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Review article

Effects of antiepileptic drugs on mitochondrial functions, morphology, kinetics, biogenesis, and survival

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ARTICLE INFO

Abbreviations:
ABAT
4-aminobutyrate aminotransferase
ACTH
Adrenocorticotropic hormone
AED
Antiepileptic drug
AHD
Alpers Huttenlocher disease
AZM
Acetazolamide
B6#
Pyridoxine
CBD
Cannabidiol
CBZ
Carbamazepine
CLB
Clobazam
CNZ
Clonazepam
CPEO
Chronic progressive external ophthalmoplegia
CSF
Cerebrospinal fluid
ECB
Eslicarbazepine
ESM
Ethosuximide
FBM
Felbamate
GABA
γ-aminobutyric acid
GAN
Ganaxolone
GBT
Gabapentin
GDH

Keywords:
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ABSTRACT

Objectives: Antiepileptic drugs (AEDs) exhibit adverse and beneficial effects on mitochondria, which have a strong impact on the treatment of patients with a mitochondrial disorder (MID) with epilepsy (mitochondrial epilepsy). This review aims at summarizing and discussing recent findings concerning the effect of AEDs on mitochondrial functions and the clinical consequences with regard to therapy of mitochondrial epilepsy and of MIDs in general.

Methods: Literature review.

Results: AEDs may interfere with the respiratory chain, with non-respiratory chain enzymes, carrier proteins, or mitochondrial biogenesis, with carrier proteins, membrane-bound channels or receptors and the membrane potential, with anti-oxidative defense mechanisms, with morphology, dynamics and survival of mitochondria, and with the mtDNA. There are AEDs of which adverse effects outweigh beneficial effects, such as valproic acid, carbamazepine, phenytoin, or phenobarbital and there are AEDs in which beneficial effects dominate over mitochondrial toxic effects, such as lamotrigine, levetiracetam, gabapentin, or zonisamide. However, from most AEDs only little is known about their interference with mitochondria.

Conclusions: Mitochondrial epilepsy might be initially treated with AEDs with low mitochondrial toxic potential. Only in case mitochondrial epilepsy is refractory to these AEDs, AEDs with higher mitochondrial toxic potential might be tried. In patients carrying POLG1 mutations AEDs with high mitochondrial toxic potential are contraindicated.

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reactive oxygen species
apoptosis
membrane potential
oxidative stress
respiratory chain

1. Introduction

Epilepsy is a common phenotypic manifestation of mitochondrial disorders (MIDs) (Finsterer and Zarrouk Mahjoub, 2013) occurring in up to half of the pediatric patients with a MID (mitochondrial epilepsy). All types of seizures described so far also occur in mitochondrial epilepsy. Treatment of mitochondrial epilepsy is generally not at variance from treatment of non-mitochondrial epilepsy (Finsterer and Zarrouk Mahjoub, 2013), but some peculiarities in the management of mitochondrial epilepsy need to be addressed (Finsterer and Mahjoub, 2013). Nonetheless, up to 90% of mitochondrial epilepsies in pediatric patients are intractable. As with all medical drugs, antiepileptic drugs (AEDs) have side effects, depending on the dosage, toxicity, and individual tolerability (Ray, 2014; Finsterer, 2012). Some of these side effects are attributable to the toxicity of AEDs to mitochondria (Finsterer, 2012). Since the prevalence of mitochondrial epilepsy is increasing with the increasing recognition and diagnosis of MIDs, it can be expected that the frequency of AED side effects will increase as well (Finsterer, 2012). Basic molecular and clinical studies have shown that AEDs may exhibit particular effects on mitochondria, which can result in a beneficial or adverse net reaction of mitochondrial functions, dynamics, morphology, or biogenesis. This review aims at summarizing and discussing previous and recent findings concerning the effect of AEDs on mitochondrial functions and the clinical consequences on AED therapy particularly of mitochondrial epilepsy and of MIDs in general.

2. Methods

The data included in this review were identified by a literature search of MEDLINE and Google Scholar using the search terms “epilepsy”, “seizures”, “convulsions”, “mitochondrial”, “respiratory chain”, “electron transport”, “oxidative phosphorylation”, “respiration” in combination with all antiepileptic drugs as listed in Table 1. Randomized (blinded or open label) clinical trials, longitudinal studies, case series and case reports were considered. Only articles published in English between 1966 and 2017 were included. Appropriate papers were studied and discussed for their appropriateness to be incorporated in this review.

3. Results

AEDs included in this review are listed in Table 1. AEDs exert their effect on mitochondria by interference with various mitochondrial pathways, structures, or functions. AEDs may affect enzymatic cascades, such as the respiratory chain or oxidative phosphorylation or non-respiratory chain pathways, such as the tricarboxic cycle or the β-oxidation. AEDs may interfere with channels, protein transporters, membrane-bound receptors, the membrane potential, they may affect the anti-oxidative defence mechanisms, or may impair mitochondrial biogenesis and apoptosis associated with appropriate changes in mitochondrial morphology, structure, and dynamics. Exceptionally, AEDs may also result in depletion of the mitochondrial DNA (mtDNA) or may increase or decrease the expression of various nuclearly encoded mitochondrial proteins. Adverse effects on mitochondria are differentiated from beneficial effects on mitochondria. An adverse effect of an AED was defined as deterioration of mitochondrial functions, structure, dynamics, or biogenesis. A beneficial effect of an AED was defined as improvement of these properties.

3.1. Effects of AEDs on the respiratory chain or oxidative phosphorylation

3.1.1. Adverse effects

The most well investigated AED with regard to interference with mitochondria is valproic acid (VPA). This is attributable to the fact that VPA is frequently used in mitochondrial epilepsy and causes the most severe side effects to MIDs. In an in-vitro study of crude mitochondrial fractions isolated from pig brains, VPA inhibited respiratory chain complex-I (RCC-I) (Hroudova and Fisar, 2010). In a study of rats, VPA, given during 75 days, decreased the respiration rate by 30% in liver mitochondria (Ponchaut et al., 1992). Additionally, administration of VPA resulted in loss of cytochrome-c-oxidase along with reduction of cytochrome aa3 (Ponchaut et al., 1992). In two studies with a HepG2 in vitro model VPA decreased O_2 consumption rates and reduced ATP-production (Komulainen et al., 2015; Li et al., 2015). Other AEDs impaired mitochondrial respiration in a similar way. In a murine hepatic microsomal system phenytoin (PHT), carbamazepine (CBZ), and phenobarbital (PB) decreased state-3 respiration (addition of respiratory substrates (e.g. succinate or pyruvate) increases respiration markedly to a high steady rate and pyridine nucleotides become reduced) and ATP synthesis (Santos et al., 2008a). In the same study PHT and PB increased state-4 respiration (respiration spontaneously and markedly decreases to a nearly constant, slow rate together with a simultaneous

Table 1
Effects of AEDs on mitochondrial functions.

	RC/OXP	Extra RC	CHRecDP	AOD	StMoApo	mtDNAcont
ACTH	−	−	−	−	−	−
AZM	−	−	+	−	+	−
B6**	−	−	−	−	−	−
CBD	+	+	−	+	+	−
CBZ	+	−	+	−	−	−
CLB	+	−	−	−	−	−
CNZ	+	−	−	−	−	−
ECB**	−	−	−	−	−	−
ESM	−	−	+	+	−	−
FBM	−	+	−	−	−	−
GAN**	−	−	−	−	−	−
GBT	+	−	+	+	−	−
LAC**	−	−	−	−	−	−
LTG	+	−	−	+	+	−
LEV	−	−	+	+	−	−
NZP	+	−	−	−	−	−
OXC	+	−	+	+	+	−
PER**	−	−	−	−	−	−
PB	+	−	+	+	−	−
PHT	+	−	+	+	−	−
PDN**	−	−	+	−	+	−
PGB	−	+	−	+	−	−
PRM	−	−	−	+	−	−
RGB	−	−	+	+	−	−
RFM**	−	−	−	−	−	−
STP**	−	−	−	−	−	−
TGB	−	−	−	+	−	−
TPM	−	−	+	−	−	−
VPA	+	+	+	+	+	+
VGB	−	−	−	+	−	+
ZNS	+	−	+	+	+	−

+: present, −: not reported or absent, **: no reports available at all, RC/OXP: respiratory chain, oxidative phosphorylation, Extra-RC: extra-respiratory chain pathways, ChRecDP: channels, receptors, mitochondrial membrane potential, AOD: anti-oxidative defense, StMoApo: structure, morphology of mitochondria and apoptosis, mtDNAcont: mtDNA content