Carbonic Anhydrase Inhibitors and Epilepsy

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Carbonic anhydrases (CAs) are a group of ubiquitously expressed metalloenzymes that catalyze the reversible hydration/dehydration of CO2/HCO3. Thus, they are involved in those physiological and pathological processes in which cellular pH buffering plays a relevant role. The inhibition of CAs has pharmacologic applications for several diseases.

Keywords: carbonic anhydrases (CAs) ; CA inhibitors (CAIs) ; epilepsy ; CA II ; CA VII ; CA XIV

1. Introduction

According to the International League Against Epilepsy (ILAE), epilepsy is a chronic brain disorder operationally defined by the occurrence of two unprovoked seizures more than 24 h apart, or one unprovoked seizure when the risk for another is known to be high (>60%) [1]. Seizures can manifest in a variety of different clinical presentations with motor, sensory, autonomic or psychic origin [2]. Seizure episodes are a result of abnormal excessive or synchronous neural activity in the brain. Seizures are classified into focal and generalized types. Focal seizures are localized in a specific cerebral area. Thus, the behavioral outcome depends on the brain regions where synchronous firing of a neuronal cell group occurs. Generalized seizures, spreading through thalamocortical connections, involve both cerebral hemispheres. Considering the specific symptoms and etiology, subclassifications of epileptic seizures are also reported [3].

The high impact of the disease on global health has provoked immense efforts from the scientific community to shed light on the complex mechanisms underlying seizure generation and to develop therapeutic strategies to pharmacologically treat epilepsy. However, antiepileptic drugs (AED) currently available and employed in clinical practice can treat only some subtypes of epilepsy and, often, pharmacological treatment may not be resolute [4]. For this reason, there is an urgent need to identify new molecular targets in order to expand the therapeutic options to treat and to defeat this dramatic pathology [5][6][7].

2. CAs and Their Role in Epilepsy

CAs catalyze a crucial reaction that basically takes place in all living organisms: the reversible hydration of carbon dioxide into bicarbonate and protons $CO_2 + H_2O \leftrightharpoons HCO_3^- + H^+$.

CA's physiological function is then essential for all species. In mammals, CAs are involved in several biological processes that directly or indirectly use components of this reaction, such as respiration, pH regulation, secretion of electrolytes and HCO_3^- dependent metabolic processes [8].

In humans and vertebrates, CAs are encoded by the α-CA gene. This class of CAs consists of 16 subtypes with different tissue and cellular locations. In the brain, several CA isoforms have been identified. CA II was the first CA isoenzyme to be associated with the brain [9]. It is expressed in neurons where it is confined to the cytoplasm [10], in oligodendrocytes [11], choroid plexus, astrocytes and in myelinated tracts [12]. The isoform CA VII has been found widely expressed in the hippocampus and cortex, exclusively at neuronal level. Other isoforms with a widespread expression throughout the brain are CA IV, with a prevalent expression in endothelial cells, the mitochondrial CA V and CA VIII, mainly found in glial cells and neurons [13][14]. Additionally, the isoforms CA III, CA X, CA IX, CA XI and CA XII have been found in cerebral tissue, although with a weak expression in normal conditions [14][15].

CA VIII, X and XI are three catalytically inactive carbonic anhydrase-related proteins (CARPs), which were speculated to function through interaction with other proteins [16]. Finally, CA XIV and CA XV were found located in the plasma membrane on neuronal bodies and on axons in the mouse and human brain [17][18].

The physiological role of cerebral CAs mainly consists in pH regulation, ion compartmentation and formation of cerebrospinal fluid.

Much of the evidence indicates that brain CAs are also involved in neuropathological processes associated with seizure generation. Epileptic conditions can increase CA levels in the brain, while their absence confers seizure resistance in animal models of epilepsy. Indeed, it has been demonstrated that CA II and CA XII levels are heightened in the epileptic brain [19] and that there is a lack of electrographic experimental induced febrile seizures in CA VII deficient mice [20].

There are multiple factors that link CAs to seizures (**Figure 1**):

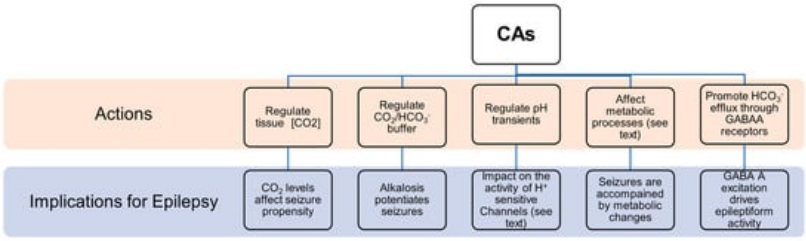

Figure 1. Schematic view of CAs actions and their involvement in epileptic processes.

(1) Seizures are accompanied by pronounced changes in ionic composition in brain compartments and by pH shift that, directly or indirectly, influence the concentration of the chemical species of the reaction catalyzed by CAs.

(2) CAs regulate CO_2 tissue concentration, and it has been demonstrated that CO_2 has a role in epilepsy. In particular, clinical evidence suggest that the enhancement of CO_2 concentration results in better seizure control [21], while low CO_2 levels are linked to higher seizure propensity [22]. The inhibition of CAs resulted in increased CO_2 concentration and a positive outcome in epilepsy management [23].

(3) It has been clearly shown that alkalosis generally potentiates seizures by increasing neuronal excitability, while acidosis has an opposite effect [24]. Since their role is in the regulation of the CO_2/ HCO_3^- buffer system, CAs are crucially involved in the control of neural excitability [25]. For instance, it has been demonstrated that CA IV and CA XIV play a role in extracellular buffering in response to neural activity [26].

(4) Mitochondrial dysfunction has been identified as one potential cause of epileptic seizures [27]. There is a vicious cycle between mitochondrial dysfunction and epileptic seizures because seizures themselves can induce mitochondrial damage that consequently triggers seizures [27]. It is known that CAs are involved in mitochondria biogenesis and physiology, and in glucose and lipid metabolism in human Sertori cells [28]. In particular, CA V A and CA V B are specifically localized in mitochondria. They hydrate carbon dioxide to yield bicarbonate ions and a proton that contribute to normal mitochondria metabolism. In the nervous system, CA V is expressed in astrocytes as well as in neurons. It has been proposed that CA V in neurons could be involved in the regulation of the intra-mitochondrial Ca^{2+} levels, thus contributing to the stability of the intracellular calcium concentration preventing neuronal degeneration and cell death [13]. Another possible function of CA V is to participate in the regulation of neuronal HCO_3^- homeostasis taking part in physiological neuronal function. Moreover, it has been reported that the intracellular regeneration of HCO_3^- and its elimination from the extracellular environment results in a repolarization in GABA responses, suggesting that CA V might also be involved in neuronal transmission [13][29].

(5) Regulating the kinetics of pH transients [25][30][31]. CAs can influence the function of a broad array of proton-sensitive transmembrane proteins implicated in neuronal signaling such as GABAARs [30][31], N-methyl-D-aspartate (NMDA) receptors [32][33], H^+-gated channels [34] and cation channels [35][36]. For example, the activity of excitatory receptors for glutamate, NMDA receptors, is inhibited by extracellular protons [37]. The initial seizure-associated extracellular alkaline shift, apparently influenced by CA activity [26], likely sustains NMDA receptors' activation during seizures. Moreover, it has been shown that CA XIV, located in close vicinity to the NMDA receptor at the synapses, regulates pH transients in the perisynaptic microenvironment and their impact on NMDA receptors' activity [33].

(6) It has been shown that glycolysis increases during seizures and that the glycolytic metabolite lactic acid can be used as an energy source [38]. A specific isoform of CAs facilitate lactate transport in astrocytes as well as in neurons [39]. In addition, CAs can intervene in lactic acid-induced acidosis, that seems to be implicated in seizure termination [38][40]. Moreover, CAs provide substrates required for the function of metabolic enzymes involved in epilepsy. For instance, a failure in pyruvate carboxylase (PC) function may lead to seizures, as demonstrated by the fact that PC deficiency is related to recurrent seizures in patients. CA V, providing HCO_3^- to pyruvate carboxylase, is involved in controlling the proper functioning of this enzyme [9] and, then, its action might have implications for epilepsy.

(7)

Numerous experimental and clinical studies support the notion that oxidative stress substantially contributes to the pathogenesis of epilepsy [41]. Studies showed that patients affected by epilepsy report a remarkable increase in levels of oxidative markers, such as malondialdehyde (MDA), protein carbonylation (PC) and nitric oxide (NO), when compared to a control group. An excessive production of free radicals could be implicated in neuronal hyperexcitability that triggers epileptogenesis. Moreover, it has been reported that overproduction of reactive oxygen species (ROS) provokes the progressive disruption of Ca^{2+} homeostasis essential for neuronal survival. In this context, it has been proposed that CAs, in particular CA VII might also have a role in the cell defence against oxidative damage thanks to its cysteine residues [42].

(8) GABAergic inhibition has been traditionally considered as the principal mechanism counterbalancing glutamatergic excitation and preventing epileptiform activity. Indeed, many of the currently used antiepileptic drugs act through enhancement of GABAergic signaling. However, much evidence has shown that epileptiform events can also be characterized by synchronous firing driven by excitatory GABA [43]. As during the first phases of development [44], excitatory action of GABA in epilepsy is due to (a) elevated intracellular chloride concentration as a result of chloride accumulation during hyperactivity [45]. High levels of intra-neuronal Cl^- leads to Cl^- efflux and then to depolarization in response to GABA binding to its type A receptor; (b) HCO_3^- permeability of GABA-A channels [46][47] that causes HCO_3^- efflux and then depolarization; (c) elevation of extracellular potassium caused by KCC2-mediated extrusion of chloride and potassium that results in membrane depolarization [48]. CAs are implicated in this abnormal epilepsy-associated GABA-A excitation. Specifically, it has been shown that they have a role in favouring the efflux of HCO_3^- ions through GABA-A receptors [49][50]. CA VII, which plays an important role in the development of febrile seizures [20], has been identified as a key molecule in GABAergic excitation and it has been suggested that CA VII developmental expression governs the electrophysiological behaviour related to neural circuit plasticity and to susceptibility to epileptogenesis [51].

3. CA Inhibitors Clinically Employed in Epilepsy Therapy

Acetazolamide (ACZ), methazolamide (MZA), zonisamide (ZNS) and topiramate (TPM) are the most known CA inhibitors, belonging to the class of sulfonamides (**Figure 2**) that act as anticonvulsants in animal models of epilepsy as well as in epileptic patients.

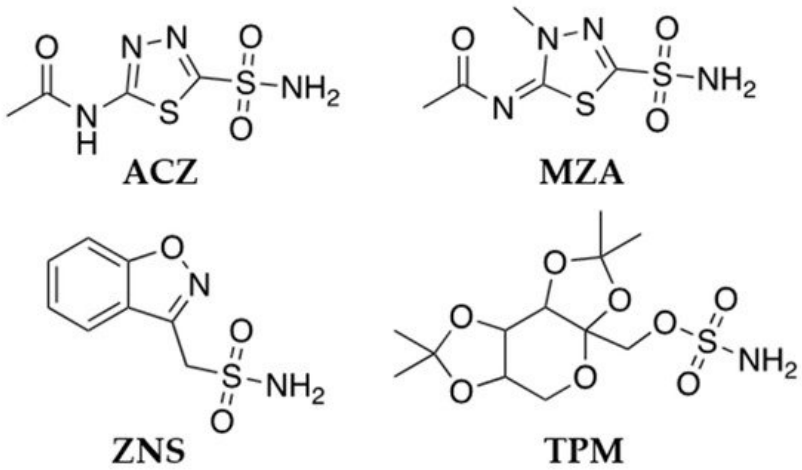

Figure 2. Chemical structure of the most known CA inhibitors.

ACZ, also known with the commercial name Diamox, was approved in 1953 as a diuretic. Actually, it is also indicated as an adjuvant for epilepsy treatment. In particular, it might be useful in partial, myoclonic, absence and primary generalized tonic–clonic seizures [9]. It seems to be particularly effective in the treatment of catamenial epilepsy in women [52]. However, since the possible side effects, including tinnitus, kidney stones, paresthesia, loss of appetite, alteration of taste [53] and the lack of an effective long-term therapy due to the development of tolerance in patients, ACZ is rarely used as an antiepileptic drug.

ACZ is able to inhibit various CA isoforms, including CA II, CAV, CAVII, CAXII and CA IV [9]. ACZ reduces the excitability of cortical neurons and suppresses neural discharges in the Maximal Electroshock (MES) model, an animal model of generalized tonic–clonic seizures [10][54]. Its anticonvulsant effect has been mainly attributed to its capacity to increase CO_2 levels in the brain and to inhibit GABA-A depolarization [54][55].

The other sulfonamide methazolamide (MZA) has inhibitory proprieties similar to those of ACZ [9]. In the literature, few articles regarding the antiepileptic effect of MZA are available. Most of them date back to the 1950s–1960s [56]. MZA was studied in animals as well as in humans: this resulted in different physicochemical properties and body distribution with respect to ACZ and seemed more active than ACZ against experimental epilepsy [57]. However, very few clinical trials on the use of MZA in epilepsy have been conducted; nowadays its clinical use is mainly restricted to the treatment of glaucoma since it is able to potently reduce intraocular pressure.

Zonisamide (ZNS) was originally synthesized in Japan in 1974. Preclinical animal studies revealed its antiseizure effect on MES in rats, mice, rabbits and dogs [58]. Several controlled clinical studies conducted in the USA and Europe demonstrated ZNS's efficacy in the treatment of partial seizures in adults. ZNS was approved by The Food and Drug Administration (FDA) in the USA in 2000 as an adjunctive therapy in the treatment of partial seizures in adults with epilepsy. Currently, it is a widely used seizure medicine, known with the common brand name "Zonegran", particularly exploited for the treatment of Temporal Lobe Epilepsy, Focal Impaired Awareness or Complex Partial Seizures Refractory Seizures, Secondarily Generalized Seizures and Simple Partial Seizures [59].

ZNS is fairly safe, well tolerated in patients and has a better, although not yet optimal, long-term efficacy profile compared to ACZ. However, its application is often accompanied by some side effects, such as headache, nausea, somnolence, dizziness and weight loss.

ZNS anticonvulsant proprieties are attributable to various molecular mechanisms: (a) it blocks low-voltage-gated sodium channels [60][61] and T-type calcium channels [62]. Both types of voltage-gated channels are implicated in controlling neuronal firing and, then, play a role in epilepsy; (b) It upregulates GABA-mediated inhibition of seizures, while reducing excitatory glutamatergic transmission. In particular, it has been shown that ZNS increases synaptic concentrations of GABA through the regulation of glutamate and GABA transporter proteins [63] and inhibits calcium-dependent, potassium-evoked extracellular glutamate release in the hippocampus [63]. It has also been demonstrated that ZNS affects GABAergic and glutamatergic neurotransmission by acting on inositol triphosphate receptor-associated neurotransmitter release [64]; (c) it acts on dopaminergic and serotonergic transmission generating antiseizure and positive psychotropic effects [65]; (d) it has free radical scavenging activities that protect neurons from the free radical damage associated to epilepsy [66]; (e) it is a potent non-specific CA inhibitor. As we reported above, it has been demonstrated that CAs are implicated in seizure generation, so, presumably, CA inhibition by ZNS might contribute to its antiepileptic activity. Clear experimental evidence that probes this last point is still lacking; indeed, the anticonvulsant effect of ZNS is not usually attributed to its CA inhibition properties [10].

Topiramate (TPM), known with the brand name Topamax, is a widely used drug for epilepsy treatment. Its use was approved in 1996 as an adjunctive and monotherapy in children as well as in adults for partial-onset seizures and for drug-resistant patients with primary or secondary generalized tonic–clonic seizures. It is considered a broad-spectrum agent, also effective as a prevention therapy for migraine headaches. Moreover, TPM is highly bioavailable and presents low protein binding [23]. Its effectiveness was probed in several animal model of epilepsy: MES model in rodents [67], amygdala kindling, a model for complex partial seizures [68], genetic absence epilepsy in rats [69], kainic acid (KA) model of temporal lobe epilepsy [70] and in an animal model for Dravet Syndrome, a severe paediatric genetic epilepsy [71]. TPM is currently used as an adjunctive therapy in children with this last form of highly pharmaco-resistant epilepsy [72]. Despite its high efficiency, fairly long-term, TPM use in patients might lead to a quite consistent list of side effects: dizziness, nervousness, anxiety and depression, confusion, coordination abnormality, loss of appetite, sensory distortion and cognitive impairment, just to mention a few. An extended release formulation (TPM-XR) has been available since 2014. TPM-XR has shown both efficacy and tolerability, though still with some adverse effects when used as either a monotherapy or an adjunctive therapy in epilepsy patients with focal or generalized seizures [73].

Topiramate inhibits all CA isoforms, in particular it strongly inhibits cerebral CA II and CA VII [9]. CO_2 retention [23], inhibition of the GABA-A mediated depolarization [74] and decrement of the initial alkalization accompanying abnormal neural activity [75], observed following TPM application, might be considered as consequences of the TPM-induced CA inhibition and might account for its anticonvulsant propriety. The anticonvulsant effect of TPM can also be due to the TPM capacity to alter neural excitability through other mechanisms, apparently unlinked with CA inhibition: TPM enhances inhibition by increasing the frequency of GABA-mediated chloride channel opening [76] by upregulating GABA levels [77] and by increasing potassium conductance [74], while it reduces neuronal excitation by inhibiting kainate-type glutamate receptors [78][79] and by blocking voltage-gated sodium channels [80] and L-type voltage-sensitive calcium channels [81].

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