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Review Article

Epilepsy and brain tumors: Two sides of the same coin

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ABSTRACT

Epilepsy is the most common symptom in patients with brain tumors. The shared genetic, molecular, and cellular mechanisms between tumorigenesis and epileptogenesis represent 'two sides of the same coin'. These include augmented neuronal excitatory transmission, impaired inhibitory transmission, genetic mutations in the *BRAF*, *IDH*, and *PIK3CA* genes, inflammation, hemodynamic impairments, and astrocyte dysfunction, which are still largely unknown. Low-grade developmental brain tumors are those most commonly associated with epilepsy.

Given this strict relationship, drugs able to target both seizures and tumors would be of extreme clinical usefulness. In this regard, anti-seizure medications (ASMs) are optimal candidates as they have well-characterized effects and safety profiles, do not increase the risk of developing cancer, and already offer well-defined seizure control. The most important ASMs showing preclinical and clinical efficacy are brivaracetam, lacosamide, perampanel, and especially valproic acid and levetiracetam. However, the data quality is low or limited to preclinical studies, and results are sometimes conflicting. Future trials with a prospective, randomized, and controlled design accounting for different prognostic factors will help clarify the role of these ASMs and the clinical setting in which they might be used.

In conclusion, brain tumor-related epilepsies are clear examples of how close, multidisciplinary collaborations among investigators with different expertise are warranted for pursuing scientific knowledge and, more importantly, for the well-being of patients needing targeted and effective therapies.

1. Introduction

The relationship between brain tumors and epilepsy has been known since the 19th century. [1]. Indeed, epilepsy is the most common symptom in patients with brain tumors. Regardless of the anatomical site of the lesion and tumor histological type, the incidence of epilepsy in brain tumors varies from 35% to 70%. Brain tumor-related epilepsies (BTREs) constitute 12% of acquired epilepsy and 4–10% of all cases of epilepsy [2,3]. The underlying mechanisms sustaining tumorigenesis and epileptogenesis are still to be fully elucidated. Given this strict relationship, drugs targeting both conditions (i.e., seizures and tumor growth and progression) would be extremely useful in clinical practice [4,5]. In this framework, anti-seizure medications (ASMs) appear to be interesting candidates. They have well-known pharmacological properties, can cross the blood–brain barrier, are already used for seizure control, and might also boast antineoplastic activity [5,6].

Thus, we conducted a literature search to review the shared mechanisms of epileptogenesis-oncogenesis and the possible antineoplastic role of ASMs. A roundtable discussion with a multidisciplinary approach was organized among the authors. The author panel comprised neurologists, neuropathologists, pharmacologists, epileptologists, and biologists with proven and recognized expertise in the field of tumoral

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epilepsy. Before the event, participants reviewed the available literature using the PubMed database as the primary source on their assigned topic. No specific term was used for the search. Their findings were presented at the time of the discussion. After the presentations, an open session enabled full discussion. The present manuscript was drafted according to the data presented during the roundtable and subsequent discussions.

2. Mechanisms underlying epilepsy in brain tumors

Epileptogenesis is a dynamic, chronic, and multifactorial process that describes the development and extension of tissue capable of generating spontaneous seizures, resulting in the development of an epileptic condition and/or its progression after it is established [7]. The incidence of brain tumors in patients with epilepsy ranges from 4% to 10%, depending on the studies [2,3]. Indeed, epileptogenesis can be sustained by any brain tumor; low-grade developmental brain tumors are most commonly associated with epilepsy [3,6,8,9]. Shared genetic, molecular, and cellular mechanisms between tumorigenesis and epileptogenesis probably underlie the relationship between these two conditions (Fig. 1). The processes by which tumors reshape the neuronal milieu towards increased activity are still largely unknown; however, recent studies are starting to shed light on several possible mechanisms.

2.1. Neuronal activity

2.1.1. Augmented excitatory transmission

Increases in neuronal activity have an important role in the proliferation and progression of glioblastoma (GBM), as synaptic and electrical integration into neural circuits promotes glioma progression (Fig. 1B). Communication between glioma and neurons is possible through neuroglioma synapses capable of inducing postsynaptic

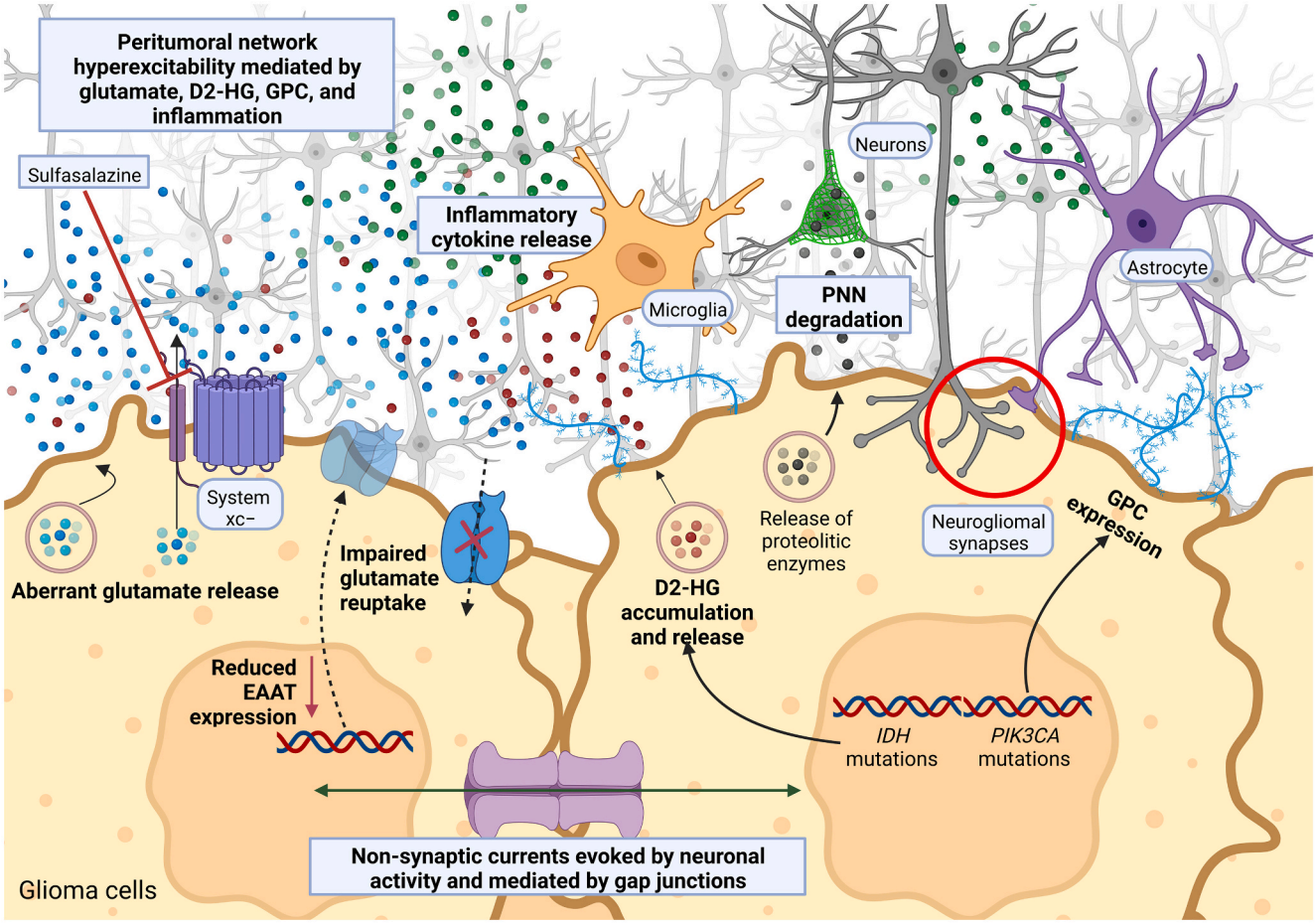

Fig. 1. Common features of peritumoral neural network hyperexcitability and tumor progression.
(A) Pathological changes in brain tumor microenvironments support hyperexcitability and epileptic discharges in nearby neurons through several mechanisms. Cancerous cells are responsible for aberrant glutamate release, also due to dysfunction in the system x_c^- (blocked by sulfasalazine). This mechanism, coupled with disrupted functionality and reduced expressions of glutamate transporters – which hinder glutamate reabsorption – causes a glutamate-rich tumor microenvironment. Such mechanism is further exacerbated in the case of *IDH*-mutated tumors, resulting in the release of D2-HG, which is able to activate ionotropic GluRs. On the other end, *PIK3CA*-mutated tumors are able to induce glypican members secretion, which drives both gliomagenesis and hyperexcitability. Cancer cells also release proteolytic enzymes, which cause perineural network degradation. Microglia and astrocytes are also able to mediate hyperexcitability through the release of proinflammatory cytokines. Finally, the tumor's post-synaptic currents mediated by neurogliomal synapses promote glioma survival and progression. These currents further spread through gap junctions expressed by tumor cells.
(B) Simplified close-up of a neurogliomal synapsis. Glutamate- and D2-HG-activated AMPA and NMDA receptors induce postsynaptic currents in cancer cells, driving tumor growth and invasion. The impaired glutamate reuptake and reduced glutamate transporters in astrocytes further exacerbate this mechanism. D2-HG is also able to upregulate the mTOR pathway sustaining epileptic activity in certain circumstances. Perampanel, a non-competitive AMPAR inhibitor, is able to reduce the AMPA-mediated hyperexcitability in both neurons and cancer cells.
D2-HG, d-2-hydroxyglutarate. AMPARs, AMPA receptors. EAAT, excitatory amino acid transporter. GPC, glypican. NMDARs, NMDA receptor. PER, perampanel. PNN, perineural network.

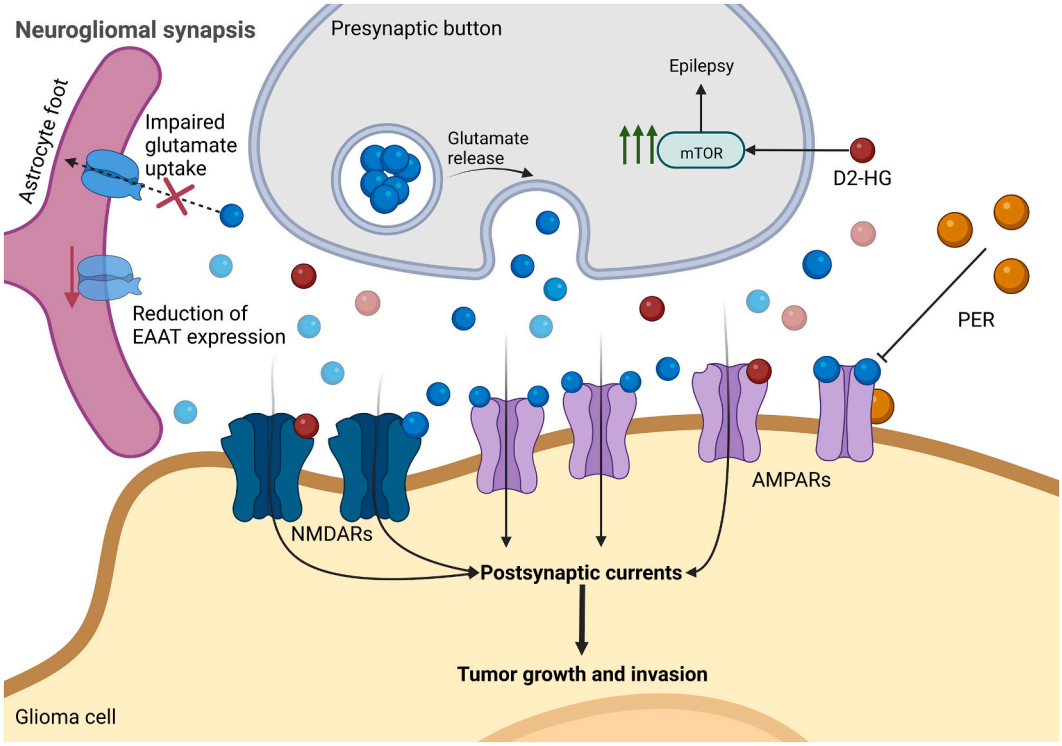

Fig. 1. (*continued*).

currents that are mediated by glutamate receptors (GluRs) of the AMPA subtype [10,11]. In this regard, AMPA antagonists, such as perampanel (PER), can reduce tumor growth and invasion [10,12]. Indeed, aberrant glutamate release from gliomas induces hyperexcitability in peritumoral networks. This release is mediated by a deficit in sodium-dependent glutamate uptake, a reduction in the glial glutamate transporter, and, most importantly, the system x_c^-, i.e., the cystine–glutamate antiporter, which exchanges extracellular cystine for intracellular glutamate. Sulfasalazine, a blocker of the system x_c^-, reduces spontaneous and evoked activity, thus showing promising anti-tumor and anti-epileptic effects [13,14] (Fig. 1A). The neuronal activity also evokes non-synaptic activity-dependent potassium currents, amplified by gap junction-mediated tumor interconnections forming an electrically coupled network (Fig. 1A). Neuronal activity, including epileptic conditions, generates synchronized calcium transients in glioma networks. Activity-regulated release of growth factors also promotes glioma growth [10,11].

2.1.2. *Impaired inhibitory transmission*

Besides augmented excitatory transmission, network hyperexcitability can result from impaired neuronal inhibition. This impaired neuronal inhibition might result in depolarizing, rather than hyperpolarizing, GABAergic activity sustained by perturbed chloride homeostasis due to changes in the expression of neuronal chloride K—Cl cotransporter 2 and Na-K-2Cl cotransporter 1 [15,16]. Another recently proposed mechanism is the loss and reduced activity of peritumoral inhibitory interneurons due to the degradation of perineuronal nets by tumor-released proteolytic enzymes [17].

2.2. *Genetic mutations*

Particular genetic traits may also sustain brain tumors and epilepsy.

2.2.1. *BRAF*

The *BRAF* gene has been shown to possess both tumor- and epilepsy-inducing features. In murine models, the $BRAF^{V600E}$ somatic mutation arising in progenitor cells during early brain development results in the acquisition of intrinsic epileptogenic properties in neuronal lineage cells and tumorigenic properties in glial lineage cells. $BRAF^{V600E}$ stimulates the expression of the RE1-silencing transcription factor, known to contribute to epileptogenesis by repressing a subset of genes coding for ion channels, receptors, and other crucial contributors to neuronal function [18,19]. Another study confirmed that $BRAF^{V600E}$ expression in neural progenitors results in a highly excitable neuronal phenotype and increased inflammatory immune response [20].

2.2.2. *Isocitrate dehydrogenase*

Mutations of the isocitrate dehydrogenase 1 (*IDH1*) and 2 (*IDH2*) genes are often found in astrocytoma, oligodendrogliomas, and GBMs [21]. In *IDH*-mutant gliomas, PI3K/AKT/mTOR signaling activity is associated with shorter progression-free survival (PFS) [22]. *IDH* mutations are associated with a higher preoperative seizure incidence [23] and a more severe phenotype of postoperative epilepsy [24]. These mutations result in the tumors' intermediate D-2-hydroxyglutarate (D2-HG) accumulation [25–27] (Fig. 1A). D2-HG is structurally similar to glutamate and is known to mimic its activity by activating GluRs, particularly *N*-methyl-D-aspartate (NMDA) receptors. D2-HG can disrupt intracellular calcium homeostasis, inhibit the mitochondrial respiratory chain, elicit the generation of reactive oxygen species, and increase the firing rate of cultured neurons, resulting in excitotoxic cell damage and neurodegeneration [28,29]. Moreover, recent data suggest that the mTOR pathway hyperactivation by D2-HG is a potential mechanism of epileptogenesis in patients with *IDH*-mutated gliomas [30], although it must remember that this singalling pathway can trigger opposing actions (i.e., neuroprotective and antiepileptogenic vs epileptogenic) on neuronal death and epileptogenesis under different conditions [31,32].

2.2.3. *PIK3CA*

PIK3CA mutations are common in GBMs as well. Tumors driven by these variants have divergent molecular properties resulting in two typical features of epileptogenesis: selective initiation of brain hyperexcitability and remodeling of the synaptic constituency. These changes

may be driven by secreted members of the glypican (GPC) family, selectively expressed in *PIK3CA*-positive tumors. In particular, within the GPC family, GPC3 has been found to drive gliomagenesis and hyperexcitability [33,34].

2.3. Astrocyte features

Despite being less investigated than neurons, astrocyte cells can become malignant and sustain epilepsy [35]. Typical astrocytes' functions are impaired in epileptic and tumoral settings. Namely, there is a loss of appropriate potassium homeostasis, accompanying changes in aquaporin, gap-junction expression and function, compromised uptake and metabolism of glutamate in astrocytes, and disrupted neurotransmitter supply, particularly in inhibitory neurons [35,36]. In addition to being potentially linked with gliosis, these biochemical changes have significant functional consequences, contributing to the circuit hyperexcitability that is the hallmark of epilepsy [36]. In astrocytic brain tumors, adenosine kinase (ADK) is upregulated in peritumoral infiltrated tissue. It is known that overexpression of ADK decreases extracellular adenosine and consequently leads to seizures. Indeed, expression of ADK in the peritumoral infiltrated tissue is significantly higher in patients with epilepsy than in patients without epilepsy [8,9]. Another mechanism relates to the seizure-related increase in reactive oxygen species and iron levels, which induce antioxidant and iron-binding capacity in astrocytes. However, astrocytes develop a pro-inflammatory phenotype upon chronic exposure. This pro-inflammatory phenotype potentially contributes to the above-cited pro-epileptogenic inflammatory processes [35,37,38].

2.4. Other factors

2.4.1. Inflammation

Inflammation also plays a role in the pathophysiology of BTRE. There is a prominent activation of both the innate and adaptive immune systems in glioneural tumors [39–41]. Astrocyte- and microglia-mediated inflammation can promote epileptogenesis and seizure recurrence, and the ensuing seizures reciprocally perpetuate neuroinflammation, especially when the endogenous resolution mechanisms fail [35,42,43]. Proinflammatory cytokines (such as IL-1β and HMGB1) and chemokines (such as CCL2) possess neuromodulatory properties; upon overproduction, they can induce peritumoral network hyperexcitability, reducing seizure threshold by modifying the function of both voltage-gated (Na^+, K^+, Ca^{2+}) and receptor-coupled ion channels (NMDA, AMPA, and GABA receptors) [35,42–45] (Fig. 1A).

2.4.2. Hemodynamics

Gliomas also impair functional hemodynamics. In glioma-infiltrated cortical regions, the neurovascular coupling becomes progressively disrupted. While seizures exhibit positive neurovascular coupling in the non-infiltrated cortex, glioma-infiltrated regions exhibit disrupted hemodynamic responses driving seizure-evoked hypoxia [46].

3. The antiproliferative action of anti-seizure medications

Malignant gliomas are extremely difficult to treat both surgically and pharmacologically. New therapies are urgently needed. However, developing novel compounds through to clinical application is highly time- and money-consuming, especially in a neurooncological setting where molecules must also be designed to be blood-brain barrier permeable [4]. A wide variety of drugs clinically used to treat non-cancerous diseases interferes with dysregulated pre-existing physiological pathways that regulate cell growth, cell death, or cell migration and cause malignant transformation. We can facilitate and accelerate the discovery of new cancer treatments through drug repurposing. Repurposed drugs have the key advantages of already being approved for clinical use, being mostly inexpensive, and having well-characterized effects and safety profiles [4]. In this perspective, ASMs are optimal candidates to be investigated, considering that they do not increase the risk of developing cancer in humans [5].

3.1. Preclinical data

3.1.1. Valproic acid

Han et al. [47] investigated the autophagic and apoptotic effects on human U251 and SNB19 cells of valproic acid (VPA), a widely used ASM. The study showed that VPA could inhibit the viability of U251 and SNB19 glioma cells in a time-and dose-dependent manner, as well as induce apoptosis through the mitochondria-dependent pathway. Moreover, VPA promoted cellular apoptosis via the activation of the Akt/mTOR pathway by decreasing their protein phosphorylation. The addition of MHY1485, an mTOR agonist that causes a strong elevation of mTOR activity, partially reduced the apoptosis ratio, suggesting that the autophagy of VPA is involved in regulating apoptosis. These findings suggest that VPA can enhance apoptosis in gliomas by promoting Akt/mTOR-induced autophagy, which could be further evaluated as an interesting therapy for these tumors [47,48]. However, as the mTOR pathway may have opposing effects on mechanisms of neuronal death and epileptogenesis, the use of mTOR-modulating drugs as potential anticancer and antiepileptogenic agents warrants further studies, as there could be circumstances in which such treatment could worsen or ameliorate neurological status, depending on the situation [31,32].

3.1.2. Levetiracetam

O(6)-methylguanine-DNA methyltransferase (MGMT) is a DNA repair protein that has an important role in tumor cell resistance. Among different ASMs with diverse MGMT regulatory actions, levetiracetam (LEV) is the most potent MGMT inhibitor [49]. LEV decreases MGMT protein and mRNA expression levels by recruiting the mSin3A/histone deacetylase 1 (HDAC1) corepressor complex, which eventually enhances p53 binding to the MGMT promoter. When the expression of mSin3A, HDAC1 or p53 is abrogated, LEV can not exert MGMT inhibition. Finally, LEV inhibites the proliferation of malignant glioma cells and increases cell sensitivity to temozolomide (TMZ), a chemotherapy agent used to treat GBM [49]. These data appear to be both in contrast [50,51] or in agreement [52] with clinical data, as discussed below.

3.1.3. Perampanel

There are some interesting new data on PER and its possible antineoplastic activity. In an in vitro study by Lange et al. [12], four ASMs with different mechanisms of action (LEV, valproic acid, carbamazepine, and PER) were tested on GBM cell lines and brain metastases cell lines derived from patients. Of the four ASMs, only PER showed systematic inhibitory effects on cell proliferation at rather low concentrations (10–30 μM), with metastatic cells being much more resistant to PER than GBM cell lines. PER was also able to reduce glucose uptake in all GBM cells. A high extracellular glutamate level was found in GBM cell lines, which was reduced by PER exposure. Despite this, apoptotic cell death was not induced [12]. Differently from Lange's results, Salmaggi et al. [53] found that treatment with 250 μM PER (or even as low as 100 μM in some cell lines) produced a marked increase in apoptosis in an in vitro study on the effect of PER and TMZ in human glioma cell lines. This discrepancy might be due to differences in the cell lines and methods used to detect apoptosis. Such PER pro-apoptotic effect is possibly due to the increased GluA2 and GluA3 expression. Indeed, the overexpression of calcium impermeable AMPARs subunit, such as GluA2, inhibits glioma cell motility and induces apoptosis [54]. Moreover, a strong synergistic effect between PER and TMZ was detected. Despite this evidence, in an in vivo study with a murine glioma model, PER was effective in abolishing tumor-associated epileptic events but did not affect tumor progression when used in combination with radiochemotherapy [55]. In the above-cited, well-designed experiment on glioma integration into the neural circuits; however, the use of PER

resulted in an approximately 50% decrease in pediatric glioma proliferation in PER-treated mice compared with vehicle-treated controls [11]. Thus, PER is an interesting molecule for brain tumors and BTRE, but more studies are needed to clarify its effects, especially regarding its possible antineoplastic activity.

3.1.4. Brivaracetam and lacosamide

The cytotoxic effect of brivaracetam and lacosamide was also tested in vitro on U87MG, SW1783, and T98G human glioma cell lines [56]. The authors found anti-migratory effects and dose-dependent cytotoxicity, although the latter was unrelated to apoptosis. Lacosamide and brivaracetam induced the modulation of several miRNAs, especially miR-195-5p and miR-107, with the former affecting the cell cycle and the latter inhibiting cell migration. Furthermore, lacosamide and brivaracetam did not modulate the expression of the chemoresistance-related molecules MRPs1–3-5, GSTπ, and P-gp. These results suggest that these molecules possess antineoplastic activity on glioma cells, and patients might benefit from treatment with brivaracetam and lacosamide in addition to standard therapeutic options [56].

3.2. Clinical data

Preliminary observations on the possible influence of ASMs on tumor outcomes date back to 2005 [57] and have been followed by other observational studies [58–60]. A combined analysis of the survival association of ASM use at the start of chemoradiotherapy with TMZ was performed in a pooled cohort of 1869 patients from four different RCTs in newly diagnosed GBMs [61]. PFS and overall survival (OS) were compared between [39] any VPA use, and no VPA use at baseline or [40] VPA use both at the beginning and after chemoradiotherapy. The authors concluded that using VPA or LEV for reasons other than seizure control in patients with newly diagnosed GBM outside clinical trials is not justifiable [61]. However, this result appears to be in contrast with other more recent investigations [50–52,62–67], as highlighted in Table 1.

3.2.1. Valproic acid

An interesting study was conducted using the Taiwan National Health Insurance Research database over 15 years and included 2379 patients with high-grade gliomas. The study investigated whether using VPA in patients under TMZ would lead to a better OS. A Cox proportional hazard regression revealed that the VPA group had a longer mean OS than the non-VPA group, with the most significant difference in patients aged between 18 and 40 years [65].

In 2015, Krauze and colleagues conducted a phase II study of concurrent radiation therapy, TMZ, and VPA in 37 patients with GBM, with interesting albeit results. The addition of VPA to standard radiation + TMZ therapy resulted in a 1-year OS rate of 86% and a 6-month PFS rate of 70% [64]. More recently, they compared the same set of patients with the modern-era standard of care data from the RTOG 0525 trial and general population data from the SEER database trial [63]. The authors concluded that the previously reported improvements in PFS and OS with the addition of VPA to concurrent radiotherapy and TMZ in their phase II study [64] were confirmed compared with both the trial population receiving standard care and the contemporary SEER cohort. Moreover, their results warranted further consideration of VPA for analysis in a phase III trial in patients with glioblastoma [63].

3.2.2. Levetiracetam

A retrospective study that collected data from 359 glioma patients treated with TMZ plus an ASM investigated whether the use of VPA correlates with tumor grade, histological progression, PFS, and OS in grade II, III, and IV glioma patients [67]. Interestingly, VPA was associated with improved survival in a dose-dependent manner. However, conversely, in grade II and III gliomas, VPA was linked to histological progression and reduced PFS, suggesting a possible differential effect of

Table 1
Overview of some studies investigating the possible antineoplastic activity of anti-seizure medications.

Study	Type of study	Aim	Study treatments	ASM antineoplastic activity
[64]	Prospective, open-label, phase II study	To evaluate the addition of VPA to standard RT and TMZ in patients with newly diagnosed GBM	VPA (+ TMZ, RT)	Yes
[61]	Pooled analysis	To explore the prognostic significance of ASMs in patients enrolled in clinical trials for newly diagnosed GBM	VPA, LEV	No
[67]	Retrospective comparative cohort study	To investigate whether the use of VPA correlates with tumor grade, histological progression, PFS, and OS in grade II, III, and IV glioma patients	VPA (+ TMZ, surgery) Patients under other ASMs used as a control group	Yes, in grade IV gliomas. No and detrimental effect in grade II–III gliomas
[51]	Retrospective, single-center, cohort study	To determine the most appropriate therapeutic measures by survival analysis to elucidate the effects of ASMs in patients with GBM	VPA, LEV, carbamazepine, gabapentin, lamotrigine, oxcarbazepine, pregabalin, topiramate, and phenytoin/fosphenitoyn (+ TMZ, RT, surgery)	No, only for LEV in patients with methylated MGMT promoter
[63]	Retrospective comparative cohort study	To compare outcomes of their previous study [64] with modern era standard of care data and general population data	VPA (+ TMZ, RT)	Yes
[65]	Retrospective population-based cohort study	To investigate whether using VPA in patients with high-grade gliomas under TMZ would lead to a better OS	VPA (+ TMZ)	Yes
[50]	Retrospective, single-center, cohort study	To assess whether LEV affects the survival of patients with *IDH* wild-type GBM treated with concurrent TMZ	LEV (+ TMZ, RT, and surgery combined) Patients under other ASMs used as a control group	Yes
[62]	Retrospective, single-center, cohort study + meta-analysis	To investigate the associations of different ASMs with OS and PFS in GBM patients	LEV, VPA, other ASMs (+ TMZ, RT, surgery)	No, only for LEV
[52]	Systematic review and meta-analysis	To quantify LEV's effect on GBM survival and characterize its safety profile to determine whether incorporating LEV into the standard of care is warranted	LEV (+ surgery)	No, only for female patients or patients with a low rate of MGMT methylation
[66]	Retrospective, single-center, cohort study	To investigate whether the duration of LEV use during the standard chemoradiation protocol affects the OS of patients with *IDH* wild-type GBM	LEV (+ standard chemoradiation protocol)	Yes

ASM, anti-seizure medication. GBM, glioblastoma. IDH, isocitrate dehydrogenase. LEV, levetiracetam. MGMT, O(6)-methylguanine-DNA methyltransferase. OS, overall survival. PFS, progression-free survival. RT, radiation therapy. TMZ, temozolomide. VPA, valproic acid.

VPA in low- and high-grade glioma patients [67]. A recent retrospective cohort study examined 418 patients treated with surgery, radiotherapy, and chemotherapy with TMZ [51]. Out of the nine ASM groups, only LEV treatment exhibited a statistically significant difference in OS in the group with a methylated MGMT promoter but not in the unmethylated MGMT promoter group, suggesting that LEV administration may prolong the survival period in GBM patients with methylated MGMT promoters undergoing TMZ chemotherapy [51]. Another retrospective study investigated whether LEV treatment affected the survival of 322 patients with surgically resected and pathologically confirmed *IDH* wild-type GBM who received TMZ-based chemoradiotherapy [50]. The multivariate analysis showed that age, complete tumor resection, MGMT promoter methylation, and LEV use were significantly associated with OS, thus supporting the use of LEV in this setting [50]. These results were confirmed by a recent meta-analysis that included 5614 patients from eight studies [62]. Outcome benefits for OS and PFS with LEV were confirmed. The authors concluded that perioperative treatment with LEV might improve the prognosis of GBM patients and recommended a prospective randomized controlled trial addressing the efficacy of LEV in GBM treatment [62]. A meta-analysis published in early 2022, including this and other studies accounting for 5804 patients with GBM, found that LEV administration did not significantly improve survival in the entire patient population, although significance was nearly reached ($p = 0.094$) [52]. Meta-regression analysis determined that LEV treatment efficacy decreased with greater proportions of MGMT methylation (and increased with greater proportions in female patients), suggesting that LEV treatment might not be effective for all patients with GBM and that LEV might instead be better suited to treat specific molecular profiles of GBM [52].

The fact that Ryu et al. and Roh et al. found that LEV improved OS in MGMT-methylated gliomas [50,51] is in contrast with the preclinical results by Bobstuc and colleague [49] and with the meta-analysis by Chen et al. [52]. In this perspective, there is an urgent need to clarify whether MGMT methylation in gliomas could be a prognostic factor for the use of LEV not only as an ASM but also as an antineoplastic agent [49,51,52].

More recently, Pallud and coworkers [66] reported longer survival in *IDH1* wild-type GBM patients receiving LEV for the entire duration of radiotherapy and chemotherapy compared with patients without LEV treatment or with shorter LEV treatment, suggesting that *IDH1* status might also be associated with a possible antitumor effect of LEV [66].

3.2.3. Perampanel

Clinical studies investigating the use of PER treatment in BTRE are not numerous and have only addressed its efficacy as an add-on therapy for glioma-associated seizures [68–74]. Therefore, clinical data on PER antineoplastic activity are scarce. Of these trials, the PERADET study [68] is the largest and the only multicentric prospective study. Thirty-six patients were treated with PER as an add-on ASM with a 12-month follow-up period. PER was shown to be efficacious by significantly reducing seizures. Besides seizure control, the PERADET study also compared subgroup stratification by oncological disease-related factors. Both patients with *IDH1* mutated and patients with MGMT methylated seemed to respond better to PER treatment [68]. The *IDH1*-mutated condition seemed to positively affect the frequency of seizures. Indeed, *IDH1*-mutated patients obtained a reduction in the mean number of seizures from 11.4 ± 12.3 to 5.9 ± 8.8 ($p = 0.02$), while IDH non-mutated patients decreased from 11.0 ± 19.3 to 1.0 ± 1.2 ($p = 0.13$). The MGMT methylated patients also significantly reduced seizures ($p = 0.04$ for both ITT and PP populations). Regarding disease progression, both groups (25 patients without tumor progression during follow-up and 11 patients with tumor progression) significantly reduced seizures at the final follow-up. Moreover, patients without a disease progression had a more significant seizure reduction than those with a disease progression ($p = 0.01$). Unfortunately, only a few patients underwent tumor molecular analysis; therefore, these data must be interpreted cautiously [68]. Indeed, these findings contrast with an observational pilot study, which did not find significant differences in the *IDH1*-mutated vs wild-type groups and the MGMT with or without promoter methylation groups [72]. However, another study found that most patients with decreased seizure activity had *IDH1*-mutant tumors, consistent with results from the PERADET study [69].

3.2.4. Summary and future agenda

In conclusion, the repurposing of drugs – including but not limited to ASMs – to achieve better outcomes in the treatment of high-grade glioma is a research avenue estimated to receive increasing attention and commitment from the clinical and scientific community over the coming years [4]. The quality of data regarding ASM use in oncological practice in the above-cited studies is low. Future study design should include prospective evaluation, separate analysis of patients undergoing protracted ASM therapy in two different scenarios (absence of seizures versus BTRE), and consider the major challenge of achieving effective drug concentrations at the target level. Solid statistical design is of paramount relevance to obtaining meaningful conclusions. Network analysis should be considered over multivariate analysis of strongly interrelated prognostic factors such as age, the magnitude of tumor removal, concurrent medications, and especially tumor grade and/or specific tumor molecular profile.

4. Conclusion

The strict relationship between epilepsy and brain tumors is sustained by several factors, including augmented neuronal excitatory transmission, impaired inhibitory transmission, genetic mutations in the *BRAF*, *IDH* and *PIK3CA* genes, inflammation, hemodynamic impairments, astrocyte dysfunction, and more, which altogether represent "two faces of the same coin". Several drugs approved for treating non-cancerous diseases are known to act on these dysregulated mechanisms; therefore, they represent a possible already available treatment that could be repurposed to tackle both seizures and tumor growth and progression. Within repurposable drugs, ASMs are optimal candidates because they have well-characterized effects and safety profiles, do not increase the risk of developing cancer, and already offer well-defined seizure control. Yet, preclinical and clinical data are preliminary, as the pathogenetic mechanisms of brain tumors and BTREs still need to be fully elucidated. Brivaracetam, lacosamide, PER, and especially VPA and LEV are the most interesting ASMs with a possible antineoplastic activity; still, data quality is low or limited to preclinical studies, especially for the formers. However, despite data uncertainty, clinicians should pay particular attention to the ASM choice according to seizure and tumor characteristics, such as location, grade, molecular profile, etc., as ASM features vary greatly and may be able to influence oncological – and thus epileptic – progression. Future trials with a prospective, randomized, controlled design accounting for different prognostic factors – tumor grade and/or specific tumor molecular profile primarily – and confronting different ASMs will help clarify the role of these medications and the clinical setting in which they might be used.

In conclusion, BTRE is a clear example of how close, multidisciplinary collaborations between investigators and clinicians of different expertise are warranted not only for the pursuit of scientific knowledge (i.e., explaining underlying pathological mechanisms and drug efficacy) but, more importantly, for the well-being of patients in need of personalized, targeted, and effective therapies.

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Authors' contributions

Conceptualization: MM; formal analysis: all authors; writing -

original draft: FP; writing - review and editing: all authors. All authors gave their approval to submit.

Declaration of Competing Interest

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