Targeting the Brain Renin–Angiotensin System in Epilepsy: Possible Anticonvulsant Effects of Valsartan in Pentylenetetrazole-Induced Convulsions

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Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Epilepsy is one of the most prevalent chronic neurological disorders and is characterized by recurrent unprovoked seizures resulting from abnormal excessive neuronal discharge within the brain. Despite the availability of multiple antiepileptic drugs (AEDs), a considerable proportion of patients continue to experience uncontrolled seizures, adverse drug reactions, cognitive impairment, and poor quality of life. Increasing evidence suggests that epileptogenesis involves complex molecular mechanisms beyond neuronal hyperexcitability, including oxidative stress, neuroinflammation, glutamate excitotoxicity, mitochondrial dysfunction, blood–brain barrier disruption, and alterations in inhibitory GABAergic neurotransmission. These mechanisms contribute not only to seizure generation but also to neuronal injury and progression of epilepsy. Consequently, recent research has focused on identifying novel therapeutic targets and repurposing established drugs with neuroprotective and anti-inflammatory properties.

Pentylenetetrazole (PTZ)-induced seizure models are among the most commonly utilized experimental models for screening anticonvulsant agents and investigating epileptogenic mechanisms. PTZ acts primarily through antagonism of GABAA receptors, leading to neuronal hyperexcitability, oxidative stress, and inflammatory activation. Experimental studies have demonstrated that modulation of oxidative and inflammatory pathways can attenuate PTZ-induced convulsions and reduce neuronal damage.

Valsartan, an angiotensin II type 1 receptor (AT1R) blocker widely used for hypertension and cardiovascular disorders, has recently attracted attention because of its neuroprotective properties. Emerging evidence indicates that valsartan may reduce oxidative stress, suppress neuroinflammation, modulate brain-derived neurotrophic factor (BDNF), and improve neuronal survival in several neurological disorders. Inhibition of central renin–angiotensin system activation by AT1 receptor blockade may therefore represent a promising therapeutic strategy in epilepsy.

This review discusses the possible anticonvulsant effects of valsartan against PTZ-induced convulsions, with emphasis on the mechanistic role of oxidative stress, neuroinflammation, glutamatergic/GABAergic imbalance, and neuronal signaling pathways. The article also highlights the pharmacological rationale for repurposing valsartan as a potential adjunctive therapeutic option in epilepsy management.

Keywords: *Renin–Angiotensin System, Epilepsy, Valsartan in Pentylenetetrazole-Induced Convulsions*

Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent unprovoked seizures resulting from abnormal and excessive electrical discharges within the brain. It represents one of the most common neurological diseases worldwide and is associated with significant medical, psychological, and social burdens. Although several antiepileptic drugs are currently available, a considerable proportion of patients continue to experience uncontrolled seizures or develop adverse effects related to long-term therapy. Consequently, there is growing interest in identifying novel pharmacological targets and repurposing established drugs that may provide both anticonvulsant and neuroprotective benefits. [1,2]

The pathophysiology of epilepsy is highly complex and involves multiple interconnected mechanisms that contribute to neuronal hyperexcitability and seizure propagation. Disturbances in excitatory and inhibitory neurotransmission, particularly glutamate overactivity and impaired GABAergic signaling, are considered major contributors to seizure generation. In addition, increasing evidence has demonstrated that oxidative stress and neuroinflammation play crucial roles in epileptogenesis. Excessive production of reactive oxygen species, inflammatory cytokines, and neuronal damage may enhance seizure susceptibility and accelerate progression of epilepsy. Therefore, therapies targeting oxidative and inflammatory pathways have attracted considerable attention in recent years. [3]

Among experimental seizure models, pentylenetetrazole (PTZ)-induced convulsions are widely used for evaluating potential anticonvulsant agents and understanding epileptic mechanisms. PTZ mainly induces seizures through antagonism of GABAA receptors, leading to neuronal hyperexcitability and synchronized epileptic activity. Furthermore, PTZ administration has been associated with oxidative stress, neuroinflammatory responses, and neuronal injury, making this model particularly valuable for investigating compounds with neuroprotective properties. [4]

Recently, the brain renin–angiotensin system has emerged as an important regulator of several neurological processes beyond cardiovascular control. Activation of angiotensin II type 1 (AT1) receptors has been linked to oxidative stress, neuroinflammation, microglial activation, and neuronal dysfunction. Accordingly, blockade of AT1 receptors may exert protective effects within the central nervous system. Valsartan, a selective angiotensin II receptor blocker, has demonstrated antioxidant, anti-inflammatory, and neuroprotective properties in several experimental studies. These findings suggest that valsartan may potentially attenuate seizure activity and neuronal damage through modulation of inflammatory and oxidative pathways. [5]

Despite the established cardiovascular uses of valsartan, its possible anticonvulsant role remains insufficiently investigated. Understanding the relationship between AT1 receptor blockade and seizure modulation may provide valuable insight into new adjunctive therapeutic strategies for epilepsy. Therefore, this review aims to discuss the possible anticonvulsant effects of valsartan against PTZ-induced convulsions and to highlight the underlying pharmacological mechanisms that may contribute to its neuroprotective actions.

Pentylenetetrazole-Induced Seizure Model and Its Pharmacological Significance

Experimental animal models are essential tools for understanding the mechanisms underlying epilepsy and for evaluating the efficacy of novel anticonvulsant agents before clinical application. Among the various seizure models, pentylenetetrazole (PTZ)-induced convulsions are considered one of the most reliable and widely utilized experimental approaches in epilepsy research. PTZ is a chemoconvulsant agent capable of producing both acute seizures and chronic kindling, thereby reproducing several behavioral and neurochemical alterations observed in human epilepsy. Due to its reproducibility and sensitivity to clinically effective antiepileptic drugs, the PTZ model has become a standard method in neuropharmacological investigations. [6]

The convulsive effect of PTZ is mainly attributed to antagonism of gamma-aminobutyric acid type A (GABAA) receptors, which leads to suppression of inhibitory neurotransmission within the central nervous system. GABA represents the principal inhibitory neurotransmitter in the brain and is essential for maintaining the balance between neuronal excitation and inhibition. Blockade of GABAA receptor-mediated chloride influx by PTZ results in neuronal hyperexcitability, synchronized epileptic discharges, and generalized convulsions. Consequently, the PTZ model is particularly useful for studying compounds capable of enhancing GABAergic activity or reducing neuronal excitability. [7]

In addition to impairment of inhibitory neurotransmission, PTZ-induced seizures are associated with significant oxidative stress and inflammatory responses within brain tissue. Experimental evidence has demonstrated that PTZ administration increases the generation of reactive oxygen species, lipid peroxidation, mitochondrial dysfunction, and inflammatory cytokine production. These pathological changes contribute to neuronal injury and may facilitate epileptogenesis and progression of seizure severity. Therefore, antioxidant and anti-inflammatory agents have attracted substantial attention as potential therapeutic approaches for seizure control and neuroprotection. [8]

Repeated administration of subconvulsive doses of PTZ can induce a phenomenon known as chemical kindling, which mimics the progressive nature of chronic epilepsy. During the kindling process, recurrent stimulation gradually lowers seizure threshold and produces long-lasting alterations in neuronal excitability and synaptic plasticity. This model provides valuable insight into the molecular and cellular mechanisms involved in epileptogenesis, neuronal remodeling, and seizure progression. Moreover, PTZ kindling has become an important experimental platform for evaluating disease-modifying therapies capable of preventing or attenuating chronic epileptic changes. [9]

Recent experimental studies have demonstrated that several neuroprotective agents attenuate PTZ-induced seizures through modulation of oxidative stress, inflammatory pathways, neurotransmitter imbalance, and neuronal apoptosis. These findings support the concept that epilepsy is not solely a disorder of electrical hyperexcitability but also involves complex biochemical

and inflammatory mechanisms. In this regard, valsartan has emerged as a promising candidate because of its antioxidant, anti-inflammatory, and neuroprotective properties, which may contribute to suppression of seizure activity and reduction of neuronal injury in PTZ-induced epilepsy models. [10]

Oxidative Stress in Epilepsy and PTZ-Induced Convulsions

Oxidative stress is considered one of the major pathogenic mechanisms involved in epileptogenesis and seizure-induced neuronal injury. During epileptic activity, excessive neuronal firing markedly increases metabolic demand and oxygen consumption within brain tissue, leading to overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS). When the production of these reactive molecules exceeds the capacity of endogenous antioxidant defense systems, oxidative damage to lipids, proteins, and nucleic acids occurs. The brain is particularly vulnerable to oxidative injury because of its high oxygen utilization, abundant lipid content, and relatively limited antioxidant reserves. [11]

Experimental and clinical studies have demonstrated that seizures are associated with significant alterations in oxidative balance. Increased lipid peroxidation, mitochondrial dysfunction, depletion of glutathione, and impairment of antioxidant enzymes such as superoxide dismutase and catalase have all been observed in epilepsy. Persistent oxidative stress may contribute not only to acute neuronal injury during seizures but also to long-term neurodegeneration and progression of epileptogenesis. Therefore, modulation of oxidative pathways has become an important therapeutic target in epilepsy research. [12]

The PTZ-induced seizure model is strongly associated with oxidative stress-mediated neuronal damage. Administration of PTZ has been shown to increase free radical generation and induce oxidative injury in several brain regions, particularly the hippocampus and cerebral cortex. Repeated PTZ exposure may further aggravate mitochondrial dysfunction and inflammatory activation, thereby lowering seizure threshold and enhancing seizure severity. Experimental studies have also demonstrated that agents possessing antioxidant activity can significantly attenuate PTZ-induced convulsions and improve neuronal survival. [13]

Oxidative stress is closely interconnected with neuroinflammatory and excitotoxic mechanisms involved in epilepsy. Excessive ROS production can activate inflammatory signaling pathways and promote release of proinflammatory cytokines, which subsequently enhance neuronal excitability and seizure susceptibility. In addition, oxidative damage may impair GABAergic inhibitory transmission and potentiate glutamate-mediated excitotoxicity, further contributing to epileptic activity. These interactions indicate that oxidative stress plays a central role in both seizure initiation and progression. [14]

Recent interest has focused on drugs with combined antioxidant and neuroprotective actions as potential adjunctive therapies in epilepsy. In this context, valsartan has demonstrated significant antioxidant properties in several experimental neurological models. Previous studies have shown that valsartan enhances endogenous antioxidant defense systems, reduces oxidative and nitrosative stress, and protects neuronal tissue against injury. Such findings support the hypothesis that valsartan may attenuate PTZ-induced seizures partly through reduction of oxidative stress and preservation of neuronal integrity. [15]

Neuroinflammation in Epilepsy

Neuroinflammation has emerged as a major contributor to the pathogenesis of epilepsy and is increasingly recognized as an important factor in seizure initiation, propagation, and epileptogenesis. Seizure activity can activate several inflammatory pathways within the central nervous system, leading to release of proinflammatory cytokines, activation of microglia and astrocytes, disruption of the blood–brain barrier, and neuronal injury. Persistent inflammatory responses may subsequently enhance neuronal hyperexcitability and lower seizure threshold, creating a vicious cycle that promotes recurrent seizures and progression of epilepsy. [16]

Among the inflammatory mediators implicated in epilepsy, interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and high mobility group box-1 (HMGB-1) are considered particularly important. These cytokines can alter neurotransmitter release, enhance glutamate excitotoxicity, impair GABAergic inhibition, and facilitate neuronal synchronization. Experimental studies have demonstrated elevated levels of inflammatory mediators in both human epilepsy and animal seizure models, indicating that neuroinflammation represents a critical component of epileptic pathology rather than simply a secondary consequence of seizures. [17]

PTZ-induced convulsions are strongly associated with activation of inflammatory pathways in brain tissue. Administration of PTZ has been shown to stimulate microglial activation and increase expression of inflammatory cytokines, resulting in neuronal injury and oxidative damage. Repeated PTZ exposure may further aggravate inflammatory responses and contribute to chronic epileptogenic changes. Consequently, several compounds possessing anti-inflammatory properties have demonstrated anticonvulsant effects in PTZ models through suppression of inflammatory signaling pathways. [18]

Recent therapeutic approaches in epilepsy research have therefore focused on modulation of neuroinflammation as a strategy for seizure control and neuroprotection. Experimental evidence indicates that reducing inflammatory cytokine production or inhibiting microglial activation may attenuate seizure severity and neuronal damage. Drugs capable of targeting both oxidative stress and inflammation may be particularly beneficial because of the close interaction between these pathological mechanisms in epilepsy. [19]

Valsartan has attracted increasing attention because of its anti-inflammatory actions within the central nervous system. Blockade of angiotensin II type 1 receptors can suppress inflammatory signaling pathways, reduce cytokine production, and inhibit microglial activation. Experimental studies have shown that valsartan attenuates neuroinflammatory responses and improves neuronal survival in several neurological disorders. These findings suggest that valsartan may potentially reduce seizure susceptibility and neuronal injury in PTZ-induced epilepsy through modulation of inflammatory mechanisms. [20]

Glutamate–GABA Imbalance in Seizure Generation

The balance between excitatory and inhibitory neurotransmission is a central determinant of neuronal stability. In normal brain function, glutamate acts as the major excitatory neurotransmitter, whereas gamma-aminobutyric acid (GABA) provides the principal inhibitory control. Epileptic seizures occur when this balance shifts toward excessive excitation or inadequate inhibition, allowing neurons to fire abnormally and synchronously. This imbalance is especially important in generalized convulsions, where widespread neuronal networks become hyperexcitable and propagate seizure activity. [21]

Glutamate-mediated excitotoxicity plays a major role in seizure initiation and seizure-related neuronal injury. Excessive glutamate release activates ionotropic glutamate receptors, allowing increased calcium influx into neurons and triggering intracellular pathways that promote oxidative stress, mitochondrial dysfunction, and cell damage. Persistent glutamatergic overactivity may therefore contribute not only to acute seizure generation but also to long-term epileptogenesis and neurodegeneration. [22]

GABAergic inhibition is equally critical in preventing uncontrolled neuronal excitation. GABAA receptors regulate chloride influx and help maintain membrane hyperpolarization, thereby limiting excessive neuronal firing. PTZ-induced seizures are strongly related to impairment of this inhibitory mechanism because PTZ acts mainly by antagonizing GABAA receptor function. Reduction of GABAergic tone increases neuronal excitability and facilitates the development of clonic and tonic convulsions. [23]

Astrocytes also contribute significantly to glutamate–GABA homeostasis. They regulate neurotransmitter recycling through the glutamate/GABA–glutamine cycle and help maintain extracellular neurotransmitter concentrations within physiological limits. Dysfunction of this astrocytic metabolic support may disturb synaptic balance and increase susceptibility to seizures. Therefore, seizure generation should be viewed not only as a neuronal disorder but also as a disturbance of neuron–glia metabolic interaction. [24]

The possible anticonvulsant relevance of valsartan may be partly related to indirect stabilization of this excitatory–inhibitory balance. By reducing oxidative stress and neuroinflammation, valsartan may limit pathological enhancement of glutamatergic signaling and protect inhibitory neuronal networks from inflammatory and oxidative injury. Although direct GABAA receptor modulation by valsartan has not been clearly established, its neuroprotective actions may create a less hyperexcitable neuronal environment and thereby reduce PTZ-induced seizure susceptibility. [25]

Brain Renin–Angiotensin System and Epilepsy

The renin–angiotensin system (RAS) is traditionally recognized for its role in cardiovascular regulation and blood pressure control; however, increasing evidence indicates that a local RAS also exists within the central nervous system. Components of the brain RAS are widely distributed in several regions involved in seizure generation and neuronal excitability, including the hippocampus, cortex, and amygdala. Activation of this system has been linked to oxidative stress, neuroinflammation, endothelial dysfunction, and neuronal injury, all of which contribute to epileptogenesis and progression of seizure disorders. [26]

Angiotensin II is considered the principal effector peptide of the RAS and exerts most of its pathological effects through activation of angiotensin II type 1 (AT1) receptors. Stimulation of AT1 receptors promotes production of reactive oxygen species, inflammatory cytokines, and excitotoxic mediators within brain tissue. Furthermore, AT1 receptor activation may enhance microglial activation and disrupt blood–brain barrier integrity, thereby facilitating neuronal hyperexcitability and seizure propagation. Consequently, excessive activation of the brain RAS has been implicated in several neurological disorders including epilepsy, stroke, and neurodegenerative diseases. [27]

Experimental evidence suggests that inhibition of the RAS may provide neuroprotective and anticonvulsant benefits. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) have demonstrated the ability to reduce oxidative injury, suppress inflammatory responses, and improve neuronal survival in different experimental models. Some studies involving ARBs such as losartan reported attenuation of seizure severity and reduction of epileptic changes, supporting the concept that AT1 receptor blockade may influence seizure susceptibility. [28]

Valsartan is a selective AT1 receptor blocker widely used in the management of hypertension, heart failure, and cardiovascular disorders. Beyond its cardiovascular effects, valsartan has demonstrated important neuroprotective properties including reduction of oxidative stress, suppression of inflammatory signaling pathways, and modulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF). These actions may contribute to stabilization of neuronal function and protection against seizure-induced neuronal injury. [29]

The possible anticonvulsant effects of valsartan may therefore result from multiple complementary mechanisms involving suppression of oxidative stress, attenuation of neuroinflammation, preservation of neuronal integrity, and modulation of excitatory signaling pathways. Considering the multifactorial nature of epilepsy, targeting the brain RAS through AT1 receptor blockade may represent a promising adjunctive therapeutic strategy in seizure disorders. Nevertheless, additional experimental and clinical studies are still required to clarify the precise mechanisms and therapeutic potential of valsartan in epilepsy management. [30]

Pharmacology of Valsartan

Valsartan is a selective angiotensin II type 1 receptor blocker that is widely used in the treatment of hypertension, heart failure, and cardiovascular risk reduction. Its primary pharmacological action is based on inhibition of angiotensin II binding to AT1 receptors, thereby reducing vasoconstriction, aldosterone secretion, sodium retention, and sympathetic activation. Unlike angiotensin-converting enzyme inhibitors, valsartan does not directly inhibit bradykinin degradation, which may

explain its lower association with cough and some bradykinin-mediated adverse effects. [31]

From a clinical pharmacology perspective, valsartan is important because it combines effective AT1 receptor blockade with a generally favorable safety profile. It is commonly administered orally and produces sustained antihypertensive activity suitable for once- or twice-daily dosing depending on the clinical indication. Although its major approved uses are cardiovascular, its pharmacodynamic actions are not limited to peripheral tissues. AT1 receptor blockade may also influence central nervous system pathways involved in oxidative stress, inflammation, and neuronal survival. [32]

The relevance of valsartan to neurological disorders is related to the presence of angiotensin II signaling pathways within the brain. Activation of AT1 receptors in neural tissue can promote inflammatory mediator release, oxidative injury, endothelial dysfunction, and microglial activation. By blocking these receptors, valsartan may reduce harmful intracellular signaling cascades that contribute to neuronal damage. These effects provide a rational basis for investigating valsartan beyond its traditional cardiovascular indications. [33]

Experimental studies have shown that valsartan can exert neuroprotective effects through enhancement of antioxidant defense mechanisms and reduction of oxidative/nitrosative stress. Such actions are especially relevant to seizure models because oxidative stress contributes to neuronal hyperexcitability, mitochondrial dysfunction, and seizure-induced neuronal injury. Therefore, the antioxidant profile of valsartan may represent one possible pathway through which it could attenuate PTZ-induced convulsions. [34]

In addition to antioxidant activity, valsartan may influence neurotrophic and inflammatory pathways. Studies have reported that valsartan can modulate brain-derived neurotrophic factor expression and reduce inflammatory signaling in experimental brain injury and neurodegenerative models. These effects suggest that valsartan may support neuronal survival and functional recovery under pathological conditions. Accordingly, its pharmacological properties support further evaluation as a possible adjunctive neuroprotective agent in epilepsy. [35]

Possible Anticonvulsant Mechanisms of Valsartan in PTZ-Induced Convulsions

The potential anticonvulsant effect of valsartan appears to involve multiple interconnected mechanisms rather than a single pharmacological pathway. Epilepsy is currently recognized as a multifactorial disorder involving oxidative stress, neuroinflammation, neurotransmitter imbalance, mitochondrial dysfunction, and neuronal apoptosis. Because valsartan possesses antioxidant, anti-inflammatory, and neuroprotective properties, it may exert beneficial effects on several pathological processes associated with seizure generation and epileptogenesis. [36]

One of the most important proposed mechanisms is attenuation of oxidative stress. Excessive production of reactive oxygen species during seizures contributes to neuronal membrane damage, mitochondrial dysfunction, and increased neuronal excitability. Experimental studies have demonstrated that valsartan enhances endogenous antioxidant defense systems and reduces oxidative and nitrosative injury within brain tissue. Reduction of oxidative stress may therefore stabilize neuronal membranes and decrease susceptibility to PTZ-induced convulsions. [37]

Valsartan may also exert anticonvulsant effects through suppression of neuroinflammatory pathways. Activation of AT1 receptors stimulates production of inflammatory cytokines and promotes microglial activation, both of which contribute to seizure propagation and neuronal injury. By blocking AT1 receptor signaling, valsartan may reduce release of inflammatory mediators and attenuate inflammatory cascades associated with epileptogenesis. This anti-inflammatory action could help limit seizure severity and protect neuronal tissue against recurrent epileptic insults. [38]

Another possible mechanism involves modulation of neurotrophic and neuronal survival pathways. Brain-derived neurotrophic factor (BDNF) plays an important role in neuronal plasticity, synaptic regulation, and neuronal survival. Alterations in BDNF signaling have been implicated in epilepsy and seizure-related neuronal remodeling. Experimental evidence indicates that valsartan can modulate BDNF expression and improve neuronal resilience under pathological conditions, suggesting a potential role in reducing seizure-induced neuronal damage. [39]

In addition, valsartan may indirectly influence excitatory and inhibitory neurotransmission within the brain. Oxidative stress and inflammation can enhance glutamatergic excitotoxicity while impairing GABAergic inhibitory pathways. Through attenuation of these pathological processes, valsartan may help restore neuronal balance and reduce hyperexcitability. Although direct modulation of GABA or glutamate receptors by valsartan has not been fully established, its overall neuroprotective profile supports a possible role in reducing seizure susceptibility in PTZ-induced epilepsy models. [40]

Valsartan and Oxidative Stress Modulation in PTZ-Induced Convulsions

Oxidative stress represents one of the most important mechanisms through which PTZ-induced convulsions produce neuronal injury and increase seizure susceptibility. During seizures, excessive neuronal firing increases oxygen consumption and mitochondrial activity, resulting in increased production of reactive oxygen species and reactive nitrogen species. If antioxidant defenses are insufficient, these reactive molecules damage neuronal membranes, proteins, and DNA, thereby worsening neuronal dysfunction and facilitating recurrent epileptic activity. [41]

The importance of oxidative stress in epilepsy is supported by evidence showing increased lipid peroxidation, reduced glutathione levels, and impaired antioxidant enzyme activity in seizure models. These biochemical changes can disturb ion gradients, impair mitochondrial energy production, and increase neuronal excitability. Therefore, antioxidant-based interventions may reduce seizure severity not only by limiting tissue injury but also by improving neuronal stability and preserving cellular homeostasis. [42]

Valsartan may provide protection against PTZ-induced oxidative injury through enhancement of endogenous antioxidant defense mechanisms. Experimental studies have shown that valsartan can attenuate oxidative and nitrosative stress in brain

tissue and improve antioxidant capacity. This effect is pharmacologically relevant because reduction of oxidative damage may preserve neuronal membrane integrity, maintain mitochondrial function, and reduce seizure-related neurodegeneration. [43]

AT1 receptor blockade may also reduce oxidative stress by inhibiting angiotensin II–mediated activation of pro-oxidant pathways. Angiotensin II signaling through AT1 receptors is associated with increased free radical generation and inflammatory activation. By blocking this pathway, valsartan may reduce reactive oxygen species production at an upstream level rather than acting only as a direct antioxidant. This mechanism may be particularly valuable in epilepsy, where oxidative stress and inflammation reinforce each other during seizure progression. [44]

Taken together, the antioxidant properties of valsartan provide a strong mechanistic explanation for its possible anticonvulsant effect in PTZ-induced convulsions. By reducing oxidative injury, supporting antioxidant defenses, and limiting angiotensin II–dependent pro-oxidant signaling, valsartan may decrease neuronal hyperexcitability and protect against seizure-induced brain damage. However, further experimental studies are needed to clarify the exact relationship between valsartan-mediated oxidative stress modulation and behavioral seizure outcomes. [45]

Valsartan and Neuroinflammatory Pathways in PTZ-Induced Convulsions

Neuroinflammation is closely linked to oxidative stress and represents another important mechanism through which PTZ-induced seizures may promote neuronal injury and epileptogenesis. Seizure activity can activate microglia and astrocytes, leading to increased release of proinflammatory mediators within brain tissue. These inflammatory signals may enhance neuronal excitability, disturb synaptic transmission, and contribute to progressive seizure susceptibility. Therefore, controlling neuroinflammation is considered an important approach in limiting seizure severity and protecting neuronal tissue. [46]

PTZ-induced convulsions are associated with activation of inflammatory pathways, including increased expression of cytokines and danger-associated signaling molecules. These mediators may amplify glutamate excitotoxicity, impair GABAergic inhibition, and promote neuronal damage. Experimental findings showing anticonvulsant effects of anti-inflammatory agents in PTZ models support the view that inflammation is not merely a consequence of seizures but may actively participate in seizure propagation and epileptogenesis. [47]

Angiotensin II signaling through AT1 receptors can contribute to neuroinflammation by stimulating cytokine release, oxidative stress, and microglial activation. This provides a pharmacological rationale for using AT1 receptor blockers as potential neuroprotective agents. By inhibiting AT1 receptor activation, valsartan may reduce inflammatory signaling and limit the downstream neuronal injury associated with repeated seizure activity. [48]

Valsartan has shown anti-inflammatory properties in experimental neurological settings, including modulation of NLRP3-related inflammatory activity and improvement of neurotrophic signaling. These actions may be particularly relevant in epilepsy, where inflammasome activation and cytokine release can increase neuronal hyperexcitability. Through suppression of inflammatory cascades, valsartan may help reduce seizure-induced brain damage and improve neuronal resilience. [49]

The anti-inflammatory mechanism of valsartan may therefore complement its antioxidant effects in PTZ-induced convulsions. Since oxidative stress and inflammation reinforce each other, simultaneous attenuation of both pathways could provide stronger neuroprotection than targeting either pathway alone. This multifunctional profile supports further investigation of valsartan as a possible adjunctive agent for seizure modulation and neuroprotection in experimental epilepsy. [50]

BDNF and Neuronal Survival Pathways

Brain-derived neurotrophic factor (BDNF) is an important neurotrophin involved in neuronal survival, synaptic plasticity, neurogenesis, and repair responses after brain injury. In epilepsy, BDNF signaling has a complex role because it may participate in both adaptive neuronal protection and maladaptive synaptic remodeling, depending on timing, brain region, and disease stage. During recurrent seizures, altered BDNF expression may reflect an endogenous attempt to protect neurons from excitotoxic and inflammatory damage. [51]

PTZ-induced convulsions are associated with neuronal stress, oxidative injury, and inflammatory activation, all of which may disturb neurotrophic signaling. Reduced neuronal support can increase vulnerability to seizure-induced injury, particularly in regions such as the hippocampus and cerebral cortex. Therefore, agents capable of preserving neurotrophic balance may help protect neurons and limit long-term epileptogenic changes. [52]

Valsartan has been reported to modulate BDNF expression and improve neuronal protection in experimental neurological models. This effect is clinically relevant because enhancement of neuronal survival pathways may reduce apoptosis, support synaptic stability, and improve functional recovery after neuronal injury. In the context of PTZ-induced seizures, valsartan-related improvement in BDNF signaling may contribute to reduced neuronal vulnerability and better resistance against seizure-associated damage. [53]

The relationship between BDNF, inflammation, and oxidative stress is particularly important in epilepsy. Excessive oxidative and inflammatory insults may impair neurotrophic signaling, while restoration of BDNF activity may improve neuronal resilience. Since valsartan can reduce oxidative stress and neuroinflammation, its effect on BDNF may be part of a broader neuroprotective network rather than an isolated mechanism. [54]

Thus, modulation of BDNF and neuronal survival pathways provides another plausible explanation for the possible anticonvulsant and neuroprotective effects of valsartan. Although direct evidence in PTZ-induced epilepsy remains limited, available experimental findings support further investigation of valsartan as a drug that may protect against seizure-related

neuronal injury through combined antioxidant, anti-inflammatory, and neurotrophic mechanisms. [55]

Blood–Brain Barrier Dysfunction and Seizure Susceptibility

Blood–brain barrier disruption is increasingly recognized as an important pathological event in epilepsy and seizure progression. Under physiological conditions, the blood–brain barrier maintains ionic stability, regulates entry of circulating molecules, and protects the neuronal microenvironment from harmful inflammatory mediators. During recurrent seizures, barrier integrity may be impaired, allowing serum proteins, immune cells, and inflammatory molecules to enter brain tissue. This disruption can promote neuronal hyperexcitability and contribute to persistence of epileptic activity. [56]

PTZ-induced convulsions may contribute to blood–brain barrier impairment through oxidative stress, inflammatory cytokine release, and endothelial dysfunction. Once the barrier is disrupted, albumin and other circulating factors may interact with astrocytes and neurons, producing changes in extracellular ion balance and synaptic excitability. These alterations may further lower seizure threshold and facilitate seizure recurrence. Therefore, maintaining blood–brain barrier integrity is considered an important component of neuroprotection in epilepsy. [57]

The brain renin–angiotensin system may influence blood–brain barrier function through effects on vascular inflammation, oxidative stress, and endothelial regulation. Angiotensin II acting through AT1 receptors can promote endothelial dysfunction and inflammatory activation, which may aggravate barrier permeability. In contrast, AT1 receptor blockade may reduce vascular oxidative injury and inflammatory signaling, thereby supporting barrier stability under pathological conditions. [58]

Valsartan may indirectly protect blood–brain barrier integrity by suppressing AT1 receptor-mediated oxidative and inflammatory pathways. Its ability to reduce oxidative stress and neuroinflammation suggests that it may limit endothelial injury and secondary neuronal exposure to circulating inflammatory factors. In PTZ-induced convulsions, such vascular protection could contribute to reduced seizure propagation and less neuronal damage. [59]

Although direct evidence linking valsartan to blood–brain barrier preservation in PTZ epilepsy models remains limited, its pharmacological profile supports this possibility. Because barrier dysfunction interacts with oxidative stress, inflammation, glutamate excitotoxicity, and neuronal injury, valsartan may provide benefit through broader stabilization of the neurovascular unit. Further experimental studies are needed to clarify whether valsartan can directly reduce PTZ-induced blood–brain barrier permeability and whether this contributes to anticonvulsant activity. [60]

Mitochondrial Dysfunction and Neuronal Apoptosis in Seizure Injury

Mitochondrial dysfunction is an important contributor to seizure-induced neuronal injury. During convulsions, excessive neuronal firing increases energy demand and calcium influx, which can overload mitochondrial function and promote reactive oxygen species generation. This mitochondrial stress may impair ATP production, disturb ion homeostasis, and increase neuronal vulnerability to recurrent epileptic activity. Therefore, preservation of mitochondrial function is considered a key element in neuroprotection during epilepsy. [61]

PTZ-induced seizures can trigger neuronal apoptosis through oxidative stress, excitotoxicity, and inflammatory signaling. Excessive intracellular calcium accumulation and mitochondrial injury may activate pro-apoptotic pathways, leading to caspase activation and neuronal loss. These changes are particularly relevant in seizure-sensitive brain regions such as the hippocampus, where neuronal damage may contribute to cognitive impairment and progression of epileptogenesis. [62]

Neuronal apoptosis is closely related to the balance between protective and damaging intracellular pathways. Anti-apoptotic proteins such as Bcl-2 help preserve neuronal survival, whereas activation of caspase-dependent mechanisms promotes cell death. Experimental studies of neuroprotective agents in seizure and brain injury models have shown that reducing apoptosis can improve neuronal survival and functional outcomes. Thus, anti-apoptotic signaling represents an important therapeutic target in epilepsy research. [63]

Valsartan may protect neurons indirectly by reducing upstream triggers of mitochondrial damage and apoptosis. Through inhibition of AT1 receptor-mediated oxidative stress and inflammation, valsartan may decrease mitochondrial injury, preserve cellular energy balance, and reduce activation of apoptotic cascades. Although direct evidence in PTZ-induced convulsions remains limited, its antioxidant and neuroprotective actions support this mechanistic possibility. [64]

The potential ability of valsartan to limit mitochondrial dysfunction and neuronal apoptosis may strengthen its role as a candidate adjunctive agent in epilepsy. Since seizure-induced neuronal injury results from overlapping oxidative, inflammatory, excitotoxic, and apoptotic mechanisms, a drug with multimodal neuroprotective properties may be particularly valuable. Further experimental studies should clarify whether valsartan can directly reduce apoptotic biomarkers and mitochondrial injury in PTZ-induced seizure models. [65]

Ion Channels, Ionic Homeostasis, and the Possible Relevance of Valsartan

Ion channel dysfunction is a central mechanism in seizure generation because neuronal excitability depends on the controlled movement of sodium, potassium, calcium, and chloride ions across neuronal membranes. Disturbance in these ion gradients can lower seizure threshold and promote repetitive neuronal firing. In epilepsy, abnormalities in voltage-gated sodium and calcium channels may enhance depolarization, while impaired potassium conductance may delay repolarization and facilitate sustained epileptic discharges. [66]

The Na^+/K^+-ATPase pump is also essential for maintaining resting membrane potential and restoring ionic balance after neuronal activity. During seizures, excessive neuronal firing disrupts sodium and potassium gradients, increases extracellular potassium accumulation, and promotes neuronal synchronization. Impairment of Na^+/K^+-ATPase activity may therefore aggravate neuronal hyperexcitability and contribute to seizure propagation. Restoration of ionic stability is consequently an

important target for neuroprotective strategies in epilepsy. [67]

Oxidative stress can directly affect ion channels and membrane pumps by damaging membrane lipids and altering protein function. In PTZ-induced convulsions, increased oxidative injury may disturb Na^+/K^+-ATPase activity and worsen ionic imbalance, thereby amplifying seizure severity. Antioxidant interventions may improve pump function and stabilize neuronal membranes, supporting the concept that oxidative stress modulation can indirectly influence electrical excitability. [68]

Valsartan does not act as a classical sodium, calcium, or potassium channel blocker; however, it may indirectly support ionic homeostasis by reducing oxidative stress and inflammation. Through attenuation of angiotensin II–mediated oxidative injury, valsartan may preserve membrane integrity and protect ion transport mechanisms from oxidative damage. This indirect stabilizing effect may be relevant in PTZ-induced seizures, where oxidative injury contributes to neuronal hyperexcitability. [69]

Therefore, the possible anticonvulsant effect of valsartan should not be interpreted as a direct ion channel-blocking action, but rather as a secondary consequence of improved neuronal microenvironment. By reducing oxidative and inflammatory stress, valsartan may help maintain ion pump activity, preserve membrane stability, and limit excessive neuronal firing. This mechanism may complement its antioxidant, anti-inflammatory, and neurotrophic effects in experimental seizure models. [70]

Comparison Between Valsartan and Conventional Antiepileptic Drugs

Conventional antiepileptic drugs primarily exert their effects through direct modulation of neuronal excitability and neurotransmission. Most classical agents act by blocking voltage-gated sodium channels, enhancing GABAergic inhibition, reducing calcium influx, or suppressing glutamate-mediated excitation. These mechanisms effectively reduce seizure frequency in many patients; however, they are often associated with adverse effects such as sedation, cognitive impairment, hepatotoxicity, and drug interactions. Furthermore, a substantial proportion of patients remain resistant to available therapies, highlighting the need for alternative or adjunctive treatment approaches. [71]

Unlike traditional antiepileptic drugs, valsartan does not directly target ion channels or neurotransmitter receptors. Instead, its possible anticonvulsant effect appears to result from modulation of secondary pathological mechanisms involved in epileptogenesis, including oxidative stress, neuroinflammation, endothelial dysfunction, and neuronal injury. This difference is pharmacologically important because epilepsy is increasingly recognized as a disorder involving multiple biochemical and inflammatory pathways in addition to electrical hyperexcitability. [72]

Several newer therapeutic strategies in epilepsy research focus on neuroprotection and disease modification rather than symptomatic seizure suppression alone. Experimental agents possessing antioxidant and anti-inflammatory properties have demonstrated beneficial effects in PTZ-induced seizure models, supporting the concept that targeting inflammatory and oxidative pathways may complement conventional seizure control. In this regard, valsartan may represent a promising adjunctive candidate because of its combined antioxidant, anti-inflammatory, and neuroprotective profile. [73]

Another important advantage of valsartan is its well-established clinical safety profile in cardiovascular medicine. Since the drug is already widely prescribed for hypertension and heart failure, substantial pharmacokinetic and safety data are available. This may facilitate drug repurposing and reduce the time and cost required for translational development compared with completely novel compounds. However, further experimental and clinical studies are still required to determine the effective anticonvulsant dose range, central nervous system penetration, and long-term neurological effects of valsartan in epilepsy. [74]

Despite these potential advantages, valsartan should not currently be considered a replacement for conventional antiepileptic drugs. The available evidence mainly supports a possible adjunctive neuroprotective role rather than direct anticonvulsant efficacy comparable to standard therapies. Nevertheless, its multimodal pharmacological actions suggest that valsartan may provide additional benefit when combined with established antiepileptic strategies, particularly in conditions where oxidative stress and neuroinflammation contribute significantly to seizure pathology. [75]

Conclusion

Epilepsy is a multifactorial neurological disorder involving complex interactions between neuronal hyperexcitability, oxidative stress, neuroinflammation, excitotoxicity, mitochondrial dysfunction, and neuronal injury. Although conventional antiepileptic drugs remain the cornerstone of therapy, many patients continue to experience inadequate seizure control and treatment-related adverse effects, emphasizing the need for novel adjunctive therapeutic strategies. Experimental evidence suggests that PTZ-induced convulsions are strongly associated with oxidative and inflammatory pathways, making these mechanisms important therapeutic targets. Valsartan, a selective angiotensin II type 1 receptor blocker, has demonstrated significant antioxidant, anti-inflammatory, neuroprotective, and neurotrophic properties in several experimental studies. Through modulation of oxidative stress, suppression of inflammatory mediators, preservation of neuronal integrity, and possible stabilization of excitatory–inhibitory balance, valsartan may exert protective effects against seizure-induced neuronal damage and epileptogenesis. Although current evidence remains largely experimental, the pharmacological profile of valsartan supports its potential as a promising adjunctive agent in epilepsy management. Further preclinical and clinical studies are required to clarify its precise anticonvulsant mechanisms, therapeutic efficacy, and future role in seizure disorders.

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