CHAPTER

7

The therapeutic and neuroprotective effects of an antiepileptic drug valproic acid in glioma patients

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Abstract

Glioma is the most common primary malignant brain tumor in adults and the patients have poor prognosis despite treatment with surgery, radiotherapy and chemotherapy. The antiepileptic drug, valproic acid (VPA) as a HDAC inhibitors is often used in glioma patients even if the patients don't have brain tumors associated epilepsy (BAE). Some previous studies have found that VPA not only has anti-epileptic effect, but also has anti-glioma growth effect through enhance radiotherapy sensitivity or other mechanism. Then VPA is reported to improve the survival of glioma patients receiving chemoradiation therapy. In addition, there are limited researches have shown that VPA has a neuroprotective effect in protect normal cells and tissues from the deleterious effects of treatment of glioma, especially radiotherapy. We'll give a brief overview of these effects of VPA in glioma patients.

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1 Introduction

Brain tumors, also known as intracranial tumors, including primary tumors derived from various intracranial tissues, such as brain tissue, meninges, etc., and secondary tumors invading the brain caused by malignant tumors of the lung, breast, digestive tract, kidney, etc. Cerebral glioma is one of the most common primary brain tumors, taking about 30% of primary tumors of the central nervous system and accounting for about 80% of the primary malignancies of the central nervous system. Glioma is also one of the most lethal human cancers and the patients have poor prognosis and difficult treatment. The median survival time of the most maliment glioma patient, glioblastoma (GBM), was at best still only 12 to 15 months despite current positive treatment with surgery, irradiation, and chemotherapy (Wen and Kesari, 2008). Although there are many new treatment methods for gliomas, including traditional Chinese medicine (Zhang et al., 2020a,b), but development of effective therapy still requires lot of efforts for the benefit of patients (Sharma et al., 2020).

Most glioma patients have symptoms of central nervous system dysfunction, such as headache, nausea, vomiting, language disorders, limb muscle weakness, ataxia, cranial nerve palsy. Epilepsy is also a common and import symptom. Epilepsy is often caused by abnormal discharge of brain neurons and they have the characteristics of sudden occurrence and repeated attacks. According to its etiology, it can be divided into primary epilepsy and secondary epilepsy. Epilepsy caused by intracranial tumors, craniocerebral trauma, cerebrovascular disease, and intracranial infections is called secondary epilepsy. The relationship between brain tumors and secondary epilepsy has already attracted the attention of physicians in the 18th century because of epilepsy is often the first symptom of brain tumors patients, especially when the lession in the functional area of the front or temporal lobe. Modern epidemiology shows that 30–40% of glioma patients initially presented with seizures (Beaumont and Whittle, 2000; Berendsen et al., 2016), and children reach 50% (Yamamoto et al., 2014). This kind of secondary epilepsy is called brain tumors associated epilepsy (BAE) which refers to the abnormal discharge of nerve cells around the focus caused by the intracranial tumor itself or its occupying effect. It can be clinically manifested as disturbance of consciousness level, limb activity, limb sensation, autonomic nerve function, etc. Therefore, it has a far-reaching impact on the patients themselves and their families. The development of epilepsy aggravates the condition, affects the patient's prognosis, and even threatens the patient's life. Therefore, the prevention of seizures in patients with brain tumors including glioma has important clinical significance. Thus, anti-epileptic drugs (AEDs) is often used to prevent seizures and brain damage in the treatment for BAE patients (Van Breemen et al., 2012). But according to the current research, it is still controversial whether AEDs should be used prophylactically in patients who have been diagnosed as brain tumors without epilepsy (Bar-Klein et al., 2014; Kong et al., 2015; Vecht and van Breemen, 2006).

Valproic acid (VPA) is a frequently used AEDs in brain toumor patients due to its effectiveness and relatively low toxicity profile. And neurosurgeons are widely used it to prevent seizures during perioperative operations. Over the years, many studies of VPA have further discovered that in addition to anti-epileptic, it also has anti-tumor, enhance radiotherapy and neuroprotection effects. This review will address several therapeutic and neuroprotective effects of VPA in glioma patients.

2 The mechanism of neuronal damage in epilepsy

According to Choi's (Choi, 1992) theory, the mechanism of neuronal damage in epilepsy is mainly refers to the ability of glutamate or related excitatory amino acids to mediate the death of central neurons under certain conditions. The combination of an excitatory amino acids and its receptor plays a decisive role in the development of epilepsy. When glutamate is released and postsynaptic excitatory effect is strengthened, then the neuronal damage is major caused by two mechanisms: (1) permeability damage: which is the early rapid excitatory toxic effect. After epilepsy attack, neuronal membrane continued to depolarize, and Na^+ flowed in a large amount through the ion channels gated by AMPA and kainate receptors, which was driven by Cl^- electric potential energy to enter the cells, so a large amount of water flowed in, resulting in acute swelling of neurons; (2) Ca^{2+} overload injury: This is a delayed injury related to a large amount of Ca^{2+} internal flow. Glutamate activates NMDA receptors, which leads to a large amount of Ca^{2+} influx, and triggers intracellular biochemical cascade reaction leading to delayed neuronal death. On average, the Ca^{2+} related injury triggered by NMDA receptors is more rapidly than the damage triggered by AMPA or kainate receptor activation. Riffault et al.(Riffault et al., 2018) describe novel insights about the brain-derived neurotrophic factor (BDNF) namely proBDNF, which ultimately led to increased seizure susceptibility. They found increased proBDNF/p75NTR signaling during development maintains a depolarizing gamma-aminobutyric acid (GABA) response in a KCC2-dependent manner in mature neuronal cells. This study shed a new light about how proBDNF/p75NTR signaling can orchestrate the GABA excitatory developmental sequence leading to depolarizing and excitatory actions of GABA in adulthood epileptic disorders.

Therefore, AEDs play an anti-epileptic role through the control of Na^+ flow, stable neuronal membrane potential and inhibits the activation of glutamate or GABA. Conventional AEDs can block the Na^+ channel of voltage-dependent nerve cells, thus reducing synaptic transmission, and affect the two inside and outside of nerve cells through Na^+-K^+-ATPase. However, if there is a certain imbalance between the role of AEDs and BAE, then epilepsy can not be controlled.

However, the pathophysiologic mechanisms of BAE are poorly understood including theories of altered peritumoral amino acids, regional metabolism, pH, neuronal or glial enzyme and protein expression, as well as immunologic activity. Schaller et al. (Schaller and Ruegg, 2003) showed BAE may also involve changes in regional metabolism, such as changes in pH value, changes in glial enzymes, glutamatergic NMDA receptor activation and other factors. Conventional AEDs are relatively poor in regulating these factors, so they can not control BAE very well.

In addition, the drug interaction between AEDs and chemotherapy drugs or other anti-tumor drugs could affects the blood concentration of AEDs and the pharmacokinetics of AEDs, and further affects the drug intake, drug metabolism or drug clearance, which makes AEDs unable to control BAE better. Finally, because of the continuous progress of the tumor, it may also increase the frequency of BAE. Further studies are needed to elucidate more clearly the mechanisms of BAE and to identify the optimal AEDs.

3 The applications of VPA in BAE patients

VPA is a commonly used AEDs, which has the advantages of easy penetration of the blood-brain barrier and no obvious inhibitory effect on the central nervous system. According to clinical medical research (Ni et al., 2018), patients with brain tumors use intravenous infusion to inject VPA into the body, which can quickly inhibit abnormal discharge of the cerebral cortex, and have a good epilepsy prevention effect. The BAE patient's various signs were normal though the monitored by electroencephalogram, electrocardiogram blood pressure and blood drug concentration, etc. A very few patients will experience mild drowsiness, but it will relieved within 24 h, and the malignancy after medication, anorexia, vomiting and other symptoms are reversible too. Therefore, VPA as a preventive drug for epilepsy caused by brain tumors, has the properties of safety and effectiveness. The application of VPA in the early postoperative period can avoid the occurrence of epilepsy to the greatest extent, and also can reduce the persistent symptoms of epilepsy making patients can return to health as soon as possible. Therefore, most physicians believe that the prevention and intervention of BAE is very effective and necessary. VPA has the following advantages (Farrelly et al., 2013): (1) It is easy to penetrate the blood-brain barrier; (2) It can not only inhibit aminobutyrate converting enzyme but also activate glutamate dehydrogenase, resulting in the increase of the inhibitory neurotransmitter aminobutyrate converting enzyme in the brain plays an antiepileptic effect; (3) the blood concentration of the drug has no inhibitory effect on the central nervous system; (4) Adverse reactions such as nausea, vomiting, anorexia and abdominal pain are reversible and VPA do not need to be stopped. The use of VPA to prevent seizures in patients with brain tumors during the perioperative period can significantly reduce the incidence of epilepsy, and provide better safety for clinical widely used.

4 VPA can improve the prognosis of glioma patients

VPA as a AEDs frequently used in glioma patients due to its effectiveness and relatively low toxicity profile (Chateauvieux et al., 2010; Vecht et al., 2014). In addition to the anti-epileptic effect, many studies have found that it can extend the survival time of glioma patients. Kerkhof et al.(Kerkhof et al., 2013) performed a survival analysis on 165 GBM patients receiving CRT with TMZ after surgery and

found that patients using VPA for at least 3 months in combination with TMZ showed a longer median survival of 69 weeks compared with 61 weeks in the group without VPA. This results adjust for age, extent of resection, and O(6)-DNA methylguaninemethyltransferase (MGMT) promoter methylation status. Barker et al. (Barker et al., 2013) also found GBM patients receiving VPA during CRT had a median OS of 23.9 months, compared with 15.1 months in patients not receiving VPA. Cox regression analysis of patients receiving CRT with TMZ revealed that VPA use during RT was associated with longer OS with seizure history. Berendsen et al. (2016) showed GBM with epilepsy was significantly associated with an increased OS compared with GBM without epilepsy too. But the survival time of glioma patients who received VPA did not differ significantly from those with seizures who did not received VPA. Thus they believed that BAE is an independent prognostic factor for longer survival in GBM and survival is not associated with VPA treatment. Lu et al. (2018) performed a meta-analysis and found that VPA was significantly associated with better OS in GBM patients by 2.4 months when managed by current standard of care. To sum up, VPA may be one of the most promising agents to improve the prognosis of glioma patients, but the prospective clinical data is still needed to confirm this.

5 The mechanism of VPA in glioma patient's survival benefit

VPA can benefit glioma patients in terms of survival, but the mechanism is not very clear. At present, the guidelines give clearer recommendations for the treatment of glioma patients and radiotherapy is one of the most important treatments. Then some in vivo and in vitro researches suggest the benefit of use VPA combined with radiation therapy for glioma patients due to radiosensitizing effect. Thotala et al. (2015) found that the combination of VPA and radiation was most effective in inhibiting tumor growth in heterotopic brain tumor models. VPA combined radiation can significantly delayed tumor growth and improved mouse survival. Further more, Van Nifterik et al. (2012) believed VPA combined with TMZ may lead to further enhancement of the radiation response. They found the combination of VPA and TMZ caused a significant radiation enhancement that was slightly more effective than that of VPA alone. VPA does not antagonize the cytotoxic effects of TMZ. Preincubation with VPA enhances the effect of both gamma-radiation and TMZ in both two glioma cell lines that differ in TMZ sensitivity caused by the absence or presence of the MGMT protein. VPA acted as a radiosensitizer in brain cancer cells.

There are, of course, some other possible mechanisms (Fig. 1). VPA is proved possible inhibit cancer cell growth by inducing apoptosis, cell cycle arrest and autophagy (Bacon et al., 2002; Catalano et al., 2005; Fu et al., 2010). VPA also can selectively kill glioma cells though enhances radiation sensitivity by modify epigenetic (Karagiannis et al., 2006) and correlated with the induction of histone hyperacetylation (Camphausen et al., 2005). Further more, Sambath et al. (Sambath et al., 2019) found that VPA can inhibit the histone deacetylases and induce apoptosis in tumor

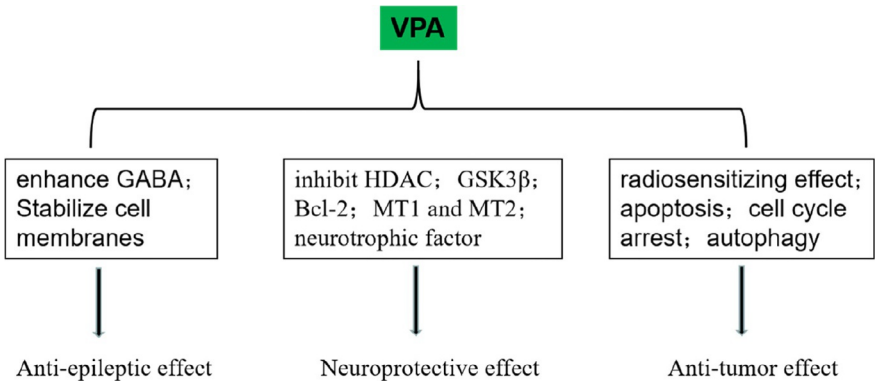

FIG. 1

A brief diagram of the mechanisms of VPA about anti-epileptic, anti-tumor, and neuroprotective effects.

cells and they constructed a photo-uncaging drug delivery system to release VPA. Kiweler et al. (2020) found that VPA as a HDAC inhibitor could interfere with DNA repair protein expression through trigger DNA damage and apoptosis alone especially in combination with established chemotherapeutics. What's more, HDAC inhibitor can disrupt the balance of cell adhesion protein expression and abrogate TGFβ-induced cellular plasticity of transformed cells. VPA played as a HDAC inhibitor also can suppress the epithelial–mesenchymal transition (EMT) process and compromise the DNA integrity of cancer cells.

6 The neuroprotective effect of VPA in glioma patients

Radiotherapy is one of the most common methods for glioma, and radiotherapy can easily cause a series of brain damages, including a certain degree of neurocognitive deficits, and many of the damage to radiotherapy is irreversible. The radiation damage in different periods of radiation therapy in glioma patients has different characteristics (Table 1). Radiotherapy causes apoptosis in the subgranular zone of the hippocampus leading to cognitive deficits. Thotala et al. (2015) found that VPA treatment protected hippocampal neurons from radiation-induced damage in both cell culture and animal models. This radioprotection is specific to normal neuronal cells and did not extend to cancer cells due to VPA treatment induced cell cycle arrest in cancer cells but not in normal neuronal cells. The level of anti-apoptotic protein Bcl-2 was increased and the pro-apoptotic protein Bax was reduced in VPA treated normal cells. VPA protects normal hippocampal neurons but not cancer cells from radiation-induced cytotoxicity both in vitro and in vivo. VPA treatment has the potential for attenuating neurocognitive deficits. Castro et al. (2005) examined the effects of VPA on the expression of the mammalian melatonin receptor subtypes,

Table 1 Characteristics of radioactive damage in different periods.

Radioactive damage	Time from radiation	Characteristics
Acute injury	During this period or just over	Reversible; edema in image
Early delayed injury	Most are within 3 months	Reversible; increased signal on fluid-attenuated inversion recovery abnormalities and T2 on MRI and get better without treatment
Late injury	More than 3 months to several years	Irreversible; Irregular circumscribed reinforced lesion on MRI

MT1 and MT2, in rat C6 glioma cells. The effects of VPA on the expression of glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) were also examined. This results suggest that the neuroprotective properties of VPA involve modulation of neurotrophic factors and receptors for melatonin, which is also thought to play a role in neuroprotection (Castro et al., 2005). Thotala et al. (2015) found that VPA can protects normal hippocampal neurons but not cancer cells from radiation-induced cytotoxicity both in vitro and in vivo. This neuroprotection and improved cognitive function was due, in part, to inhibition of HDAC and GSK3β, the latter of which is only inhibited in normal cells. By the way some studies showed that VPA could promotes hair growth, and thus has the potential to reduce the radiotherapy side effect of hair loss during the treatment of glioma.

7 The side effects of VPA and neuroprotective effects of other AEDs

Even though VPA is highly effective on against epilepsy and has some anti-glioma effect. Even if its tolerance is good, it still has some rare reactive reactions. For example, VPA is able to alter hematopoietic homeostasis by modifying the cell population balance in the myeloid compartment. This may lead to a potential failure of erythropoiesis in patients with cancer or chronic inflammatory diseases having a well-described propensity to anemia (Chateauvieux et al., 2011).

Traditional AEDs, such as carbamazepine, sodium phenytosin and VPA, have been the preferred drug for the treatment of epilepsy. In recent years new AEDs, such as tiagabine, topiramate, lamotrigine, felbamate, etc., found that they not only have anti-epileptic effect, but also have neuroprotective effects like many other drugs showed neuroprotective effects in nervous system diseases (Zhang et al., 2019). Thiagabine plays a role in treatment of epilepsy by inhibiting the reuptake of GABA by glial cells and neurons and increasing the concentration of GABA at the synaptic site. As a new type of AEDs, a study showed that tiagabine can improved neurobehavioral outcome and reduced brain infarction volume in post-ischemia treatment

model. This research suggest that post-ischemic administration of tiagabine have neuroprotective effects (Yang et al., 2000). In addition, thiagabine can reduce the temperature of brain, and hypothermia is an effective brain protection measure. It has been proved that the use of thiagabine to induce hypothermia to play the role of brain protection (Inglefield et al., 1995). Felbamate is a new dicarbamate anticonvulsant with low toxicity being used in human clinical anti-epilepsy. There are a lot of animals (Inglefield et al., 1995; Yang et al., 2000) and in vitro (Wallis et al., 1992) showed that the neuroprotective effect of felbamate was significant. Felbamate provided neuroprotection may though enhance the inhibitory effect of GABA and block *N*-methyl-D-aspartate receptor. After bilateral common carotid artery occlusion, the use of felbamate can reduce the cell death of hippocampal CA1 area, and this effect increases with the increase of dose (Wasterlain et al., 1996). Lamotrigine plays an antiepileptic role by regulating Na^+ channel, stabilizing membrane potential and inhibiting the excitability of glutamate. Lamotrigine can play a neuroprotective role by reduce mortality, reduce apoptosis, improve neurological function and memory function (Crumrine et al., 1997; Shuaib et al., 1995). The antiepileptic effects of topiramate are various, mainly for blocking Na^+ and Ca^{2+} channels, strengthening the Cl^- influx and antiexcitatory amino acids mediated by GABA. Topiramate can reduce the severity of epilepsy and delay the interval of epilepsy in a dose-dependent manner. In animal experiments, topiramate can reduce the damage of neurons in hippocampus, especially in CA area. The neuroprotective effect of topiramate was showed it can reduced the degree of motor injury and the severity of epileptic attack in animal model (Edmonds et al., 2001).

8 Conclusion

VPA play as a widely used AEDs in glioma patients and show strong survival benefits in glioma patients. There are some evidence currently suggests that VPA may confers a significant neuroprotective effect in the treatment of glioma, but there is a need for more, larger, prospective studies to validate the result.

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