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Commentary

Zonisamide: Aspects in neuroprotection

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ABSTRACT

Zonisamide is widely used as an antiepileptic drug. Two studies published recently in Experimental Neurology focus on the drug's neuroprotective effect. In the present commentary, we discuss the significance of their findings and aspects of zonisamide in neuroprotection.

Introduction

Zonisamide (1,2-benzisoxazole-3-methanesulfonamide) was developed in the 1970s as anticonvulsant agent (Uno et al., 1979). After extensive studies it became available in 1989 for the treatment of intractable epilepsy in Japan and received over 10 years later approval in the USA and Europe for adjunctive treatment of partial seizures in adults (Murata, 2004). Besides treatment of epilepsy, there has been a growing interest in the therapeutic potential of zonisamide for treating non-seizure conditions, such as intractable neuropathic pain (Atli and Dogra, 2005), headache (Drake et al., 2004), obesity and binge eating disorder (McElroy et al., 2006) and Parkinson's disease (PD) (Murata et al., 2001).

Particular in PD, studies reporting positive effects of zonisamide have become more frequent. PD is a slowly progressive neurodegenerative movement disorder and clinically characterized by progressive motor dysfunction (bradykinesia, resting tremor, rigidity, and postural instability), mainly linked to the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), which leads to the depletion of dopamine in the striatum, the main target of the axonal projections arising from the SNc (Rodriguez-Oroz et al., 2009). Despite the availability of effective symptomatic drugs, there is presently no cure for PD, and all attempts to slow the neuronal cell loss in clinically significant manner have failed so far (Hauser et al., 2009; Olanow, 2009; Olanow et al., 2009).

Murata et al. found that zonisamide has beneficial effects in PD (Murata et al., 2001, 2007). In two double-blind, randomized, multicenter trials, carried out on PD patients, who showed insufficient response to L-DOPA treatment, zonisamide significantly improved motor functions determined by beneficial changes in the total score of the Unified Parkinson's Disease Rating Scale (UPDRS) Part III, from baseline to the final assessment point, when compared with placebo (Murata et al., 2001, 2007). The overall incidence of adverse events was not significantly different between zonisamide 25 mg once daily and placebo groups in the phase IIb/III trial.

Mechanisms of action

The antiepileptic effect of zonisamide involves blockage of voltage-dependent Na^+ and T-type Ca^{2+} channels (Kothare and Kaleyias, 2008), which have a pivotal role in membrane excitability, suggesting that zonisamide disrupts neuronal synchronized firings and epileptic activity resulting in a limitation of spread or propagation of seizures (Kothare and Kaleyias, 2008). This effect possibly contributes to the neuroprotective potential of zonisamide, but in PD additional protective mechanisms seem to be of high relevance. Novel insights indicate that both, dopaminergic and non-dopaminergic mechanisms could equally be involved. BOX 1 presents an overview of possible mechanistic effects which may be responsible for the neuroprotective potential of zonisamide.

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Box 1
Mechanistic effects of zonisamide.

GABAergic system
- No affinity for GABA receptors (Rock et al., 1989)
- Enhances GABA release binding allosterically GABA receptor (Yamamura et al., 2009)

ACh system
- No effect on acetyl-cholinesterase activity (Zhu et al., 2002)
- Enhances ACh release (Zhu et al., 2002)

Dopaminergic system
- No affinity for dopamine receptors (D_1–D_5) or activity on dopamine transporter (Okada et al., 1995; Yamamura et al., 2009)
- Enhances dopamine release (Okada et al., 1995)
- Inhibits monoamine oxidase type B (MAO-B) (Okada et al., 1995; Murata et al., 2001; Sonsalla et al., 2010)

Ischemic conditions
- Reduces neonatal hypoxic–ischemic brain damage (Hayakawa et al., 1994)
- Ameliorates brain infarction and the event of neurological deficit after transient focal cerebral ischemia (Minato et al., 1997)
- Reduces neuronal damage by decreasing ischemia-induced extracellular glutamate accumulation and interruption of excitotoxic pathways (Owen et al., 1997)

Oxidative stress
- Scavenges free radicals such as hydroxyl ($OH^{\bullet}$) and nitric oxide (NO) but not superoxide ($O2^{\bullet-}$) (Mori et al., 1998)
- Inhibits nitric oxide synthase (NOS) activity (Noda et al., 1999)
- Shows inhibitory effect on lipid peroxide formation (Komatsu et al., 1995)
- Reduces 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels, a marker for oxidative DNA damage in iron-induced epileptogenic foci (Komatsu et al., 2000)

Several investigations have been made concerning the influence of zonisamide on the dopaminergic system. A direct dopamine-like effect of zonisamide is rather improbable, as zonisamide shows no affinity to dopamine receptors (D_1–D_5) or dopamine transporters (Okada et al., 1995; Yamamura et al., 2009). Still, therapeutic doses of zonisamide are able to increase *in vivo* the levels of dopamine (DA) and its metabolites in the striatum both intracellularly and extracellularly (Okada et al., 1995). This effect was not observed in rats with 6-hydroxydopamine (6-OHDA)-induced denervation of dopaminergic fibers (Gluck et al., 2004). Nevertheless, in the striatum of 6-OHDA-treated rats, DA levels increased if zonisamide was co-administered with L-DOPA (Gluck et al., 2004). This increase in striatal DA levels *in vivo* may explain a certain symptomatic benefit induced by zonisamide in PD, particularly when co-administered with L-DOPA.

One way of investigating the neuroprotective effects, i.e. the potential to protect the viability and function of diseased neurons, is to study the rescuing properties of a presumable protective agent in the presence of a neurotoxin. Protective effects of zonisamide have been tested against the dopaminergic neurodegeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice (Yano et al., 2009; Sonsalla et al., 2010). Zonisamide attenuated the deleterious effect on MPTP-induced depletion in DA, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the striatum and reduced the loss of TH positive neurons and the reactive astrogliosis in the striatum and substantia nigra (Yano et al., 2009).

Zonisamide has been shown to inhibit monoamine oxidase type B (MAO-B) (Okada et al., 1995; Murata, 2004), which is required to transform the pro-drug MPTP into its active toxic metabolite. A clinical trial demonstrated that zonisamide was effective even in PD patients who had been treated with the MAO-B inhibitor selegiline, suggesting that the MAO-B inhibitory effect of zonisamide may not be its only relevant mechanism (Murata et al., 2007).

Furthermore, recent experimental studies suggest that zonisamide protects against dopamine quinone formation induced by an excess amount of cytosolic DA outside the synaptic vesicles (Asanuma et al., 2008), which has been proposed to be a mechanism of toxicity for MPP^+ (Lotharius and O'Malley, 2000).

Additionally, neuroprotective effects of zonisamide have been demonstrated by an attenuation of neonatal hypoxic–ischemic damage in experimental animals (Hayakawa et al., 1994). It is also possible that zonisamide acts neuroprotective by scavenging free radicals such as hydroxyl or nitric oxide, thought to be extremely harmful for neuromembranes, and by inhibiting nitric oxide synthase activity (Mori et al., 1998; Noda et al., 1999). In an animal model of epilepsy, zonisamide reduced the formation of 8-hydroxy-2′-deoxyguanosine, a marker for oxidative damage of DNA (Komatsu et al., 2000).

However, the detailed molecular mechanisms of the neuroprotective properties of zonisamide remain unclear. Various hypotheses have been proposed, but the supporting data are not yet sufficient enough to draw a distinct conclusion.

Novel insights in the neuroprotective potential

In a study published recently in Experimental Neurology, Costa et al. (2010) reported the electrophysiological effects of zonisamide on rat corticostriatal slice preparations, focusing on striatal spiny neurons which are involved in diseases such as Parkinson's (PD) and Huntington's (HD). They stated a dose-dependent depression by zonisamide on a current-evoked repetitive firing discharge, by neither affecting the resting membrane potential nor the input resistance of striatal spiny neurons. By investigating the excitatory glutamatergic field potentials (FP) initiated by stimuli, they found an obvious decrease in the presence of 100 µM and 300 µM zonisamide. In further experiments Costa et al. (2010) studied the effect of zonisamide on the excitatory postsynaptic potential (EPSP) and detected a reduction of the amplitude in a dose-dependent manner. They inferred that pre- and postsynaptic sites of action are involved in the EPSP depression.

A very interesting part of the work of Costa et al. (2010) is the analysis of the effect of zonisamide on the FP amplitude after the activation of glutamatergic inputs, in the presence of an acute intoxication with rotenone and 3-nitropropionic acid (3-NP). Rotenone is known to inhibit the mitochondrial complex I (Santiago et al., 1995). Chronic treatment of rodents with rotenone results in nigrostriatal dopaminergic degeneration, formation of ubiquitin- and α-synuclein-positive nigral inclusions and motor deficits (Sherer et al., 2003) and is therefore considered as a model for PD. Costa et al. (2010) found zonisamide to be neuroprotective in concentrations ranging between 0.1 and 10 µM, because in these concentrations the FP amplitude could still be detected. Surprisingly, higher doses of zonisamide (100 µM) showed a detrimental effect, as they reduced the FP amplitude even stronger than rotenone. Overall zonisamide showed a bell-shaped dose–response curve, wherein the maximal effect could be found approximately at a concentration of 1 µM. The authors hypothesized that a neuroprotective mechanism of zonisamide against rotenone involves enhancement of GABA mediated inhibition via activation of $GABA_A$ receptors as they detect a blocking of neuroprotective action by the competitive $GABA_A$ antagonist bicuculline.

However, zonisamide failed to show neuroprotection against 3-NP (Costa et al., 2010), a known inhibitor of mitochondrial complex II