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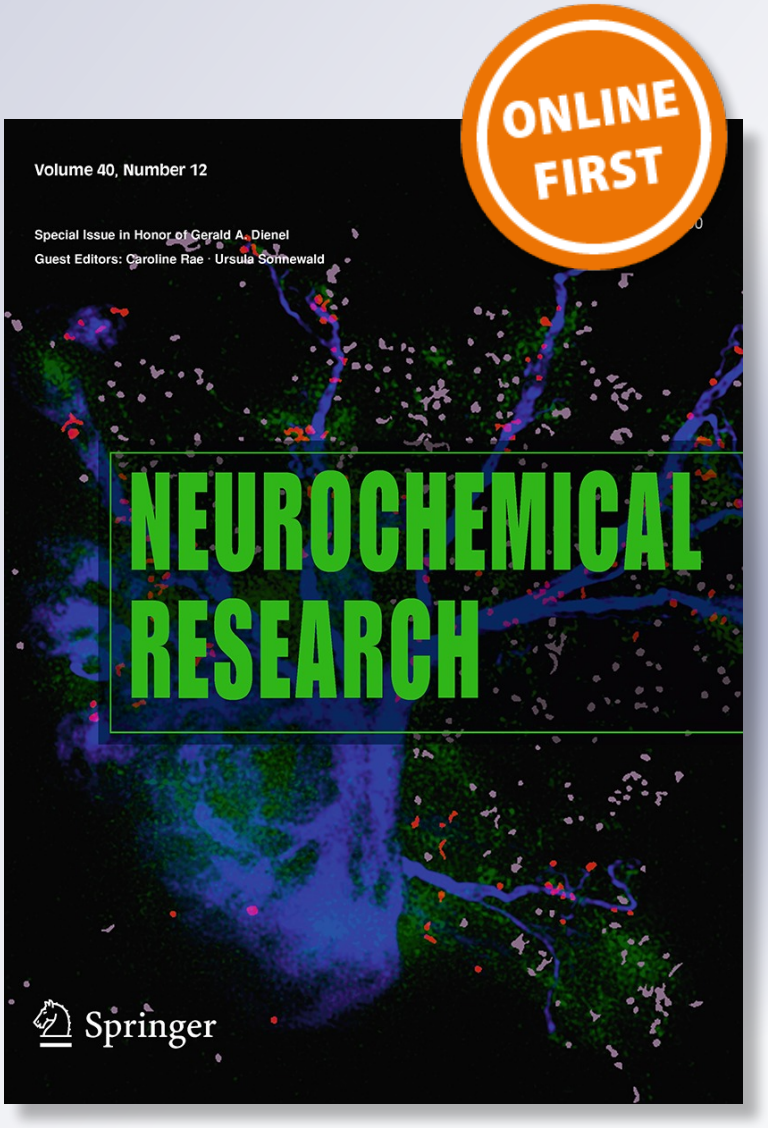

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ORIGINAL PAPER

Neuroprotection as a Potential Therapeutic Perspective in Neurodegenerative Diseases: Focus on Antiepileptic Drugs

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Abstract Neuroprotection is conceived as one of the potential tool to prevent or slow neuronal death and hence a therapeutic hope to treat neurodegenerative diseases, like Parkinson's and Alzheimer's diseases. Increase of oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammatory changes, iron accumulation, and protein aggregation have been identified as main causes of neuronal death and adopted as targets to test experimentally the putative neuroprotective effects of various classes of drugs. Among these agents, antiepileptic drugs (AEDs), both the old and the newer generations, have shown to exert protective effects in different experimental models. Their mechanism of action is mediated mainly by modulating the activity of sodium, calcium and potassium channels as well as the glutamatergic and GABAergic (gamma-aminobutyric acid) synapses. Neurological pathologies in which a neuroprotective action of AEDs has been demonstrated in specific experimental models include: cerebral ischemia, Parkinson's disease, and Alzheimer's disease. Although the whole of experimental data indicating that neuroprotection can be achieved is remarkable and encouraging, no firm data have been produced in humans so far and, at the present time, neuroprotection still remains a challenge for the future.

Keywords AEDs · Neuroprotection · Experimental animal models

Introduction

The increasing knowledge about the basic neuronal changes underlying the degenerative process of various neurological diseases has greatly stimulated the research aimed at identifying drugs which may stop, or at least slow, the cascade of events leading to neuronal death. Indeed, the relative preservation of neuronal integrity and/or function over time against an ongoing neurodegenerative insult, is a widely explored treatment option to prevent or slow disease progression and secondary injuries in many central nervous system (CNS) disorders, such as the classical neurodegenerative diseases Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), and also multiple sclerosis (MS) and epilepsy [1–4]. Additionally, a therapeutic approach based on neuroprotection has been conceived since decades to limit the neuronal damage consequent to acute insults, like ischemic stroke, intracerebral haemorrhage (ICH), and traumatic brain injury (TBI) [5]. Continued effort in research has being done to find any method effective in preventing the onset or progression of neurodegenerative diseases or secondary injuries. Among the many compounds so far investigated, antiepileptic drugs (AEDs) have been shown to effectively counteract cell apoptosis/necrosis in various in vitro and in vivo experimental models of specific neurological diseases [5]. Rare attempts to demonstrate a useful effect have been made also in humans.

Concerning the mechanism of action, AEDs counteract the pathologically disturbed neuronal excitability by modulating

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the activation of ion channels, receptors and intracellular signalling pathways [6]. A single AED can display multiple mechanisms. Sodium, calcium and potassium channels, and the glutamatergic and GABAergic (gamma-aminobutyric acid) synapses are the main targets of AEDs in CNS.

Aim of the present manuscript is to provide an updated review of the most relevant data on the neuroprotective effects exerted by AEDs in experimental models of neuronal damage. The potential implications of these effects in human pathology are considered at the present time a therapeutic hope for various neurological diseases which today exhibit a negative prognosis.

General Concepts of Neuroprotection

The neurodegenerative process which underlies various neurological disorders is the result of a complex cascade of pathological events, including increase of oxidative stress, mitochondrial dysfunction, excito-toxicity, inflammatory changes, iron accumulation, and protein aggregation [7, 8]. This series of events leads to cell death and, ultimately, to a progressive neuronal depletion. A potential therapeutic tool is counteracting one or more steps of the degenerative process with the obvious consequence of neuronal protection. Neuroprotection, therefore, is attempted most frequently by targeting oxidative stress and excito-toxicity, which both are able to directly cause neuron cell death or trigger a cascade of events leading to protein misfolding, proteasomal malfunction, mitochondrial dysfunction, or glial cell activation, ultimately causing neuron cell apoptosis. More recently, neuroinflammation has been recognized to play a role in the pathogenesis of various neurodegenerative diseases, like PD, AD, and amyotrophic lateral sclerosis, and also in other CNS disorders, like cerebral ischemia [8]. Neuroprotective treatments commonly exploit glutamate antagonists, i.e. voltage-gated ion channel blockers or GABA receptor agonists, and antioxidants, with the aim to attenuate excitotoxicity and oxidative stress, respectively. Additional strategies include the use of anti-inflammatory molecules, caspase inhibitors, trophic factors, or anti-protein aggregation agents [8]. Figure 1 illustrates the various mechanisms of individual AEDs, which potentially might play a role in exerting their neuroprotective effects in different neurological pathological processes.

Experimental Models of Neurodegenerative Disorders

Acute Damage Models

Rodent animal models of ischemia are the most widely used. Global ischemia may be induced by blocking, for a defined time period, either carotid arteries and vertebral arteries or only the carotid arteries. Experimental focal ischemia is commonly studied during permanent or transient occlusion of a middle cerebral artery (pMCAO, tMCAO) by an intraluminal suture or with a vascular clip [9, 10].

In vitro models of cerebral ischemia are commonly represented by either primary cultures of post-mitotic neurons from different regions of rat or mouse brain (cortex, striatum, septum, hippocampus, etc.) or brain slices, particularly the hippocampal slices, exposed to oxygen and glucose deprivation (OGD) [11, 12].

One of the most commonly used animal models of hypoxic-ischemic encephalopathy is the permanent unilateral carotid artery ligation with a subsequent exposure to a hypoxic environment (8 % oxygen) in neonatal rat pups. This model creates a unilateral infarct in the hemisphere ipsilateral to the ligation, typically concentrated in cortical and hippocampal areas of the brain [13].

Intracerebral haemorrhage (ICH) are usually induced in rodent animals by transclival puncture of arteries with a piece of glass or a stainless steel cannula introduced through a burr hole into the brain [14]. Various rodent models of TBI have been developed and targeted at improving our understanding of molecular cascades that are initiated by head trauma, including fluid percussion injury, cortical impact injury, weight drop-impact acceleration injury, and blast injury [15].

Chronic Damage Models

Experimental models of PD are represented by dopaminergic neuron cell cultures or animals, usually rodents, treated with environmental or synthetic neurotoxins or genetically engineered to lack or overexpress known PD-related genes [16–18]. Neurotoxin-based models include the treatment of cell cultures, or animal administration, with either 6-hydroxydopamine (6-OHDA), 1-methyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat or rotenone, that are able to produce an oxidative stress by irreversibly targeting mitochondrial chain respiratory complexes and to cause dopaminergic neuron cell death [19, 20]. In genetic models of PD the genes coding for either α-synuclein, parkin, LRKK2, PINK1, DJ-1, that have been found mutated in familial PD, are overexpressed or knocked out to characterize specific molecular events that lead to the death of dopaminergic neurons [20, 21]. Similarly, toxic AD models are generally represented by primary or immortalized cultures of cortical neurons exposed to amyloid-beta (Aβ) peptides or oligomers, while genetic AD models are based on the use of transgenic methodologies targeting amyloid precurson protein, presenilin, tau or APOE genes, in rodents, usually in mice, and also in cell cultures [22].

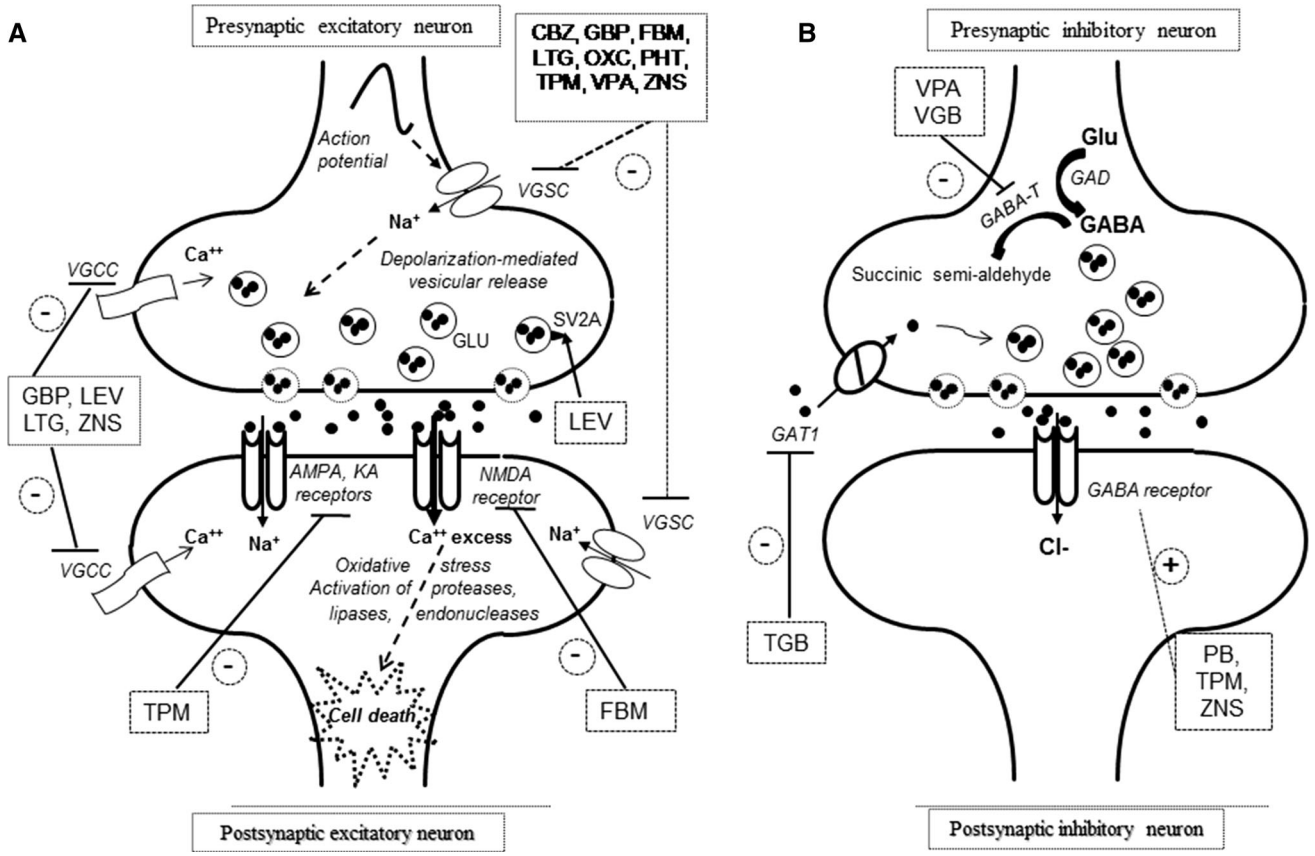

Fig. 1 Molecular targets of AEDs. AEDs mostly work targeting several molecules at the excitatory synapse (**a**), including voltage-gated sodium channels (VSGC), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors, and NMDA (*N*-methyl-D-aspartate) receptors. Their inhibitory action is able to prevent or attenuate excitoxic cell death by decreasing depolarization-induced Ca^{++} massive influx and vesicular release of glutamate (GLU). The binding to L-type voltage-gated Ca^{++} channels is thought to be associated with a decrease in GLU. Levetiracetam is the only AED binding to the synaptic vesicle glycoprotein 2A (SV2A), which might have a role in GLU release. Excitatory neurotransmission at the postsynaptic membrane can be limited by topiramate, acting on AMPA and kainate receptors. Some AEDs also have targets at inhibitory synapses (**b**). The metabolism of GABA in presynaptic terminals and glial cells is decreased by tiagabine -mediated inhibition of GABA transporter (GAT1, also known as SLC6A1), leading to a decrease in GABA uptake into presynaptic terminals and surrounding glia, and by GABA-transaminase (GABA-T) irreversible inhibition mediated by vigabatrin and valproic acid. Topiramate and zonisamide enhance inhibitory neurotransmission by allosterically modulating $GABA_A$ receptor-mediated Cl^- currents. GAD, glutamic acid decarboxylase. The abbreviations of all antiepileptic drugs: *CBZ* carbamazepine, *OXC* oxcarbazepine, *FBM* felbamate, *PHT* phenytoin, *GBP* gabapentin, *LTG* lamotrigine, *LEV* levetiracetam, *PB* phenobarbital, *TGB* tiagabine, *TPM* topiramate, *VPA* valproate, *ZNS* Zonisamide

Toxic HD models are represented by cortical or striatal neuron cell cultures or rodent animals treated with 3-nitropropionic acid (3-NP), a suicidal inhibitor of mitochondrial complex II, or excitotoxins, such as kainate (KA), ibotenate or quinolinate. Genetic HD models are mostly represented by neuronal cell cultures or animals overexpressing mutant, such as BACHD mice, or wild-type huntingtin [23, 24].

Experimental models have been developed that mimic status epilepticus (SE). The common pharmacological models of SE are kainic acid, pilocarpine and perforant path stimulation. These models are being used to study the mechanisms of neuronal injury and susceptibility, synaptic reorganization, the hippocampal sclerosis, the seizure-induced changes in gene expression and neurogenesis, and the development of new anticonvulsant drugs [25].

Several animal models have been used to investigate the molecular and cellular adaptations of nociceptive pathways. Inflammatory pain models use subcutaneous injections of inflammatory agents, such as formalin, capsaicin, or complete Freund's adjuvant (CFA), usually into the hind or forepaw, whereas neuropathic pain models typically involve surgical injury of a spinal or peripheral nerve. These models result in reliable nociceptive sensitization; mimicking key components of the chronic pain experience in humans [26].

The experimental autoimmune encephalomyelitis (EAE) model is the most widely-used animal model to investigate

the possible pathogenic mechanisms operating in MS, characterized by mononuclear cell infiltration into the CNS and axon demyelination. EAE is induced by either the administration of myelin protein or peptide in adjuvant or by the adoptive transfer of encephalitogenic T cell blasts into naïve recipients [27].

The Clinical Concept of Disease Progression in Neurology

Neurodegenerative diseases are defined as disorders with a typically progressive selective loss of neurons and distinct involvement of functional systems defining clinical presentation. Biochemical, genetic, and molecular pathological examinations have contributed to expand in a more complete way this definition [28]. The clinical picture is a direct expression of the anatomo-functional system affected by the degenerative process rather than reflecting the molecular/biochemical pathologic background. As a consequence of disease progression, additional anatomical regions will be affected, leading to complex constellations of symptoms and possibly hampering the correct diagnosis. On these grounds, a theoretically main therapeutic strategy is that of using drugs which may stop or at least slow disease progression. However, even if various attempts were carried out, there is almost no drug for which the efficacy has been confirmed in clinical trials [29]. Concerning AEDs, lamotrigine, for example, did not prevent loss of cerebral or spinal cord volume over 24 months in patients suffering from secondary progressive MS [2]. In a double-blind controlled study an adjunctive treatment with low dose of zonisamide to levodopa has induced improvement of all the cardinal symptoms of PD [30], but a slowing effect on the disease has not been clearly demonstrated.

Individual AEDs and Neuroprotective Effects

Table 1 summarizes the neuroprotective effects exerted experimentally by individual AEDs in specific experimental models of various neurological diseases.

Carbamazepine (CBZ) and Oxcarbazepine (OXC)

The mechanism of action of CBZ and the structurally related OXC is multiple: block of voltage sensitive Na^+ channels resulting in modulation of neural membrane excitability, increase of K^+ conductance, modulation of Ca^{2+} channel function, reduction of glutamatergic transmission; they both inhibit repetitive neuronal firing and counteract the spread of discharges [31].

Neuroprotection against OGD was observed in slices treated with CBZ, which induced a small reduction of excitatory postsynaptic potential amplitude without changes of paired-pulse facilitation [32]. The CBZ neuroprotective potential has also been demonstrated in the rotenone model of PD. The onset of rotenone-induced membrane depolarization, that was concomitant with an increased release of both excitatory amino acids and dopamine, was significantly delayed by CBZ in a manner dependent on the modulation of endogenous GABA in cortico-striatal brain slices [19]. Administration of CBZ and OXC improved the clinical status and reduced immune infiltrates in mice affected by EAE induced by rat myelin oligodendrocyte glycoprotein inoculation [33]. OXC- and CBZ-mediated inhibition of microglial activity as well as neural sodium loading was shown to slow EAE progression when drugs were administered during periods of the inflammatory penumbra after active lesion formation in myelin-specific T cell receptor transgenic mice [34]. CBZ has been reported to reduce the expression of IL-1β and TNF-α from basal conditions in the hippocampus of rats and the increase in pro-inflammatory cytokines induced by lipopolysaccharide (LPS) injection [35]. Neuroprotection exerted by CBZ was also demonstrated in KA-induced neurotoxicity in mice through increased phosphorylation of the signal transducer and activator of transcription-3 (Stat3), which contributes with other factors, like NF-κB and HIF-1α, to regulate the expression of genes that mediate cell survival [36]. Interestingly, some data indicate that CBZ is able to exert neurotrophic effects, leading to an increase in neural plasticity and dendrite outgrowth [37].The effect might be mediated by enhancing the levels of synaptic proteins, i.e. BDNF, PSD-95, NLG1, β-neurexin, and SYP, against cytotoxicity induced by nutrient deprivation in hippocampal cultures; similar effects were obtained by administration of VPA [37].

OXC at a concentration up to 300 μM reduced cell death induced by OGD in hippocampal slices [38].

Felbamate (FBM)

FBM inhibits both Na^+ and Ca^{2+} channels, enhances GABA-mediated events through a barbiturate-like modulatory effect on the $GABA_A$ receptor and reduces glutamate-mediated excitation [39, 40]. The neuroprotective effects of FBM have been demonstrated in several ischemic brain models, including a gerbil model of global ischemia, bilateral carotid ligations in rat pups, the OGD model in hippocampal slices [31, 41, 42]. Interestingly, it has been shown that FMB serum concentrations similar to those reported in FBM monotherapy for seizures display neuroprotection against CA1 traumatic neuronal injury [43].

Table 1 Antiepileptic drugs and experimental models of specific neurological pathologies in which a neuroprotective effect has been demonstrated

AED	Experimental model	Neurological pathology	References
CBZ	Cortico-striatal brain slices exposed to rotenone	Parkinson's disease (PD)	[1–4]
OXC	Autoimmune encephalomyelitis induced by inoculation of rat MOG in C57/Bl6 mice; myelin-specific T cell receptor transgenic mice; LPS injection in rat hippocampus	Multiple sclerosis	
FBM	CA1 traumatic neuronal injury by fluid percussion	Traumatic brain injury	[5–8]
	Bilateral carotid ligations in rat pups	Cerebral ischemia	
	Gerbil model of global ischemia		
	Oxygen/glucose deprivation (OGD) model in hippocampal slices		
GBP	Surgical ligation of left L5 nerve in male Sprague–Dawley rats	Neuropathic pain	[9, 10]
	Injection of 3-nitropropionic acid in rats	Nigrostriatal degeneration (HD, PD)	
LTG/ REMA	Permanent or transient MCAO in rats and gerbils	Focal and global cerebral ischemia	[10–16]
	Unilateral occlusion of the left common carotid artery		
	Oxygen/glucose deprivation (OGD) model in striatal slices	Hypoxic-ischemic encephalopathy	
	Experimental subarachnoid hemorrhage in rabbits		
	3-Nitropropionic acid administration in rat striatum	Subarachnoid hemorrhage	
	KCl/electric stimulation in migraine type 1 mutant mice		
		Nigrostriatal degeneration (HD, PD)	
		Migraine-related ischemia	
LEV	Closed head injury and subarachnoid hemorrhage in mice	Traumatic brain injury	[17–22]
	Controlled cortical impact injury in rats	Ischemia and hypoxic-ischemic brain injury	
	Permanent MCAO in rats; neonatal hypoxia–ischemia rat model		
	Cultures of hippocampal neurons exposed to amyloid-β	Alzheimer's disease	
	Mice overexpressing amyloid-β		
PB, TGB/ VGB PHT	Oxygen-.glucose deprivation in corticostriatal brain slices	Ischemia, excitotoxic cell death	[23–27]
	NMDA administration in isolated chick embryo retina		
	Right carotid ligation in newborn rats	Neonatal cerebral hypoxia ischemia	
	Autoimmune encephalomyelitis		
		Multiple sclerosis	
TPM	Hypoxic-ischemic white matter injury	Cerebral ischemia	[5, 6, 28–30]
	Global ischemia	Lithium-pilocarpine model	
	Focal cerebral ischemia		
	Status epilepticus		
VPA	Middle cerebral artery occlusion in rats	Cerebral ischemia	[31–43]
	Induction of ICH in adult male rats; rat primary cortical neurons and rat brain exposed to hemin	Intracerebral haemorrhage	
	Transgenic HD mouse model	Huntington's disease (HD)	
	Transgenic AD mouse models		
		Alzheimer's disease (AD)	
ZNS	THB treatment of dopaminergic CATH.a cells	Parkinson's disease	[44–56]
	Rotenone treatment in corticostriatal brain slices and differentiated SH-SY5Y cells;	Hyperoxic brain death	
	MPTP treatment in SH-SY5Y and PC12 cells, mice and marmosets		
	6-OHDA treatment in astrocytes and rat mesencephalic organotypic slice cultures of substantia nigra		
	Transgenic PD mice models		
	Rat model of hyperoxia-induced neonatal brain injury		

LPS lipopolysaccharide, *MCAO* middle crebral artery occlusion, *MOG* myelin oligodendrocyte glycoprotein, *MPTP* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *6-OHDA* 6-hydroxydopamine, *THB* tetrahydrobiopterin

Gabapentin (GBP)

GBP (1-(aminomethyl)cyclohexaneacetic acid), a structural analog of GABA, potentiates GABA transmission. Early treatment with GBP offered some protection against neuropathic pain induced in male Sprague–Dawley rats by a surgical ligation of left L5 nerve [44]. Moreover, GBP at doses of 100 mg/kg significantly alleviated all behavioural manifestations of neuropathic pain induced by chronic constriction injury in rats [45]. GBP and lamotrigine have been seen to significantly counteract the oxidative stress, the impairment of mitochondrial complex enzyme activities and the increase of TNF-α level induced by 3-NP in the striatum of rats [46]. Different data suggest that the mechanism involved is an increase in GABA transmission [11, 46, 47].

Lamotrigine (LTG)

Data indicating the neuroprotective effects of LTG have been obtained in several experimental models. Post-insult treatment with LTG, a triazine compound acting as voltage-dependent sodium channel blocker, has been reported to strongly reduce damage of hippocampal CA1 and CA3 cells and prevent CA3 cell loss in a pMCAO rat model, thus exerting a beneficial action against ischemia induced cognitive impairment [48]. Low concentrations of both LTG and remacemide, another compound with anticonvulsant properties, were found to exert an additive neuroprotective action against the irreversible field potential loss and cell swelling induced by OGD [49]. These experimental data support the hypothesis that a negative modulation of excitatory transmission, in the absence of a relevant interference with normal synaptic transmission, can be neuroprotective against ischemia [5, 49, 50]. LTG treatment also attenuates selective CA1 neuronal loss in the gerbil hippocampus by preventing tMCAO-induced increase in post-synaptic intrinsic excitability of CA1 pyramidal neurons [51]. LTG also attenuated cerebral vasospasm after experimental subarachnoid hemorrhage in rabbits [52], and reduced the hippocampal tissue levels of glutamate and aspartate, without effects on GABA or glutamine levels, in a rat model of neonatal hypoxic-ischemic encephalopathy [53]. Pre-treatment with either LTG, remacemide or the active desglycinyl metabolite of remacemide (d-REMA) was able to decrease, in a dose-dependent manner, LDH release as well as edema and the number of necrotic and pyknotic nuclei in the ganglion layer induced by NMDA, KA, or alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid in isolated chick retina [54]. Combinations of d-REMA and LTG showed additive rather than potentiation effects against NMDA-induced cell injury [54]. Pre-treatment of rat cerebellar granule cells with LTG caused a time- and concentration-dependent inhibition of glutamate excitotoxicity with nearly full protection at higher doses ($\geq$ 100 μM); neuroprotection by LTG involved histone deacetylase inhibition and downstream up-regulation of anti-apoptotic protein Bcl-2 [55]. Chronic treatment with topiramate or LTG reduced the susceptibility to KCl-induced or electric stimulation-induced ischemic depolarizations in both wild-type and familial hemiplegic migraine type 1 mutant mice; consequently, both tissue and neurological outcomes were improved [56]. The neuroprotective potential of LTG also involves elevation of the ratio of astroglial differentiation to neuronal differentiation under retinoic acid stimulation [57], and stimulation of neurogenesis in the granule cell layer of the dentate gyrus [58].

Levetiracetam (LEV)

LEV, a piracetam (S-enantiomer pyrrolidone) derivative, is an inhibitor of presynaptic calcium channels, its neuromodulatory and neuroinhibitory effects are due to its binding to the synaptic vesicle protein SV2A [59]. LEV displayed a neuroprotective action against brain injury induced by intraperitoneal administration of KA in rats, since it prevented the loss of reduced glutathione and concomitantly decreased malonildialdehyde and IL-1beta mRNA levels, and cell damage in rat cortex and diencephalon [60]. LEV reduced, in a dose-dependent fashion, both the amplitude and duration of repetitive paroxysmal depolarization shifts, as well as the N-, and partially P/Q-type high-voltage-activated (HVA) Ca^{2+} currents in single pyramidal neurons from rat neocortical slices [61]. The inhibitory effects of LEV were mimicked by CBZ, LTG, and topiramate in rat corticostriatal brain-slice models of OGD [32]. These results suggest that the concomitant inhibition of fast Na^{+} and HVA Ca^{2+}conductances is a critical step for neuroprotection against ischemia. The specific therapeutic benefits of LEV against post-stroke seizures has been suggested in human and experimental studies [62, 63]. Daily LEV treatment had also favourable effects on structural and molecular parameters TBI, i.e. closed head injury and subarachnoid haemorrhage (SAH), likely through modulation of both excitatory and neuroinflammatiory pathways [64, 65]. Interestingly, a novel mechanism by which LEV displays its action is represented by LEV ability to remove the Zn^{2+}-induced suppression of GABA(A)-mediated presynaptic inhibition with consequent presynaptic decrease in glutamatergic transmission [66]. LEV displayed antiapoptotic effects in a neonatal rat model of hypoxic-ischemic brain injury in the early period, and dose-dependently improved behavioral performance in the late period [67]. LEV also exerted a beneficial action against Aβ-induced death of cultured hippocampal neurons

[68]. Additional data indicate that LEV blocks depletion of $Kv_{4.2}$ a dendritic potassium channel important for regulating dendritic excitability and synaptic plasticity-associated with dendritic hyperexcitability in mice overexpressing amyloid-β [69].

Phenobarbital (PB) and Phenytoin (PHT)

PB, a barbiturate acting through an increase in GABA activity, was first reported to diminish MPTP ion-induced neurotoxicity in rats [70]. PB pre-treatment resulted in a behavioural neuroprotection against KA-induced deficits in acquisition learning, tested by Morris water maze in mice [71]. Notably, lower PB doses (30 mg/kg) resulted protective against stroke in PD12 CD1 mice, while higher doses (60 mg/kg) were not effective [72]. Moreover, PBinhibited KA-induced increase in lipid peroxidation, depletion of reduced glutathione, and hippocampal CA-3 neuron death [73]. Early PB administration after cerebral hypoxia/ischemia enhanced the neuroprotective efficacy, in term of better sensorimotor performance and less ipsilateral cerebral hemisphere cortical damage, in newborn rats [74].

Concerning PHT, it is known that the drug can induce brain atrophy in patients after long-term use [75]. Nonetheless, some literature data have indicated that also PHT might exert neuroprotective effects in experimental autoimmune encephalomyelitis [76, 77]. In humans, randomized controlled trials of PHT failed to show that the use of this anticonvulsant drug exerts any antiepileptogenic effect in injured brain [78].

Tiagabine (TGB)

TGB counteracts neuronal and glial uptake of GABA, thus prolonging the presence of GABA in the synaptic cleft, trough inhibition of the GAT-1, GABA transporter, on presynaptic neurons and glial cells [79, 80]. In a model of status epilepticus, TGB reduced CA1 and CA3c pyramidal cell loss [81, 82]. Also, it reduced brain infarctionvolume in a focal ischemia model in rats in a dose-dependent manner [42]. Other studies have shown that the drug is effective in reducing CA1 hippocampal cell mortality both in focal and in global ischemia [41]. Post-ischemic hypothermia has been hypothesized to be partially responsible for the neuroprotective action of TGB [82]. TGB displayed, like vigabatrin (VGB), CBZ, FBM and LTG, significant neuroprotective effects in the OGD model [11, 38].

Topiramate (TPM)

Several mechanisms of action are attributed to TPM: modulation ofAMPA/kainate- and $GABA_A$-activated ion channels and voltage activated Na^+ and Ca^{2+} channels, activation of K^+ conductance, inhibition of depolarizing GABAA-mediated responses, potentiation of the effects of endogenous GABA through a novel binding site on the GABAA receptor complex, alteration of the phosphorylation state of the kainate receptor [83–85]. Given these multiple effects, the drug exerts its protective action by reducing excitatory amino acid release, ischemic depolarization and calcium overload in the ischemic cells and by increasing the brain's GABAergic activity. A body of data obtained in different experimental models clearly indicate that TPM is protective against selective hypoxic-ischemic white matter injury, OGD [86], AMPA/kainate receptor mediated cell death and Ca^{2+} influx, hemorrhagic incidence in focal cerebral ischemia [87] and global ischemia [41]. A protective effect of TPM was also demonstrated in different hippocampus layers in a model of status epilepticus in rats [3, 88, 89].

Valproate (VPA)

VPA is a voltage-dependent sodium channel blocker, able to increase GABA brain levels and also to act as a potent histone deacetylase (HDAC) inhibitor. VPA has been reported to induce a small reduction of excitatory postsynaptic potential amplitude in corticostriatal brain-slice models of ischemia [32]. Moreover, pre-treatment prior to insult and post-insult treatment with VPA reduced rat brain infarct size and improved functional outcome in both t- and p-MCAO ischemia models [90, 91]. Treatment with VPA immediately after reperfusion reduced the infarct area only in tMCAO model [92].VPA exerts its neuroprotective action against brain ischemia by multiple mechanisms: (1) direct targeting of HDAC, which facilitates transcription factor binding to gene promoters and regulates the expression of numerous neurotrophic and neuroprotective factors [93–95]; (2) suppression of glutamate neurotoxicity by up-regulation of α-synuclein, inhibition of oxidative stress and induction of stress response proteins [96–99]; (3) induction of anti-apoptotic proteins and inhibition of pro-apoptotic proteins [90, 91, 100, 101]; (4) suppression of both microglial activation and up-regulation of pro-inflammatory transcription factors NF-κB and enzymes iNOS and COX2 [93, 102, 103]; (5) blood–brain barrier protection by inhibition of cerebral ischemia-induced NF-κB activation, MMP9 up-regulation and tight junctions degradation [95]; (6) pro-angiogenic effects involving VEGF up-regulation and MMP-9 inhibition following HDAC inhibition [95]; (7) pro-neurogenic effects by activation of the ERK1/2 pathway [104–107]; 8) enhancement of mesenchymal stem cell migration [108, 109]. VPA treatment also provides a therapeutic strategy to attenuate ICH injury due to its ability of partially block cell death

induced by hemin, released from hemoglobin, by down-regulating hemoxygenase-1 protein expression via ERK1/2 and JNK activation [101, 110]. Additional data have indicated that VPA inhibits amyloid-β production, tau phosphorylation, and neuritic plaque formation, and improves memory and learning deficits in AD mouse models; regulation of NGF expression, stimulation of neurite outgrowth, and inhibition of both mitochondrial and endoplasmic reticulum pathway of apoptosis are the identified mechanisms [111–117]. Interestingly, VPA has also been shown to ameliorate survival and motor performance in HD transgenic mice [118].

Zonisamide (ZNS)

ZNS, a benzisoxazole chemically unrelated to any of the other AEDs, displays a pleiotropic action since it is able to inhibit voltage-dependent sodium channels, prevent influx of calcium through T-type calcium channels, enhance GABAergic and monoaminergic transmission, scavenge free radicals and modulate nitric oxide (NO) levels [119]. ZNS has been shown to exert neuroprotective effects in animal models of hypoxic-ischemic damage [120–124] and to inhibit NO synthase in the hippocampus following NMDA administration [125]. Post-treatment with ZNS attenuated KA-induced apoptosis in rat primary hippocampal neurons [126]. Various studies have provided evidence in favour of ZNS neuroprotective effects against PD [127]. In particular, the drug is able to protect dopaminergic neurons against damage and/or death induced by a variety of toxic injuries, like exposition to rotenone, MPTP, 6-OHDA, aggregated α-synuclein and other substances, in different in vitro and animal models [128–135]. Interestingly, ZNS protective effects in PD models also involve an antioxidant action through free-radical scavenger activity, up-regulation of anti-oxidant proteins (metallothionein-2, copper/zinc superoxide dismutase, manganese superoxide dismutase, glutathione peroxidase), and abrogation of changes in mitochondrial membrane potential as well as increase in lipoperoxide and oxidized glutathione levels induced by mitochondrial toxins [130, 131, 133, 135]. These features makes ZNS a promising drug for the treatment of the most important age-related neurodegenerative diseases, given the increased evidence supporting a critical pathogenic role for oxidative stress and nitrosative stress in these disorders [136]. In particular, changes in the redox status of glutathione, the major endogenous antioxidant, have been shown contribute to disruption of systemic redox homeostasis which can be associated to alterations on vulnerable neurons. Moreover, redox proteomics approaches have indicated that cellular degeneration, in brain regions selectively affected in neurodegenerative disorders, is a function of mitochondrial oxidative modified proteins [137]. Moreover, ZNS was able to effectively inhibit monoamine oxidase B activity, significantly delay the pace of dopaminergic neuron degeneration induced by expression of A53T α-synuclein, and attenuate toxicity independently of the formation and maturation of α-synuclein aggregates in PD rodent models [138, 139]. Chronic ZNS administration improved the survival of dopaminergic neurons and motor function in the Engrailed mutant mouse, a genetic PD model, probably through the increase of brain-derived neurotrophic factor signaling in the brain [140]. Other protective effects of ZNS in PD experimental models include increase in astroglial cysteine transport, leading to increased glutathione synthesis, inhibition of microglial activation, increased dopamine release and blockade of calcium channels [141].

Conclusion

The characterization of molecular mechanisms activated by AEDs may be useful to define new classes of drugs that not only suppress seizures but also specifically act to protect neural tissues against injuries. Thus, there is a growing interest in the potentially therapeutic value of AEDs for the prevention of injury responses, that would result in disease modification [142]. Preclinical findings have shown that some AEDs, acting as blockers of voltage-gated ion channels or enhancers of GABAergic neurotransmission, are able to exert neuroprotective effects by modulating cell survival signaling cascades, oxidative stress pathways, and protein quality control mechanisms [142]. In this regard, further investigations are acknowledged to address whether or not some AEDs, i.e. VPA and ZNS, are also able to induce the expression of vitagenes, including heat shock proteins (Hsps), sirtuins, Nrfs as well as the thioredoxin/thioredoxin reductase system. This system has been shown to play a key role in neuroprotection through the modulation of endogenous cellular defense pathways involved in adaptive response to stress [143, 144].

AEDs also facilitate or enhance anti-inflammation, angiogenesis, neurogenesis, blood–brain barrier integrity, and disease-specific neuroprotection. The activation of these mechanisms may have therapeutic potential for the treatment of the classical neurodegenerative diseases such as AD, PD, HD, but also other neurological diseases in which neurodegeneration plays an important pathogenic role, like MS and stroke. As illustrated above, experimental data are abundant and strongly suggest that neuroprotection by AEDs can be a possible future therapeutic strategy to prevent neuronal damage and hence to delay or stop the neurodegenerative process. At the present time, however, no firm data have been produced in humans and

neuroprotection still remains an important challenge for the future. Moreover, an important issue to be taken into account when administrating antiepileptics, is hormesis. This is a biphasic dose response characterized by a low dose stimulation and a high dose inhibition. Given the key role played by hormesis in the adaptive response to stress, promoting survival through the neutralization of many endogenous and environmental challenges by toxic agents [145], much attention should be paid to a careful setting of AED therapeutic doses. Moreover, beneficial effects resulting from a combined administration of drugs or only pretreatment with protective molecules should be considered in order to confer protection against neuronal cell death induced by environmental toxins.

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