regulation of neural excitement by regulating Ca ion hoemostasis on the neural membrane, and by regulating the release of neurotransmitters (6). In the brain, there are four distinct subclasses of these channels, L,P/Q, N (with high voltage-sensitivity) and T type (with low voltage-sensitivity, opens at lower depolarization). Gabapeptin and pregabalin exert their effect by binding to α2δ subunit of P/Q Ca channel, thus modifying and stabilizing them in their inactive form (7). Ethosuximide modulates T type of Ca channels and, by blocking them, it exerts its anticonvulsant effect (8).

GABA is the main inhibitory neurotransmitter of the brain, which, when released in the synaptic space/cleft, acts though two receptor types, iontropic GABAa and metabotropic GABAb (the third type, GABAc, is expressed in the retina). So, for example, bensodiazepines increase receptor affinity of GABAa for GABA, topiramate also exerts its effect through GABAa. Barbiturates are less selective to GABAa receptors, they exert their effect through prolonging its activation. Some other AEDs exert their effect by blocking neuron's and glia's reception of GABA, as well as its metabolizing, tiagabine (TGB), vigabatrin (VGN).

Taking into account that potassium channels are involved in the process of neuron repolarization, and that they have a significant role in maintenance of membrane potential at rest, some of AEDs, i.e. phenytoin, also exert their effect also by modulating the activities of K channels.

HCN channels expressed in the hippocampus and thalamus are also a significant locus of action of AEDs, because of their Na and K ion permeability. By means of these receptors, lamotrigine (partial and absence seizures) and gabapeptin exert their effects. Blocking of the receptor of the main excitatory neurotransmitter glutamate in the brain (NMDA; non- NMDA, kainite and metabotropic), is the locus of action of phelbamate, topiramate (9).

Mechanisms of drug action and prediction of the effects of AEDs in clinical conditions

Experimental and clinical evidence confirm the effectiveness of drugs which block voltage and "user dependent" Na channels in preventing partial seizures, with or without secondary generalization. Their effectiveness has also been confirmed in the treatment of primary generalized tonic clonic seizures (Table 2).

On the other hand, the drugs which act through potentiation of GABAergic inhibition, VGN and TGB, are also effective in the treatment of partial seizures, even though their potential effectiveness in treating primary generalized tonic clonic seizures is not adequately documented.

Although many AEDs affect Cavchannels, for the majority of these substances the importance of this effect in the total clinical effectiveness is not yet determined. There is clear evidence that T type of Ca channels plays the key role in the maintenance of synchronized paroxysmal discharges through thalamo-cortical circuits, and that drugs which block T type of Ca channels in thalamic neurons are effective anti-absence drugs.

Studies performed on animal models (10) point to the high effectiveness of GABAb receptorantagonists in the therapy of absence seizures. Since refractory absence seizures represent a small segment of AEDs market, this class of substances is not examined in the clinical studies (11).

There is a significant number of potential AEDs which are currently undergoing the phase of clinical trial, and which are considered to act through mechanism different from the ones in Table 1. Preliminary evidence was obtained by estimating clinical effectiveness of drugs against partial seizures. Those drugs include the ones which act as blockers of the synaptic vesicle protein (SVA), collapsing response-mediatory protein-2 (CRMP-2), selective AMPA receptor antagonists, and the ones which inhibit neural discharge by increasing conductivity of K through channels KCNQ2/3 i KCNQ3/5 (12).

Although some of these drugs have already been introduced into the clinical practice, or they are currently in phase III of preclinical trials, it is still too early to determine the corelation between these mechanisms and the profiles of clinical effectivenessin relation to different types of seizures.

Mechanism of AEDs action and their combination

Although the majority of people can be treated with one drug, a certain percentange of patients require a combined therapy so as to achieve the best clinical response (13). Greater clinical benefit should be achieved by using the combination of drugs with different and, possibly, complementary mechanisms compared to the combination of drugs which act through the same primary mechanism.

In an extensive review which deals with these issues and which is focused on the results of animal studies (14) it was concluded that: 1) The combination of Na channel blockers and drugs which potentiate GABAergic effects may have advantages; 2) The combination of two GABAergic drugs or the combination of AMPA antagonists and NMDA antagonists may potentiate effectiveness, but reduce tolerance; 3) The combination of two Na channel blockers seems to be the least prospective.

Table 1. The main mechanisms of AED action

- The first generation of AEDs

	Blockade of voltage Na+ channels	Increase of the GABA level, in brainor synapses	Selective potentiation of GABA-A's mediated response	Direct facilitation of the influx Cl-	Blockade of $Ca2^+$channels				Other mechanisms
					N	L	T	P/Q	
BZD	-	-	+	-	-				-
CBZ	++	?	-	-		+			+
ETS	-	-	-	-			++		-
PB	-	+	+	+	-				+
PHT	+	-	-	-	?				+
VPA	?	+	?	-			+		++

- The second generation of AEDs

	Blockade of voltage Na+ channels	Increase of the GABA level, in brain or synapses	Selective potentiation of GABA-A's mediated response	Direct facilitation of the influx Cl-	Blockade of $Ca2^+$channels				Other mechanisms
					N	L	T	P/Q	
FBM	++	+	+	-		+			+
GBP	?	+	-	-	++			++	+
LTG	+	+	-	-	++		++	++	+
LEV	-	?	+	-	+				++
OXC	++	?	-	-	+			+	+
PGB	-	-	-	-	++			++	?
TGB	-	++	-	-	-				-
TPM	++	+	+	-		+			+
VGB	-	++	-	-	-				+
ZNS	++	?	-		++		++	++	+

++ primary action, + secondary action, - action is not described, ? controversial facts

Table 2. Spectrum of effectiveness of old and new AED's in treating some of the basic types of seizures

	Partial seizures (with or without secondary generalization)	Primary generalized tonic - clonic seizures	Absence seizures	Mioclonic seizures/ jerks	Drop attacks	Infantile spasms
The first generation of AEDs						
BZD*	+	+	+	+	+	?
CBZ	+	+	A	A	- (?)	-
ETS	-	-	+	+ (?)	-	-
PB	+	+	A	+(?)	+ (?)	-
PHT	+	+	A	A	+ (?)	-
VPA	+	+	+	+	+	+
The second generation of AEDs						
FBM	+	+	+(?)	+(?)	+	-
GBP	+	?	-	A	-	-
LTG**	+	+	+	-(?)	+	?
LEV	+	+(?)	?	+	?	?
OXC	+	+	A	A	- (?)	-
PGB	+	?	-	A (?)	-	-
TGB	+	?	A	A	- (?)	?
TPM	+	+	?	+ (?)	+	?
VGB	+	+ (?)	A	A	- (?)	+
ZNS	+	+	+(?)	+	?	?

* Benzodiazepines can precipitate tonic seizures in patients with Lennox-Gastaut syndrom.
** Lamotrigine can aggravate different types of seizures in patients with grave mioclonic epilepsy
+ effectiveness, - no effects, ? not known, A- aggravation

Table 3. Combination of AEDs for which there are reports on clinical adventages

Combination of drugs	Type of seizure	Level of evidence
CBZ + VPA	Partial seizures	Relatively well documented
VPA+ ETS	Absence	Relatively well documented
VPA + LTG	Many types of seizures	Well documented
CBZ + VGB	Partial seizures	Speculative
LTG + VGB	Partial seizures	Controversive
TGB + VGB	Partial seizures	Anecdotal
LTG+ GBP	Partial seizures	Anecdotal
LTG + TPM	Partial seizures	Anecdotal

T*able 4.* Adverse effects which can be predicted by the knowledge of side pharmacological characteristics of an individual AED

Drug	Pharmacological characteristics	Adverse effects
CBZ, OXC	Antidiuretic effect	Hypo Na
TPM, ZNS	Inhibition of carbon anhidrosis	Urolithiasis, paresthesia
PB, PHT, CBZ (i mnogi drugi AEL)	Hem decrease	Attack precipitation in patients withintermittent porphyria
VPA	Inhibition of glucuronyl transferase	Increase of serum concentration of LTG

Abbreviations list (Epilepsia 1993, 34(6): 1151)

Abbreviation	*Name*	*Abbreviation*	*Name*
AED	Antiepileptic drugs	LZP	Lorazepam
AZM	Acetazolamide	MDL	Midazolam
BZD	Benzodiazepines	OCBZ	Oxcarbazepine
CBZ	Carbamazepine	PB	Phenobarbital
CLB	Clobazam	PGB	Pregabalin
CZP	Clonazepam	PHT	Phenytoin
DZP	Diazepam	PRM	Primidone
ESM	Ethosuximide	TGB	Tiagabine
FBM	Felbamate	TPM	Topiramate
GBP	Gabapentin	VPA	Valproic acid
LEV	Levetiracetam	VGB	Vigabatrin
LCS	Lacosamide	ZNS	Zonisamide
LTG	Lamotrigine		

However, it can be concluded that there is not enough evidence from the well-controlled studies, and, therefore, the rational mechanistic approach to combined therapy is hardly practicable because of "the incomplete knowledge of patho-physiology of seizures, as well as the accurate mechanism of action of an AED". It is clear that all AED combinations are not equivalent in terms of their clinical benefits and tolerance profiles (15).

Some studies suggest that the combination of two Na channel blockers, like CBZ and OXC (16), or CBZ and LTG (17), in a certain percentage of patients may result in potentiation of adverse effects in the central nervous system.

On the other hand, there is not enough evidence concerning the recommendation of choice of an individual combination (18). There are certain announcements in the recommendation which agree on the fact that the combination of AEDs and a similar profile of unwanted drugs (i.e. barbiturate and benzodiazepine, or carbamazapine and phenytoin) should be avoided in the therapeutic treatment, and that agents which have been empirically proved to have synergic effectiveness or antagonistic profile of adverse effects should be potentiated.

Many AEDs are susceptible to significant pharmacokinetic interactions, which are unfavourable from the clinical perspective, and pharmacodynamic interactions (at the locus of drug action), which, clinically, may be both favourable and unfavourable (19). It has been shown in the animal studies that VPA ans LTG have synergic anticonvulsant effects, while their neurotoxic potential is antagonized (20). These results have been confirmed in clinical studies, the combination of VPA and LTG is especially

effective in controlling partial or generalized seizures, which are resistent to maximum tolerable doses of each drug, respectively (21,22).

The same combination of AEDs is complicated for/by pharmacokinetic interactions (19), which, according to the preliminary reports, may be in unison with high teratogenic risk (23). Prevalence of teratogenicity as a result of AEDs use is higher in the case of VPA and CBZ combination (24). A larger number of other AED combinations is associated with favourable pharmacodynamic interactions (Table 3), even though the level of evidence is low.

AEDs mechanism of action and prediction of adverse effects

There is still no clear profile of adverse effects caused by a specific meachanism of action of each individual AED. However, there are examples of the emergence of motor incoordination in patients who use Na channel blockers; there are frequent cases of gaining weight, sedation or depressive mood after the use of drugs which potentiate the effects of GABA, and development of behavioural disorders which occur after the use of NMDA receptor antagonists.

Useful prediction about the possibility of the emergence of the certain adverse effects can be made according to the information about side pharmacological effects of an individual AED. For example, CBZ, and OCBZ, to a large extent, show antidiuretic characteristics, which are clinically manifested as hydrous sonic imblance and osmolality disorder in patients who use these drugs (25). Additional examples are shown in Table 4. Mechanisms involved in the antidiuretic effect of OCBZ (26): 1) changes in the osmoreceptor sensitivity, 2) direct simulation of ADH release from the hypophysis, 3) increased sensitivity of kidney receptors to ADH, 4) direct effect (independent of ADH) on the distal tubule cells, 5) prolongation of ADH half-life, through degradation decrease. The use of VPA also achieves its hyponatriemic effect, probably through the same mechanisms (27).

Clinically significant pharmacokinetic drug interactions are often the consequence of induction or inhibition of metabolic enzymes of liver or other organs. Drugs metabolyzed by the system cytochrome P450 can provoke seizures.

Acute intermittent porphyria is an AD human disease, which is usually manifested before puberty. People with this illness are heterozygotes (they have 50% of the normal enzyme activity). This is the effect of the hereditary partial uroporphyrinogen I synthase deficiency. In the case of the enzyme deficiency, AmLev acid and porphobilinogen start to accumulate, while there is not enough HEM. In this way, decreased HEM bioavailability makes the drugs and hormones which need proteins consisting HEM for their metabolism (i.e. cytochrome P-450) provoke acute deterioration. The emergence of seizures is interpreted by: 1) increased AmLev quantity which blocks GABA receptors, 2) decreased HEM which affects neurotransmitters (triptophan – serotonin), 3) electrolyte disorder due to vomiting (28).

As discussed in Patsalos and Perucca's article (19) this is the area where mechanistic information has large proven value for the safer use of drugs in clinical conditions.

Conclusion

In contrast to other therapeutic areas, epilepsy is still an area where therapeutic algorithms canot be designed through pathophysiological mechanistic approach. It is very unlikely that in the near future doctors will be advised to treat the given epileptic syndrome with a "sodium channel blocker", "AMPA receptor antagonist", "GABA transmission blocker", or the "combination of sodium channel blocker and P glycoprotein inhibitor".

A more detailed understanding of the mechanisms which form the basis of a good or bad individual therapeutic response can be crucial for choosing the appropriate AED.

Preliminary evidence suggest that, when it comes to patients with refractory epilepsy (29), the cause can be a disorder at the level of ionic channels which are insensible to the effects of the medication used, or the genetically determined abnormality of a receptor subunit. According to this evidence, dysfunctional ionic channels may be the new target of antiepileptic treatments.

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PATOFIZOLOŠKI ILI EMPIRIJSKI PRISTUP U FARMAKOTERAPIJI EPILEPSIJA?

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Poznavanje etiopatogeneze epilepsije i terapijski tretman ove bolesti evoluirali su od čisto mehanističkog pristupa do vremena kada se dosta zna o patofiziološkoj osnovi ove bolesti, mehanizmima epileptogeneze, generalizaciji i propagaciji napada.

Cilj rada bio je da ukaže na neka razmatranja kako poznavanje mehanizma dejstva antiepileptičkih lekova (AEL) može pomoći u predikciji kliničkog odgovora na AEL i ultimativno poboljšati lečenje epilepsije.

Za razliku od drugih terapijskih područja, epilepsija još uvek nije područje gde se terapijski algoritmi mogu dizajnirati putem patofiziološkog mehanicističkog pristupa. Malo je verovatno da će u bližoj budućnosti lekari imati preporuke da dati epileptički sindrom leče "blokatorom Na kanala", "antagonistom AMPA receptora", "blokatorom preuzimanja GABA", ili "kombinacijom blokatora Na kanala sa inhibitorom P glikoproteina".

Kako preliminarni dokazi sugerišu da kod nekih bolesnika sa refraktornim oblikom epilepsije uzrok može biti poremećaj na nivou jonskih kanala koji su neosetljivi na efekte primenjenog leka, ili, pak, genetski determinisana abnormalnost neke receptorske subjedinice, novi ciljni horizonti antiepileptičnog tretmana mogli bi biti disfunkcionalni jonski kanali. *Acta Medica Medianae 2012;51(1):59-65.*

***Ključne reči**: epilepsija, epileptogeneza, antiepileptična terapija*