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CRITICAL REVIEW

Neurovascular unit dysfunction as a mechanism of seizures and epilepsy during aging

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Abstract

The term neurovascular unit (NVU) describes the structural and functional liaison between specialized brain endothelium, glial and mural cells, and neurons. Within the NVU, the blood-brain barrier (BBB) is the microvascular structure regulating neuronal physiology and immune cross-talk, and its properties adapt to brain aging. Here, we analyze a research framework where NVU dysfunction, caused by acute insults or disease progression in the aging brain, represents a converging mechanism underlying late-onset seizures or epilepsy and neurological or neurodegenerative sequelae. Furthermore, seizure activity may accelerate brain aging by sustaining regional NVU dysfunction, and a cerebrovascular pathology may link seizures to comorbidities. Next, we focus on NVU diagnostic approaches that could be tailored to seizure conditions in the elderly. We also examine the impending disease-modifying strategies based on the restoration of the NVU and, more in general, the homeostatic control of anti- and pro-inflammatory players. We conclude with an outlook on current pre-clinical knowledge gaps and clinical challenges pertinent to seizure onset and conditions in an aging population.

KEYWORDS

aging, Alzheimer's disease, blood-brain barrier, cognitive decline, inflammation, late-onset epilepsy, neurodegeneration, seizures, stroke, traumatic brain injury

1 | INTRODUCTION

Older adults account for 12% and 20% of the United States and Europe population, respectively.[1,2] By 2050, one in six individuals will be 65 years of age or older.[3,4] These numbers are important considering that the incidence of seizures and epilepsy increases from 50 years of age, and it becomes the highest in subjects older than 65 because of epileptogenic brain insults and diseases.[3] This clinical fact, and its limited understanding, stirs discussion about pathological mechanisms and trajectories, risk of cognitive impairment, and the adequacy of available antiseizure medications for treating older patients.[3] From this context, we examined whether neurovascular unit (NVU) dysfunction during aging [5-8] could play a role in the onset of seizures and epilepsy. We searched for relevant literature using PubMed and Google Scholar databases. We focused on, but did not limit to, the past decade. We used combinations of two or more keywords[9] (eg, seizures, aging, late-onset epilepsy, neurovascular unit, blood-brain barrier (BBB), inflammation, glial cells, stroke, traumatic brain injury, neurodegeneration, tau-hyperphosphorylation, amyloid beta, Alzheimer's disease, and vascular dementia) to retrieve and select pertinent knowledge, including perspective views, hypotheses, and knowledge gaps. We first summarize the structural and cellular elements of the healthy NVU. Next, we focus on clinical and experimental examples supporting the involvement of NVU dysfunction, within a pro-inflammatory environment and not limited to BBB permeability, in the occurrence of seizures and epilepsy during aging. Finally, we discuss diagnostic and therapeutic opportunities that could be further studied and potentially applied to an aging population, proposing a contextualization to seizure conditions.

Key points

1. Neurovascular unit (NVU) dysfunction is a converging disease-associated element contributing to seizures during aging.
2. Acute brain insults and disease progression promote or intersect with seizures during aging.
3. Blood-brain barrier dysfunction and brain inflammation could be hallmarks of age-related seizures and neurodegenerative diseases.
4. Refining NVU diagnostics and therapies is essential to control seizures and epilepsy in the aging population.

2 | THE NEUROVASCULAR UNIT: AN OVERVIEW OF CELLULAR COMPONENTS AND FUNCTIONS

The NVU is unique to the brain and is a complex functional and multi-cellular anatomic structure. The NVU includes vascular cells (brain microvessel endothelial cells [BMECs]) with mural cells (pericytes and smooth muscle cells) that are in close contact with BMECs, glial cells (astrocytes, microglia, and oligodendrocytes), perivascular macrophages, and neurons (Figures 1 and 2). Within the NVU, the BBB includes a vast system of capillaries and postcapillary venules regulating the passage of molecules and cells in and out of the brain. The BBB is characterized by a highly selective endothelial-pericyte-astrocyte layering, separating the peripheral blood from the brain

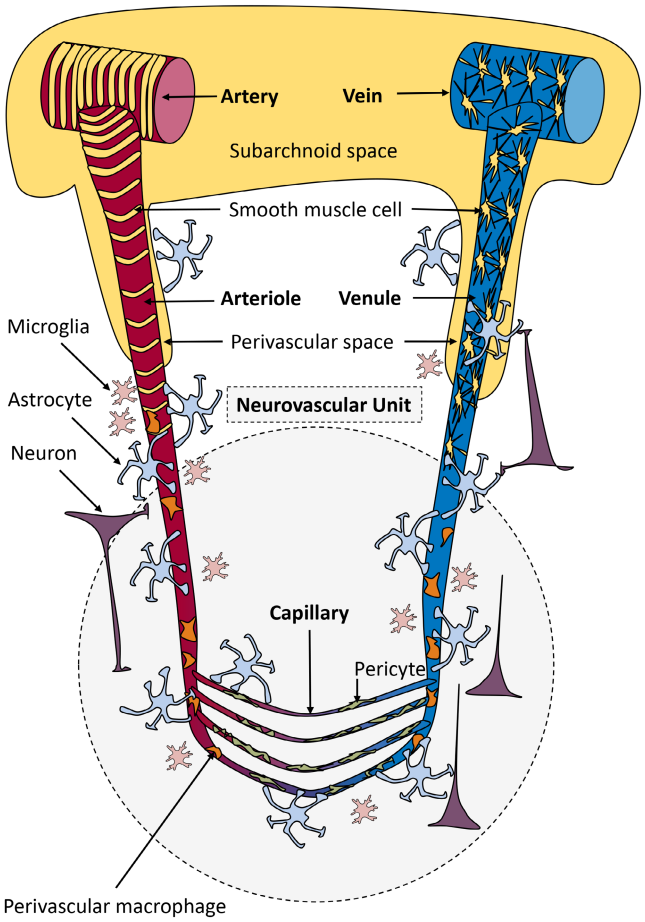

FIGURE 1 Schematic overview of the cerebrovasculature. The brain receives blood supply from the carotid and vertebral arteries, which regulate blood flow via the contraction of smooth muscle cells. Arteries leave the subarachnoid space to penetrate the brain parenchyma, branching into arterioles and capillaries. At this site, the endothelium is surrounded by a multi-cellular assembly (see Figure 2), forming the neurovascular unit. Blood is collected in venules and distributed via veins to exit the brain

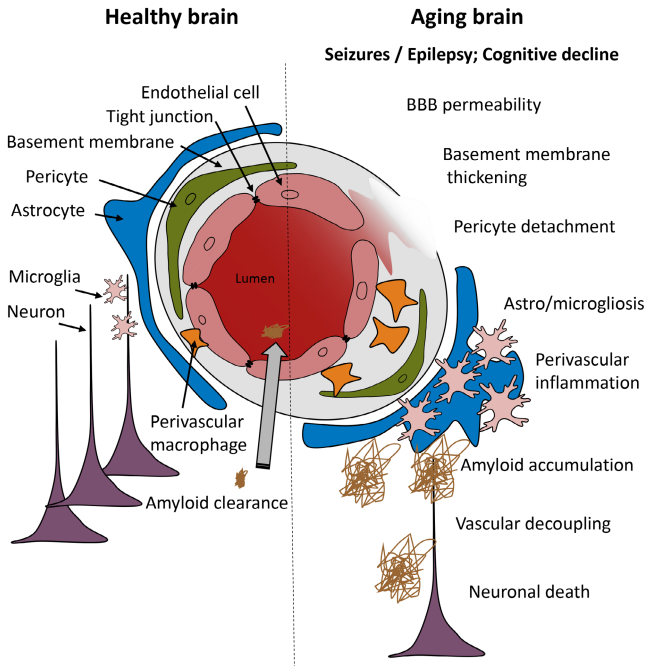

FIGURE 2 The neurovascular unit in the healthy and aging brain: intersections with seizure conditions. Left: in the healthy brain, endothelial cells are connected by tight junctions and form the blood-brain barrier (BBB). These endothelial cells are surrounded by pericytes (and perivascular macrophages) embedded in the basement membrane. Astrocytic endfeet cover the basement membrane and enclose the blood vessel, and neighboring microglia provide immune surveillance. Changes in local neuronal activity lead to subsequent changes in cerebral blood flow, a process that is called neurovascular coupling. Furthermore, several transporters are active, for example, to clear amyloid from the brain. Right: detrimental processes during aging can intersect with seizure pathophysiology. These changes include increased BBB permeability, basement membrane thickening, pericyte detachment, astrocytosis and microgliosis, perivascular inflammation, amyloid and tau accumulation, and neuronal death, which may converge to seizure, epilepsy and/or cognitive decline

parenchyma (Figure 2; see Ref. 10). The BBB is a gateway, and the first cell type encountered when entering the brain from the blood is the BMEC. These cells are connected via tight and adherens junctions, restricting the paracellular diffusion of ions (eg, Na^+, K^+, and Cl^-), macromolecules, and polar solutes, but allowing oxygen/CO_2 via diffusion (see Ref. 10 and11). Tight junction proteins have a size-selective permeability to uncharged molecules of up to 4 nm, suggesting that larger molecules can passively traverse only when the permeability of the BBB increases or via ad hoc transport or metabolic mechanisms.[12–14] BMECs produce a variety of molecules, including inflammatory mediators, growth factors, and extracellular matrix proteins, that modulate diverse molecular pathways and allow adaptations during physiological and pathological stimuli (see[15,16]). BMECS are encased by a continuous basement membrane, consisting of an inner layer produced by BMECs and pericytes and a parenchymal layer shaped by astrocytes (Figure 2).[17,18] The basement membrane consists of laminin, collagen IV, nidogen, and heparan sulfate proteoglycans that support mutual interactions between BMECs, pericytes, and astrocytes.[15,18,19] The basement membrane is a physical barrier with an ideal location for signaling processes.[20] Pericytes are mural cells located within the basement membrane, where they interact with BMECs and astrocytic end-feet to participate in structural and homeostatic BBB functions (Figure 2; and[21,22]). Pericytes communicate directly with BMECs through gap junctions and adjacent pericytes via peg-and-socket contacts.[22] They are essential for the normal development and function of the brain arterioles and capillaries, including tightness or permeability properties and cerebral blood flow regulation.[22,23] Pericytes interplay with immune cells[24 25]; they may have macrophage-like properties[26] and rapidly relay inflammatory signals from the periphery.[27] Astrocytes ensheath with their endfeet perivascular pericytes, the basal lamina, and neuronal processes (Figures 1 and 2). They are centrally positioned between neurons and BMECs. They are essential for neurovascular coupling, the dynamic control of local blood flow in response to increased metabolic needs due to neural activity.[28–30] They express ion channels, transporters, and receptors, enabling their critical roles in modulating synaptic activity via potassium buffering, pH regulation, neurotransmitter uptake, gliotransmitter release, and maintenance of neuronal homeostasis.[30] Astrocytes produce inflammatory mediators and extracellular matrix proteins, with either BBB-promoting or BBB-disrupting effects, depending on the signals received from neurons, microglia, and endothelial cells (see[15,16,30]). In addition, they are essential for perivascular clearance via the glymphatic system.[31] Microglia and oligodendrocytes neighbor the BBB. Microglia are the primary brain immune effector cells that become activated and undergo a morphological and functional transformation during brain injuries and diseases (see Ref. 32). Oligodendrocytes are responsible for forming myelin sheets that provide support and insulation to axons in the central nervous system.[32] Finally, perivascular macrophages lie on, or close to, the outer (abluminal) surface of blood vessels.[33] Like pericytes, they can regulate blood vessel permeability and immune functions by producing inflammatory mediators and performing phagocytosis.[32,33] These fundamental descriptions (comprehensively reviewed in Ref. 20 and 34–36) illustrate the cellular complexity of the BBB interface within the NVU, underpinning direct liaisons between regional cerebrovascular functions and permeability, inflammation, and neuronal activity regulations. Failure of these precise cellular and homeostatic interactions during

pathological conditions favors abnormal neuronal firing or seizures.

3 | NEUROVASCULAR DYSFUNCTION IS A RISK FACTOR FOR SEIZURES AND EPILEPSY DURING AGING: CLINICAL CLUES.

Particularly in the aging population, brain insults or diseases can promote seizures and late-onset epilepsy (LOE).[37] A significant subset of LOE remains of uncertain origin,[38] and clinical evidence indictates that cerebrovascular dysfunction could represent an underlying and converging pathological substrate.[6,39] This is coherent with the fact that an increase in BBB permeability favors seizure activity or abnormal neuronal transmission by homeostatic and inflammatory dysregulations (see Ref. 6, 24, and 40–44). Acute (eg, stroke and traumatic brain injury) and long-term (eg, neurodegenerative disorders, chronic traumatic encephalopathy) pathologies can be epileptogenic and are associated with an increased risk for seizures and epilepsy in the elderly (Figure 3).[3,45] These acute and chronic conditions can present with NVU dysfunction intertwined with brain inflammation. Here, we focus on cerebrovascular diseases, traumatic brain injury, and neurodegenerative disorders.

Cerebrovascular diseases (subarachnoid hemorrhage, intracerebral hemorrhage, occlusion and stenosis of cerebral arteries, transient cerebral ischemia[46]) are known risk factors for LOE.[47] Post-stroke epilepsy (PSE) accounts for up to 50% of LOE cases.[45,48] The risk for seizures and PSE increases with age, estimated to be six times higher in patients >60 years than younger subjects.[49] Adult subjects with hypertension presented a 2-fold risk of developing epilepsy. Hypertension was proposed as a potentially modifiable vascular risk factor.[45] Patients with hemorrhagic stroke or presenting hemorrhagic transformation are at higher risk of seizures[50] (eg, within 7 days from the stroke episode[51]). The presentation of early seizures post-stroke significantly increases the incidence of delayed PSE. Seizures are most common when the stroke occurs at the middle cerebral artery branch, associated with disturbances in the microcirculation.[50–52] At the cellular level, an early post-stroke seizure may result from the sudden increase of BBB permeability, leading to a loss of parenchymal ionic and neurotransmitter homeostasis. It can be associated with local pro-inflammatory elements.[52] Proteomic studies performed on mechanically retrieved thrombi unveiled the presence of pro-inflammatory cytokines, adhesion molecules, and T cells, supporting the existence of a local inflammation that can negatively impact the brain endothelium.[53–55] Cerebrovascular permeability and inflammation are proposed mechanisms for PSE and seizures.[34,53]

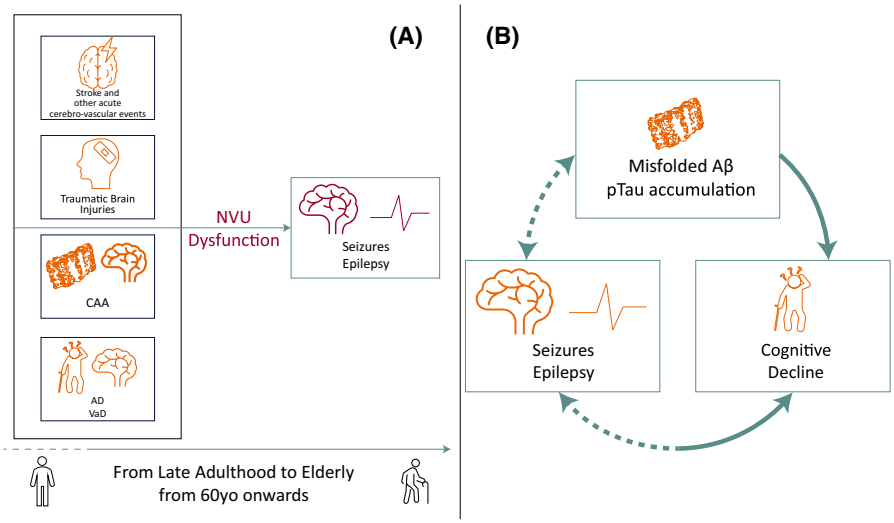

FIGURE 3 Neurovascular dysfunction as a converging risk factor for late-onset seizures or epilepsy and cognitive decline. (A) An acute insult (e.g., stroke, traumatic brain injury, generalized status epilepticus) or a progressive disease (e.g., cerebral amyloid angiopathy, CAA; vascular dementia, VaD; Alzheimer's disease, AD) to the aging brain can precipitate seizures by a mechanism encompassing neurovascular unit (NVU) dysfunction, including increased blood-brain barrier (BBB) permeability, within an inflammatory environment. (B) Summary of bidirectional associations (to be demonstrated: dotted lines; likely or demonstrated: solid lines) and the vicious cycle between seizures, neurodegenerative pathways, and cognitive decline over time. Seizure activity may accelerate brain aging or promote markers of neurodegeneration, and neurodegenerative pathologies present with abnormal neuronal discharges or seizures

3.1 | Traumatic brain injury

Due to reduced autonomy and increased motor disabilities, older individuals are at high risk of falls[56] and traumatic brain injury (TBI). The latter is a leading cause of subdural and intracranial hemorrhage, diffuse cerebral edema, and skull fracture, all risk factors of post-traumatic epilepsy (PTE) in the aging population.[47,57] Although the risk for a single early seizure following TBI is higher at a young age (<5 years), PTE can develop in older individuals.[57] A computerized tomography (CT)–scan visible cortical insult is associated with a greater risk of developing PTE.[58] Experimentally and clinically, BBB dysfunction was indicated as one early event post-TBI, potentially underpinning the development of neurological defects or seizures over time.[59,60] Evidence shows a topographic association between cerebrovascular hypoxia, rapidly occurring post-TBI, and long-term changes of gamma waves.[59] Repeated TBI during early ages (eg, contact sports) or lifespan (eg, military, repeated accidents) can lead to chronic traumatic encephalopathy (CTE), a condition characterized by the accumulation of hyperphosphorylated tau (p-tau),[61] with extensions to Alzheimer's disease (AD). Clinically, CTE presents with impairments in cognition, behavior, mood, and in some cases, chronic headache and motor and cerebellar dysfunction.[61] Patients with CTE are at higher risk of developing epilepsy, with a suspected pathophysiological implication of repeated BBB damage consequent to TBI.[62,63]

3.2 | Neurodegenerative disorders

AD and vascular dementia (VaD) present with cerebrovascular alterations.[64–67] AD displays structural or permeability modifications of the BBB,[68] associated with accumulation or inadequate clearance of misfolded Aβ.[64] Neurovascular dysfunction can precede the clinical diagnosis of AD.[64,66,69] VaD is the result of widespread microangiopathy-related cerebral dysfunction (eg, vascular leukopathy), and it is associated with cardiovascular risk factors (hypertension, smoking, dyslipidemia, overweight).[70] Cerebral amyloid angiopathy (CAA), with misfolded amyloid beta at the pial and cortical vessels,[68] represents a risk factor for AD and hemorrhagic stroke, with an extension to seizure onset.[71]

Bidirectional associations between seizures, AD, and VaD are suspected.[72] Poorly controlled seizures are a risk factor for neurodegenerative diseases. In AD, seizures can occur during early, or pre-symptomatic disease stages.[73] The relative risk of seizures for patients with AD, VaD, or no dementia is 5.6/1000, 7.5/1000, and 0.8/1000 individuals each year, respectively.[74–77] Furthermore, abnormal tau phosphorylation exists in temporal lobe epilepsy (TLE) brain specimens, with subjects presenting comorbidities evocative of neurodegenerative conditions.[75, 76] Nevertheless, the prevalence of p-tau and amyloid plaques in human TLE remains debated.[78] These studies provide pathological elements of comparison and overlap between clinical TLE, AD-like patterns, and chronic encephalopathy.[73.79,80]

BBB dysfunction, specifically in the hippocampus, is associated with mild cognitive impairment.[81] A recent 2-year follow-up study performed in patients with cerebral small vessel disease, showed white and cortical gray matter BBB permeability associated with cognitive and executive function decline.[82] Hippocampal capillary dysfunction exists in individuals with early cognitive defects, irrespective of Aβ and tau-related biomarkers, suggesting BBB dysfunction as an initial biomarker of disease .[83] In addition, a transient EEG slowing of the cortical network occurs in AD patients, correlated with cognitive impairment.[84] Collectively, this clinical evidence delineates a context where acute insults and disease progression converge into NVU dysfunction as a possible unifying mechanism contributing to abnormal neuronal activities (Figure 3).

4 | NVU DYSFUNCTION IN THE AGING AND EPILEPTOGENIC BRAIN: EXPERIMENTAL EVIDENCE.

Experimentally, aging and seizures present overlapping NVU cellular changes or adaptations (Figure 2). With age, density and coverage of BMECs and pericytes decrease,[85] resulting in BBB dysfunction, particularly in brain regions vulnerable to age-related deteriorations, such as the hippocampus.[81,86] Furthermore, the expression of transporters located at the luminal and abluminal endothelial sides decreases,[7] leading to reduced uptake of nutrients into the brain and accumulation of waste products. In addition, thickening of the basement membrane ensues with aging, resulting in stiffening of the vasculature, underlined by increasing systolic blood pressure.[7] Although the number and size of astrocytes increase during aging,[87] a decline in the number of oligodendrocytes and heterogeneity of microglia can occur,[88,89] altogether leading to changes in brain clearance via the glymphatic system, reduced myelination, and altered immune surveillance. An inadequate response of the aging cerebrovasculature to specific vasodilators has been shown, such as reduced NO-mediated dilatation, oxidative stress, and vascular inflammation.[8] These events will decrease neurovascular coupling efficiency, further aggravated by myelin loss.[90]

BBB dysfunction during aging triggers the hyperactivation of transforming growth factor β (TGFβ) signaling in astrocytes and causes neural dysfunction and age-related pathology in rodents.[6] Infusion of serum albumin into the young rodent brain (mimicking BBB leakiness) induced astrocytic TGFβ signaling and an aged brain phenotype including aberrant electrocorticographic activity, vulnerability to seizures, and cognitive impairment.[6] Infusion of albumin into the cerebral ventricles of young rats led to a transient slowing of the cortical network. This event was also observed in cortical brain regions with BBB dysfunction in patients with AD and epilepsy and in three rodent models.[84]

Alterations in the composition of the extracellular matrix (ECM) are evident during aging and epileptogenesis, triggered by matrix metalloproteinases, endopeptidases that are critical for tissue formation, neuronal network remodeling, and BBB permeability.[91] Higher matrix metalloproteinase (MMP) expression and activity are associated with BBB permeability[92] via degradation of the basal lamina and tight junction proteins and promote the infiltration of neutrophils into the brain parenchyma,[93] which can contribute to epileptogenesis. This is corroborated by studies performed in MMP knockout mice in which BBB dysfunction, brain inflammation, and epileptogenesis could be attenuated or decreased after an initial insult.[94,95]

Pericytes are a cellular entry point and offer an opportunity to study new BBB restorative pharmacological strategies in central nervous system (CNS) diseases.[34,96,97] In general, the perivascular deconstruction, redistribution, and reactivity of pericytes, in coordination with glial cells, negatively impacts BBB permeability and contributes to brain inflammation.[97,98] Deficiency of pericytes during aging leads to brain hypoperfusion, resulting in secondary neurodegenerative changes.[99] Pericyte (NG2DsRed) detachment from the capillary occurs after experimental status epilepticus in the hippocampus and cortices.[24,34,44,100,101] In this condition, pericytes lose their bump-on-a-long appearance and perivascular processes, becoming hypertrophic over time.[40,44,102] The latter is qualitatively similar to the pericyte pathology reported after experimental traumatic brain injury or neurodegenerative disease during aging.[97,103] In a model of TLE, pericytes detach from the capillary during seizure progression.[24] Loss of pericyte coverage is followed by the formation of new cells at the capillary level after status epilepticus, disclosing complex dynamics and equilibriums of damage and repair processes.[100] At the functional level, a redistribution of mural cells modifies vasoreactivity and blood flow when endothelin-1 or glutamate was applied in vivo after status epilepticus.[100] Increased BBB permeability is preceded by capillary constriction with indications of pericyte damage mediating loss of capillary integrity, with involvement of pericyte mitochondrial depolarization.[104] In addition to their critical structural functions, pericytes have immunological features, and they can participate in peripheral or brain inflammation (see[98, 105]). Pericytes can express inflammatory mediators and present antigens.[98] For example, during experimental TLE progression, pericytes, microglia, and astrocytes become reactive and form a perivascular multi-cellular assembly.[24,34,106] The activated microglial cells accumulate at the outer BBB wall, potentially eliminating the damaged pericytes.[24] This regional multi-cellular cluster corresponds to areas with increased BBB permeability. Similar events occur in experimental autoimmune encephalopathy[107,108] and AD,[109,110] where the perivascular accumulation of microglial cells topographically overlays with the entry of blood fibrinogen or albumin into the brain parenchyma.

Along with the perivascular multi-cellular assembly developing during seizure conditions, increased platelet-derived growth factor receptor beta (PDGFRβ) expression and ectopic collagen III and IV perivascular deposits suggest the existence of pro-fibrotic mechanisms.[44,111] A perivascular multi-cellular activation in response to seizures could promote a localized scarring process, negatively affecting vascular tone[100] and neurovascular coupling.[104] Pro-inflammatory cytokines, such as IL-1β, can promote pericyte damage and microglia-pericyte assemblies,[24] along with BBB permeability changes.[112–118]

A pericyte-endothelial pathology also occurs in experimental and human neurodegenerative disorders, including AD.[83,97] Elegant studies revealed how the BBB directly contributes to, or even precedes, the onset or the progression of cognitive decline in AD patients with the apolipoprotein E (*APOE*) ε4 variant.[69,119] Furthermore, soluble PDGFRβ, a pericyte damage biomarker, was elevated in the cerebrospinal fluid of AD *APOE* ε4 carriers, predictive of subsequent cognitive decline. Experimentally, *APOE* ε4 accelerates BBB dysfunction, reduces cerebral blood flow over time, and promotes behavioral defects. This evidence illustrates a pathological neurovascular intersection between aging, AD, and epilepsy, supporting the hypothesis that regional BBB breakdown represents a mechanism, or a risk factor, for developing or accelerating neurodegenerative pathways.[72,75,76]

Aging is associated with gliosis, with complex transcriptome adaptations over time (see Ref. 120 and 121). A higher number of $GFAP^+$ astrocytes and Iba-1^+ microglia in the cortex of aging mice and increased receptor for advanced glycation end products were also reported.[122] These events are involved in the inflammatory response, brain entry of thrombin and albumin in hippocampal parenchyma, and indicate BBB permeability.[123] These changes were also observed in the cortex of APP/PS1 mice (an AD model), followed by the formation of Aβ plaques.

In the hippocampus, the appearance of Aβ plaques preceded these alterations.[123] Furthermore, at the peak of inflammation in APP/PS1 mice, microglial cells are activated, increasing BBB permeability.[123] Similarly, astrogliosis and microgliosis occur in models of epilepsy,[30] promoting epileptogenesis via disturbance of energy metabolism and gliotransmission, BBB permeability, dysregulation of blood flow, and the release of pro-inflammatory molecules.[30] Glial cells play an essential role in the elimination of Aβ.[124] Impaired amyloid-beta efflux and clearance, diminished cerebrospinal fluid (CSF) production, decreased enzymatic and metabolic activities, augmented influx of peripheral Aβ through the BBB, and overexpression of amyloid precursor protein contribute to cognitive decline.[99,123]

The role of perivascular macrophages during aging and epileptogenesis is less studied. Of interest, the number of hippocampal CD163-positive perivascular macrophages positevely correlates with BBB permeability in rats with recurrent spontaneous seizures.[125] In addition, the expression of CD68-positive monocytes/macrophages, chemokine (C–C motif) ligand 2, and CD163-positive perivascular macrophages correlated with the number of spontaneous seizures,[125] suggesting that these factors may contribute to epileptogenesis. Collectively, these data illustrate the multi-facet involvement of NVU cells during the aging processes, with specific overlaps and contextualization to epilepsies. This emerging knowledge requires systematic studies to define the cellular mechanisms and pharmacological targets tailored to seizure conditions during aging.

5 | OVERVIEW OF MODALITIES AND BIOMARKERS TO ASSESS NVU DYSFUNCTION: RELEVANCE TO SEIZURES AND AGING.

NUV dysfunction is etiological to brain diseases, and it enables the diagnosis of neurological disorders.[126] Over the last decades, new imaging and molecular biomarkers have emerged to track NVU dysfunction during age-related pathological conditions; now there is an opportunity to clinically and experimentally apply imaging and blood biomarkers to late-onset seizures and epilepsies. Depending on the required spatial and temporal resolution, experimental imaging tools vary from two-photon microscopy, laser speckle contrast imaging, to intrinsic optical imaging; translational and clinical modalities include positron emission tomographic (PET), single-photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI).[127–130] These techniques can be applied to study structural and functional modifications of the NVU during aging and epileptogenesis, such as BBB permeability, cerebral blood flow (CBF) alterations, inflammation, neuronal and axonal changes, as well as gradual, pathological processes such as the presence of amyloid and tau-related markers.[6,99,130–135] Recent developments include multi-photon laser scanning microscopy (MPLSM) and functional ultrasound imaging (fUSi).[128,136] MPLSM can be used for in vivo imaging of cellular dynamics and morphology, together with CBF.[128] fUSi is an innovative imaging modality based on Doppler ultrasound, capable of recording vascular brain activity over large scales (eg, tens of cubic millimeters) at unprecedented spatial and temporal resolution for such volumes (up to 10 μm pixel size at 10 kHz).[128] By merging these two technologies, researchers may have access to a more detailed view of the various processes at the neurovascular level.[128] Although these techniques were developed and tested in head-fixed animals, fUSi is also feasible in freely moving animals.[128]

Longitudinal MRI studies in rats after status epilepticus show that BBB dysfunction in the piriform network is a sensitive and specific predictor for epilepsy,[112,137] whereas diffused pathology is associated with a lower risk.[112] A multi-parametric MRI combined with machine-learning analysis revealed distinct pathological modifications of BBB permeability, blood volume fractions, and apparent diffusion coefficient in the hippocampal epileptogenic zone and seizure-propagating brain regions devoid of lesion.[40] In a TLE model, these imaging identifiers spatiotemporally overlapped with trajectories of brain inflammation, amyloidogenic, and tau-hyperphosphorylation changes unfolding over time.[138] These results are coherent with the evidence showing that vascular dysfunction is an element favoring neurodegenerative modifications over time, advocating for a regional cerebrovascular link between seizures and associated comorbidities.[97] Significant effort is currently devoted toward the prediction and risk assessment of AD and the transition from mild cognitive impairment to AD,[139] as well as in epilepsy, to define epileptogenic and seizure propagation regions based on BBB measures in experimental TLE.[40]

Considering PET, there are multiple imaging agents, including small molecules, peptides, affibodies, aptamers, antibodies, and nanoparticles.[130] Novel agents are being developed or under investigation, which may help identify NVU alterations at the molecular level. The gap between experimental models and patients for these novel imaging modalities is significant; the field of brain imaging is advancing swiftly, with the explicit goal of targeting increasingly larger volumes of tissue with high spatial and temporal resolution.[128]

Blood or peripheral fluids biomarkers of NVU dysfunction represent another emerging tool with diagnostic and prognostic values. In conditions of increased

BBB permeability, a panel of astrocyte, neuronal, and pericyte proteins can exit the brain into the peripheral blood, where they can be detected (see Ref. 126 for review). Although blood biomarkers of BBB permeability have not been studied in the specific context of LOE, significant indications exist for neurodegenerative and aging conditions.[72] In blood, phosphorylated tau (p-tau181, p-tau217) represents a biomarker for diagnosing or staging AD patients.[126] CSF Aβ42:Aβ40 ratio can discriminate AD from other neurological disorders. Furthermore, blood and CSF neurofilament light chains and GFAP correlate with AD staging.[126] A few studies focused on pediatric or young adults with epilepsies.[41,42,44] A systematic review indicated an increase of blood S100B, a BBB permeability biomarker.[140] MRI T1 peri-ictal imaging in drug-resistant epileptic patients correlates with blood S100B, indicating BBB permeability during a seizure.[141] Increased S100B blood levels in pediatric TLE were reported minutes after a complex partial seizure.[142] Blood S100B levels were increased in a pediatric population of intractable focal epilepsy.[143] Furthermore, accumulating evidence outlined specific blood microRNAs (miRNA) as biomarkers of neurovascular and neuroinflammatory modifications across epilepsies (see Ref. 144–146 for a comprehensive review). These emerging approaches are essential for identifying biomarkers of NVU dysfunction, with a prospect application to epilepsies in the aging population.

6 | NVU PHARMACOLOGY IN EPILEPSY: AVAILABLE MOLECULES FOR THE HOMEOSTATIC CONTROL OF BRAIN INFLAMMATION

Considering the ramifications of NVU dysfunction in seizure and neurodegenerative disorders, restoring cerebrovascular integrity within a broader control of brain inflammation could represent a strategy to prevent, curb, or halt disease progression. The pharmacological management of epilepsy can be age-dependent. Here, we hypothesize that treatments aimed at restoring NVU functions might reduce or prevent seizures during aging. Past studies point to a plethora of candidate molecules, novel or repurposed, exerting BBB protective and general anti-inflammatory effects. Here, we examine this existing evidence and the possible benefits of contemporary molecules in seizure disorders, although recognizing that pre-clinical studies performed during aging are unavailable. Table 1 identifies four categories: pro- and anti-inflammatory equilibrium pathways, PDGF/TGF pathways, oxidative stress pathways, and matrix metalloproteinases. BBB permeability and neuroinflammation intersect during seizures and broad-spectrum (e.g., corticosteroids[147,148]), or specific anti-inflammatory molecules (e.g., anakinra/VX-765[149–152] or antibodies against integrins, α4 or VCAM-1[153]), as well as the immunosuppressant and mTOR inhibitor rapamycin[137,154,155] can ameliorate BBB integrity, and reduce ictogenesis or epileptogenesis in experimental models. Some promising results exist for specific compounds in clinical studies with drug-resistant epilepsies (Table 1). Boosting the endogenous anti-inflammatory mechanisms represents an emerging approach, using peripheral T-regulatory cells[156] or Annexin-A1.[157–159] Other therapeutic approaches are PDGF/TGF targeting (using PDGF-BB,[100] Imatinib,[44] IPW,[6] or losartan,[112,160–165] antioxidant treatment vitexin[166] or carveol[167]), or matrix metalloproteinase inhibition[95,168] that were shown to reduce BBB permeability and brain inflammation, ictogenesis, or epileptogenesis.[169] However, the efficacy of these molecules in curbing age-related pathological changes or aggravations remains to be investigated.

7 | FUTURE DIRECTIONS AND CONCLUSIONS

Although the incidence of seizures in the aging population increases, pre-clinical studies on this phenomenon lag behind. A caveat of the proposed framework is that NVU dysfunctions occur in various pathologies, not necessarily leading to epilepsy, and substantial research is needed to fully understand how the NVU modifies during aging and how this can contribute, or not, to seizures or epileptogenesis. It is also essential to develop minimally invasive, clinically applicable methods for diagnosing the extent and localization of NVU dysfunction. Pre-clinical studies have shown that detecting and quantifying NVU alterations is feasible. Novel developments are being implemented in the clinic (e.g., quantitative contrast-enhanced MRI), which may help identify novel biomarkers for epileptogenesis or treatment response in the aging population. Existing and urgent questions are: whom should we treat? When should we start treatment, at which dose, and for how long? Coupling accurate diagnosis to specific therapy will allow tailoring the type, dose, and duration of treatment to each patient, increasing the likelihood that personalized medicine could become a new approach for the prevention and treatment of epilepsy in the elderly. Essential factors to be considered are lifestyle, diet, exercise, and being cognitively active. The latter elements and their impact on the NVU functions and age-related pathologies remain to be fully studied.

In conclusion, we have presented an overview of the pathophysiological intersections between the NVU, brain

TABLE 1 NVU and inflammation-homeostatic targets applicable to epilepsies

Drug		Group	Specific mechanism	Reported effects in experimental studies	Experimental model	Epilepsy-related clinical trials or usage
Rapamycin	Target Inflammatory Mediators or Boosting Endogenous Anti-inflammatory Mechanisms	Immunosuppressant	mTOR antagonist	Reduces BBB permeability and epileptogenesis	Rat electrical[154] and kainic acid SE model[137,155]	Tuberous sclerosis complex[170–173]
Anakinra/VX-765		Interleukin-1 receptor antagonist	Human interleukin-1 receptor antagonist (IL-1Ra)	Reduces BBB permeability, inflammation, ictogenesis, epileptogenesis	Rat pilocarpine SE model,[149,150] mouse kainic acid SE model,[151] guinea pig ex-vivo brain model[149,152]	Febrile infection-related epilepsy Syndrome (FIRES),[174–176] Temporal Lobe Epilepsy[177]
Dexamethasone		Glucocorticoid	Decreased *JMJD3* gene expression. Suppression of MMP-2, MMP-3, and MMP-9 gene activation	Reduces BBB permeability, ictogenesis, and epileptogenesis Preserves tight junctions' integrity	Rat pilocarpine SE model,[148] rat febrile seizure model[147] In vitro BBB model[178–180]	Epileptic encephalopathies,[181,182] FIRES[183]
Annexin-A1 (ANXA1)		Endogenous glucocorticoid anti-inflammatory player	Inhibition of the small G protein RhoA	Reduces BBB permeability inflammation, neurodegeneration, ictogenesis, and epileptogenesis Restores cell polarity, cytoskeleton integrity, and paracellular permeability	Mouse kainic acid SE model,[157] rat pilocarpine SE model,[158] ANXA-/- mice[159] In vitro BBB model[159]	None
Integrins, α_4 or VCAM-1 antibody		Modulation of vascular adhesion molecules	Blockade of T-cells vascular interplay	Reduces BBB permeability, ictogenesis, and epileptogenesis	Mouse pilocarpine SE model[153]	None
T-regulatory cells		Endogenous anti-inflammatory $CD4^+$, $CD25^+$ $FoxP3^+$ leukocytes	Suppress activation, proliferation and cytokine production from T cells	T-cell depletions increase seizure activity and inflammation	Mouse kainic acid SE model[156]	None

(Continues)

TABLE 1 (Continued)

Drug		Group	Specific mechanism	Reported effects in experimental studies	Experimental model	Epilepsy-related clinical trials or usage
PDGF-BB	PDGF/TGF Targeting	PDGFR agonist	Pericyte trophism during acute damage	Reduces pericyte loss and vascular pathology after SE Restores BBB function in an endothelial monolayer	Mouse kainic acid SE model[100] In vitro BBB model[184]	None
Imatinib		Kinase inhibitor	Inhibition of PDGF signaling. Anti-inflammatory/ pericyte	Reduces vascular fibrosis	Organotypic hippocampal culture with kainic acid[44]	Epilepsy with chronic myeloid leukemia,[185] glioblastoma[186,187]
IPW		TGF-b receptor inhibitor	Inhibition of TGFβR signaling	Reduces transient paroxysmal slow wave events, ictogenesis, and TGFβ signaling improve cognition	Serum albumin brain infusion in mice[6]	None
Losartan		Antihypertensive	Angiotensin II antagonist	Reduces BBB permeability, inflammation, oxidative stress, neuronal loss, ictogenesis, and epileptogenesis	Albumin or bile salt application on the cortex of rats[160] rat pilocarpine SE model,[161,162] rat amygdala kindling model,[163] rat pentylenetetrazol kindling model,[164] rat kainic acid SE model,[165] rat paraoxon SE model[112]	None
Vitexin	Oxidative Stress Targeting	Flavonoid	Antioxidant	Reduces BBB permeability, inflammation, ictogenesis	Rat hypoxia-ischemia model[166]	None
Carveol		Terpenoid	Antioxidant	Reduces BBB permeability, inflammation and ictogenesis	Rat pentylenetetrazol kindling model[167]	None

TABLE 1 (Continued)

Drug		Group	Specific mechanism	Reported effects in experimental studies	Experimental model	Epilepsy-related clinical trials or usage
IPR-179 (or ACT-03)	Extracellular matrix Targeting	Matrix metalloproteinase inhibitor	MMP2/9 inhibitor	Reduces MMP9 expression, ictogenesis, and epileptogenesis	Rat hippocampal kindling model and mouse kainic acid SE model[95]	None
Doxycline		Matrix metalloproteinase inhibitor	Broad-spectrum MMP inhibitor	Reduces perineuronal net less, synaptic reorganization, neuronal loss, ictogenesis	Rat amygdala kindling model[168]	None

Abbreviations: BBB, blood-brain barrier; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; PDGF-BB, platelet-derived growth Factor-BB; PDGFR, platelet-derived growth factor receptor; SE, status epilepticus; TGF, transforming growth factor; VCAM, vascular cell adhesion molecule.

inflammation, epilepsy, and seizures during aging. The discovery of new disease mechanisms will pave the way to original opportunities for biomarkers predicting epilepsy onset and related cognitive dysfunction. It is essential to develop novel therapeutic strategies to curb or prevent seizure onset and epilepsy in the aging population.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Neither of the authors has any conflict of interest to disclose.

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REFERENCES

1. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet (London, England). 2009;374:1196–208.
2. Krauss G. Epilepsy is not resolved. Epilepsy Curr. 2014;14:339–40.
3. Sen A, Jette N, Husain M, Sander JW. Epilepsy in older people. Lancet. 2020;395:735–48.
4. United Nations DoEaSA, Population Division. World Population Ageing 2019: Highlights. In Editor (Ed)^(Eds) Book World Population Ageing 2019: Highlights; 2019.
5. Erdo F, Denes L, de Lange E. Age-associated physiological and pathological changes at the blood-brain barrier: A review. J Cereb Blood Flow Metab. 2017;37:4–24.
6. Senatorov VV Jr, Friedman AR, Milikovsky DZ, Ofer J, Saar-Ashkenazy R, Charbash A, et al. Blood-brain barrier dysfunction in aging induces hyperactivation of TGFbeta signaling and chronic yet reversible neural dysfunction. Sci Transl Med. 2019;11:eaaw8283.
7. Banks WA, Reed MJ, Logsdon AF, Rhea EM, Erickson MA. Healthy aging and the blood-brain barrier. Nat Aging. 2021;1:243–54.
8. Enciu AM, Gherghiceanu M, Popescu BO. Triggers and effectors of oxidative stress at blood-brain barrier level: relevance for brain ageing and neurodegeneration. Oxid Med Cell Longev. 2013;2013:297512.
9. The US Population Is Aging. Available at: https://www.urban.org/policy-centers/cross-center-initiatives/program-retirement-policy/projects/data-warehouse/what-future-holds/us-population-aging
10. Daneman R. The blood-brain barrier in health and disease. Ann Neurol. 2012;72:648–72.
11. Coomber BL, Stewart PA. Morphometric analysis of CNS microvascular endothelium. Microvasc Res. 1985;30:99–115.
12. Van Itallie CM, Anderson JM. Claudins and epithelial paracellular transport. Annu Rev Physiol. 2006;68:403–29.
13. Van Itallie CM, Holmes J, Bridges A, Gookin JL, Coccaro MR, Proctor W, et al. The density of small tight junction pores varies among cell types and is increased by expression of claudin-2. J Cell Sci. 2008;121:298–305.
14. Ghosh C, Puvenna V, Gonzalez-Martinez J, Janigro D, Marchi N. Blood-brain barrier P450 enzymes and multidrug transporters in drug resistance: a synergistic role in neurological diseases. Curr Drug Metab. 2011;12:742–9.
15. Baeten KM, Akassoglou K. Extracellular matrix and matrix receptors in blood-brain barrier formation and stroke. Dev Neurobiol. 2011;71:1018–39.
16. van Vliet EA, Aronica E, Vezzani A, Ravizza T. Review: Neuroinflammatory pathways as treatment targets and biomarker candidates in epilepsy: emerging evidence from preclinical and clinical studies. Neuropathol Appl Neurobiol. 2018;44:91–111.
17. Del Zoppo GJ, Milner R, Mabuchi T, Hung S, Wang X, Koziol JA. Vascular matrix adhesion and the blood-brain barrier. Biochem Soc Trans. 2006;34:1261–6.
18. Sorokin L. The impact of the extracellular matrix on inflammation. Nat Rev Immunol. 2010;10:712–23.
19. Wu C, Ivars F, Anderson P, Hallmann R, Vestweber D, Nilsson P, et al. Endothelial basement membrane laminin alpha5 selectively inhibits T lymphocyte extravasation into the brain. Nat Med. 2009;15:519–27.
20. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015;7:a020412.
21. Armulik A, Genove G, Mae M, Nisancioglu MH, Wallgard E, Niaudet C, et al. Pericytes regulate the blood-brain barrier. Nature. 2010;468:557–61.
22. Winkler EA, Bell RD, Zlokovic BV. Central nervous system pericytes in health and disease. Nat Neurosci. 2011;14:1398–405.
23. McConnell HL, Kersch CN, Woltjer RL, Neuwelt EA. The translational significance of the neurovascular unit. J Biol Chem. 2017;292:762–70.
24. Klement W, Garbelli R, Zub E, Rossini L, Tassi L, Girard B, et al. Seizure progression and inflammatory mediators promote pericytosis and pericyte-microglia clustering at the cerebrovasculature. Neurobiol Dis. 2018;113:70–81.
25. Ozen I, Deierborg T, Miharada K, Padel T, Englund E, Genove G, et al. Brain pericytes acquire a microglial phenotype after stroke. Acta Neuropathol. 2014;128:381–96.
26. Balabanov R, Washington R, Wagnerova J, Dore-Duffy P. CNS microvascular pericytes express macrophage-like function, cell surface integrin alpha M, and macrophage marker ED-2. Microvasc Res. 1996;52:127–42.
27. Duan L, Zhang XD, Miao WY, Sun YJ, Xiong G, Wu Q, et al. PDGFRbeta cells rapidly relay inflammatory signal from the circulatory system to neurons via chemokine CCL2. Neuron. 2018;100(183–200):e188.
28. Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. Glial and neuronal control of brain blood flow. Nature. 2010;468:232–43.
29. Gordon GR, Howarth C, MacVicar BA. Bidirectional control of arteriole diameter by astrocytes. Exp Physiol. 2011;96:393–9.

30. Verhoog QP, Holtman L, Aronica E, Van Vliet EA. Astrocytes as guardians of neuronal excitability: mechanisms underlying epileptogenesis. Front Neurol. 2020;11:591690.
31. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The glymphatic system: a beginner's guide. Neurochem Res. 2015;40:2583–99.
32. Koizumi T, Kerkhofs D, Mizuno T, Steinbusch HWM, Foulquier S. Vessel-associated immune cells in cerebrovascular diseases: from perivascular macrophages to vessel-associated microglia. Front Neurosci. 2019;13:1291.
33. Lapenna A, De Palma M, Lewis CE. Perivascular macrophages in health and disease. Nat Rev Immunol. 2018;18:689–702.
34. Giannoni P, Badaut J, Dargazanli C, De Maudave AF, Klement W, Costalat V, et al. The pericyte-glia interface at the blood-brain barrier. Clin Sci (Lond). 2018;132:361–74.
35. Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-brain barrier: from physiology to disease and back. Physiol Rev. 2019;99:21–78.
36. van Vliet EA, Aronica E, Gorter JA. Blood-brain barrier dysfunction, seizures and epilepsy. Semin Cell Dev Biol. 2015;38:26–34.
37. Beghi E, Giussani G. Aging and the epidemiology of epilepsy. Neuroepidemiology. 2018;51:216–23.
38. Copeland LA, Ettinger AB, Zeber JE, Gonzalez JM, Pugh MJ. Psychiatric and medical admissions observed among elderly patients with new-onset epilepsy. BMC Health Serv Res. 2011;11:84.
39. Gibson LM, Allan SM, Parkes LM, Emsley HCA. Occult Cerebrovascular Disease and Late-Onset Epilepsy: Could Loss of Neurovascular Unit Integrity Be a Viable Model? Cardiovasc Psychiatry Neurol. 2011;2011:1–7.
40. Boux F, Forbes F, Collomb N, Zub E, Maziere L, de Bock F, et al. Neurovascular multiparametric MRI defines epileptogenic and seizure propagation regions in experimental mesiotemporal lobe epilepsy. Epilepsia. 2021;62:1244–55.
41. Marchi N, Tierney W, Alexopoulos AV, Puvenna V, Granata T, Janigro D. The etiological role of blood-brain barrier dysfunction in seizure disorders. Cardiovasc Psychiatry Neurol. 2011;2011:482415.
42. Friedman A, Kaufer D. Blood-brain barrier breakdown and blood-brain communication in neurological and psychiatric diseases. Cardiovasc Psychiatry Neurol. 2011;2011:431470.
43. Giannoni P, Badaut J, Dargazanli C, De Maudave AFH, Klement W, Costalat V, et al. The pericyte-glia interface at the blood-brain barrier. Clin Sci (London, England). 1979;2018(132):361–74.
44. Klement W, Blaquiere M, Zub E, deBock F, Boux F, Barbier E, et al. A pericyte-glia scarring develops at the leaky capillaries in the hippocampus during seizure activity. Epilepsia. 2019;60:1399–411.
45. Stefanidou M, Himali JJ, Devinsky O, Romero JR, Ikram MA, Beiser AS, et al. Vascular risk factors as predictors of epilepsy in older age: The Framingham Heart Study. Epilepsia. 2021;63(1):237–43.
46. World Health O. ICD-10: international statistical classification of diseases and related health problems: tenth revision. In Editor (Ed). Book ICD-10: international statistical classification of diseases and related health problems : tenth revision, Geneva: World Health Organization; 2004.
47. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. N Engl J Med. 1998;338:20–4.
48. Brodie MJ, Elder AT, Kwan P. Epilepsy in later life. Lancet Neurol. 2009;8:1019–30.
49. So EL, Annegers JF, Hauser WA, O'Brien PC, Whisnant JP. Population-based study of seizure disorders after cerebral infarction. Neurology. 1996;46:350–5.
50. Serafini A, Gigli GL, Gregoraci G, Janes F, Cancelli I, Novello S, et al. Are early seizures predictive of epilepsy after a stroke? Results of a Population-Based Study. Neuroepidemiology. 2015;45:50–8.
51. Mohamed C, Kissani N. Early seizures in acute stroke. Pan Afr Med J. 2015;20:136.
52. Yang H, Rajah G, Guo A, Wang Y, Wang Q. Pathogenesis of epileptic seizures and epilepsy after stroke. Neurol Res. 2018;40:426–32.
53. Dargazanli C, Zub E, Deverdun J, Decourcelle M, de Bock F, Labreuche J, et al. Machine learning analysis of the cerebrovascular thrombi proteome in human ischemic stroke: an exploratory study. Front Neurol. 2020;11:575376.
54. Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. Nat Rev Cardiol. 2021;18(9):666–82.
55. Gibson LM, Hanby MF, Al-Bachari SM, Parkes LM, Allan SM, Emsley HC. Late-onset epilepsy and occult cerebrovascular disease. J Cereb Blood Flow Metab. 2014;34:564–70.
56. Panel on Prevention of Falls in Older Persons AGS, British Geriatrics S. Summary of the updated American geriatrics society/British geriatrics society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc. 2011;59:148–57.
57. Johnston A, Smith PEM. Epilepsy in the elderly. Expert Rev Neurother. 2010;10:1899–910.
58. Xu T, Yu X, Ou S, Liu X, Yuan J, Huang H, et al. Risk factors for posttraumatic epilepsy: A systematic review and meta-analysis. Epilepsy Behav. 2017;67:1–6.
59. Ichkova A, Rodriguez-Grande B, Zub E, Saudi A, Fournier ML, Aussudre J, et al. Early cerebrovascular and long-term neurological modifications ensue following juvenile mild traumatic brain injury in male mice. Neurobiol Dis. 2020;141:104952.
60. Tomkins O, Feintuch A, Benifla M, Cohen A, Friedman A, Shelef I. Blood-brain barrier breakdown following traumatic brain injury: a possible role in posttraumatic epilepsy. Cardiovasc Psychiatry Neurol. 2011;2011:765923.
61. Stern RA, Daneshvar DH, Baugh CM, Seichepine DR, Montenigro PH, Riley DO, et al. Clinical presentation of chronic traumatic encephalopathy. Neurology. 2013;81:1122–9.
62. Marchi N, Bazarian JJ, Puvenna V, Janigro M, Ghosh C, Zhong J, et al. Consequences of repeated blood-brain barrier disruption in football players. PLoS One. 2013;8:e56805.
63. Alyenbaawi H, Kanyo R, Locskai LF, Kamali-Jamil R, DuVal MG, Bai Q, et al. Seizures are a druggable mechanistic link between TBI and subsequent tauopathy. Elife. 2021;10:e58744.
64. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol. 2018;14:133–50.
65. Kalaria RN. The pathology and pathophysiology of vascular dementia. Neuropharmacology. 2018;134:226–39.
66. Hussain B, Fang C, Chang J. Blood-brain barrier breakdown: an emerging biomarker of cognitive impairment in normal aging and dementia. Front Neurosci. 2021;15:688090.

67. Giannoni P, Claeysen S, Noe F, Marchi N. Peripheral routes to neurodegeneration: passing through the blood-brain barrier. Front Aging Neurosci. 2020;12:3.
68. Giannoni P, Arango-Lievano M, Neves ID, Rousset MC, Baranger K, Rivera S, et al. Cerebrovascular pathology during the progression of experimental Alzheimer's disease. Neurobiol Dis. 2016;88:107–17.
69. Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney MD, Chakhoyan A, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. Nature. 2020;581:71–6.
70. Iemolo F, Duro G, Rizzo C, Castiglia L, Hachinski V, Caruso C. Pathophysiology of vascular dementia. Immun Ageing. 2009;6:13.
71. Yamada M. Cerebral amyloid angiopathy: emerging concepts. J Stroke. 2015;17:17–30.
72. Romoli M, Sen A, Parnetti L, Calabresi P, Costa C. Amyloid-beta: a potential link between epilepsy and cognitive decline. Nat Rev Neurol. 2021;17:469–85.
73. Joutsa J, Rinne JO, Hermann B, Karrasch M, Anttinen A, Shinnar S, et al. Association between childhood-onset epilepsy and amyloid burden 5 decades later. JAMA Neurol. 2017;74:583–90.
74. Imfeld P, Bodmer M, Schuerch M, Jick SS, Meier CR. Seizures in patients with Alzheimer's disease or vascular dementia: A population-based nested case-control analysis. Epilepsia. 2013;54:700–7.
75. Gourmaud S, Shou H, Irwin DJ, Sansalone K, Jacobs LM, Lucas TH, et al. Alzheimer-like amyloid and tau alterations associated with cognitive deficit in temporal lobe epilepsy. Brain. 2020;143:191–209.
76. Tai XY, Koepp M, Duncan JS, Fox N, Thompson P, Baxendale S, et al. Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: a study of temporal lobe resections. Brain. 2016;139:2441–55.
77. Casillas-Espinosa PM, Ali I, O'Brien TJ. Neurodegenerative pathways as targets for acquired epilepsy therapy development. Epilepsia Open. 2020;5:138–54.
78. Silva JC, Vivash L, Malpas CB, Hao Y, McLean C, Chen Z, et al. Low prevalence of amyloid and tau pathology in drug-resistant temporal lobe epilepsy. Epilepsia. 2021;62(12):3058–67.
79. Gan L, Cookson MR, Petrucelli L, La Spada AR. Converging pathways in neurodegeneration, from genetics to mechanisms. Nat Neurosci. 2018;21:1300–9.
80. Lam AD, Cole AJ, Cash SS. New approaches to studying silent mesial temporal lobe seizures in Alzheimer's disease. Front Neurol. 2019;10:959.
81. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, et al. Blood-brain barrier breakdown in the aging human hippocampus. Neuron. 2015;85:296–302.
82. Kerkhofs D, Wong SM, Zhang E, Uiterwijk R, Hoff EI, Jansen JFA, et al. Blood-brain barrier leakage at baseline and cognitive decline in cerebral small vessel disease: a 2-year follow-up study. Geroscience. 2021;43(4):1643–52.
83. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med. 2019;25:270–6.
84. Milikovsky DZ, Ofer J, Senatorov VV Jr, Friedman AR, Prager O, Sheintuch L, et al. Paroxysmal slow cortical activity in Alzheimer's disease and epilepsy is associated with blood-brain barrier dysfunction. Sci Transl Med. 2019;11:eaaw8954.
85. Stewart PA, Magliocco M, Hayakawa K, Farrell CL, Del Maestro RF, Girvin J, et al. A quantitative analysis of blood-brain barrier ultrastructure in the aging human. Microvasc Res. 1987;33:270–82.
86. Verheggen ICM, de Jong JJA, van Boxtel MPJ, Gronenschild E, Palm WM, Postma AA, et al. Increase in blood-brain barrier leakage in healthy, older adults. Geroscience. 2020;42:1183–93.
87. Middeldorp J, Hol EM. GFAP in health and disease. Prog Neurogibol. 2011;93:421–43.
88. Rodriguez-Arellano JJ, Parpura V, Zorec R, Verkhratsky A. Astrocytes in physiological aging and Alzheimer's disease. Neuroscience. 2016;323:170–82.
89. Kettenmann H, Hanisch UK, Noda M, Verkhratsky A. Physiology of microglia. Physiol Rev. 2011;91:461–553.
90. Zimmerman B, Rypma B, Gratton G, Fabiani M. Age-related changes in cerebrovascular health and their effects on neural function and cognition: A comprehensive review. Psychophysiology. 2021;58:e13796.
91. Rempe RG, Hartz AMS, Soldner ELB, Sokola BS. Matrix metalloproteinase-mediated blood-brain barrier dysfunction in epilepsy. J Neurosci. 2018;38:4301–15.
92. Mun-Bryce S, Rosenberg GA. Gelatinase B modulates selective opening of the blood-brain barrier during inflammation. Am J Physiol. 1998;274:R1203–11.
93. Gurney KJ, Estrada EY, Rosenberg GA. Blood-brain barrier disruption by stromelysin-1 facilitates neutrophil infiltration in neuroinflammation. Neurobiol Dis. 2006;23:87–96.
94. Broekaart DW, Korotkov A, Gorter JA, van Vliet EA. Perivascular inflammation and extracellular matrix alterations in blood-brain barrier dysfunction and epilepsy. In: Janigro D, Nehlig A, Marchi N, editors. Inflammation and epilesy: new vistas. Switzerland: Springer Nature Switzerland; 2021. p. 71–106.
95. Broekaart DW, Bertran A, Jia S, Korotkov A, Senkov O, Bongaarts A, et al. The matrix metalloproteinase inhibitor IPR-179 has antiseizure and antiepileptogenic effects. J Clin Invest. 2021;131:e138332.
96. Sweeney MD, Ayyadurai S, Zlokovic BV. Pericytes of the neurovascular unit: key functions and signaling pathways. Nat Neurosci. 2016;19:771–83.
97. Sweeney MD, Montagne A, Sagare AP, Nation DA, Schneider LS, Chui HC, et al. Vascular dysfunction-The disregarded partner of Alzheimer's disease. Alzheimers Dement. 2019;15:158–67.
98. Rustenhoven J, Jansson D, Smyth LC, Dragunow M. Brain pericytes as mediators of neuroinflammation. Trends Pharmacol Sci. 2017;38:291–304.
99. Marques F, Sousa JC, Sousa N, Palha JA. Blood-brain-barriers in aging and in Alzheimer's disease. Mol Neurodegener. 2013;8:38.
100. Arango-Lievano M, Boussadia B, De Terdonck LDT, Gault C, Fontanaud P, Lafont C, et al. Topographic reorganization of cerebrovascular mural cells under seizure conditions. Cell Rep. 2018;23:1045–59.
101. Milesi S, Boussadia B, Plaud C, Catteau M, Rousset MC, De Bock F, et al. Redistribution of PDGFRbeta cells and NG2DsRed pericytes at the cerebrovasculature after status epilepticus. Neurobiol Dis. 2014;71:151–8.
102. Librizzi L, de Cutis M, Janigro D, Runtz L, de Bock F, Barbier EL, et al. Cerebrovascular heterogeneity and neuronal excitability. Neurosci Lett. 2018;667:75–83.

103. Zehendner CM, Sebastiani A, Hugonnet A, Bischoff F, Luhmann HJ, Thal SC. Traumatic brain injury results in rapid pericyte loss followed by reactive pericytosis in the cerebral cortex. Sci Rep. 2015;5:13497.
104. Prager O, Kamintsky L, Hasam-Henderson LA, Schoknecht K, Wuntke V, Papageorgiou I, et al. Seizure-induced microvascular injury is associated with impaired neurovascular coupling and blood-brain barrier dysfunction. Epilepsia. 2019;60:322–36.
105. Smyth LCD, Rustenhoven J, Park TI, Schweder P, Jansson D, Heppner PA, et al. Unique and shared inflammatory profiles of human brain endothelia and pericytes. J Neuroinflammation. 2018;15:138.
106. Garbelli R, de Bock F, Medici V, Rousset MC, Villani F, Boussadia B, et al. PDGFRbeta(+) cells in human and experimental neuro-vascular dysplasia and seizures. Neuroscience. 2015;306:18–27.
107. Merlini M, Rafalski VA, Rios Coronado PE, Gill TM, Ellisman M, Muthukumar G, et al. Fibrinogen induces microglia-mediated spine elimination and cognitive impairment in an alzheimer's disease model. Neuron. 2019;101:1099–108 e1096.
108. Davalos D, Ryu JK, Merlini M, Baeten KM, Le Moan N, Petersen MA, et al. Fibrinogen-induced perivascular microglial clustering is required for the development of axonal damage in neuroinflammation. Nat Commun. 2012;3:1227.
109. Ryu JK, McLarnon JG. A leaky blood-brain barrier, fibrinogen infiltration and microglial reactivity in inflamed Alzheimer's disease brain. J Cell Mol Med. 2009;13:2911–25.
110. Halder SK, Milner R. A critical role for microglia in maintaining vascular integrity in the hypoxic spinal cord. Proc Natl Acad Sci USA. 2019;116:26029–37.
111. Dias DO, Kim H, Holl D, Werne Solnestam B, Lundeberg J, Carlen M, et al. Reducing pericyte-derived scarring promotes recovery after spinal cord injury. Cell. 2018;173:153–65 e122.
112. Bar-Klein G, Lublinsky S, Kamintsky L, Noyman I, Veksler R, Dalipaj H, et al. Imaging blood-brain barrier dysfunction as a biomarker for epileptogenesis. Brain. 2017;140:1692–705.
113. Kastanauskaite A, Alonso-Nanclares L, Blazquez-Llorca L, Pastor J, Sola RG, DeFelipe J. Alterations of the microvascular network in sclerotic hippocampi from patients with epilepsy. J Neuropathol Exp Neurol. 2009;68:939–50.
114. Marchi N, Angelov L, Masaryk T, Fazio V, Granata T, Hernandez N, et al. Seizure-promoting effect of blood-brain barrier disruption. Epilepsia. 2007;48:732–42.
115. Ivens S, Kaufer D, Flores LP, Bechmann I, Zumsteg D, Tomkins O, et al. TGF-beta receptor-mediated albumin uptake into astrocytes is involved in neocortical epileptogenesis. Brain. 2007;130:535–47.
116. Pavlovsky L, Seiffert E, Heinemann U, Korn A, Golan H, Friedman A. Persistent BBB disruption may underlie alpha interferon-induced seizures. J Neurol. 2005;252:42–6.
117. Seiffert E, Dreier JP, Ivens S, Bechmann I, Tomkins O, Heinemann U, et al. Lasting blood-brain barrier disruption induces epileptic focus in the rat somatosensory cortex. J Neurosci. 2004;24:7829–36.
118. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. Nat Rev Neurol. 2011;7:31–40.
119. Montagne A, Zhao Z, Zlokovic BV. Alzheimer's disease: A matter of blood-brain barrier dysfunction? J Exp Med. 2017;214:3151–69.
120. Clarke LE, Liddelow SA, Chakraborty C, Munch AE, Heiman M, Barres BA. Normal aging induces A1-like astrocyte reactivity. Proc Natl Acad Sci USA. 2018;115:E1896–905.
121. Boisvert MM, Erikson GA, Shokhirev MN, Allen NJ. The aging astrocyte transcriptome from multiple regions of the mouse brain. Cell Rep. 2018;22:269–85.
122. Matias I, Morgado J, Gomes FCA. Astrocyte heterogeneity: impact to brain aging and disease. Front Aging Neurosci. 2019;11:59.
123. Janota CS, Brites D, Lemere CA, Brito MA. Glio-vascular changes during ageing in wild-type and Alzheimer's disease-like APP/PS1 mice. Brain Res. 2015;1620:153–68.
124. Ries M, Sastre M. Mechanisms of abeta clearance and degradation by glial cells. Front Aging Neurosci. 2016;8:160.
125. Broekaart DWM, Anink JJ, Baayen JC, Idema S, de Vries HE, Aronica E, et al. Activation of the innate immune system is evident throughout epileptogenesis and is associated with blood-brain barrier dysfunction and seizure progression. Epilepsia. 2018;59:1931–44.
126. Janigro D, Bailey DM, Lehmann S, Badaut J, O'Flynn R, Hirtz C, et al. Peripheral blood and salivary biomarkers of blood-brain barrier permeability and neuronal damage: clinical and applied concepts. Front Neurol. 2020;11:577312.
127. Netto JP, Iliff J, Stanimirovic D, Krohn KA, Hamilton B, Varallyay C, et al. Neurovascular unit: basic and clinical imaging with emphasis on advantages of ferumoxytol. Neurosurgery. 2018;82:770–80.
128. Urban A, Golgher L, Brunner C, Gdalyahu A, Har-Gil H, Kain D, et al. Understanding the neurovascular unit at multiple scales: Advantages and limitations of multi-photon and functional ultrasound imaging. Adv Drug Deliv Rev. 2017;119:73–100.
129. Yoon JH, Jeong Y. In vivo imaging for neurovascular disease research. Arch Pharm Res. 2019;42:263–73.
130. Lu FM, Yuan Z. PET/SPECT molecular imaging in clinical neuroscience: recent advances in the investigation of CNS diseases. Quant Imaging Med Surg. 2015;5:433–47.
131. van Vliet EA, Dedeurwaerdere S, Cole AJ, Friedman A, Koepp MJ, Potschka H, et al. WONOEP appraisal: imaging biomarkers in epilepsy. Epilepsia. 2017;58:315–30.
132. Kelly P, Hudry E, Hou SS, Bacskai BJ. In vivo two photon imaging of astrocytic structure and function in Alzheimer's disease. Front Aging Neurosci. 2018;10:219.
133. Bankstahl M, Breuer H, Leiter I, Markel M, Bascunana P, Michalski D, et al. Blood–brain barrier leakage during early epileptogenesis is associated with rapid remodeling of the neurovascular unit. eNeuro. 2018;5(3):ENEURO.0123-18.2018.
134. MacDonald ME, Pike GB. MRI of healthy brain aging: A review. NMR Biomed. 2021;34:e4564.
135. Chagnot A, Barnes SR, Montagne A. Magnetic resonance imaging of blood-brain barrier permeability in dementia. Neuroscience. 2021;474:14–29.
136. Malojcic B, Giannakopoulos P, Sorond FA, Azevedo E, Diomedi M, Oblak JP, et al. Ultrasound and dynamic functional imaging in vascular cognitive impairment and Alzheimer's disease. BMC Med. 2017;15:27.
137. van Vliet EA, Otte WM, Wadman WJ, Aronica E, Kooij G, de Vries HE, et al. Blood-brain barrier leakage after status epilepticus in rapamycin-treated rats I: Magnetic resonance imaging. Epilepsia. 2016;57:59–69.

138. Canet G, Zub E, Zussy C, Hernandez C, Blaquiere M, Garcia V, et al. Seizure activity triggers tau hyperphosphorylation and amyloidogenic pathways. Epilepsia. 2022. doi:10.1111/epi.17186. 2022 Feb 28. Online ahead of print.
139. Carnevale L, Lembo G. Innovative MRI techniques in neuroimaging approaches for cerebrovascular diseases and vascular cognitive impairment. Int J Mol Sci. 2019;20:2656.
140. Liang KG, Mu RZ, Liu Y, Jiang D, Jia TT, Huang YJ. Increased serum S100B levels in patients with epilepsy: a systematic review and meta-analysis study. Front Neurosci. 2019;13:456.
141. Ruber T, David B, Luchters G, Nass RD, Friedman A, Surges R, et al. Evidence for peri-ictal blood-brain barrier dysfunction in patients with epilepsy. Brain. 2018;141:2952–65.
142. Calik M, Abuhandan M, Sonmezler A, Kandemir H, Oz I, Taskin A, et al. Elevated serum S-100B levels in children with temporal lobe epilepsy. Seizure. 2013;22:99–102.
143. Calik M, Abuhandan M, Kandemir H, Guzel B, Solmaz A, Celik H, et al. Interictal serum S-100B protein levels in intractable epilepsy: a case-control study. Neurosci Lett. 2014;558:58–61.
144. Enright N, Simonato M, Henshall DC. Discovery and validation of blood microRNAs as molecular biomarkers of epilepsy: Ways to close current knowledge gaps. Epilepsia Open. 2018;3:427–36.
145. Henshall DC. MicroRNA and epilepsy: profiling, functions and potential clinical applications. Curr Opin Neurol. 2014;27:199–205.
146. Henshall DC, Hamer HM, Pasterkamp RJ, Goldstein DB, Kjems J, Prehn JHM, et al. MicroRNAs in epilepsy: pathophysiology and clinical utility. Lancet Neurol. 2016;15:1368–76.
147. Garcia-Curran MM, Hall AM, Patterson KP, Shao M, Eltom N, Chen K, et al. Dexamethasone attenuates hyperexcitability provoked by experimental febrile status epilepticus. eNeuro. 2019;6:ENEURO.0430-19.2019.
148. Marchi N, Granata T, Freri E, Ciusani E, Ragona F, Puvenna V, et al. Efficacy of anti-inflammatory therapy in a model of acute seizures and in a population of pediatric drug resistant epileptics. PLoS One. 2011;6:e18200.
149. Marchi N, Fan Q, Ghosh C, Fazio V, Bertolini F, Betto G, et al. Antagonism of peripheral inflammation reduces the severity of status epilepticus. Neurobiol Dis. 2009;33:171–81.
150. Dyomina AV, Zubareva OE, Smolensky IV, Vasilev DS, Zakharova MV, Kovalenko AA, et al. Anakinra reduces epileptogenesis, provides neuroprotection, and attenuates behavioral impairments in rats in the lithium-pilocarpine model of epilepsy. Pharmaceuticals (Basel). 2020;13:340.
151. Iori V, Iyer AM, Ravizza T, Beltrame L, Paracchini L, Marchini S, et al. Blockade of the IL-1R1/TLR4 pathway mediates disease-modification therapeutic effects in a model of acquired epilepsy. Neurobiol Dis. 2017;99:12–23.
152. Librizzi L, Noe F, Vezzani A, de Curtis M, Ravizza T. Seizure-induced brain-borne inflammation sustains seizure recurrence and blood-brain barrier damage. Ann Neurol. 2012;72:82–90.
153. Fabene PF, Navarro Mora G, Martinello M, Rossi B, Merigo F, Ottoboni L, et al. A role for leukocyte-endothelial adhesion mechanisms in epilepsy. Nat Med. 2008;14:1377–83.
154. van Vliet EA, Forte G, Holtman L, den Burger JC, Sinjewel A, de Vries HE, et al. Inhibition of mammalian target of rapamycin reduces epileptogenesis and blood-brain barrier leakage but not microglia activation. Epilepsia. 2012;53:1254–63.
155. van Vliet EA, Otte WM, Wadman WJ, Aronica E, Kooij G, de Vries HE, et al. Blood-brain barrier leakage after status epilepticus in rapamycin-treated rats II: Potential mechanisms. Epilepsia. 2016;57:70–8.
156. Xu D, Robinson AP, Ishii T, Duncan DS, Alden TD, Goings GE, et al. Peripherally derived T regulatory and gammadelta T cells have opposing roles in the pathogenesis of intractable pediatric epilepsy. J Exp Med. 2018;215:1169–86.
157. Zub E, Canet G, Garbelli R, Blaquiere M, Rossini L, Pastori C, et al. The GR-ANXA1 pathway is a pathological player and a candidate target in epilepsy. FASEB J. 2019;33:13998–4009.
158. Gimenes AD, Andrade BFD, Pinotti JVP, Oliani SM, Galvis-Alonso OY, Gil CD. Annexin A1-derived peptide Ac2-26 in a pilocarpine-induced status epilepticus model: anti-inflammatory and neuroprotective effects. J Neuroinflammation. 2019;16:32.
159. Cristante E, McArthur S, Mauro C, Maggioli E, Romero IA, Wylezinska-Arridge M, et al. Identification of an essential endogenous regulator of blood-brain barrier integrity, and its pathological and therapeutic implications. Proc Natl Acad Sci USA. 2013;110:832–41.
160. Bar-Klein G, Cacheaux LP, Kamintsky L, Prager O, Weissberg I, Schoknecht K, et al. Losartan prevents acquired epilepsy via TGF-beta signaling suppression. Ann Neurol. 2014;75:864–75.
161. Hong S, JianCheng H, JiaWen W, ShuQin Z, GuiLian Z, HaiQin W, et al. Losartan inhibits development of spontaneous recurrent seizures by preventing astrocyte activation and attenuating blood-brain barrier permeability following pilocarpine-induced status epilepticus. Brain Res Bull. 2019;149:251–9.
162. Sun H, Wu H, Yu X, Zhang G, Zhang R, Zhan S, et al. Angiotensin II and its receptor in activated microglia enhanced neuronal loss and cognitive impairment following pilocarpine-induced status epilepticus. Mol Cell Neurosci. 2015;65:58–67.
163. Nozaki T, Ura H, Takumi I, Kobayashi S, Maru E, Morita A. The angiotensin II type I receptor antagonist losartan retards amygdala kindling-induced epileptogenesis. Brain Res. 2018;1694:121–8.
164. Joshi D, Katyal J, Arava S, Gupta YK. Effects of enalapril and losartan alone and in combination with sodium valproate on seizures, memory, and cardiac changes in rats. Epilepsy Behav. 2019;92:345–52.
165. Tchekalarova JD, Ivanova NM, Pechlivanova DM, Atanasova D, Lazarov N, Kortenska L, et al. Antiepileptogenic and neuroprotective effects of losartan in kainate model of temporal lobe epilepsy. Pharmacol Biochem Behav. 2014;127:27–36.
166. Luo WD, Min JW, Huang WX, Wang X, Peng YY, Han S, et al. Vitexin reduces epilepsy after hypoxic ischemia in the neonatal brain via inhibition of NKCC1. J Neuroinflammation. 2018;15:186.
167. Alvi AM, Al Kury LT, Alattar A, Ullah I, Muhammad AJ, Alshaman R, et al. Carveol attenuates seizure severity and neuroinflammation in pentylenetetrazole-kindled epileptic rats by regulating the Nrf2 signaling pathway. Oxid Med Cell Longev. 2021;2021:9966663.
168. Pollock E, Everest M, Brown A, Poulter MO. Metalloproteinase inhibition prevents inhibitory synapse reorganization and seizure genesis. Neurobiol Dis. 2014;70:21–31.
169. Marchi N, Johnson AJ, Puvenna V, Johnson HL, Tierney W, Ghosh C, et al. Modulation of peripheral cytotoxic cells and ictogenesis in a model of seizures. Epilepsia. 2011;52:1627–34.

170. Franz DN, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Adjunctive everolimus therapy for tuberous sclerosis complex-associated refractory seizures: Results from the postextension phase of EXIST-3. Epilepsia. 2021;62:3029–41.
171. Franz DN, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Everolimus for treatment-refractory seizures in TSC: Extension of a randomized controlled trial. Neurol Clin Pract. 2018;8:412–20.
172. Curatolo P, Franz DN, Lawson JA, Yapici Z, Ikeda H, Polster T, et al. Adjunctive everolimus for children and adolescents with treatment-refractory seizures associated with tuberous sclerosis complex: post-hoc analysis of the phase 3 EXIST-3 trial. Lancet Child Adolesc Health. 2018;2:495–504.
173. French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet (London, England). 2016;388:2153–63.
174. Kenney-Jung DL, Vezzani A, Kahoud RJ, LaFrance-Corey RG, Ho ML, Muskardin TW, et al. Febrile infection-related epilepsy syndrome treated with anakinra. Ann Neurol. 2016;80:939–45.
175. Lai YC, Muscal E, Wells E, Shukla N, Eschbach K, Hyeong Lee K, et al. Anakinra usage in febrile infection related epilepsy syndrome: an international cohort. Ann Clin Transl Neurol. 2020;7:2467–74.
176. Dilena R, Mauri E, Aronica E, Bernasconi P, Bana C, Cappelletti C, et al. Therapeutic effect of Anakinra in the relapsing chronic phase of febrile infection-related epilepsy syndrome. Epilepsia Open. 2019;4:344–50.
177. Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: a summary of the Eleventh Eilat Conference (EILAT XI). Epilepsy Res. 2013;103:2–30.
178. Hue CD, Cho FS, Cao S, Dale Bass CR, Meaney DF, Morrison B 3rd. Dexamethasone potentiates in vitro blood-brain barrier recovery after primary blast injury by glucocorticoid receptor-mediated upregulation of ZO-1 tight junction protein. J Cereb Blood Flow Metab. 2015;35:1191–8.
179. Na W, Shin JY, Lee JY, Jeong S, Kim WS, Yune TY, et al. Dexamethasone suppresses JMJD3 gene activation via a putative negative glucocorticoid response element and maintains integrity of tight junctions in brain microvascular endothelial cells. J Cereb Blood Flow Metab. 2017;37:3695–708.
180. Barna L, Walter FR, Harazin A, Bocsik A, Kincses A, Tubak V, et al. Simvastatin, edaravone and dexamethasone protect against kainate-induced brain endothelial cell damage. Fluids Barriers CNS. 2020;17:5.
181. Gofshteyn JS, K. KG, Marquis BO, J. JL, Gourley D, Grinspan Z, et al. Measurable outcomes for pediatric epileptic encephalopathy: a single-center experience with corticosteroid therapy. Epileptic Disord. 2021;23:111–22.
182. Chen J, Cai F, Jiang L, Hu Y, Feng C. A prospective study of dexamethasone therapy in refractory epileptic encephalopathy with continuous spike-and-wave during sleep. Epilepsy Behav. 2016;55:1–5.
183. Horino A, Kuki I, Inoue T, Nukui M, Okazaki S, Kawawaki H, et al. Intrathecal dexamethasone therapy for febrile infection-related epilepsy syndrome. Ann Clin Transl Neurol. 2021;8:645–55.
184. Shen J, Xu G, Zhu R, Yuan J, Ishii Y, Hamashima T, et al. PDGFR-beta restores blood-brain barrier functions in a mouse model of focal cerebral ischemia. J Cereb Blood Flow Metab. 2019;39:1501–15.
185. Taguchi K, Kouroki M, Ohmura T, Jono H, Endo F, Saito H. Carbamazepine-imatinib interaction in a child with chronic myeloid leukemia. Pediatr Int. 2014;56:e33–6.
186. Pursche S, Schleyer E, von Bonin M, Ehninger G, Said SM, Prondzinsky R, et al. Influence of enzyme-inducing antiepileptic drugs on trough level of imatinib in glioblastoma patients. Curr Clin Pharmacol. 2008;3:198–203.
187. Reardon DA, Egorin MJ, Desjardins A, Vredenburgh JJ, Beumer JH, Lagattuta TF, et al. Phase I pharmacokinetic study of the vascular endothelial growth factor receptor tyrosine kinase inhibitor vatalanib (PTK787) plus imatinib and hydroxyurea for malignant glioma. Cancer. 2009;115:2188–98.

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