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Different Mechanisms Underlying the Antiepileptic and Antiparkinsonian Effects of Zonisamide

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1. Introduction

Zonisamide (ZNS, 3-sulfamoylmethyl-1,2-benzisoxazole) was developed by Dainippon Pharma (Osaka, Japan: currently Dainippon Sumitomo Pharma) and is currently used as an antiepileptic drug (AED) in Japan, South Korea, USA and Europe (Seino, 2004; Seino & Leppik, 2007). Indeed, the wide antiepileptic spectrum of ZNS has been established (Brodie, 2004; Karceski et al., 2005; Seino, 2004; Seino & Leppik, 2007; Willmore, 2004). Several clinical studies have also reported the wide clinical spectrum of ZNS against psychiatric and non-epileptic neurological disorders, including mood disorders (Ghaemi et al., 2008; Ghaemi et al., 2006; Kanba et al., 1994; McElroy et al., 2005), essential tremors (Bermejo, 2007), and its protective effects against ischemic cerebral damage (Willmore, 2004) and Parkinson’s disease (Murata, 2004; Murata et al., 2007). In Japan, ZNS was approved for Parkinson’s disease in 2009 by the Ministry of Health, Labor and Welfare. In this chapter, we review the dose-dependent effects of ZNS on neurotransmission and differences in the mechanisms underlying its antiepileptic and antiparkinsonian effects.

2. Antiepileptic mechanisms of ZNS

The major mechanism underlying the antiepileptic effects of ZNS (Rogawski & Porter, 1990) is inhibition of the voltage-gated Na⁺ channel (Rock et al., 1989; Schauf, 1987). However, subsequent pharmacological studies have demonstrated that the target molecules of ZNS include T-type voltage-sensitive Ca²⁺ channel (Kito et al., 1996; Suzuki et al., 1992), Ca²⁺ induced Ca²⁺ releasing system (CICR) (Yamamura et al., 2009b; Yoshida et al., 2005), carbonic anhydrase (Yamamura et al., 2009a), redox (Tokumaru et al., 2000; Ueda et al., 2005; Ueda et al., 2003), neuronal depolarization-induced glutamate release (Okada et al., 1998; Yoshida et al., 2005), enhancement of release of inhibitory neurotransmitters, e.g., GABA (Yoshida et al., 2005), dopamine and serotonin (Murakami et al., 2001; Okada et al., 1999; Okada et al., 1992; Okada et al., 1995) and lack of affinity to GABAₐ receptor (Rock et al., 1989).

With regard to its antiparkinsonian action, ZNS enhances both the turnover and release of dopamine, and inhibits MAO-B activity and dopaminergic oxidative stress (Asanuma et al.,...
While the typical dose of ZNS is 300 to 600 mg/day for patients with epilepsy (Seino et al., 1988), a significant improvement in motor symptoms is reported in patients of Parkinson’s disease treated with only 25 to 100 mg/day of ZNS (Murata, 2004; Murata et al., 2007).

**Table 1. Possible antiepileptic mechanism of ZNS**

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Table 1. Possible antiepileptic mechanism of ZNS
2.1 Effects of ZNS on ion channels

Preclinical studies suggested that ZNS inhibits the propagation of epileptic hyperexcitability through neuronal membrane stabilization and prevention of synchronization of firing (Macdonald, 2002; Rock et al., 1989; Rogawski & Porter, 1990; Schauf, 1987). Ample evidence indicates that the modulation of activities of several types of ion channels is the major mechanism of the antiepileptic effect of ZNS (Macdonald, 2002; Rogawski & Porter, 1990; Seino & Leppik, 2007).

2.1.1 Effects of ZNS on voltage-gated Na\(^+\) channel

The antiepileptic effects of ZNS on partial seizures are due to inhibition of voltage-gated Na\(^+\) channels. In in vitro electrophysiological studies, ZNS reduced sustained repetitive firing by inhibiting voltage-gated Na\(^+\) channels (Rock et al., 1989; Schauf, 1987). These inhibitory effects of ZNS probably increase the threshold of neuronal action potentials and lead a shift in the steady-state fast inactivation threshold of voltage-gated Na\(^+\) channels (Macdonald, 2002; Rogawski & Porter, 1990; Seino & Leppik, 2007). The inhibitory effects of ZNS on Na\(^+\) currents is probably induced by preferential binding to inactive voltage-gated Na\(^+\) channels that produces use- and voltage-dependent blockade and slows the rate of recovery from inactivation (Macdonald, 2002).

2.1.2 Effects of ZNS on voltage-sensitive Ca\(^{2+}\) channel

The role of voltage-sensitive Ca\(^{2+}\) channel in epilepsy is entirely consistent with its ability to orchestrate numerous neuronal events thought to be altered in seizures such as neurotransmitter release, dendritic physiology, gene expression and notably epileptic seizure-induced neuronal apoptosis (Zhang et al., 2000). ZNS inhibits high-threshold voltage-sensitive Ca\(^{2+}\) channel (L-type Ca\(^{2+}\) channel)(Kito et al., 1996; Rossier et al., 1996). ZNS also inhibits low-threshold voltage-sensitive Ca\(^{2+}\) channel (T-type Ca\(^{2+}\) channel) in a concentration-dependent manner (Kito et al., 1996; Rossier et al., 1996; Suzuki et al., 1992). The T-type Ca\(^{2+}\) channel is activated by small depolarization of the neuronal plasma membrane; and the resulting Ca\(^{2+}\) influx generates low threshold spikes that can trigger a burst of action potentials mediated by Na\(^+\) channels (Perez-Reyes, 2003). Therefore, antiepileptic actions of ZNS against childhood absence epilepsy and catastrophic childhood epilepsy are mediated through its inhibitory effects on T-type Ca\(^{2+}\) channel (Rogawski & Loscher, 2004a, b; White, 1999).

2.1.3 Effects of ZNS on CICR

The intraneuronal Ca\(^{2+}\) mobilization comprises both Ca\(^{2+}\) influx via voltage-sensitive Ca\(^{2+}\) channels and ligand-gated ion channels, as well as output from intracellular Ca\(^{2+}\) stores associated with the endoplasmic reticulum, namely the CICR, which is comprised of the ryanodine receptor (RyR) and inositol 1,4,5-trisphosphate receptor (IP3R) (Berridge, 1998). Several studies have indicated recently that functional abnormalities of CICR contribute to the rise in intraneuronal Ca\(^{2+}\) concentration associated with epileptic seizures (Matsumoto & Nagata, 1999; Matsumoto et al., 1996; Mori et al., 2005). Transient up-regulation of both c-Fos and RyR-3 gene expression was observed in the hippocampus of the kainate-induced epilepsy model (Mori et al., 2005). Antagonists of both RyR and IP3R had no effect on the induction or persistence of epileptiform discharges, but both types of antagonists prevent seizure-induced neuronal death (Pal et al., 2001; Pelletier et al., 1999). During resting stage,
ZNS activates IP3R but has no effect on RyR (Yamamura et al., 2009c; Yoshida et al., 2005). Contrary to the resting stage, during neuronal hyperexcitability, ZNS inhibits the activities of both IP3R and RyR (Yamamura et al., 2009c; Yoshida et al., 2005). These actions of ZNS are similar to other antiepileptic drug, topiramate (Okada et al., 2005).

2.2 Effects of ZNS on other neuromodulating systems

2.2.1 Effects of ZNS on the redox system

Current research associates free radical damage with epilepsy (Komatsu et al. 1995; Sudha et al. 2001), and the use of antioxidants early in the treatment of seizure-related neuronal injury is an attractive strategy, since epileptic seizures cause neuronal cell damage through the production of free radicals (Komatsu et al., 2000; Sudha et al., 2001). ZNS protects neurons against free-radical damage by scavenging the hydroxyl and nitric oxide radicals and such action is dose-dependent (Leppik, 2004; Mori et al., 1998; Noda et al., 1999). Especially, ZNS provides scavenging effects against cytosolic and plasma membrane-targeting free radicals in epileptogenic foci (Komatsu et al., 2000; Tokumaru et al., 2000; Ueda et al., 2005; Ueda et al., 2003). The radical scavenging properties operate in not only the ZNS-related antiepileptic activity but also its neuroprotective action against hypoxic/ischemic brain damage (Hayakawa et al., 1994; Owen et al., 1997).

2.2.2 Effects of ZNS on carbonic anhydrase

It was initially thought that the inhibitory effects of ZNS on carbonic anhydrase do not contribute to the antiepileptic action of ZNS, since the IC$_{50}$ value of ZNS is 188 times less potent than that of acetazolamide (Masuda & Karasawa, 1993). However, subsequent studies demonstrated that different affinities to carbonic anhydrase subtypes (Casini et al., 2003; Supuran, 2008). The Ki values for ZNS on cytosolic hCAII (35 nM), mitochondrial hCAV (20 nM) and plasma membrane binding hCAIX (5.1 nM) (Casini et al., 2003; Supuran, 2008) are lower than the therapeutic-relevant plasma concentrations of ZNS (Okada et al., 1999; Okada et al., 2003; Yamamura et al., 2009a). Activation of GABA$_A$ receptor opens its Cl$^-$ channel, which is permeable to both HCO$_3^-$ efflux and Cl$^-$ influx (Staley et al., 1995). Under physiological conditions, the hyperpolarizing action of the Cl$^-$ influx abolishes the depolarizing effect of HCO$_3^-$ efflux (Staley et al., 1995). In contrast to physiological conditions, continuous neuronal hyperactivation, e.g., epileptic seizure, results in an increase in intraneuronal Cl$^-$ concentration (Ge et al., 2006; Ge et al., 2007; Okada et al., 2003). A rise in Cl$^-$ concentration in the synaptic active zone stimulates GABA$_A$ receptor to produce depolarizing action (Ge et al., 2006; Ge et al., 2007). Inhibition of carbonic anhydrase reduces intraneuronal HCO$_3^-$ concentration with enhancement of Na$^+$-independent Cl$^-$/HCO$_3^-$ exchange (Leniger et al., 2004). Thus, ZNS prevents the epileptic hyperexcitability-induced conversion of GABA$_A$ receptor activity from inhibitory to excitatory activity (Yamamura et al., 2009a).

2.3 Effects of ZNS on neurotransmitter system

The generation of epileptic seizures could be due to a relative imbalance between excitatory and inhibitory neurotransmission, resulting in increased neuronal excitability and abnormally frequent patterns of discharge (Hirose et al., 2000; Okada et al., 2002). Glutamate is one of the main excitatory neurotransmitters, and excessive release of glutamate seems to precipitate seizures in epileptic patients and in animal models of epilepsy (Hirose et al.,
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2000; Okada et al., 2002). In contrast to glutamate, various other neurotransmitters, e.g., GABA, dopamine, serotonin and acetylcholine, are involve in the regulation of inhibitory transmission (Hirose et al., 2000; Okada et al., 2002; Okada et al., 2010).

2.3.1 Effects of ZNS on glutamatergic system

Both systemic administration of therapeutically-relevant dose and local perfusion of therapeutically-relevant concentration of ZNS reduced depolarization induced glutamate release in the hippocampus and frontal cortex (Okada et al., 1998; Yamamura et al., 2009a; Yamamura et al., 2009b; Yamamura et al., 2009c; Yoshida et al., 2005). It has been demonstrated that continuous stimulation induced by glutamate release has several components: (1) a Ca\(^{2+}\)-dependent initial rise, which is neuronal activity-independent, (2) this initial rise is followed by a series of Ca\(^{2+}\)-dependent phasic rises associated with neuronal activity, and (3) a small overflow of glutamate that persists in a Ca\(^{2+}\)-independent manner (Obrenovitch et al., 1993; Obrenovitch et al., 1996; Okada et al., 1998; Zilkha et al., 1995). Especially, the third component, which is Ca\(^{2+}\)-independent and neuronal activity-independent glutamate release, is probably spreading depression induced release (Okada et al., 1998). Therapeutically relevant concentrations of ZNS inhibit these three types of glutamate effects in the hippocampus (Okada et al., 1998).

2.3.2 Effects of ZNS on GABAergic system

ZNS has dual action against GABAergic transmission; enhancement of GABA release and protection against conversion GABA\(_A\) receptor activity from inhibitory to excitatory action. ZNS tends to enhance the inhibitory function of GABA\(_A\) receptor through interaction at allosteric or other binding sites (Mimaki et al., 1988) and GABAergic transmission via down-regulation of GABA transporter (Ueda et al., 2003). Inhibition of carbonic anhydrase reduces intraneuronal HCO\(_3^-\) concentration with enhancement of Na\(^+\)-independent Cl\(^-\)/HCO\(_3^-\) exchange (Leniger et al., 2004). Although there is no direct evidence that it activates GABA\(_A\) receptor-associated neuronal events, ZNS enhances the Cl\(^-\) currents associated with GABA\(_A\) receptor (Mimaki et al., 1988). These actions of ZNS are possibly modulated by inhibition of carbonic anhydrase activity similar to topiramate (Sills et al., 2000). Both systemic administration of therapeutically-relevant dose and local perfusion of therapeutically-relevant concentration of ZNS increased and decreased the basal and depolarization-induced releases of GABA in the hippocampus and frontal cortex, respectively (Okada et al., 1998; Yamamura et al., 2009a; Yamamura et al., 2009b; Yamamura et al., 2009c; Yoshida et al., 2005). Furthermore, the inhibitory interneurons release GABA (Hirose et al., 2000; Okada et al., 2002; Staley et al., 1995; Zhu et al., 2008).

2.3.3 Effects of ZNS on monoamine release

Systemic administration of ZNS affects monoamine release in the hippocampus, frontal cortex and striatum in a biphasic dose-dependent manner (Kawata et al., 1999; Murakami et al., 2001; Okada et al., 1999; Okada et al., 1992; Okada et al., 1995; Okada et al., 2002). At therapeutically-relevant dose, ZNS increases extracellular levels of monoamines, whereas ZNS at supra-therapeutic dose decreases monoamine release (Kawata et al., 1999; Murakami et al., 2001; Okada et al., 1999; Okada et al., 1992; Okada et al., 1995; Okada et al., 2002). Similar to its effect on the release of monoamines, both acute and chronic administration of therapeutically-relevant doses of ZNS enhance the turnover of dopamine and serotonin (i.e.,
monoamine synthesis) (Okada et al., 1999; Okada et al., 1992; Okada et al., 1995). In addition, ZNS inhibits monoamine oxidase activity. These stimulatory effects of ZNS on monoaminergic transmission, via enhancement of monoamine synthesis and release with inhibition of monoamine degradation, are observed after chronic administration (Okada et al., 1999; Okada et al., 1992; Okada et al., 1995).

### 3. Antiparkinsonian mechanisms of ZNS

In an open clinical trial of a combination of ZNS (50-200 mg/day) with antiparkinsonian drugs showed lessening of symptoms, wearing off of Parkinson’s disease, and more than 30% improvement of total score of the Unified Parkinson’s Disease Rating Score up to 3 years (Murata, 2004; Murata et al., 2001). The addition of ZNS to L-DOPA treatment in patients experiencing “wearing-off” fluctuations resulted in lessening of motor fluctuation and significant improvement of the duration, severity, and activities of daily living in “off” time and the score of motor examination. A more recent double blind controlled study from Japan demonstrated that the combination of lower than antiepileptically-relevant dose of ZNS (25-100 mg/day) and L-DOPA improved all cardinal symptoms of Parkinson’s disease (Murata et al., 2007). Based on these clinical evidences, ZNS was released for use in Japan in March 2009 as a novel antiparkinsonian agent.

In a series of studies, we have reported a dose-dependent biphasic action for ZNS on striatal dopaminergic system, e.g., ZNS at 25–50 mg/kg (i.p.) increased whereas at 100 mg/kg (i.p.) it decreased striatal dopamine release. However, ZNS at lower than antiepileptically-relevant dose of ZNS failed to modulate striatal dopaminergic transmission (Murakami et al., 2001; Okada et al., 1999; Okada et al., 1992; Okada et al., 1995; Yamamura et al., 2009b). These results suggest possible differences in the mechanisms of the antiepileptic and antiparkinsonian actions of ZNS. In this regard, the mechanism of the antiparkinsonian action of ZNS remains poorly understood.

Table 2. Possible antiparkinsonian mechanism of ZNS

<table>
<thead>
<tr>
<th>Ion channel blockade</th>
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<tr>
<td>Inhibition of T-type voltage-sensitive Ca²⁺ channel</td>
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<tr>
<td>Inhibition of dopamine-quinone formation</td>
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<tr>
<td>Enhancement of glutathione synthesis</td>
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<td>Enhancement of transmission in indirect pathway</td>
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3.1 Inhibition of dopamine quinone formation

Under normal conditions, dopamine is stable in the synaptic vesicle; however, administration of L-DOPA to patients with Parkinson’s disease damages the dopaminergic neuronal system (Sulzer et al., 2000). In patients with Parkinson’s disease treated with L-DOPA, a large amount of dopamine remains in the cytosol away from the synaptic vesicle, since the damaged dopaminergic system has only a small dopamine pool for storage (Asanuma et al., 2008; Asanuma et al., 2003; Ogawa et al., 2005; Sulzer et al., 2000).

Despite the beneficial effects of L-DOPA, the toxicity of excess L-DOPA and dopamine has been well documented in many in vitro and in vivo animal studies using parkinsonian models (Asanuma et al., 2008; Asanuma et al., 2003; Ogawa et al., 2005; Sulzer et al., 2000).
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Free excess dopamine is easily metabolized via type-B monoamine oxidase (MAO-B) or by auto-oxidation to produce cytotoxic reactive oxygen species (ROS), and then forms neuromelanin (Sulzer et al., 2000). In the oxidation of dopamine by MAO-B, dopamine is converted to DOPAC to generate general ROS hydrogen peroxide (Sulzer et al., 2000). Conversely, non-enzymatic and spontaneous auto-oxidation of L-DOPA and dopamine produces superoxide and reactive quinones, dopamine-quinone and DOPA-quinone, (Asanuma et al., 2003; Ogawa et al., 2005; Sulzer et al., 2000; Tse et al., 1976). The highly reactive dopamine-quinone or DOPA-quinone itself exerts predominant cytotoxicity in dopaminergic neurons and surrounding neurons, since these quinones are generated from free cytosolic dopamine away from the synaptic vesicle or from L-DOPA (Sulzer et al., 2000). ZNS prevents dopamine-quinone formation induced by excess amount of cytosolic dopamine outside the synaptic vesicles (Asanuma et al., 2008).

3.2 Enhancement of glial glutathione synthesis
Glutathione acts as an antioxidant against ROS–induced neurodegeneration. Astrocytes, but not neurons, express cystine/glutamate exchange transporter, which takes up cystine, reduces it to cysteine, and consequently supplies cysteine, the substrate for glutathione synthesis, in neurons. Glutathione synthesis in neurons is dependent on the expression of the cystine/glutamate exchange transporter on astrocytes (Shih et al., 2006; Wang & Cynader, 2000). Other studies demonstrated that glutathione and its synthesis-related molecules provide protection for astrocytes against age-dependent nigrostriatal dopaminergic neuro-degeneration (Chinta et al., 2007; Solano et al., 2008). ZNS markedly increased glutathione levels by enhancing the astroglial cystine/glutamate exchange transporter and astroglial proliferation via S100β production or secretion. ZNS acts as a neuroprotectant against oxidative stress and progressive dopaminergic neurodegeneration (Asanuma et al., 2010).

3.3 Enhancement of transmission striato-pallidal indirect pathway
Parkinson’s disease is characterized neuropathologically by a relative and selective loss of dopaminergic projection neurons within the substantia nigra pars compacta (SNc), and the formation of cytoplasmic inclusions within many surviving neurons (Gibb, 1991). The reduced population of dopaminergic neurons in SNc leads to the development of classical symptoms of Parkinson’s disease through functional abnormalities in striatal output pathways, which are composed of direct and indirect pathways (Hauber, 1998). In the rat brain, the direct pathway is composed of striatal GABAergic neurons, which project to the substantia nigra pars reticulata (SNr), a region under dopamine D1 receptor-mediated stimulatory regulation (Hauber, 1998). The indirect pathway comprises the striatal GABAergic neurons that project to the globus pallidus (GP) and are under dopamine D2 receptor-mediated inhibitory regulation, the pallidal GABAergic neurons that project to the nucleus subthalamicus (STN) and the subthalamic glutamatergic neurons that project to GP and SNr (Hauber, 1998). Indeed, depletion of dopaminergic transmission produces over-inhibition of pallido-subthalamic GABAergic and disinhibition of subthalamonigral glutamatergic projections in the indirect pathway (DeLong, 1990; Hauber, 1998). Enkephalin is colocalized and acts as cotransmitter with GABA in striatal neurons that project to GP; however, enkephalin reduces the GABAergic inhibition in the indirect pathway via
inhibition of GABA release (Maneuf et al., 1994). Based on these effects, the δ opioid receptor and its endogenous agonist enkephalin have been proposed as a suitable target in the symptomatic therapy of Parkinson’s disease (Hille et al., 2001; Maneuf et al., 1994). Local administration of antiepileptic-relevant concentrations of ZNS in the striatum increases dopamine release, whereas the use of antiparkinsonian-relevant concentration of ZNS does not affect striatal dopamine release (Yamamura et al., 2009b). Local administration of both antiparkinsonian- and antiepileptic-relevant concentrations of ZNS in the striatum reduces the extracellular levels of GABA in STN and glutamate in SNr, but decreases extracellular levels of GABA in GP without affecting their level in SNr (Yamamura et al., 2009b). These concentration-dependent effects of ZNS on extracellular neurotransmitter levels are independent of dopamine and δ2 receptors; however, blockade of δ1 receptor inhibited the effects of ZNS (Yamamura et al., 2009b). Activation of δ1 receptor enhances the effects of ZNS on neurotransmitter level. Based on these results, we suggest that ZNS does not affect the direct pathway but inhibits the δ1 receptor-mediated indirect pathway.

4. Conclusion

It has been well established that ZNS is the first line antiepileptic drug in the treatment of partial, absence and generalized epilepsies. In addition, ZNS is a potentially useful agent in the treatment of Parkinson’s disease. Its antiepileptic potential has been demonstrated in several clinical studies and meta-analysis studies; however, the antiparkinsonian potential has been demonstrated in only one randomized, placebo-controlled study.

The mechanisms of the antiepileptic action of ZNS have been investigated through various basic experiments, whereas the antiparkinsonian mechanisms remain to be clarified. Interestingly, the dose of ZNS used for the treatment of patients with Parkinson’s disease is lower than its therapeutic range against epilepsy. To our knowledge, the pharmacological profile within the antiparkinsonian dose has demonstrated only an increase in glutathione synthesis and enhancement of transmission through the indirect pathway. Enhancement of the indirect pathway is probably involved in the improvement of symptoms of Parkinson’s disease. In contrast, activation of glutathione synthesis prevents the progression of Parkinson’s disease rather than improves symptoms. Therefore, ZNS likely improves long-term prognosis. More information is required to clarify the effects of ZNS on long-term prognosis of patients with Parkinson’s disease (the long-term efficacy of ZNS). Based on clinical experience in the treatment of epilepsy for more than 20 years in Japan, ZNS is a relatively safe and well tolerated drug.

5. References


Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological evidence for an increasing prevalence of epilepsy throughout the world, and evidence of increasing morbidity and mortality in many countries as a consequence of higher incidence of infectious diseases, head injury and stroke. We decided to edit this book because we identified another way to approach this problem, covering aspects of the treatment of epilepsy based on the most recent technological results from developed countries, and the basic treatment of epilepsy at the primary care level in rural areas of South Africa. Therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis, as a leading cause of epilepsy in developing countries. Many experts from the field of epilepsy worked hard on this publication to provide valuable updated information about the treatment of epilepsy and other related problems.

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