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REVIEW

An Update on Stiripentol Mechanisms of Action: A Narrative Review

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ABSTRACT

Stiripentol (Diacomit®) (STP) is an orally active antiseizure medication (ASM) indicated as adjunctive therapy, for the treatment of seizures associated with Dravet syndrome (DS), a severe form of childhood epilepsy, in conjunction with clobazam and, in some regions valproic acid. Since the discovery of STP, several mechanisms of action (MoA) have been described that may explain its specific effect on seizures associated with DS. STP is mainly considered as a potentiator of gamma-aminobutyric acid (GABA) neurotransmission: (i) via uptake blockade, (ii) inhibition of degradation, but also (iii) as a positive allosteric modulator of $GABA_A$ receptors, especially those containing α3 and δ subunits. Blockade of voltage-gated sodium and T-type calcium channels, which is classically associated with anticonvulsant and neuroprotective properties, has also been demonstrated for STP. Finally, several studies indicate that STP could regulate glucose energy metabolism and inhibit lactate dehydrogenase. STP is also an inhibitor of several cytochrome P450 enzymes involved in the metabolism of other ASMs, contributing to boost their anticonvulsant efficacy as add-on therapy. These different MoAs involved in treatment of DS and recent data suggest a potential for STP to treat other neurological or non-neurological diseases.

Keywords: Stiripentol; Epilepsy; GABA; Ion channels; Metabolism; Lactate dehydrogenase; Cytochrome P450s

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Key Summary Points

Stiripentol (STP) is a potentiator of GABAergic transmission and inhibits voltage-gated sodium and calcium channels.

STP also modulates brain energy metabolism and lactate dehydrogenase.

A pharmacodynamic interaction exists between STP and benzodiazepines such as clobazam.

As a cytochrome P450 inhibitor, STP also potentiates other antiseizure medications via pharmacokinetic interactions.

In addition to its anticonvulsant effects in Dravet syndrome, STP may have other potential therapeutic indications.

INTRODUCTION

Stiripentol (STP), 4,4-dimethyl-1-[3,4-(methylenedioxy)phenyl]-1-penten-3-ol, is an α-ethylene alcohol first synthesized in the late 1970s [1]. As a result of the presence of a chiral center, STP has two enantiomers, *R*(+)-STP and *S*(−)-STP (Fig. 1); the racemate of these is used medically [2].

Early investigations showed anticonvulsant effects of STP in rodents and identified its first mechanisms of action (MoA) involving the gamma-aminobutyric acid (GABA)-ergic system [3]. The antiseizure properties of STP were confirmed in the alumina-induced epilepsy model in the monkey [4] and the first data suggesting its efficacy against epilepsy in humans were published shortly thereafter [5–7].

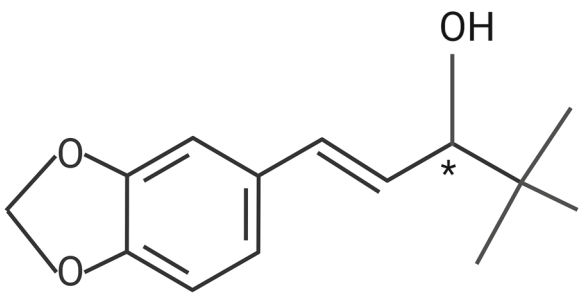

Fig. 1 Structural formula of stiripentol (molecular weight 234 g/mol) (the star indicates the stereogenic carbon, making the molecule chiral)

On the basis of its anticonvulsant properties in preclinical and clinical studies as well as pharmacokinetic and safety evaluation in healthy volunteers [8] and epileptic patients [9], STP was tested in a randomized clinical trial in humans, where it showed efficacy against seizures in Dravet syndrome (DS) [10, 11]. DS is a rare form of childhood epilepsy that develops in the first 20 months of life and is subsequently associated with significant comorbidities of intellectual disability (variable degrees but often severe) ataxia, circadian rhythm disorders, and autism-like social interaction deficits [12]. Noteworthy, DS is associated with a high risk of status epilepticus (SE)-associated mortality and sudden unexpected death in epilepsy (SUDEP) [13]. STP was first approved in the European Union (as Diacomit®) in 2007 for use in conjunction with clobazam and valproate, as adjunctive therapy of refractory tonic–clonic seizures in patients with DS [14]. It obtained a market authorization in the USA in combination with clobazam in 2018 with orphan drug status for treatment of DS [15]. From a clinical point of view, 30 years of real-world experience demonstrated the efficacy and safety of STP in reducing seizure frequency and abolishing SE in adulthood when patients were treated starting from 6 months of age [16, 17]. An international consensus of experts now recognizes STP as the second-line antiseizure medication (ASM) in DS [18, 19].

Earlier studies in the 1970s indicated that the MoA underlying the antiepileptic properties of STP involved the GABAergic system, the major inhibitory neuronal system in the mammalian central nervous system (CNS) [3]. Indeed, STP inhibits the synaptosomal reuptake of GABA as well as its degradation in glial cells by acting on GABA transaminase, both effects leading to a higher cerebral GABA concentration [3, 20]. At that time, interactions between STP and glucose metabolism were already suggested to underlie

its anticonvulsant effects [21]. Later, STP was shown to inhibit a variety of hepatic cytochrome P450 enzymes (CYPs), thereby affecting the metabolism of other drugs [22, 23].

The current review provides an update of the recent advances in knowledge concerning the MoAs of STP and addresses the relevance of effective concentrations from preclinical studies and their translation to human titration. Furthermore, on the basis of the analysis of its different MoAs, the potential clinical interest of STP in other diseases is discussed.

METHODS

This is a narrative review of the literature including the new data on the MoAs of STP based on relevant publications identified through an electronic search of PubMed (from 1978 to 2023). This article is therefore based on previously conducted studies and does not contain any new human or animal data.

STP POTENTIATES GABAERGIC TRANSMISSION VIA DIFFERENT MOAS

One of the characteristics of STP is its capacity to potentiate GABAergic transmission in different ways. GABA is the principal inhibitory neurotransmitter in the brain that is synthetized within GABAergic axon terminals, stored in synaptic vesicles, and released into the synapse upon depolarization, where it acts on specific receptors. Among those, the $GABA_A$-type receptors permit chloride entry into the postsynaptic neuron that leads to hyperpolarization of the cell membrane and therefore dampens its activity. GABA is then recaptured by the presynaptic neuron and astrocytes to be degraded or reused via the Krebs (or tricarboxylic acid) cycle (Fig. 2a). For a recent review on GABA and its role in epilepsy, the reader is referred to [24].

Increase of Brain GABA Levels

Two mechanisms have been identified to explain the increase of GABA cerebral levels observed following administration of STP: (i) inhibition of its reuptake by interacting with GABA transporters (GAT) and (ii) blockade of GABA transaminase (GABA-T), the main enzyme of GABA degradation (Fig. 2a) [3, 20]. GAT1 and GAT3 are the main GABA transporters expressed in the brain [24]. An ex vivo study found that STP does not interact with GAT1 in hippocampal neurons, suggesting the inhibition of another, unidentified, GAT subtype [25].

Potentiation of $GABA_A$ Receptors

$GABA_A$ receptors are heteropentamers in the majority of cases comprising two α, two β, and either one γ or a δ subunit [26, 27]. The subunits exhibit a high heterogeneity including α1–6, β1–3, γ1–3, δ, π, ε, θ, and ρ1–3 subunits (Fig. 2b) [26–28]. Structural studies have shown that GABA has two binding sites at α/β subunit extracellular interfaces, and benzodiazepines have a specific site at the α/γ extracellular interface [29–31]. A photolabelling competition study with other ligands showed that STP is likely to bind α/β, similar to barbiturates [32] and β/γ transmembrane domain, while nothing is shown about δ subunit binding (Fig. 2b) [33].

Quilichini and colleagues showed that STP enhances postsynaptic $GABA_A$ receptor-mediated transmission, by increasing the duration and the frequency of miniature GABAergic inhibitory postsynaptic currents (mIPSCs) [25]. STP prolonged the time of $GABA_A$ receptor activation in a concentration-dependent manner with a barbiturate-like mechanism and an absence of interaction with the BZDs or neurosteroid sites. To better understand the subunit selectivity of STP potentiation, an in vitro study in transfected HEK-293 T cells showed that STP increases $GABA_A$ receptor-mediated currents with a more prominent effect if the receptors contained an α3 subunit and to a lesser degree, α1/2/4/5/6 subunits [34]. Similarly, a higher

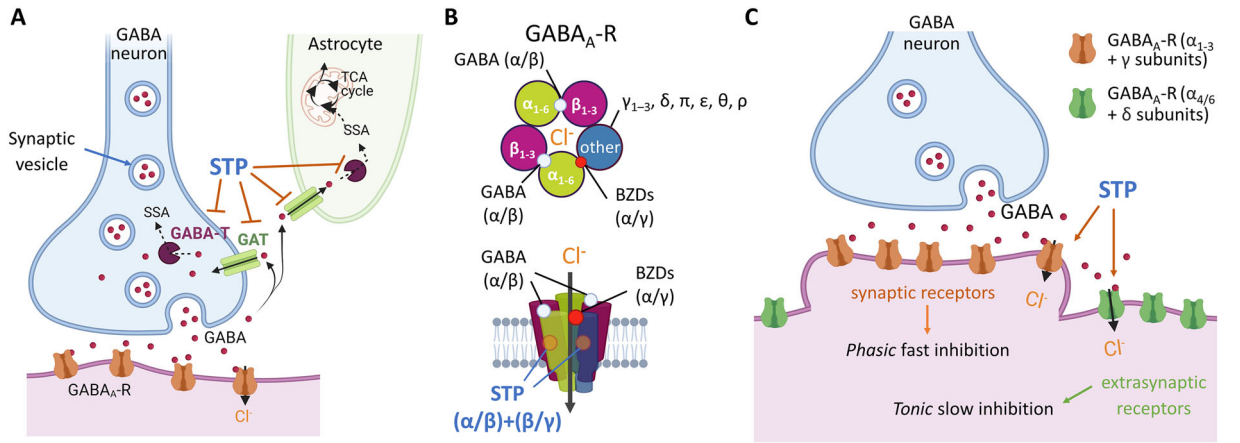

Fig. 2 Potentiation of GABA neurotransmission. **A** Representation of GABAergic transmission, where stiripentol (STP) inhibits GABA transaminase (GABA-T) and the GABA transporter (GAT). **B** $GABA_A$ receptor ($GABA_A$-R) is a heteropentamer (top), where GABA binds between α and β subunits, benzodiazepines (BZDs) between α and γ, and STP most likely binds α/β and β/γ transmembrane domains (bottom). **C** At the postsynaptic level, STP binds to $GABA_A$ receptor at synaptic and extrasynaptic localizations, leading to both phasic and tonic inhibitions. *SSA* succinic semialdehyde, *TCA* tricarboxylic acid

activity of STP at δ-containing $GABA_A$ receptors was also evidenced.

The brain distribution of $GABA_A$ receptors with distinct physiological roles is regionally specific and each subtype mediates different pharmacological properties. For example, receptors containing α1–3 subunits are localized in the synapse and mediate fast synaptic inhibition (termed phasic inhibition). In contrast, $GABA_A$ receptors containing α4–6 subunits are largely peri- and/or extrasynaptic and mediate a form of tonic inhibition through persistent activation by low concentrations of ambient extracellular GABA [35, 36]. Most γ-subunit-containing receptors are localized in the synapse while the δ subunit co-assembles predominantly with α4/α6 subunits to reside at peri- or extrasynaptic sites [35, 36]. Altogether, these studies suggest that the presence of GABA is necessary for the action of STP. Binding of STP to $GABA_A$ receptor locks the receptor into a conformation with much higher affinity for GABA. STP functions as a positive allosteric modulator of both synaptic (α1–3 and γ subunits) and extrasynaptic (α4/6 and δ subunits) $GABA_A$ receptors, suggesting that it could potentiate both *phasic* and *tonic* GABA-mediated inhibitory currents (Fig. 2c).

Critical Role of GABA in Dravet Syndrome

Dravet syndrome (DS) has a genetic etiology, with patients carrying a de novo loss-of-function pathogenic variant within *SCN1A* gene in over 80–85% of cases [11, 37]. *SCN1A* encodes a voltage-gated sodium channels α1 subunit ($Na_v1.1$), which is expressed in GABAergic inhibitory interneurons in the hippocampus and neocortex [38]. The $Na_v1.1$ haploinsufficiency in these interneurons contributes to a decrease in inhibition, which could lead to an overall excess excitability, ultimately leading to the generation of seizures [39]. Therefore, GABA enhancement by inhibition of reuptake, prevention of degradation, or increase in GABA receptor activity is a logical approach to control seizures. These potentiating effects of STP on the inhibitory GABAergic transmission contribute largely to its anticonvulsant profile and efficacy in the treatment of DS.

In addition, the recurrence of tonic–clonic seizures which can be prolonged or repeated, leading to SE particularly in the patient's first 5 years, is a critical feature of DS [11, 12, 19]. Although BZDs are the first-line therapy for the treatment of SE, they fail to stop SE in at least 30% of cases [40]. By whole-cell recording of

hippocampal slices from rats with prolonged SE and resistant to BZDs (pilocarpine model), Grosenbaugh et al. showed that STP potentiated GABAergic phasic IPSCs and tonic GABAergic current by acting at a different site from the BDZ binding one, thus confirming earlier findings [25, 41]. It is interesting to note that both IPSC potentiation and anticonvulsant activity of STP were greater in young animals compared to adults [41]. In addition, these same authors revealed that STP enhanced glutamate release as evidenced by an increase in the frequency of spontaneous miniature excitatory postsynaptic currents. This suggests that STP could affect both inhibitory and excitatory transmission.

Although acting on a different binding site, STP showed synergy with BZDs. Indeed, BZDs are positive allosteric modulators of $GABA_A$ receptor containing γ subunit but are inactive on receptors containing α4, α6, or δ subunits [42, 43]. While first studies showed some additive effects of STP and BZDs [25, 34], Fisher (2011) revealed that co-application of STP with different BZDs, including clobazam, produced a greater maximal enhancement of receptor activity than any of these agents on their own [44]. Together, these studies demonstrated that both STP and BZDs target separate sites of $GABA_A$ receptors leading to a potentiation of GABAergic currents [25, 34, 41, 44].

STP AND ION CHANNELS: ANTISEIZURE AND NEUROPROTECTIVE EFFECTS

Another MoA of STP involves ion channels and a potential for neuroprotective effects in the context of neuronal injury associated with seizures [45, 46]. Following traumatic brain injury, an important cell flux of Na^+ and Ca^{2+} via, in part, voltage-gated sodium and calcium channels, drives necrotic cell death and leads to long-term cell dysfunction in surviving cells [47, 48]. Using in vitro neuronal-glial cultures of rat cortex exposed to oxygen–glucose deprivation or high levels of glutamate, it was shown that the percentage of survival of neuronal tissue is significantly increased in the presence of STP [45].

STP exhibits only a weak binding affinity to *N*-methyl-D-aspartate (NMDA) receptors and no affinity for other glutamate receptors, suggesting that its neuroprotective effects are unlikely underlined by antagonism of glutamatergic transmission [45]. On the other hand, STP displayed a strong affinity for the voltage-gated sodium channel site 2 [49, 50], thus blocking sodium flux and reducing intracellular calcium levels in hippocampal neurons exposed to NMDA [45]. This suggests that the neuroprotective effects of STP would imply a reduction in calcium-induced neurotoxicity. Furthermore, STP could modulate Na^+ and Ca^{2+} flux probably by binding to channels whose type has not been identified yet.

This effect on voltage-gated sodium channels (VGSC) may seem paradoxical for the treatment of patients with DS which is, as mentioned above, mostly due to a loss of function of $Na_v1.1$ channel subtype. Yet, the type of VGSC targeted by STP has not been identified. It is known that $Na_v1.2$, $Na_v1.3$, and $Na_v1.6$ channel subtypes are found in abundance in excitatory neurons of the CNS and participate in the generation of both somatodendritic and axonal action potentials [51, 52]. For instance, a new epileptic encephalopathy caused by a de novo mutation in the *SCN8A* gene, which encodes $Na_v1.6$, has been described in patients with epilepsy [53, 54]. Theoretically, selective blockade of one of these sodium channel types (resulting in inhibition of glutamate release) could lead to a rebalance of excitatory/inhibitory transmission and contribute to seizure control.

In animal models of absence epilepsy, Riban et al. showed that STP could interact with T-type voltage-gated calcium channels ($Ca_v3.1$, $Ca_v3.2$, $Ca_v3.3$) [55]. Indeed, this type of voltage-gated calcium channel is strongly implicated in the thalamocortical oscillations that underly the expression of the spike-and-wave discharges that characterize absence seizures, an important feature of DS [56–58]. Using electrophysiological methods such as patch clamp recordings, this study showed an inhibitory effect of STP on the currents mediated by T-type voltage gated calcium channels [55].

STP REGULATES GLUCOSE ENERGY METABOLISM AND LACTATE DEHYDROGENASE

It is now increasingly recognized that impaired brain energy homeostasis in the brain plays a key role in the pathogenesis of epilepsy [59–61]. As a reminder, D-glucose and L-lactate are the main fuel that provide energy to most cells in the body and particularly in neurons and astrocytes [62]. It was shown that STP affects enzymes involved in glucose metabolism in the brain of rats treated with the convulsant pentylenetetrazol [21, 63]. In particular, STP reduced the activation of glucose–phosphatase dehydrogenase (G6PD) and thus avoided the excessive overconsumption of glucose in the brain of convulsing animals: STP exhibited "a neuro/glial glucose-sparing effect" (Fig. 3a). Furthermore, STP inhibits another neoglucogenesis enzyme, lactate dehydrogenase (LDH) which is highly activated during seizures [21]. In neurons and glial cells, LDH is responsible for the bidirectional conversion of pyruvate and lactate with concomitant interconversion of NADH and NAD^+ depending on the concentration gradient [64]. LDH is a tetramer composed of two different subunits A and/or B which can assemble into five different combinations termed LDH1 (also known as LDHB) to LDH5 (or LDHA) differentially expressed all over the body (e.g., heart, brain, muscle, liver, platelets) [65–67]. LDHs are part of the astrocyte-neuron lactate shuttle, a key metabolic pathway for energy supply [68] (Fig. 3a).

While the first studies did not identify which isoform of LDH was targeted by STP, an inhibitory effect of STP on LDH1 and LDH5 isoenzymes was described in vitro [69] (Fig. 3a). This report also showed the specificity of the effect of STP among 20 other anticonvulsant drugs. More recently, the effects of STP on the production of lactate associated with activation of LDHA observed in some tissue and cell dysfunctions was confirmed in glioblastoma models. Guyon et al. evidenced a reduction in lactate production potentially due to LDH inhibition, at STP effective concentrations [70]. In addition, in an angiogenesis cellular model, STP altered lactate/pyruvate pathway via its action on LDHs [71]. Likewise, in a rat model of cerebral ischemia, Dhir et al. found that STP reduced in vivo LDHA levels in the ischemic rat brain tissue [72].

Besides its role in regulating the homeostasis of lactate and pyruvate, LDHA is also a key enzyme responsible for converting glyoxylate to oxalate in the cytoplasm, the last step of oxalate metabolism in liver (Fig. 3b) [73]. The exposure of cultured hepatocytes (HepG2 cells) to STP resulted in a dose-dependent and significant decrease in oxalate production (Fig. 3b). The modulation of h-LDHA expression in HepG2 cells transfected with a siRNA targeting the LDHA human gene suggested the specific effect of STP on this isoenzyme [74]. Noteworthy, STP is now used as a reference substance in studies evaluating LDH inhibitors in cultured hepatocytes [75, 76].

ANCILLARY MECHANISM OF ACTION

A recent in vitro study has evidenced the increase in the enzymatic activity of protein-L-isoaspartyl methyltransferase (PIMT) in the presence of STP with a resulting neuroprotective effect [77]. Using biophysical techniques, the authors showed that STP can stabilize PIMT by binding close to the cofactor binding site, thus leading to increased enzymatic activity. PIMT is a repair enzyme which converts altered isoaspartyl residues to normal aspartyl ones. These altered residues induce fibrillation of peptides and proteins affecting intracellular pathways leading to cell dysfunction up to cell death. In the context of anti-NGF-induced neurotoxicity in PC12 cells or Aβ42-induced one in primary rat cortical neurons, this study showed that PIMT's neuroprotective effect, as measured by increased cell survival, is enhanced by STP.

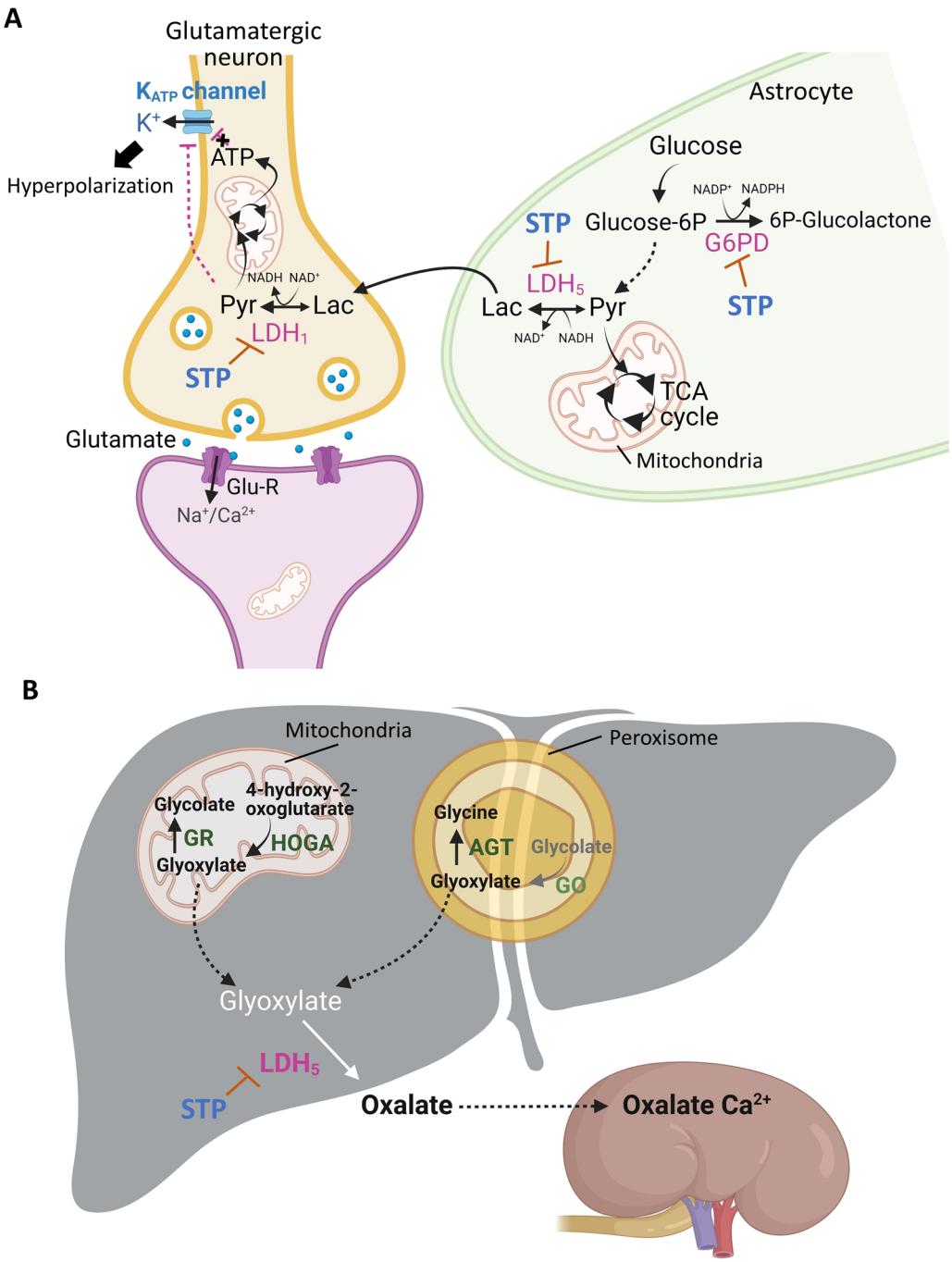

Fig. 3 Impact of stiripentol (STP) on brain metabolism and lactate dehydrogenase (LDH) in the brain (**A**) and liver (**B**). **A** Lactate shuttle from astrocyte to neurons, where STP inhibits G6PD and LDHs, leading to alteration in brain metabolism, and hyperpolarization of glutamatergic neurons via K_{ATP} channel activation. **B** STP inhibits LDH_5 in hepatocytes, leading to decreased oxalate production and to reduced oxalate-calcium accumulation in kidney. *AGT* alanine-glyoxylate aminotransferase, *ATP* adenosine triphosphate, *G6PD* glucose-6-phosphate dehydrogenase, *Glu-R* glutamate receptor, *GO* glycolate oxidase, *GR* glyoxylate reductase, *HOGA* 4-hydroxy-2-oxoglutarate aldolase, *Lac* lactate, *NAD* nicotinamide adenine dinucleotide, *NADP* nicotinamide adenine dinucleotide phosphate, *Pyr* pyruvate, *TCA* tricarboxylic acid

STP ALSO POTENTIATES THE EFFECT OF OTHER MEDICATIONS

In addition to the GABAergic system, STP has also indirect pharmacological effects through metabolic drug interactions. We will now describe these effects as they have relevant clinical consequences for patients treated with several medications.

Metabolic drug interactions are most often associated with adverse events. However, in some instances including STP in DS, they can also have therapeutic purposes. In addition to its pharmacodynamic effects in combination with other anticonvulsant drugs (clobazam, clonazepam, diazepam), STP inhibits the hepatic metabolism of other ASMs (Fig. 4). Consequently, the lower degradation of these antiseizure drugs leads to an increased bioavailability and stronger effects at their respective targets. Indeed, STP inhibits several CYP isoenzymes such as CYPs 1A2, 2C9, 2C19, 2D6, and 3A4 in vitro [23, 78] and CYPs 1A2 and 3A4 in vivo [23]. The inhibitory effects of STP on CYP3A4 and, more potently, on CYP2C19 are involved in the interactions between STP and clobazam and its active metabolite *N*-desmethylclobazam, as described in vitro and in vivo in patients with DS (Fig. 4) [79, 80]. Therefore, this metabolic interaction needs to be considered in the titration of both drugs in co-therapy. As a matter of fact, it is recommended to decrease the dosage of clobazam when STP is initiated, thus limiting the adverse effects associated with high clobazam plasma levels [14, 15].

Many other drugs are metabolized by CYP isoenzymes. In particular, sodium valproate (VPA), an often-prescribed ASM, is subject to oxidation/hydroxylation through CYP2C9 and CYP2C19 [81, 82]. Inhibition of these isoenzymes by STP is likely to increase VPA levels as suggested by a clinical study in patients with DS [83], although there is some debate on this

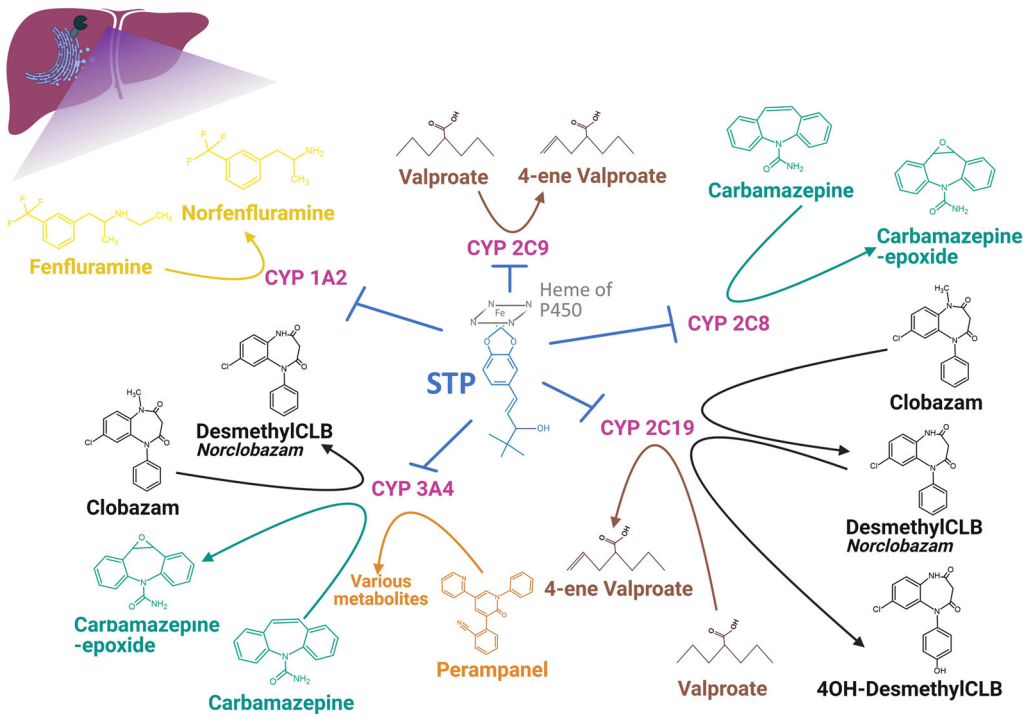

Fig. 4 Pharmacokinetic interactions of stiripentol (STP) with antiseizure medications. STP inhibits different cytochrome 450 (CYP) enzymes, by interaction with its heme (middle), leading to increased concentrations of other antiseizure medications

result [10]. The inhibitory effect of STP on the CYP2C8 and CYP3A4-dependent metabolism of carbamazepine (CBZ), another well-prescribed ASM, was also reported in human liver microsomes and in epileptic patients [23, 84–86]. Studies on epilepsy animal models showed greater anticonvulsant effects following combination of the two compounds, depending on the dose ratio of STP and CBZ used. Furthermore, the plasma and brain levels of CBZ were increased in the presence of STP, whatever the dose ratio of these two compounds [87]. This was confirmed by a clinical study where CBZ was co-administered with STP [88]. Fenfluramine is metabolized by CYP1A2, and to a lesser degree by CYP2C9 and CYP2C19 [89]. Its plasma level in healthy subjects increased when co-administered with STP [90]. Finally, a recent clinical study showed that the serum levels of perampanel increased with STP doses in epileptic patients including those with DS [91]. The inhibiting effect of STP on CYP 3A4, the main CYP isoenzyme involved in the perampanel metabolism, probably explains this effect [92].

The different MoAs for STP are summarized in Fig. 5.

DISCUSSION

Because STP has several impacts on the brain, as well as peripheral organs, we will now discuss their roles in the context of other neuropathologies or peripheral diseases.

Correlation Between Experimental Concentrations and Therapeutic Exposure

When measured in epileptic patients, total plasma STP concentrations of 4–25 μg/mL (corresponding to 17–106 μM) are found at effective doses around 50 mg/kg/day (Table 1). Noteworthy, STP serum concentrations are dependent of patient age and body weight [93, 94]. Globally, STP effective concentrations for the MoAs presented above (summarized in Table 2) are in the same order of magnitude as the blood concentrations in humans at therapeutic doses, particularly those related to actions at the GABAergic system (25–130 μM) and ionic channels (3–69 μM). However, the effective concentrations on the LDH target (42–500 μM) are globally higher than therapeutic concentrations while it is the converse with the CYPs target (0.3–100 μM). This conclusion should be nuanced if free (unbound) concentrations of STP are considered. Indeed, as 99% of STP is bound to plasma proteins, the free concentrations of STP in the brain or hepatic tissue range between 0.2 and 1 μM [95]. Although it is generally considered that only the free (unbound) drug transported into tissues is responsible for its pharmacological activity, it has been shown that some anti-inflammatory compounds and steroid hormones have much higher tissular than plasmatic concentrations, possibly because of their strong lipophilicity [96, 97]. This is similar for STP which exhibits lipophilic properties with an estimated partition coefficient ($\log P$) of 2.94 and is practically insoluble in water (49.2 mg/L) [98, 99]. The brain-to-plasma concentration ratio of STP in rat varied from approximately 0.5 to 1.2, i.e., around unity [41, 46, 100–102]. Therefore, concentrations of 17–106 μM are also achievable in the brain. In contrast, a liver/plasma ratio of 35 was measured 1 h after intravenous injection of STP in rats [103], thus impacting the degree of partition of STP between hepatocyte and plasma and increasing the concentration at the enzyme site (CYPs or LDH5) as compared with free plasma concentration.

Overall, when considering the different in vitro effective concentrations with the therapeutic levels in patients, one can rank the different direct MoAs according to a decreasing order of sensitivity: allosteric $GABA_A$ receptor potentiation > inhibition of ionic (Na^+ and Ca^{2+}) channels ≫ attenuation of energy metabolism or LDH activity. Indirect MoA can be applied in the case of polytherapy effects via CYP hepatic metabolism. Further studies are needed to delineate the respective part of each target underlying the pharmacological and therapeutic properties of STP, considering its different targets and different organs.

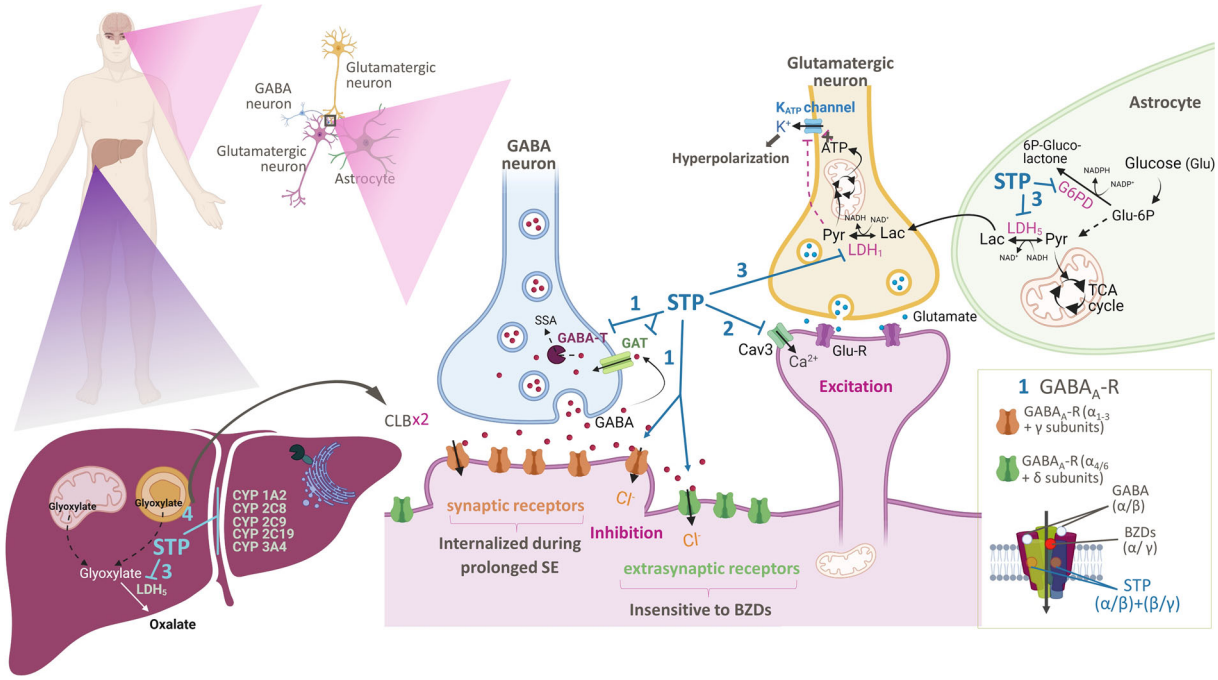

Fig. 5 Summary of the different mechanisms of action of stiripentol (STP) **1** STP is a potentiator of GABAergic transmission, by reducing GABA degradation (inhibition of GABA transaminase, GABA-T), inhibiting GABA transporter (GAT), and as a positive allosteric modulator of $GABA_A$ receptors ($GABA_A$-R). STP can target both synaptic and extrasynaptic receptors, likely by binding of transmembrane subunits (bottom right). **2** STP inhibits ion channels, such as postsynaptic T-type calcium channels: $Ca_v3.1$, 3.2, and 3.3. **3** STP can alter brain energy metabolism, by inhibiting glucose-6-phosphate dehydrogenase (G6PD) and lactate dehydrogenase (LDH), involved in lactate (Lac)-pyruvate (Pyr) shuttle. In the liver, STP also inhibits LDH_5 which is responsible for oxalate production. **4** STP makes pharmacokinetic interactions with concomitant antiseizure medications, such as clobazam (CLB), by inhibiting several cytochrome 450 (CYP) enzymes. *BZDs* benzodiazepines, *ATP* adenosine triphosphate, *NAD* nicotinamide adenine dinucleotide, *NADP* nicotinamide adenine dinucleotide phosphate, *TCA* tricarboxylic acid

Antiepileptic Activity of STP: DS and Beyond

As indicated above, the antiepileptic effect of STP is observed at tissue concentrations compatible with its various MoAs, apart from inhibition of LDH which requires higher concentrations. The usual association of STP with clobazam and/or valproate may target the imbalance between excitatory and inhibitory activities often associated with epileptic seizures [104, 105]. In particular, STP and CLB have additive activity on $GABA_A$ receptor because they bind to different sites, with subsequent synergistic effect against seizures [106, 107]. STP also increases plasma concentrations of clobazam and *N*-desmethylclobazam via inhibition of CYP enzymes. Hence, the pharmacokinetic interactions may also indirectly contribute to the antiseizure activity [79, 108].

Beyond the co-therapy with CLB which is known for its efficacy in DS, STP seems to also have independent benefits when administered alone [108, 109]. In preclinical studies, STP alone inhibits the different seizure types found in DS: febrile seizures [110–112], prolonged generalized clonic seizures [41, 46], and absence seizures [55]. It is important to note that the efficacy of STP against febrile seizures is higher in young animals [110]. This age-dependency could be explained by the higher sensitivity of STP towards α3 subunits of the $GABA_A$

Table 1 Comparison between the effective doses of STP and their corresponding total plasma concentrations in epileptic patients

Effective doses range (mg/kg/day)	Plasma concentration range, µg/mL [µM]	Diseases	References
≈ 37	5 [21]	Epileptic patients (non-DS)	[5]
34–78	4–22 [17–94]	Absence seizures in children	[7]
62–76	7–10 [29–42]	Epileptic patients (non-DS)	[6]
50	8–12 [34–51]	Patients with DS	[10]
80	6–16 [25–68]	Childhood partial epilepsy	[88]
50	4–25 [17–106]	Patients with DS	[145]

DS Dravet syndrome

receptors, that are highly expressed during brain development [113].

In patients with DS, STP was found to be effective in the prevention of SE [114]. Preclinical studies also indicate that STP alone can prevent SE in young animals [46], but can also terminate SE and BZD-resistant SE [41]. The selectivity of STP for α3 and δ subunits containing $GABA_A$ receptors could explain this effect. Indeed, the development of pharmacoresistance during SE appears to be partly due to a selective decrease in BZD-sensitive populations of $GABA_A$ receptors, sparing a population of receptors that is not modulated by these drugs [115]. It has been suggested that SE decreases surface expression of $GABA_A$ receptors containing γ2 subunits [116]. In contrast, other populations of $GABA_A$ receptors, such as those containing the α3, α4, and δ subunits, remain functional throughout SE [117]. Moreover, inhibition of $Ca_v3.2$ and $Ca_v3.3$ calcium channels, which are upregulated during prolonged SE in animal models [118, 119], can also contribute to STP efficacy against SE. These properties of STP likely support its therapeutic interest for the treatment of supra-refractory SE (SE ≥ 24 h) combined with other antiseizure drugs, as shown in recent studies [120–122]. In addition, Auvin and colleagues (2013) reported that STP reduced neuronal injury in the hippocampus due to prolonged SE in rats [46]. Neuroprotective effects were also demonstrated in an in vitro model of brain injury associated with seizures [45]. These biological properties of STP could involve blockade of sodium and calcium channels, without excluding its effects on the GABAergic system [45, 123, 124].

While the potentiation of GABAergic transmission aggravates absence seizures [125, 126], BZDs suppress them [127] as well as drugs acting as positive allosteric modulators via α2/3/5 subunit-containing $GABA_A$ receptors [128]. STP alone was found to decrease the number of absence seizures in two rat models. The impact of STP on T-type voltage gated calcium channels could also explain its anti-absence properties [55]. Interestingly, this anti-absence effect of STP was also found in a small cohort of patients suffering from atypical absence seizures [7].

While STP efficacy in DS and related seizures is now well recognized [18, 19, 114], other forms of epilepsy could benefit from STP therapy. An early randomized placebo-controlled trial showed a potential effect of STP in combination with carbamazepine (CBZ) in childhood partial epilepsy [88]. Pharmacokinetic interactions between STP and CBZ could explain this effect, while further studies are required to confirm this potential efficacy. Interestingly, a new clinical trial involving co-therapy of STP

Table 2 Summary of in vitro effective concentrations of STP on different targets

In vitro effective concentration (μM)	Targets	References
IC_{50} = 50	GABA transporter	[3]
30–100–300	$GABA_A$ receptor	[25]
EC_{50} = 35.5	$GABA_A$ (α1β3γ2) receptor	[34]
EC_{50} = 24.6	$GABA_A$ (α3β3γ2) receptor	[34]
100	$GABA_A$ (α3β3δ) receptor	[34]
EC_{50} = 45	$GABA_A$ current in young animals	[41]
EC_{50} = 102	$GABA_A$ current in adults	[41]
EC_{50} = 60/130	$GABA_A$ (α/β and β/γ transmembrane domain) receptor	[33]
3–10–300	VGSC/VGCC	[45]
IC_{50} = 69	$Ca_v3.1$	[55]
IC_{50} = 64	$Ca_v3.2$	[55]
IC_{50} = 37	$Ca_v3.3$	[55]
500	LDHA/B	[69]
42–427	Oxalate synthesis (LDHA)	[74]
500	Lactate production (LDHA/B)	[70]
K_i between 7 and 140	CYP 1A2/2C9/2C19/3A4/2D6	[23]
IC_{50} = 5.11	CYP3A4 (CBZ to CBZE)	[85]
IC_{50} = 37.1	CYP2C8 (CBZ to CBZE)	[85]
IC_{50} = 1.6	CYP3A4 (CLB to NCLB)	[79]
IC_{50} = 3.2	CYP2C19 (CLB to NCLB)	[79]
IC_{50} = 0.27	CYP2C19 (NCLB to 4HNLCB)	[79]

VGSC voltage gated sodium channels, *VGCC* voltage gated calcium channels

and CBZ in focal epilepsy is ongoing (https://clinicaltrials.gov/study/NCT05419180).

Concerning STP inhibition of brain metabolism and LDHs enzymes, it is important to consider that they are observed at higher concentrations than the other MoAs. It is now recognized that excessive neuronal discharges require adequate energy sources and their depletion in astrocytes is associated with seizure termination [59, 60]. The importance of the metabolic pathway in the control of seizures has been recently illustrated by the increase of LDHA expression in the hippocampus in a model of mesial temporal lobe epilepsy in the mouse [129]. Although the use of metabolic targets to treat epilepsy is a matter of debate [130, 131], another recent study using a metabolomic analysis in a DS mouse model demonstrated that this disease can be associated with complex alterations in glucose and tricarboxylic acid cycle metabolism underlying a greater seizure susceptibility [132]. While inhibition of LDH was described as a cause of seizure cessation in rodent models [69], high concentrations (500 μM) of STP were needed, suggesting that other MoAs were involved in its in vivo antiepileptic effects.

Use of STP Beyond Seizures?

Beyond the antiseizure effects described above, inhibition of LDH offers interesting perspectives in the treatment of other pathologies. We present here two disorders on which a significant amount of data has been published that suggests a possible therapeutic role of STP: primary hyperoxaluria and glioblastoma.

Primary hyperoxaluria is a rare and severe genetic disease where increases in glyoxylate and oxalate hepatic production induce renal failure with consequent morbidity and mortality [133]. Studies have shown that LDH5 was involved in the last step of oxalate production [73]. Preclinical data and first clinical observations have demonstrated the efficacy of STP for the treatment of this disease [74]. These preliminary results motivated the initiation of clinical studies. In the case of primary hyperoxaluria, the site of action of STP is the liver, where its concentrations reach the high levels needed to inhibit LDH [103].

Another pathology linked to LDH is glioblastoma, a severe form of brain cancer with dramatic outcomes [70]. It has been shown that cancer cells take up glucose and transform it into lactate even under aerobic conditions known as the Warburg effect [65, 66]. Critical to its highly glycolytic phenotype is LDHA, which catalyzes the last step of glycolysis. In many types of spontaneous cancers, an elevated activity of LDHA, and to a lesser degree LDHB, is observed as compared to normal tissues [134–138]. Three independent preclinical studies have shown that STP reduces lactate production with a subsequent decrease in glioblastoma invasion and growth in vitro and in vivo in mice [70, 139, 140]. A few years earlier, Bonuccelli et al. (2017) had revealed the efficacy of STP in reducing the activity and the propagation of cancer stem-like cells in an in vitro approach [141]. Additional studies will be needed to evaluate the potential of STP for clinical benefit in patients with glioblastoma and possibly other cancers.

Because of its effects on glucose energy metabolism and lactate dehydrogenase, efficacy of STP was found in other models of diseases including cerebral ischemia [71, 142], Alzheimer's disease [77], neuropathic pain [143], and Lyme disease and *Borrelia burgdorferi* infection [144]. These studies remain exploratory and, to our knowledge, are not yet supported by clinical data.

CONCLUSION

Several different targets including the GABAergic system, ion channels, and, at higher tissue levels, LDH enzyme were identified for STP. The relevant correlation between in vitro and in vivo preclinical studies and clinical data obtained in patients with DS confirms that the GABAergic system and ion channels represent critical MoAs of STP in this form of epilepsy. On the basis of the multitarget action of STP, investigations have been recently pursued in other animal models of epilepsy and comorbidities such as sudden unexpected death in epilepsy, suggesting additional potential therapeutic effects of STP. Deciphering these mechanisms could not only identify potential new therapeutic applications but also consolidate the use of STP for DS. Patients affected by rare diseases currently poorly treated may also benefit from the introduction of STP-based innovative treatments combined or not with other drugs. STP's multimodal MoAs are not mutually exclusive, but rather act synergistically in its antiseizure and non-seizure effects providing to this compound a strong therapeutic potential.

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Declarations

Conflict of Interest. Alexandre Bacq, Vincent Castagné, Marie-Emmanuelle Le Guern and Marc Verleye are or were Biocodex members. Antoine Depaulis is a scientific advisor for Biocodex. Elaine C Wirrell has received reimbursement for serving on Data Safety and Monitoring Boards for Amicus, Acadia, Neurocrine, Longboard and GRIN.

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