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Canine idiopathic epilepsy as a natural animal model for human epilepsy: a metabolic perspective beyond the brain

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Canine idiopathic epilepsy as a natural animal model for human epilepsy: a metabolic perspective beyond the brain

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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.

DATA AVAILABILITY

The data that support the findings from this review are available in the referenced publications. No new data was generated.

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AUTHOR CONTRIBUTION

All authors had full access to the data and take responsibility for the integrity of the data and the accuracy of the scientific interpretation formulated. Study concept and design: G.C and F.V. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: G.C. and F.V. Figures: G.C and F.V. Critical revision of the manuscript for important intellectual content: All authors. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

F.V. has recently finished a doctoral research project, regarding the role of the gastro-intestinal microbiome and nutrition in canine idiopathic epilepsy, which was financially supported by Nestlé Purina Petcare Europe. M.H. is a Member of the Advisory Board of Nestlé Purina Petcare Europe. M.H. has been paid for several consulting services by a variety of pet food companies. The authors have no other financial or personal relationships with other people or organizations that could inappropriately influence or bias the content of the paper.

Abstract

Emerging evidence indicates that epilepsy extends beyond the brain, involving systemic metabolic, immune, and microbiome perturbations that shape neuronal excitability and treatment response. Canine idiopathic epilepsy (CE) offers a naturally occurring, genetically diverse model with strong electrophysiological, pharmacological, and clinical homology to human epilepsies. In this review, we synthesise canine and human data on metabolic pathways (amino acids, lipids, vitamins, minerals, trace elements), the gut–brain axis and neurotransmitter signalling, inflammation and immunity, oxidative stress, the endocannabinoid system, and microRNAs. Across these systems, consistent alterations are reported in CE, paralleling human findings and supporting a view of epileptogenesis that expands beyond the brain. We highlight opportunities for translation, like biomarkers and stratifiers, dietary/metabolic interventions (e.g., MCT-based nutrition), microbiome modulation, and immunometabolic targets, alongside critical pitfalls: small, heterogeneous cohorts, antiseizure medication confounding, variable fasting or diet status, breed effects and correlation without causal testing. Taken together, CE can bridge experimental models and clinical practice, advancing epilepsy research beyond the brain toward mechanism-guided, multisystem therapeutics, offering a win-win for both species alike.

Key points:

Epilepsy, dog, human, preclinical, metabolome, animal model

Introduction

Epilepsy is one of the most common chronic neurological disorders in humans, highly affecting the quality of life of patients and their families (Boele et al., 2025). While epilepsy affects around 50 million people worldwide (World Health Organization, 2019), the underlying aetiology remains unclear in 32% of cases (Syvertsen et al., 2015). Additionally, the currently available antiseizure medications (ASMs) remain unable to fully control epileptic seizures in approximately one third of people with epilepsy (Löscher et al., 2020). These numbers stress the importance of further research to better characterize the pathophysiology of epilepsy and its management. Recent evidence supports a more integrative perspective on epilepsy (Boguszewicz et al., 2019; Chojnowski et al., 2025; Fujita et al., 2019; Maa et al., 2021), recognizing that its pathophysiological manifestations extend beyond the central nervous system (CNS) and are also reflected in systemic metabolic alterations (Eid, 2022). Characterization of these metabolic pathways, systems, and states may help to further elucidate the underlying aetiologies, inform the development of novel therapeutic strategies, and ultimately improve the clinical management of epilepsy.

Human epilepsy encompasses a heterogeneous group of disorders characterized by diverse aetiologies and complex pathophysiological mechanisms (Hirsch et al., 2022). The variability in clinical presentation and underlying causes among individuals underscores the need for a tailored therapeutic approach considering the specific patient and disease characteristics, as such evolving towards personalised medicine (McGinn et al., 2022). Emerging technologies such as metabolomics, especially when integrated with established disease models, offer promising avenues to advance diagnostic and therapeutic options in epilepsy (Eid, 2022).

Canine idiopathic epilepsy (CE) is an umbrella-term encompassing genetic epilepsy, suspected genetic epilepsy, and epilepsy of unknown cause (Berendt et al., 2015). Its diagnosis is based on internationally recognized criteria to exclude structural or reactive causes resulting in epileptic seizures (De Risio et al., 2015). As such, CE represents a robust, naturally occurring model for human epilepsy types of genetic or unknown origin. Its translational value is supported by converging electrophysiological, pharmacological, and clinical evidence (Charalambous et al., 2023; Devinsky et al., 2018; Löscher, 2022; Potschka et al., 2013). Notably, for example, dietary supplementation with medium-chain triglycerides has demonstrated efficacy across species, including rodents, dogs, and humans (Han et al., 2021). Simultaneously, the intestinal canine microbiome resembles the human microbiome better than that of rodents (Coelho et al., 2018), reinforcing the relevance of the canine model to study potential pathways and systems of interest, like the gut-brain axis. However, direct cross-species comparisons of metabolic profiles remain limited, despite growing interest in molecular endotyping, i.e. identification of distinct biological subtypes, to refine epilepsy classification and treatment strategies (Wagstyl et al., 2024).

The dog offers several advantages as a translational model: (1) spontaneous seizure occurrence eliminates the need for artificial induction; (2) clinical manifestations closely resemble those observed in human epilepsy; (3) shared environmental exposures with humans enhance ecological validity; and (4) dietary intake can be standardized using fixed-formulation, nutritionally complete diets, an approach less feasible in human patients due to dietary heterogeneity and variable compliance. These latter factors (3 and 4) are particularly critical, as environmental and dietary variables are recognized as major confounders in human clinical research (Obeso et al., 2021). Importantly, the use of naturally affected dogs creates reciprocal benefits: insights translate to human epilepsy and simultaneously improve clinical outcomes in veterinary practice. This dual-impact, real-world model complements and extends traditional experimental approaches.

This review synthesizes current evidence on metabolic pathways, systems, and states implicated in epilepsy across dogs and humans, identifying areas of convergence and divergence. By mapping shared mechanisms and species-specific features, we aim to clarify the translational value of the canine model and outline priorities for its integration into future epilepsy research. Ultimately, this framework is

intended to advance understanding of disease aetiology and mechanisms, and to facilitate biomarker discovery and therapeutic target development in both veterinary and human medicine.

Methods and search criteria

This review aims to characterize systemic metabolic and neurobiological alterations identified in CE, with a particular emphasis on parallels with human epilepsy research. A two-step methodological approach was therefore employed.

In the first step, a systematic literature review was conducted (August 2025) to identify studies investigating metabolic pathways in canine IE, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Figure 1). The research question guiding this step was: "In dogs with idiopathic epilepsy (P), can we identify original studies comparing aspects of the metabolism (I) to a control group of healthy dogs (C), to detect alterations in specific metabolites or metabolic pathways (O)?". The search strategy included the terms: "Dog OR canine," and "Epileps*," whereby a filter for original research was applied. Searches were performed via Web of Science and PubMed (MEDLINE database). Inclusion criteria were: (1) original research articles and (2) studies involving dogs diagnosed with idiopathic epilepsy in accordance with the international guidelines (De Risio et al., 2015) and (3) healthy dogs as a control group. Studies focusing solely on genotyping or medical imaging techniques were excluded.

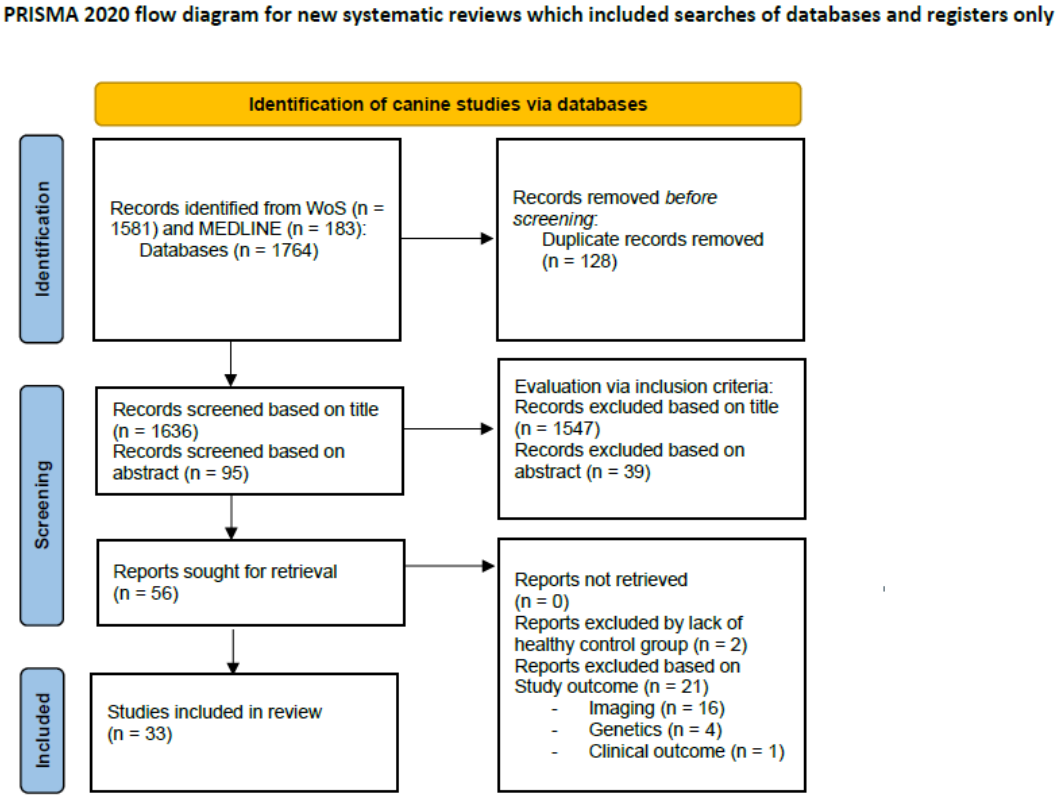


Fig. 1: PRISMA Flowchart showing the applied literature search strategy (first step). Adapted from Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

In the second step, metabolic pathways, systems and/or states of interest identified in the canine literature were further examined for their relevance to human epilepsy. For each of these, a targeted literature search was conducted using keywords to assess whether these alterations have also been reported in human epilepsy studies. The identified metabolic pathways, systems and/or states will be discussed in this manuscript, organized according to the affected functional aspects.

Canine and human idiopathic epilepsy: overlapping metabolic mechanisms

The literature retrieved on CE through our search strategy yielded 33 publications (summarized in table 1), encompassing analyses of cerebrospinal fluid (CSF), brain tissue, blood, and fecal samples. All studies were conducted on client-owned dogs affected by idiopathic epilepsy in comparison with a healthy control group. Some studies additionally included extra control groups, like dogs with structural epilepsy or meningoencephalitis of unknown origin. Several studies further stratified the CE population into subcategories, such as ‘controlled’ or ‘mild phenotype’ versus ‘uncontrolled’ or ‘drug-resistant,’ and ‘treated’ versus ‘untreated.’ The number of dogs with idiopathic epilepsy enrolled in individual studies ranged from 4 to 92, while healthy control groups included 4 to 127 dogs. Across these investigations, specific metabolic and physiological mechanisms were identified, many of which appear interrelated and intricately involved in the pathogenesis of epilepsy.

Inflammatory and immune pathways, together with mitochondrial function and related oxidative stress, emerge as central mechanisms in epilepsy and appear to form a self-perpetuating cycle (Figure 2). Metabolic disturbances in amino acids, lipids, minerals, trace elements, and vitamins may act as triggers within this cycle. Additional alterations in the endocannabinoid system, microbiota–gut–brain axis, neurotransmission, and post-transcriptional regulation further contribute to epileptogenesis and may modulate these interactions. In this review, the most important components of this self-perpetuating cycle are examined across separate sections: inflammatory and immune pathways, microbiota-gut-brain axis, oxidative stress, lipid metabolism, amino acid and protein metabolism, minerals, trace elements and vitamins, neurotransmission, endocannabinoid system, and microRNA. In each section, we first summarise the existing research on CE and subsequently compare these findings with evidence from studies on people with epilepsy (PWE), with the aim of delineating cross-species similarities and divergences.

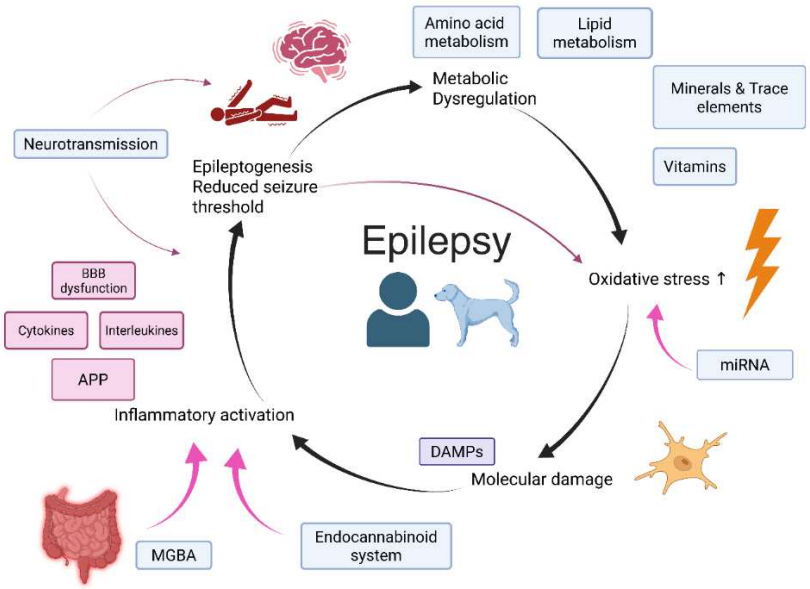


Fig. 2: Self-perpetuating cycle in the pathogenesis of epilepsy in dogs and humans. miRNA: micro RNA; DAMPs: Damage associated molecular patterns; MGBA: microbiota-gut-brain axis; BBB: blood-brain barrier; APP: acute phase proteins. Created in BioRender.com.

Inflammatory and immune pathways

Neuroinflammation

Neuroinflammation has long been recognized as a contributing factor in epilepsy, first as a consequence of recurrent seizures, perpetuating a self-reinforcing inflammatory cycle (Vezzani & Granata, 2005). Additionally, evidence from experimental animal models indicated that neuroinflammation also precedes seizure onset, implicating it as a potential initiator of epileptogenesis (Vezzani et al., 2011). In the brain, microglia activation results in the release of damage-associated molecular patterns (DAMPs) (Klegeris, 2021), cytokines (Giffard et al., 2008) and effector pathways, like COX-2 (Rawat et al., 2019). Among the DAMPs implicated in epilepsy, High Mobility Group Box 1 (HMGB1) and Heat Shock Protein 70 (HSP70) have emerged as key mediators in experimental rodent models and PWE (Maroso et al., 2010). Moreover, the blood-brain barrier (BBB) function is hampered in PWE (Bar-Klein et al., 2017) and CE (Hanael et al., 2019), as such causing peripheral immune cells and molecules to enter the brain.

Canine epilepsy

Although CE is traditionally considered a non-inflammatory epilepsy subtype (De Risio et al., 2015), emerging evidence suggests a more nuanced pathophysiological profile, with each epileptic seizure inducing secondarily inflammatory processes (von Rüden et al., 2023). Regarding epilepsy neuroinflammation, three canine studies were identified. One study revealed increased HSP70

expression, a key DAMP, in the piriform lobe in CE (von Rüden et al., 2020). Second, the CSF concentration of TNF-α, a pro-inflammatory cytokine, was increased in CE versus healthy dogs (Merbl et al., 2014). Third, serum creatine kinase (CK), a biomarker for tissue damage, was shown to be increased in CE (Paltrinieri et al., 2017). Notably, this increase was primarily caused by an increase in the isoenzyme predominantly found in the brain, i.e. CK-BB, thus revealing neuron damage and leakage via the BBB. However, CE could not be differentiated from other CNS diseases like inflammatory or degenerative disorders based on CK (Paltrinieri et al., 2017).

Human epilepsy

Similarly to dogs, human research highlighted an important role for neuroinflammation within the pathophysiology of epilepsy (Aguilar-Castillo et al., 2024; Costagliola et al., 2022), for which similarities and divergences are depicted in table 2. Similar to CE, increased HSP70 levels have been identified in the CNS of PWE. One study found overexpressed HSP70 in epileptic vs. non-epileptic brain tissue from people with focal drug-resistant epilepsy (Hossain et al., 2020), while another study identified increased HSP70 immunoreactivity in the surgically removed hippocampi of patients with mesial temporal lobe epilepsy (Dericioglu et al., 2013). Additionally, the CSF of PWE following status epilepticus showed significantly higher HSP70 levels compared to either controls or PWE experiencing epileptic seizures not including status epilepticus (Rejdak et al., 2012). Moreover, increased CSF pro-inflammatory cytokines, including TNF-α, like in CE, have been detected in multiple types of PWE (Aguilar-Castillo et al., 2024; Kalsariya et al., 2025; Ye et al., 2025).

Peripheral inflammation

As highlighted by the primary aim of this review, disturbances in epilepsy extend beyond the CNS, and this is equally true for inflammatory processes (Vezzani, 2020). Accordingly, peripheral inflammatory markers may offer complementary insights. Similar to neuroinflammatory processes, peripheral inflammation typically begins with the recruitment of inflammatory cells and the release of pro-inflammatory cytokines, which in turn drive the synthesis of acute-phase proteins (APP) such as C-reactive protein (CRP), haptoglobin, and ceruloplasmin (Kushner, 1993). To avoid redundancy, APP other than CRP will be addressed under ‘protein metabolism’. The release of APP is ultimately followed by metabolic alterations, thereby further reinforcing the self-perpetuating inflammatory cycle (Figure 2).

Canine epilepsy

The inflammatory haematological cells in CE are characterised by a significant greater neutrophil to lymphocyte ratio (Despa et al., 2024), revealing primarily neutrophil-mediated inflammation. Additionally, increased DAMPs, i.e. serum HMGB1 (Koo et al., 2020), and cytokines, serum IL-1β (Kostic et al., 2019), have been identified in CE. IL-1 β was increased regardless of epilepsy aetiology,

showing no differences between idiopathic and structural epilepsy (Kostic et al., 2019). While serum CRP did not significantly increase in dogs with idiopathic epilepsy versus healthy dogs (Segers et al., 2017), elevated serum CRP levels were detected in dogs with structural epilepsy, suggesting seizure-induced inflammation may differ between epilepsy subtypes (Despa et al., 2024; Mahon et al., 2023). However seizure severity in dogs with idiopathic epilepsy had an influence, with dogs experiencing cluster seizures showing higher serum CRP levels than dogs without clusters (Despa et al., 2024).

Metabolic studies further support an inflammatory component in CE, by identifying elevated plasma lipids, i.e. oleoylethanolamide (OEA), a PPAR agonist with anti-inflammatory properties, and 11,12-DHET (Yonezawa et al., 2024). For the latter, bioactivity is not well documented, while 11,12 epoxyeicosatrienoic acid (11,12 EET), a substrate for 11,12-DHET, has been shown to suppress seizures in mouse hippocampus (Mule et al., 2017). Furthermore, drug-resistant CE was characterised by elevated plasma xanthurenic acid and reduced vitamin B6 levels (Verdoodt, Bhatti, et al., 2025). These suggest inflammatory activation of the kynurenine pathway (Rios-Avila et al., 2013), the major metabolic pathway for tryptophan schematically displayed in Figure 3. Additionally, 4-guanidinobutanoic acid, a proinflammatory substrate for the blood-brain barrier creatine transporter (Schepers et al., 2010; Tachikawa & Hosoya, 2011), was increased in drug-resistant CE (Verdoodt, Bhatti, et al., 2025). Fecal metabolomics of the same study population revealed increased histamine in drug-resistant CE, together with higher serotonin in mild CE (Verdoodt, Hesta, et al., 2025), indicating altered tryptophan metabolism and intestinal inflammation potentially linked with the severity of disease (Blasco et al., 2020; Conesa et al., 2023).

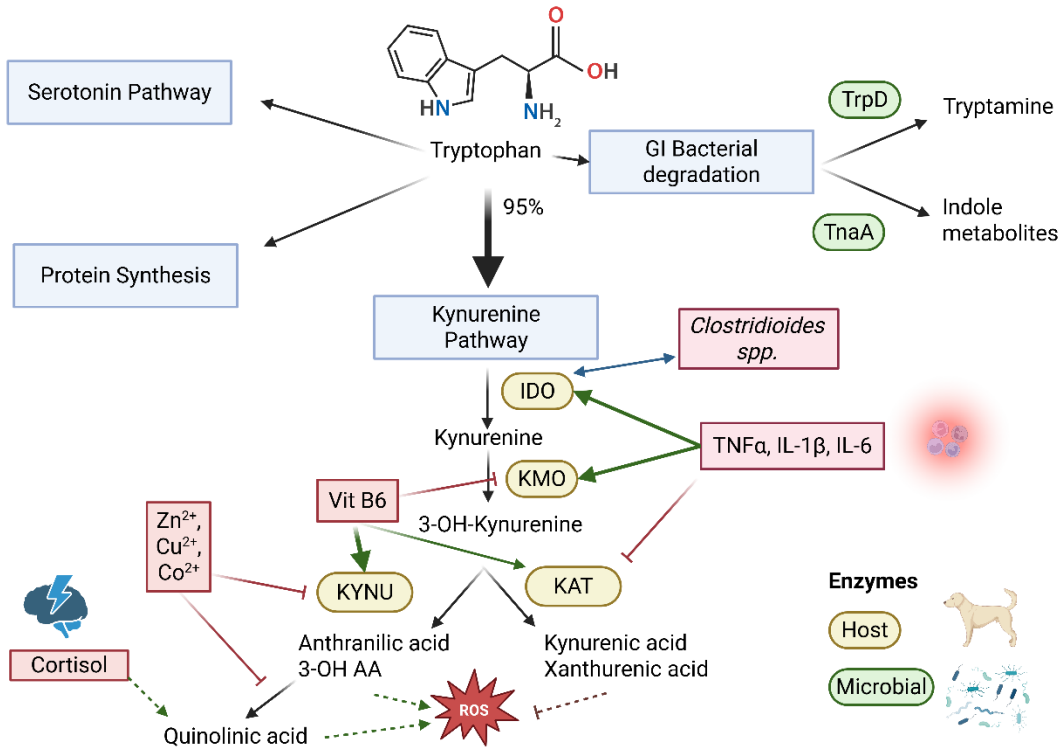


Fig. 3: Schematic overview of the primary host and gastrointestinal microbial tryptophan metabolism, with focus on the kynurenine pathway, and its interactions with inflammation, (oxidative) stress, gastrointestinal microbiota, vitamins and minerals. TrpD: Tryptophan decarboxylase; TnaA: Tryptophanase; IDO: Indoleamine 2,3-dioxygenase; TNF: Tumor Necrosis Factor; IL: Interleukin; KMO: Kynurenine 3-monooxygenase; OH: hydroxy; Vit: vitamin; KAT: Kynurenine aminotransferase; Kynu: Kynurenine hydrolase; 3-OH AA: 3-hydroxy anthranilic acid. Created in BioRender.com.

Human epilepsy

Starting with the inflammatory haematological cell types, similar to CE, higher neutrophil to lymphocyte ratios in PWE were indicated by recent meta-analyses (Hosseini et al., 2022; Li, Wei, et al., 2025). Moreover, this ratio was significantly elevated in patients with same-day seizure recurrence (Alemdar et al., 2025). However, the relationship between epileptic seizures and neutrophil to lymphocyte ratio does not appear linear (X. Wang et al., 2025).

At cytokine level, like in CE, increased IL-1β and TNFA-α were detected in the serum of PWE (Cao et al., 2025). In addition, significantly higher blood CRP levels were found in adults with epilepsy, but not children (Zhong et al., 2019). In contrast, a study in 2022 did find significantly higher serum CRP levels in childhood epilepsy, and decreased CRP following treatment with levetiracetam (Zhou et al., 2022).

The specific plasma lipids detected in CE, i.e. 11,12 DHET and OEA, however, were not yet identified in PWE. Conversely, xanthurenic acid, a kynurenine pathway metabolite, was also increased in children with epileptic spasm syndrome (J. Yan et al., 2022), with a significant increase in children non-responsive to adrenocorticotropic hormone (Wan et al., 2024). These findings suggest a link between epilepsy, the kynurenine and corticoid stress metabolism in both species.

Inflammation and antiseizure medication

The potential influence of ASM on inflammation is considered limited and ASM specific, while the efficacy of ASM was hampered in mouse models with induced inflammation (De Caro et al., 2019; M. Yan et al., 2025). Chronic levetiracetam administration in a rodent model stimulated xanthurenic acid production by brain cells (Fukuyama & Okada, 2018). In the canine study detecting increased plasma xanthurenic acid, it was increased only in drug-resistant CE, of which only 7/27 received levetiracetam (Verdoodt, Bhatti, et al., 2025). This suggests that levetiracetam administration is unlikely to account for the observed increase. Conversely, valproic acid has been shown to reduce inflammatory microglia overaction via histone deacetylase inhibition *in vitro* (Chen et al., 2007) and, together with carbamazepine, reduce the levels of proinflammatory cytokines produced by human peripheral immune cells *in vitro* (Popović et al., 2025). To the best of our knowledge, these anti-inflammatory effects have not been corroborated in a clinical setting.

Innate immune system

In recent years, research has strengthened the hypothesis that immuno-inflammatory mechanisms, including both the innate and adaptive immune system, contribute to both the onset of epileptic seizures as well as to epileptogenesis (Levite & Goldberg, 2022). Hereby, the complement cascade, pro-inflammatory cytokines and T-cells, and neuronal autoantibodies seem to be related to epilepsy.

Canine epilepsy

The complement cascade, a key interface between innate immunity and inflammation, revealed significantly increased serum C3 and C4 levels in CE, regardless of ASM status or seizure timing (Kang et al., 2024). Notably, dogs with a mean seizure frequency ≥ 3/month exhibited higher C3 levels, implicating complement activation in disease severity (Kang et al., 2024).

Human epilepsy

The blood complement cascade was shown to be involved in the discrimination of PWE *vs*. controls (Kopczynska et al., 2018), as well as in children suffering from febrile seizures (Şahin et al., 2025). In adults with idiopathic generalized epilepsy specifically, decreased C3 and C4 serum levels were detected (Liguori et al., 2017). More recently, lower complement components were detected in patients with DR epilepsy, together with a sex-dependent effect (Pinzon-Hoyos et al., 2025). These findings are contrasting the increased C3 levels detected in CE (Kang et al., 2024), potentially revealing a species-specific complement response.

Adaptive immune system

Canine epilepsy

In CE, one study reported significantly higher serum and CSF IL-17 concentrations, elevated stimulated Th17 cell counts, and a slight positive correlation between Th17 cell count and seizure severity (Knebel et al., 2022). Another study on CE reported undetectable concentrations of D-dimers in the CSF (de la Fuente et al., 2012), while more recently hyperfibrinolysis in CE treated with phenobarbital (García et al., 2024) was detected. One canine case of epilepsy caused by an autoimmune encephalitis has been described (Huenerfauth et al., 2022). However, a prospective study evaluating paired CSF and serum samples, could not detect neuronal autoantibodies in CE, using murine and human antigens (Hemmeter et al., 2023). Conversely, a retrospective study additionally evaluating paired CE CSF and serum samples, detected CSF-specific immunoglobulin G-type oligoclonal bands in 21% of CE cases with drug-resistance. However, no evidence of association with ASM response could be detected (Föhr et al., 2025). These outcomes may reflect true limited importance of autoimmune encephalitis in CE and/or methodological limitations due to non-homologous antigen use.

Human epilepsy

The observations in PWE and experimental models align with CE. In humans, IL-17A promotes hippocampal damage, disrupts BBB integrity, and contributes to epileptogenesis (Lu et al., 2023). Certain ASM (carbamazepine, levetiracetam) can also influence coagulation parameters, including D-dimer, PT, and APTT (Li, Zhong, et al., 2025).

Regarding autoantibodies, PWE show variable prevalence among patients. Well-characterized antibodies are primarily observed in human autoimmune encephalitis (e.g., anti-NMDAR, LGI1, CASPR2) (Çarçak et al., 2025). Notably, in cats an LGI1-autoantibody limbic encephalitis, paralleling its human counterpart, is recognized (Glantschnigg-Eisl et al., 2023), while the role for autoimmune encephalitis in CE is limited. Human non-encephalitic epilepsy cohorts on the other hand often exhibit low prevalence of antibodies, influenced by antigen selection and laboratory techniques (Cabezudo-García et al., 2021).

Microbiota-gut-brain axis

The microbiota-gut-brain axis (MGBA) provides a bidirectional communication pathway between the gastrointestinal (GI) tract, the enteric nervous system (ENS) and the central nervous system (CNS) via the vagal and spinal afferent nerves, the GI immune system, the hypothalamic–pituitary–adrenal cortical axis and bacterial metabolites in the circulation (Agirman et al., 2021). The GI microbiota, i.e. the collection of microorganisms residing in the GI tract, represent an important factor within this axis (O'Mahony et al., 2015). The MGBA is moreover greatly influenced by nutrition in both dogs and people (Coelho et al., 2018; Schneider et al., 2024). Recently, interest in the MGBA in the context of epilepsy has been increasing rapidly, both in human (Zhu et al., 2024) and veterinary medicine (Blanquet et al., 2025; Gernone et al., 2022). The pathways involved in the MGBA are not yet fully elucidated, but important interactions with oxidative stress, inflammatory and immune pathways are recognized.

Gastrointestinal microbiota

Studies show a potentially important role of the GI microbiota in the pathogenesis and management of epilepsy. Differences in GI microbiota composition have been demonstrated in CE (García-Belenguer et al., 2021; Silvestrino et al., 2025; Verdoodt, Hesta, et al., 2025) and PWE (Mousavi et al., 2025) compared to healthy controls. Moreover, interventions altering the composition of the GI microbiota, aiming to reduce the epileptic seizure frequency, have been described in CE (Blanquet et al., 2025) and PWE (Mousavi et al., 2025). These findings support a potential role for dysbiosis, i.e. disease-promoting imbalance in the GI microbiota composition (Weiss & Hennet, 2017), in epileptogenesis despite the fact that inconsistent GI microbiota alterations were revealed in CE and PWE. These inconsistencies

between studies likely reflect technical limitations of 16S rRNA sequencing data, in addition to potential biological variation. Moreover, the GI microbiota of drug-resistant PWE was significantly altered compared to drug-sensitive PWE, indicating a potential role for the normalization of the GI microbiota towards that of healthy individuals in the management of epilepsy (Gong et al., 2021; Peng et al., 2018).

Pre-clinical rodent models

Different rodent studies further established a role for the GI microbiota in epileptogenesis and seizure susceptibility. One study in mice receiving a ketogenic diet, i.e. a low carbohydrate and high fat diet resulting in the production of ketone bodies (Rho, 2017), showed that the anticonvulsive effect of this diet was mediated by GI microbiota alterations in *Akkermansia* and *Parabacteroides* (Olson et al., 2018). Similarly, another preclinical study showed that fecal microbial transplantation (FMT) from stressed to non-stressed rats accelerated kindling and increased the duration of induced seizures, while vice versa, fecal transplants from non-stressed to stressed rats could counteract the proepileptic effects of stress (Medel-Matus et al., 2018). Lastly, in a rat model for posttraumatic epilepsy, the pre-existent fecal microbial abundancies of specific members of the *Lachnospiraceae* family could predict the risk for developing epilepsy following traumatic brain injury (Medel-Matus et al., 2022).

Canine epilepsy

Studies in CE related to the MGBA have primarily studied and identified microbial changes. Overlapping findings have been detected, although all studies relied on 16S rRNA sequencing, which is inherently prone to interstudy variability caused by sample preparation as well as bioinformatics and taxonomic databases used (Forry et al., 2024; Hoisington et al., 2024; Roume et al., 2023). Hereby, CE showed lower fecal *Prevotella spp.* and *Phascolarctobacterium* (García-Belenguer et al., 2021, 2025; Silvestrino et al., 2025; Verdoodt, Hesta, et al., 2025), while an additional increase in fecal *Escherichia-Shigella* and *Cl. sensu stricto 1* was noted in CE (Silvestrino et al., 2025; Verdoodt, Hesta, et al., 2025). Importantly, the functional impact of the GI microbiota on host metabolism is expected to be more relevant than compositional changes alone. In this context, metabolomics provides a powerful approach to elucidate these functional interactions (Zierer et al., 2018). This has indeed been implemented in CE too, revealing alterations in histamine and tryptophan metabolism likely related to changes in the GI microbiota, as described below (Verdoodt, Hesta et al., 2025; Verdoodt, Bhatti et al., 2025).

Human epilepsy

Previously, structural and functional similarity of the canine and human GI microbiota as well as similar reactions to diet were shown (Coelho et al., 2018). Indeed, PWE showed some overlapping GI microbiota alterations with CE. Two studies identified decreased fecal *Phascolarctobacterium* in PWE compared to healthy controls (Cui et al., 2022; K. Zhou et al., 2023), while an increase in fecal *Escherichia-Shigella* was noticed additionally (Cui et al., 2022), paralleling the findings in CE. In

contrast, another study identified lower fecal *Escherichia-Shigella* and higher *Prevotella spp*. in PWE compared to healthy controls (Gong et al., 2020), while the same research group later identified a restorative effect of ketogenic diet in children with epilepsy on the GI microbiota composition, including increased fecal *Alloprevotella spp*. (Gong et al., 2021). The *Alloprevotella* genus is closely related to *Prevotella* and exerts similar functions, like the production of short chain fatty acids (Tett et al., 2021). Additionally, an earlier diet intervention trial in children with epilepsy revealed increased fecal *Prevotella spp*. following a ketogenic diet (Xie et al., 2017). Like for many bacterial genera, considerable functional species and even subspecies strain-level variation exists within the genus *Prevotella* (Tett et al., 2021), which could explain these apparent contrasting findings in different epilepsy studies.

Additional alterations, not paralleled (yet) in CE, have been detected in PWE. A Mendelian randomization study detected a causal relationship with increased epilepsy risk for bacteria from the Class *Betaproteobacteria* and Order *Burkholderiales* (Zeng et al., 2023), while the elevation of fecal bacterial genera promoting neuroinflammation in PWE was additionally highlighted in a recent meta-analysis (Mousavi et al., 2025). These bacterial alterations highlight the relevance of the MGBA in the pathophysiology of PWE, which is, at least partially, mirrored in CE.

Bacterial tryptophan metabolites

In addition to the tryptophan and kynurenine metabolites discussed earlier (Figure 2), multiple bacterial tryptophan metabolites have additionally been altered in CE and PWE. In CE, fecal indole-3-carboxylic acid, which is a bacterial metabolite of tryptophan, was reduced (Verdoodt, Hesta, et al., 2025), while plasma 2,6-dihydroxybenzoic acid, which is a diet-associated metabolite microbially derived from phenolic compounds (Wan et al., 2021), was decreased as well (Verdoodt, Bhatti, et al., 2025). These findings suggest a different intestinal microbial function in CE. Notably, in CE, higher fecal indole, another microbial tryptophan metabolite, was associated with reduced seizure frequency (Verdoodt, Hesta, et al., 2025), which is in line with findings from PWE. A recent metabolomics study in paediatric epilepsy highlighted a role for tryptophan metabolism and the MGBA, by identifying lower plasma indole levels in children with epilepsy compared to age-matched healthy controls (Chojnowski et al., 2025). In children with cerebral palsy, on the other hand, increased indole concentrations were observed in drug-resistant cases (Peng et al., 2023). Together, these findings seem to support a role for tryptophan metabolism as link between the GI microbiota and the brain (Gao et al., 2020), in both CE and PWE.

Peripheral histamine

While peripheral histamine involvement could be hypothesized for CE, based on increased fecal histamine in these dogs (Verdoodt, Hesta, et al., 2025), human studies on this remain limited. Existing literature for PWE primarily focuses on central histaminergic signalling, including one study showing

higher 1-methylhistamine in brain tissue of humans with temporal lobe epilepsy (Bañuelos-Cabrera et al., 2016) and case reports or small-scale clinical studies investigating the effects of histamine receptor antagonists (Yang et al., 2022). Two rat models indicate a seizure protective effect for histamine and its precursor (Ago et al., 2006; Chen et al., 2002). Generally, a complex interaction between central histamine, neural excitability and epilepsy exists, whereby the effect is mediated by the location and type of receptors ($H_{1,2,3}$ or H_4-R) (Yang et al., 2022). However, histamine levels in feces are unlikely to be related to the central histaminergic system. Interestingly, high GI concentrations of histamine have been shown to disrupt tight junctions, and thus hamper intestinal barrier integrity (Grosheva et al., 2020; Schirmer et al., 2020). Therefore, the findings in CE are suspected to be related to an indirect effect via inflammatory signalling and the MGBA, while this has not (yet) been detected in PWE.

Oxidative stress

Oxidative stress is defined as an imbalance between oxidants and antioxidants in favour of the former, leading to disruption of redox signalling and control and/or molecular damage (Beal, 1998). It is closely associated with mitochondrial function and plays a significant role in the pathogenesis of CNS disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease, Friedreich's ataxia, and amyotrophic lateral sclerosis (Beal, 1998). Moreover, oxidative stress has been implicated in the mechanisms underlying epilepsy and epileptogenesis in a rat model (Liang et al., 2000).

Canine epilepsy

In veterinary neurology, recent studies have documented an altered serum oxidative profile in CE compared to healthy controls, with increased levels of advanced oxidation protein products (AOPP) and reduced antioxidant markers such as thiol groups (R-SH), glutathione, paraoxonase-1 (PON-1), and butyrylcholinesterase (BChE) activity (Radaković et al., 2023). A more recent CE metabolomic study confirmed significant alterations in oxidative stress–related plasma metabolites, i.e. elevated gluconic acid and xanthurenic acid, and decreased carnosine and 2,6-dihydroxybenzoic acid (Verdoodt, Bhatti, et al., 2025). Consistently, Yonezawa et al. (2024) reported significantly increased concentrations of nitric oxide metabolites (nitrite + nitrate; NOx) in CSF for CE and meningoencephalitis of unknown origin (MUO) compared to healthy controls. In contrast, plasma NOx levels did not differ significantly among healthy controls, CE, and MUO (Yonezawa et al., 2024).

Human epilepsy

In PWE, increased AOPP levels, as seen in CE, were associated with increased ROS and myeloperoxidase activity (Ercegovac et al., 2010). Notably, AOPP levels have been shown to decrease following surgical resection of epileptogenic foci in humans (López et al., 2007) further supporting their role as potential biomarkers. The role for lipid peroxidation in PWE, like CE, shows inconsistent

results (Borowicz-Reutt & Czuczwar, 2020; C.-S. Liu et al., 1997; H. Sun et al., 2022), suggesting the need for more sensitive or specific lipid peroxidation markers in epilepsy research. In addition, natural antioxidants like resveratrol, N-acetylcysteine, and sulforaphane have shown neuroprotective and anticonvulsant properties in PWE and rodent models (Borowicz-Reutt & Czuczwar, 2020; Folbergrová et al., 2023; Pauletti et al., 2019).

Oxidative stress and antiseizure medication

Although oxidative stress is not considered a primary mechanism of action for currently available ASM, several studies demonstrate that ASM can modulate redox pathways. Valproate, for example, has been shown to reverse glutathione depletion and lipid peroxidation in PTZ-induced rodent seizure models (Devi et al., 2006; Luft et al., 2019; Mazhar et al., 2017; Pahuja et al., 2012). Similar antioxidant activity has been observed for phenytoin, phenobarbital, carbamazepine (Mazhar et al., 2017), lamotrigine (Goel et al., 2009) and diazepam (Rajasekaran, 2005).

Lipid metabolism

The causes and pathophysiological mechanisms underlying lipid metabolism dysregulation in epilepsy remain incompletely understood (Lourenço et al., 2024). Nevertheless, lipid metabolism alterations have been implicated in several pathogenetic mechanisms underlying epileptogenesis and constitute pivotal factors contributing to disease progression (Meier et al., 2024). Both the quality and quantity of lipids are involved in this process and can lead to the production of reactive oxygen species (ROS), which exacerbate oxidative stress, inflammation, and cell death, all implicated in the pathophysiology of epilepsy (Guo et al., 2023; Meier et al., 2024). In addition, disturbances of the MGBA have been reported to influence host lipid metabolism, including shifts in short-chain fatty acid (SCFA) pathways (Zhai et al., 2024).

Disruptions in lipid metabolism in epilepsy primarily involve triglycerides, cholesterol, sphingolipids, and fatty acids (Meier et al., 2024). In CE, one study identified significantly higher fasting serum triglyceride concentrations in ASM treated dogs (Kluger et al., 2008). Likewise, several observational studies in PWE have documented elevated plasma triglyceride levels in subsets of patients, particularly those with drug-resistant epilepsy, suggesting a potential association between lipid dysregulation and drug-resistance (Guo et al., 2023; Sarecka-Hujar et al., 2022). However, such associations may be confounded by the metabolic effects of chronic ASM therapy (Chochoł et al., 2025). In CE, phenobarbital administration has been shown to significantly decrease the fecal abundance of *Clostridiales* and increase fecal SCFAs (Watanangura et al., 2022).

Growing evidence supports a role for SCFAs, including acetate, propionate, and butyrate, in mechanisms relevant to epilepsy. Supporting this hypothesis, fecal supernatants from dogs with

idiopathic epilepsy have been demonstrated to activate enteric neurons, suggesting that microbiota-derived metabolites, potentially including SCFAs, may exert direct neuroactive effects along the MGBA (Elfers et al., 2024). Experimental studies in rodent models indicate that reduced SCFA availability is associated with increased seizure susceptibility, whereas supplementation with specific SCFAs, particularly butyrate, can exert anticonvulsant and neuroprotective effects (Medel-Matus et al., 2018). Consistent with these findings, both humans and dogs with epilepsy exhibit alterations in gut microbiota composition that may affect SCFA-producing taxa, as discussed in the preceding sections (Gong et al., 2021; Peng et al., 2018; Verdoodt, Hesta, et al., 2025; C. Zhou et al., 2022).

Both in PWE and CE, dietary interventions that modify triglyceride composition, particularly ketogenic diets or those based on medium-chain triglycerides, have shown potential antiepileptic benefits and an acceptable safety profile (Han et al., 2021). These findings might support the hypothesis that specific lipid alterations could modulate neuronal excitability in both species. Moreover, the dog represents a valuable translational model for evaluating and refining therapeutic strategies that target lipid-mediated neuronal mechanisms (Han et al., 2021).

Amino acid and protein metabolism

Alterations in amino acid and protein metabolism have emerged as a potential key feature in the pathophysiology of epilepsy (Lai et al., 2022; Verdoodt, Bhatti, et al., 2025). Increasing evidence from human and animal studies indicates that these metabolic disturbances extend beyond secondary effects of seizure activity and may actively contribute to epileptogenesis and disease progression. Dysregulated protein expression, processing, and degradation are implicated in neuroinflammatory responses, blood–brain barrier dysfunction, and neurodegenerative mechanisms, while altered amino acid metabolism affects neurotransmitter synthesis, excitatory–inhibitory balance, mitochondrial function, and redox homeostasis (Lai et al., 2022; Sarlo & Holton, 2021). Together, these tightly interconnected pathways highlight a central and integrative role for amino acids and proteins in shaping seizure susceptibility, treatment response, and long-term neurological outcomes in epilepsy.

Protein metabolism

Amyloid-β

Elevated levels of β-amyloid (Aβ) have been associated with epilepsy in both PWE and CE, as well as in murine models (Aroor et al., 2023; Farhan et al., 2025; Phochantachinda et al., 2023). In drug-resistant CE, systemic alterations in amyloid metabolism have been reported, as evidenced by significantly increased plasma Aβ42 concentrations compared with healthy controls (Phochantachinda et al., 2023). Furthermore, an early-onset neurodegenerative disorder associated with PITRM1 (a mitochondrial protease involved in peptide degradation) dysfunction has been described, characterized

by mitochondrial impairment, Aβ accumulation, and fatal epilepsy, although currently only reported in a single breed with a specific epilepsy syndrome (Hytönen et al., 2021). Similarly, in PWE, increased expression of the amyloid precursor protein has been detected in temporal lobe and hippocampal tissue from humans with drug-resistant epilepsy, supporting the hypothesis that Aβ precursor protein may contribute to the pathophysiological mechanisms underlying drug-resistance in PWE (Aroor et al., 2023; Sima et al., 2014). Recent evidence suggests that elevated Aβ levels in adulthood represent a risk factor for late-onset epilepsy, while amyloid pathology also correlate with cognitive impairment in PWE (Farhan et al., 2025). In line with these clinical observations, in APP/PS1 transgenic mice, the presence of Aβ plaques has been correlated with an increased frequency and duration of epileptiform discharges, further reinforcing the link between Aβ pathology and seizure susceptibility (Gureviciene et al., 2019). The increase in Aβ levels in both species may explain the observed correlation for PWE and CE with Alzheimer's disease in humans, and its equivalent in dogs: canine cognitive dysfunction syndrome (CCD) (Dolev et al., 2013; Hickman et al., 2023). In humans, epileptic seizure activity itself has been shown to trigger neurodegenerative processes by generating aberrant electrical currents and promoting both the production and release of Aβ (Gourmaud et al., 2020; Gureviciene et al., 2019). Moreover, the presence of Aβ42 has been demonstrated to enhance neuronal excitability in a rodent model of Alzheimer's disease, thereby facilitating the development and progression of epilepsy (Minkeviciene et al., 2009). Canine studies have further supported these associations. The dynamics of plasma Aβ concentrations in dogs mirror those observed in aging humans, both with and without AD (Alsulami et al., 2025; Panek et al., 2021). Additionally, dogs affected by drug-resistant epilepsy have been shown to exhibit an increased risk of developing CCD at a younger age compared with neurologically normal dogs (Packer et al., 2018).

Haptoglobin

Baka et al. conducted two distinct studies on CE, performing proteomic analyses on both serum and CSF from the same cohort. Epileptic dogs were divided into three groups: CE treated with ASM, untreated CE, and structural epilepsy. Comparison with healthy controls revealed significant alterations in both CSF and serum across all groups for several proteins, including haptoglobin (HP) (Baka et al., 2021, 2024). The multifunctional protein HP exhibits anti-inflammatory properties that facilitate Aβ clearance (Bai et al., 2023; Song et al., 2015) and exerts antioxidant effects by binding free haemoglobin, thereby preventing oxidative tissue damage (Melamed-Frank et al., 2001). Its role in epilepsy remains to be fully elucidated, as current evidence in PWE remains inconsistent. Previous studies in PWE have reported an association between reduced plasma HP levels and the occurrence of epileptic seizures (Panter et al., 1985; Saccucci et al., 2004; Sadrzadeh et al., 2004), whereas others have shown increased HP levels associated with refractory epilepsy in children (Saengow et al., 2021) and IE in adults (Sadrzadeh et al., 2004). Conversely, some investigations have found no significant association between HP and seizure occurrence (Anderson et al., 2009). Experimental evidence

suggests that decreased HP may impair clearance of free haemoglobin in the CNS, potentially contributing to epileptogenesis, while elevated HP may reflect immune activation and BBB dysfunction (Lee et al., 2021; Sadrzadeh et al., 2004).

Matrix metallopeptidase 2

The zinc-dependent endopeptidase MMP-2 which is decreased in treated CE, is known to be involved in extracellular matrix degradation and BBB integrity (Dixit et al., 2016; Duits et al., 2015). It also exhibits anti-inflammatory effects via interactions with interleukin-4 and interleukin-13 (Kovacs, 2000), and is upregulated in various neurological and inflammatory disorders in humans (Dixit et al., 2016; Kanoh et al., 2008; Patil et al., 2015), as well as in human non-infectious conditions with an inflammatory component (Niebroj‐Dobosz et al., 2010; Trentini et al., 2016). However, MMP-2's role in epileptogenesis remains unclear (Beroun et al., 2019). In the studies by Baka et al. mentioned above, a downregulation of MMP-2 was observed in the CSF of treated dogs with CE. This reduction may reflect the effects of ASM, the time elapsed since the last epileptic seizure, or excessive utilization with slow resynthesis (Baka et al., 2021).

Amino acid metabolism

Parallel to the proteomic studies, canine metabolomics research revealed alterations in amino acids comparing CE and healthy dogs in multiple biofluids, i.e. CSF, plasma and feces (Hasegawa et al., 2014; Verdoodt, Bhatti, et al., 2025; Verdoodt et al., 2024; Verdoodt, Hesta, et al., 2025). Notably, disruptions in levels of lysine, threonine, leucine, methylated and acetylated amino acids, phenylalanine and glutamate were identified in plasma and CSF using a targeted approach (Hasegawa et al., 2014; Verdoodt, Bhatti, et al., 2025). Importantly, CSF metabolic differences between idiopathic and structural epilepsy in dogs highlight an impact of the pathophysiological mechanism beyond the occurrence of epileptic seizures as such (Hasegawa et al., 2014). Additionally, altered urinary levels of glycine and serotonin, as well as a decreased γ-aminobutyric acid (GABA)-glutamate ratio, have been reported in CE (Schmidt et al., 2022). Similar metabolic disturbances have been identified in PWE and other animal models, including disruptions in alanine, aspartate, and glutamate metabolism, together with disruptions in glycine, serine, and threonine metabolism (Lai et al., 2022; Sarlo & Holton, 2021; Wang et al., 2016).

Analysing individual amino acids in greater detail across studies reveals both convergent and divergent metabolic alterations associated with epilepsy. A human Mendelian randomized study suggested a causal impact for increased leucine with epilepsy (C. Zhang et al., 2024). This aligns with the higher plasma leucine detected in CE (Verdoodt, Bhatti, et al., 2025), thus potentially supporting a similar pathophysiology. However, from a therapeutic perspective, in PWE, leucine, together with lysine, could enhance a ketogenic diet's ability to treat epileptic seizures (Clanton et al., 2017). For lysine, an

imbalance in acetylation and deacetylation has been described in PWE (J. Wang et al., 2023). Additionally, lysine metabolism disorders, such as SEDT1B-related syndrome, are associated with epilepsy (Weerts et al., 2021). Similar pathophysiological mechanisms could potentially explain the increase in N_6-acetyl-lysine that was detected in plasma in CE (Verdoodt, Bhatti, et al., 2025). Dysregulation of protein lysine acetylation, potentially driven by altered deacetylase activity or increased mitochondrial acetyl-CoA, may promote excessive N_6-acetyl-L-lysine formation, enhancing protein turnover and thereby raising plasma concentrations (Choudhary et al., 2014; D. Guo et al., 2025).

In contrast, threonine alterations appear to differ between species and disease states. While threonine levels were reported to be increased in CE, serum threonine concentrations were decreased in PWE compared with healthy controls (Wei et al., 2012). Moreover, a transient reduction in serum threonine has been observed following seizures in PWE, whereas no significant changes were detected under basal conditions (Avalos et al., 2025). These metabolic discrepancies may be related to the time elapsed since the last epileptic seizure, consistent with observations in a rodent model of temporal lobe epilepsy, which demonstrated distinct alterations in glycine, serine, and threonine metabolism at 48 h (i.e., increased glycine) versus 6 weeks (i.e., no significant changes in glycine) after status epilepticus (Antmen et al., 2025).

Tryptophan

As addressed in the preceding sections and schematically illustrated in Figure 3, tryptophan metabolism (particularly the kynurenine pathway) lies at the interface of inflammation, oxidative stress, and the microbiota–gut–brain axis. Comparative evidence from canine and human studies consistently highlights the involvement of this pathway in epilepsy across species.

The kynurenine pathway generates bioactive metabolites that modulate immune responses and neuroactive signalling, thereby linking peripheral metabolic alterations to CNS function. Alterations in tryptophan–kynurenine metabolism have been reported in adults with status epilepticus (Hanin et al., 2024), PWE (Wei et al., 2012), drug-resistant epilepsy (Zhu et al., 2025), and children with epilepsy (Chojnowski et al., 2025). A metabolic shift toward increased kynurenic acid production has been described in children with drug-resistant epilepsy responding to a ketogenic diet (Żarnowska et al., 2019), while elevated fecal kynurenic acid levels were also reported in children with cerebral palsy and epilepsy (Peng et al., 2023).

Beyond kynurenine pathway metabolites, serotonin, a major downstream product of tryptophan metabolism, has also been implicated in epilepsy. Serotonin exists in two functionally and anatomically distinct pools: a central serotonergic system, synthesized in the brain by tryptophan hydroxylase 2 (TPH2), and a peripheral serotonergic system, accounting for ~90–95% of total body serotonin and predominantly produced in gastrointestinal enterochromaffin cells via tryptophan hydroxylase 1

(TPH1) (Berger et al., 2009; Gershon & Tack, 2007). Peripheral serotonin does not cross the blood–brain barrier; therefore, changes in fecal, urinary, or circulating serotonin primarily reflect gut-derived and microbiota-modulated tryptophan metabolism rather than direct alterations in central serotonergic neurotransmission (Berger et al., 2009). While central serotonergic mechanisms are discussed in detail in the Neurotransmission section, accumulating evidence supports a relevant role for peripheral serotonin dysregulation in epilepsy. In dogs, faecal serotonin was increased in CE with a mild epileptic phenotype, whereas fecal indole-3-carboxylic acid was decreased in both mild and drug-resistant dogs compared to healthy controls (Verdoodt, Hesta, et al., 2025). Additionally, altered urinary serotonin levels further support dysregulation of downstream tryptophan metabolism in CE (Schmidt et al., 2022). In humans, changes in platelet serotonin content, serum serotonin levels, and urinary serotonin metabolites have been reported in epilepsy and have been linked to seizure burden, autonomic dysfunction, and systemic inflammatory states (Hesdorffer et al., 2011; Petrucci et al., 2020). In addition, peripheral serotonergic dysregulation has been implicated in the pathophysiology of sudden unexpected death in epilepsy, highlighting the relevance of non-central serotonin pools in epilepsy-related morbidity (Petrucci et al., 2020). Collectively, current data support a potential role of peripheral serotonin dysregulation as part of the broader alterations in tryptophan metabolism observed in PWE and dogs with CE.

Finally, several vitamins and minerals involved as enzymatic cofactors in tryptophan metabolism, including vitamin B6, pantothenic acid, magnesium, iron, and zinc, have been reported to be altered in both CE and PWE, potentially contributing to dysregulation of downstream metabolic pathways (Majewski et al., 2016).

Minerals, trace elements and vitamins

Emerging research highlights that trace elements, particularly selenium, iron, copper and zinc are associated with both the development of epilepsy and changes in seizure susceptibility in PWE, CE and rodent models (W. Liu et al., 2023). Antiseizure interventions, including ASM and the ketogenic diet, have been shown to modify serum concentrations of these elements, suggesting that the maintenance of trace element homeostasis may play a role in both the prevention and the therapeutic management of epilepsy (Kawahara et al., 2023). In addition to trace elements, several vitamins have also been implicated in epilepsy, with deficiencies or imbalances potentially influencing neuronal excitability and seizure thresholds (Miller et al., 2024; Ran et al., 2024).

Canine epilepsy

Evidence for the involvement of vitamins in CE is limited, however, one study mentioned vitamin B6 as a key metabolite, with markedly reduced plasma concentrations observed in CE compared to healthy

dogs (Verdoodt, Bhatti, et al., 2025). No other studies evaluating vitamins in CE could be retrieved. Conversely, minerals and trace elements have been evaluated in multiple CE studies. First, a study by Vitale et al. (2019) reported significantly elevated serum copper, manganese, selenium, and zinc concentrations in CE (Vitale et al., 2019) compared to healthy controls. Increased micromineral levels were subsequently corroborated by Rosendahl et al. (2023), who demonstrated higher whole-blood concentrations of copper and selenium, an increased Cu/Zn ratio, and lower whole-blood chromium concentrations in CE (Rosendahl et al., 2023b). Additional evidence from studies assessing trace element concentrations in the hair of dogs with CE further supports the occurrence of such alterations (Rosendahl et al., 2023a). From these studies, blood copper and hair arsenic concentrations, however, seemed to be linked to ASM rather than epilepsy as such. Notably, only selenium concentrations in CE were above the established reference range for healthy dogs in all sample types. Surprisingly, negative long term health effects have solely been described with selenium deficiency rather than toxicity (Todd et al., 2012; van Zelst et al., 2016). Therefore, future studies should include markers for selenium bioactivity and urinary excretion to provide insights into the biological meaning of selenium's alteration in CE.

Human epilepsy

Copper and Zinc

In PWE, elevated blood copper levels have been reported, with some evidence linking this increase to specific ASM (Ilhan et al., 2004; Prasad et al., 2014; Seven et al., 2013). Phenobarbital therapy, for instance, can enhance ceruloplasmin oxidation, thereby elevating serum ceruloplasmin and copper concentrations (Tutor-Crespo et al., 2003). Importantly, the Cu/Zn ratio has been considered a more sensitive biomarker than the individual mineral concentrations, with significant increases documented in children with epilepsy, compared to healthy controls (El-Masry et al., 2018; Prasad et al., 2014). However, it should be noted that these measurements are limited to blood, which may not always accurately reflect tissue mineral status due to the body's homeostatic regulation (López-Alonso et al., 2025).

Copper plays an essential role in brain health, contributing to neurotransmitter synthesis, synaptic activity modulation, and nerve myelination. Both copper deficiency and excess can have deleterious effects on neuronal integrity and function (Gromadzka et al., 2020). Excess copper can enhance reactive oxygen species (ROS) production, despite the antioxidant properties of Cu-Zn superoxide dismutase, triggering pro-inflammatory responses and potentially increasing the risk of neurotoxicity and epilepsy (Płonka-Półtorak et al., 2013). Conversely, copper deficiency can impair mitochondrial respiration, reduce antioxidant defence, and disrupt neurotransmitter metabolism, ultimately leading to neuronal dysfunction and enhanced seizure susceptibility (Kumar & Gross, 2006; Prohaska & Smith, 1982).

Zinc, on the other hand, exhibits antioxidant and anti-inflammatory properties, and the Cu/Zn ratio has been proposed as a biomarker of oxidative stress and inflammation (Jeong et al., 2021; Malavolta et al., 2010), both of which, as discussed previously, are implicated in epileptogenesis. Interestingly, zinc supplementation has been associated with reduced epileptic seizure frequency in PWE, while seizure activity returned upon withdrawal of supplementation (Elshorbagy et al., 2015).

Selenium

Selenium status in PWE remains a subject of debate. One recent meta-analysis reported reduced selenium concentrations in PWE (Gündoğdu et al., 2023; Jia et al., 2020), whereas another study conversely found significantly higher levels in PWE compared with controls (Gündoğdu et al., 2023). Earlier studies in paediatric patients with intractable epilepsy additionally showed low serum selenium concentrations (Elshorbagy et al., 2015), and moreover, clinical improvement has been reported in selenium deficient PWE following supplementation (Ramaekers et al., 1994; Weber et al., 1991; Yürekli & Nazıroğlu, 2013). Such discrepancies may be related to selenium's narrow safety margin in humans, unlike dogs (Barchielli et al., 2022; Zentrichová et al., 2021). Indeed, impaired selenoprotein expression, reduced selenium availability, disruption of sodium selenate biosynthesis, or impaired brain selenium transport has been implicated in the pathogenesis of epilepsy and other neurodevelopmental disorders (Schweizer et al., 2021). Conversely, excessive selenium can promote oxidative stress through glutathione depletion, suppress cholinergic signalling, and induce cholinergic neuron degeneration (Lakshmi et al., 2015). Maintaining optimal selenium levels is critical to harness its antioxidant benefits without incurring neurotoxic risks (Estevez et al., 2012).

Vitamin B6

Vitamin B6, more specifically its active form pyridoxal-5′-phosphate (PLP), appeared capable of modulating the neurotoxic triad of excitotoxicity, oxidative stress, and inflammation that underlies epileptogenesis (Holton, 2021), as schematically illustrated in Figure 4. First, PLP could restore the excitatory–inhibitory balance, by facilitating the conversion of glutamate into GABA (André et al., 2001; Löscher et al., 2006; Martin, 1987). Second, PLP reduces homocysteine levels, preventing NMDA receptor overactivation and excessive neuronal excitation (Deep et al., 2019; Zaric et al., 2019). Third, PLP enhances glutathione synthesis, as such protecting neurons from oxidative damage (Kannan & Jain, 2004; Mahfouz & Kummerow, 2004; Tunali, 2014; Turkyilmaz et al., 2021). Moreover, PLP has been shown to enhance epileptic seizure control by modulating cytokine production, as such causing anti-inflammatory effects (Al-Daghri et al., 2016; Ueland et al., 2017). However, water-soluble, high-dose administration of vitamin B6 can additionally cause reversible neurological side effects in humans and dogs (Turck et al., 2025; Yun et al., 2020). Therefore, optimal dosing would be primordial to attain therapeutic benefits. The levels of PLP may be influenced by ASM in PWE, although findings vary across drug types and study designs (Albersen et al., 2015; Husebye et al., 2021; Linnebank et al., 2012; Mintzer et al., 2012; Tamura et al., 2000). Most studies report significantly lower PLP levels in PWE,

particularly in those receiving enzyme-inducing ASM, like phenytoin or carbamazepine (Mintzer et al., 2012; Tamura et al., 2000).

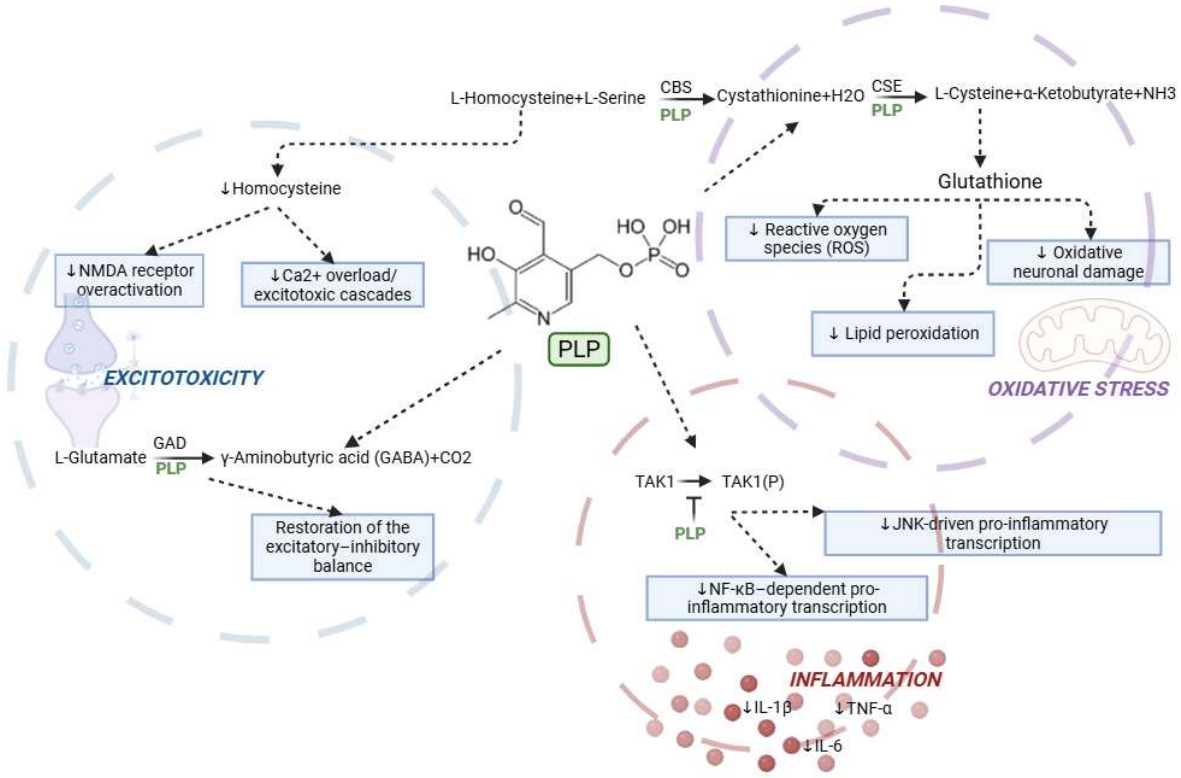


Fig. 4: Schematic overview of pyridoxal-5′-phosphate (PLP)-dependent pathways modulating the neurotoxic triad underlying epileptogenesis. PLP: pyridoxal-5′-phosphate; NMDA: N-methyl-D-aspartate; GAD: glutamate decarboxylase; CBS: cystathionine β-synthase; CSE: cystathionine γ-lyase; TAK1: transforming growth factor-β–activated kinase 1; TNF: tumor necrosis factor; NF-κB: nuclear factor kappa B; JNK: c-Jun N-terminal kinase; IL: interleukin. Created in BioRender.com.

Neurotransmission

Alterations in neurotransmitter systems play a key role in the pathophysiology of PWE and CE. Dysregulation of inhibitory (GABA, glycine) and excitatory (glutamate, aspartate) neurotransmission, as well as imbalances in monoamines such as serotonin, norepinephrine, and epinephrine, have consistently been reported in epileptic individuals of both species.

Glutamate and glutamic acid

Across human and animal studies, altered glutamate and glutamic acid levels have been consistently documented in the blood (Avalos et al., 2025; Verdoodt, Bhatti, et al., 2025; Wang et al., 2016) and CSF (Hasegawa et al., 2014; Lalwani et al., 2020; Sarlo & Holton, 2021; Shirayama et al., 2005; Yang et al., 2018) of individuals with epilepsy. Under physiological conditions, excess glutamate is actively

cleared from the CNS into systemic circulation. However, the relationship between central and peripheral glutamate is complex: while blood glutamate concentrations may partially reflect brain metabolism, they are also influenced by peripheral sources (e.g., muscle, liver, and gut) and by the selective transport properties of the blood–brain barrier (McKenna, 2013; Rimmele & Rosenberg, 2016). As the primary excitatory neurotransmitter in the CNS (McKenna, 2013), glutamate accumulation is central to epileptogenesis. Perturbations in the excitatory–inhibitory equilibrium, particularly altered GABA-glutamate ratios, constitute a core mechanism underlying seizure initiation (Sarlo & Holton, 2021). Beyond its central actions, glutamate also serves as an excitatory neurotransmitter within the enteric nervous system, where enteric neurons express glutamatergic receptors and transporters analogous to those found in the central nervous system (Ding et al., 2021; M.-T. Liu et al., 1997). Glutamatergic signalling along the MGBA has been proposed as a mechanism by which metabolic and neuroactive signals in the periphery may influence brain function (Baj et al., 2019). Furthermore, studies in rodent models indicate that gastric glutamate can activate afferent pathways that are suppressed by vagotomy, consistent with vagal modulation of central responses to gut stimuli (Kondoh et al., 2009).

Canine epilepsy

Urinary neurotransmitter profiling in CE revealed a decreased GABA/glutamate and norepinephrine/epinephrine (NE/E) ratio (Schmidt et al., 2022). The same study further indicated that sex and ASM therapy may modulate these concentrations (Schmidt et al., 2022). Furthermore, two earlier studies investigated neurotransmitter alterations in CE. Among these, Ellenberger et al. (2004) confirmed altered CSF concentrations of GABA and glutamate, as well as changes in their ratio (Ellenberger et al., 2004). Similarly, Morita et al. (2005), employing cerebral micro dialysis, electroencephalographic recordings, and immunohistochemical analyses, documented elevated extracellular concentrations of glutamate and aspartate in CE brains, which were associated with an increased spike frequency (Morita et al., 2005).

Human epilepsy

Although the function for GABA and glutamate in maintaining the brains inhibitory-excitatory balance has been well established, studies in PWE on glutamate and GABA are limited to small cohorts with suboptimal statistical power, and an incomplete understanding of how central and peripheral concentrations relate to each other (Sarlo & Holton, 2021). The observation of analogous neurochemical alterations in CE suggests that dogs may constitute a translational model for investigating glutamate–GABA dysregulation and guiding the development of targeted interventions (Sarlo & Holton, 2021; Verdoodt, Bhatti, et al., 2025).

Epinephrine and norepinephrine

Epinephrine and norepinephrine are closely linked to epilepsy in both humans and dogs. In PWE, noradrenergic system dysregulation has been hypothesized to be correlated with common comorbidities such as sleep disturbances and cognitive deficits (Borodovitsyna et al., 2017; Gannon et al., 2015; Roliz & Kothare, 2022; Salvin et al., 2011). Similarly, in CE, increased urinary epinephrine concentrations likely cause the altered urinary norepinephrine/epinephrine ratio (Schmidt et al., 2022) and, like in PWE, these are associated with common comorbidities, including sleep disturbances, ADHD-like behaviours, and anxiety (Hobbs et al., 2022; Packer et al., 2018, 2019; Schmidt et al., 2022).

Glycine

Glycine is an inhibitory neurotransmitter that, when dysregulated, can induce epileptic seizures through multiple mechanisms at both low and high concentrations (Pourhamzeh et al., 2022; Roth & Xia, 2004). Elevated urinary glycine levels detected in CE may be associated with seizure onset, cognitive impairment, and hyperactivity, consistent with clinical observations in PWE (Packer et al., 2018; Schmidt et al., 2022, 2023; Watson et al., 2018). Evidence from human and murine studies indeed indicates that dysfunction of glycine receptors is associated with epileptic phenotypes, and several receptor subtypes have been proposed as potential therapeutic targets (Fraser et al., 2025; Fraser & Harvey, 2025; Mizzi & Blundell, 2025; Shen et al., 2015). Further evidence supporting the involvement of glycine in epilepsy pathogenesis comes from the existence of a hereditary disorder of glycine metabolism in humans, known as nonketotic hyperglycinaemia (Farris et al., 2020). This condition leads to the accumulation of glycine in the body, resulting in refractory epileptic seizures, hyperactivity, elevated levels of glycine in the urine, and, in adults, cognitive impairment (Krawiec & Anastasopoulou, 2025). In contrast to PWE, in whom valproate, an ASM, has been shown to markedly increase both urinary and plasma glycine concentrations (Chapman, 1986), no comparable effect has been documented in CE treated with first- or second-line ASM (i.e. phenobarbital or potassium bromide) approved for the management of CE (Schmidt et al., 2022).

Serotonin

As mentioned in previous sections, serotonin represents a key downstream product of tryptophan metabolism; however, beyond its peripheral metabolic role, it also exerts critical functions as a central neurotransmitter relevant to epilepsy. In humans, reduced serotonin levels are associated with various psychiatric disorders . Furthermore, in PWE alterations in the serotonergic system have been shown to lower the epileptic seizure threshold and contribute to frequently co-occurring neurobehavioral comorbidities (Buchanan et al., 2014; Richerson & Buchanan, 2011). The International League Against Epilepsy has suggested that selective serotonin reuptake inhibitors (SSRIs) may be used with caution for the treatment of anxiety in certain PWE. These drugs are already widely used to manage behavioural

and psychological disorders in both species (DeFilippis & Wagner, 2014; Simpson et al., 2007; Watson et al., 2018).

Experimental evidence in PWE indicates that SSRIs or serotonin–norepinephrine reuptake inhibitors (SNRIs) can reduce the severity of epilepsy by alleviating depressive symptoms (Maguire et al., 2021; Tallarico et al., 2023). Additionally, in dogs, fluoxetine (an SSRI) has been reported to be effective in treating fly-snapping syndrome, a condition considered to represent limbic epilepsy by some but a compulsive behavioural disorder by others (Wrzosek et al., 2015).

Endocannabinoid system

Endogenous endocannabinoid metabolism

The endocannabinoid system is a neuromodulatory network composed of endocannabinoids, like anandamide, 1- and 2-arachidonoyl glycerol, their receptors (CB1, CB2), and associated enzymes, which regulates synaptic transmission and maintains homeostasis in the central and peripheral nervous system. It plays a key role in modulating neuronal excitability, inflammation, and seizure susceptibility (Zeng & Chen, 2025). Importantly, species-specific differences in CB1 expression have been documented, particularly regarding regional distribution, cellular localization, and density. In dogs, CB1 is widely expressed in the cerebral cortex, hippocampus, basal ganglia, cerebellum, hindbrain, spinal cord, peripheral nerves, and glial cells (Di Salvo et al., 2024; Freundt-Revilla et al., 2017; Pirone et al., 2016), whereas in humans CB1 is predominantly neuronal and concentrated in the hippocampus, cortex, amygdala, basal ganglia, and cerebellum (Chou et al., 2022; Straiker et al., 2012). Moreover, CB1R expression in humans is dynamic rather than static: it varies during development, with aging, and in response to stress or environmental experiences (M. Zhang et al., 2024). Therefore, while dogs could serve as a model to study differential receptor modulation between healthy and CE, they are not suitable for direct comparison of CB1 receptor localization across species.

Canine epilepsy

In CE, higher CSF anandamide was detected, and this increase was even more pronounced in dogs with a severe phenotype, i.e. status epilepticus and/or cluster seizures, or long disease history (Gesell et al., 2013). More recently, distinct modification in the hippocampal CB1 receptors was highlighted for CE compared to structural epilepsy. Dogs with IE showed decreased CB1 receptor expression in the CA1 region, in contrast to dogs with structural epilepsy showing increased expression (Kostic et al., 2023).

Human epilepsy

In humans with newly diagnosed temporal lobe epilepsy, decreased CSF anandamide was detected (Romigi et al., 2010). This seems contrasting to the increased CSF anandamide in CE, however, the authors of the CE study suggest a physiological counter-mechanism to attempt to regulate epileptic

seizure thresholds. This would indeed not yet be present in the acute phase of the disease studied in PWE. The alteration of CB1 receptors is considered complex and depending on the aetiology in PWE (Maglóczky et al., 2010), with e.g. a downregulation in the hippocampus of people with temporal lobe epilepsy (Ludányi et al., 2008), similar to the distinct receptor modification seen in CE. However, for CB1 expression no direct cross-species comparison is possible, as stressed by the differences in regional distribution, cellular localization, and density (Di Salvo et al., 2024).

Phytocannabinoids

Both in PWE and CE, cannabidiol, i.e. a phytocannabinoid, emerged as a novel management strategy, highlighting potential efficacy in epileptic seizure reduction, but also adverse effects like somnolence and gastro-intestinal symptoms (Jensen et al., 2025; Saranti et al., 2025). Most research up to date argues against the relevance for CB1 and CB2 receptors in the anticonvulsive effect of phytocannabinoids (Potschka et al., 2022). Other receptors, including the G protein receptor 55 (GPR55) and transient receptor potential Vannilloid-1 (TRPV1) (Bazelot & Whalley, 2016; Gray & Whalley, 2020), together with an interaction via adenosine signalling (Gaston & Szaflarski, 2018) are hypothesized as the major pathways leading to its anticonvulsive effects.

MicroRNA

MicroRNAs (miRNAs) play a crucial role in the post-transcriptional regulation of genes involved in neuronal metabolic pathways, including mitochondrial function, glycolysis, and oxidative stress responses. Emerging evidence indicates that altered miRNA expression contributes to metabolic dysregulation observed in epilepsy, affecting neuronal energy homeostasis and excitability. These findings suggest that miRNA–metabolism interactions represent a key molecular link between bioenergetic imbalance and epileptogenesis (J. Wang & Zhao, 2021).

Canine epilepsy

A recent study has investigated microRNAs (miRNAs) in CE (García-Gracia et al., 2024). The study focused on seven miRNAs previously identified as dysregulated in both human and murine epilepsy (Brennan et al., 2020; De Benedittis et al., 2021; Ioriatti et al., 2020; Martins‐Ferreira et al., 2020; Zheng et al., 2019). Six of these (miR-16, miR-27a-3p, miR-93-5p, miR-132, miR-142, and miR-574-3p) were found to be altered in CE, with five showing significant downregulation. Notably, a panel combining miR-93-5p, miR-142, and miR-574 demonstrated promising diagnostic performance (García-Gracia et al., 2024).

In earlier work on CE, Gutierrez-Quintana et al. (2021) investigated miR-134, a miRNA upregulated in rodent models of drug-resistant epilepsy and in human temporal lobe epilepsy. Plasma levels of miR-

134 were significantly higher in drug-resistant CE compared to controls and drug-responsive dogs (Gutierrez-quintana, 2022). Additionally, Pasierbinska et al. (2023) profiled blood miRNAs in drug-naive and treated CE in a pilot study, identifying miRNAs that distinguish CE from healthy dogs (e.g., miR-381, miR-214, miR-224), and those differentiating drug-resistant versus drug-responsive cases (e.g., miR-223, miR-129, miR-210). These results support a potential role of miRNAs in the molecular mechanisms underlying CE and drug-resistance, establishing a basis for further biomarker discovery and therapeutic studies.

Human epilepsy

In PWE, several miRNAs have been implicated in neuronal plasticity, dendritic spine morphology, synaptic regulation, and excitability. Similar to CE, miR-134 (a neuron-enriched miRNA involved in dendritic spine development through targets such as LIMK1)is consistently upregulated in brain tissue of patients with drug-resistant temporal lobe epilepsy, reflecting synaptic remodelling associated with hyperexcitability (Jimenez-Mateos et al., 2012; Y. Sun et al., 2016). Circulating levels of miR-134 are also elevated in plasma or serum of patients with drug-resistant epilepsy, suggesting potential as a biomarker for pharmacoresistance (De Benedittis et al., 2021). Additionally, miR-129-2-3p is upregulated in cortical tissue and plasma of patients with refractory temporal lobe epilepsy. ROC analyses indicate miR-129-2-3p can discriminate PWE from controls with good sensitivity and specificity (Y. Sun et al., 2016).

For miR-223, findings in PWE are inconsistent across studies, but it has been reported to be overexpressed in serum of patients with temporal lobe epilepsy and may differentiate drug-resistant from drug-responsive cases. Similarly, miR-210, a hypoxia-regulated miRNA, shows limited and inconsistent evidence in PWE (Brennan et al., 2020; Yakovleva et al., 2022), with most functional data derived from animal models where it modulates neuronal survival and GABAergic signalling post-seizure (Brennan et al., 2020).

In summary, studies in PWE strongly support a role for miR-134 and miR-129-2-3p in pathophysiology and drug resistance, while canine evidence remains preliminary. Systematic cross-species studies are needed to establish the translational relevance for biomarker discovery and targeted interventions.

Conclusion and future insights

In conclusion, the synthesis of canine and human data underscores CE as a robust, naturally occurring translational model for PWE, that extends our understanding of epilepsy beyond the brain. Conserved disturbances for CE and PWE across inflammatory and immune networks include markers like IL-17, HSP70 and TNF-α, as well as a primarily neutrophil-induced inflammation. However, the involvement of the complement cascade seems to differ in CE and PWE, thus interspecies translation requires caution. Additionally, disruption of the tryptophan-kynurenine has been implicated in CE and PWE, while the precise mechanism is not yet fully understood in both species, highlighting an important opportunity for a harmonized cross-species approach. Likewise, both species show involvement of amyloid-β formation and cognitive comorbidities. Within the MGBA, a role for *Phascolarctobacterium* and *Prevotella* was highlighted in CE and PWE. Considering the inherent limitations of microbiota identification, future work should emphasize the functional implications of these microbial alterations, whereby a cross-species approach would be beneficial. Lastly, potential convergence was suggested for vitamin B6 metabolism and miRNA, but additional data from CE is needed to further establish these hypotheses.

Priorities for future research include: (1) Harmonized cross-species, longitudinal cohorts with standardized phenotyping, including epileptic seizure semiology, comorbidities, diet information, and ASM exposure, to address current study heterogeneity and common confounding factors; (2) Multi-omics pipelines integrating metabolomics, proteomics, trace-element and vitamin status, microbiome and microRNAs to derive robust biomarker panels and responder stratifiers; (3) Randomized, clinical trials of nutritional and metabolic interventions, like e.g. the MCT-diet, and GI microbiome modulation (pre- and probiotics, FMT); and (4) Translational validation of emerging targets, like miRNA-134, immunomodulation, and endocannabinoid regulation, with attention to species-specific characteristics highlighted in this review. Taken together, CE has the potential to bridge experimental models and clinical practice, as such enhancing epilepsy research in both species.

Tables

Table 1. Summary of canine studies identified through PRISMA-based literature search

Reference	Category	Population	Sample type	Main alteration
Kostic et al. 2023	Endocannabinoid	HC=7; IE=5; SE=7	Brain tissue	↓CB1R in IE dogs
Paltrinieri et al. 2017	Inflammation	HC=10; IE=14	Serum	↑ total CK and CK-BB
Weber et al. 2012	Energy	HC, IE, SRMA, CNS neoplasia, IVDD, MUO, BM	CSF	↓CSF:serum glucose ratio
Morita et al. 2005	Neurotransmitters	HC=3; IE=4; SE=4	Blood	↑Extracellular glutamate/aspartate
Hemmeter et al. 2023	Immunology	HC=57; IE=58	Blood	No neural autoantibodies detected
Knebel et al. 2022	Immunology	HC=10; IE=57	CSF; Serum	↑Th17 cells and ↑IL-17
Kang et al. 2024	Immunology	HC=29; IE=49	Serum	↑C3 and C4
de la Fuente et al. 2012	Immunology	HC=7; IE=15	CSF; Blood	Elevated D-dimer; no CSF-blood correlation
Kostic et al. 2019	Inflammation	HC=6; IE=30	CSF; Serum	↑IL-1β
Despa et al. 2024	Inflammation	HC=8; IE=29; RE=10	Blood	↑CRP in SE; ↑NLR
Koo et al. 2020	Inflammation	HC=26; IE=14	Serum	↑HMGB1
von Rüden et al. 2020	Inflammation	HC=28; IE=21	Brain tissue	↑TLR4

Segers et al. 2017	Inflammation	HC=28; IE=38	Serum	No consistent ↑CRP
Merbl et al. 2014	Inflammation	HC=12; IE=7	CSF; Serum	↑TNF-α and ↑IL-6
Yonezawa et al. 2024	Lipid & OS	HC=9; IE=11	CSF; Plasma	Dysregulated lipid metabolites
Kluger et al. 2008	Lipid & OS	HC=57; IE=57	Serum	↑Triglycerides (Tx IE)
Verdoodt et al. 2025	AA, inflam, OS, vit	HC=39; IE=49	Plasma	Oxidative stress signature
Hasegawa et al. 2014	AA	HC=18; IE=16; SE=19	CSF	Altered amino-acid profile
Gesell et al. 2013	Endocannabinoid	HC=16; IE=40	CSF	Altered AEA/2-AG
Verdoodt et al. 2025	MGBA	HC=39; IE=49	Feces	Dysbiosis; altered SCFA pathways
Schmidt et al. 2022	Neurotransmitters	HC=127; IE=63	Urine	Distinct neurotransmitter profile
Ellenberger et al. 2004	Neurotransmitters	HC=20; IE=94; genetic IE=35	CSF	↓GABA and ↓Aspartate
García-Belenguer et al. 2021	MGBA	HC=12; IE=19	Feces	↓GABA- and SCFA-producing bacteria
Muñana et al. 2020	MGBA	HC=13; IE=13	Feces	No major Lactobacillus differences
Silvestrino et al. 2025	MGBA	HC=17; IE=19	Feces	↓Microbial diversity; ↑pro-inflammatory taxa
Rosendahl et al. 2022	Minerals & vit	HC=19; IE=19	Blood	Altered Cu, Se, Cr
Rosendahl et al. 2023	Minerals & vit	HC=42; IE=63	Hair	Mineral imbalances

Vitale et al. 2019	Minerals & vit	HC=50; IE=92	Serum	Altered Se, Cu
García-Gracia et al. 2024	miRNA	HC=8; IE=15	Plasma	Distinct miRNA profile
Radaković et al. 2023	Lipid & OS	HC=15; IE=15	Blood	Systemic oxidative stress
Phochantachinda et al. 2023	Proteome	HC=4; IE=4	Plasma	Altered amyloid/inflammatory proteins
Baka et al. 2024	Proteome	HC=9; IE=17	Serum	Differential expression of protein markers
Baka et al. 2021	Proteome	HC=10; IE=17	CSF	Immune/ECM pathway alterations

Summary of the 33 original research studies identified through the PRISMA-based literature search, each comparing metabolic features of dogs with idiopathic epilepsy to healthy controls across cerebrospinal fluid, blood, brain tissue, or fecal samples. **Abbreviations:** 2-AG = 2-arachidonoylglycerol; AA = amino acids; AEA = anandamide; BM = bacterial meningoencephalomyelitis; C3/4 = complement factor 3/4; CB1R = cannabinoid 1 receptor; CK (-BB) = creatine kinase – (brain isoform); CNS = central nervous system; CRP = C-reactive protein; CSF = cerebrospinal fluid; Ctl = controlled; ECM = extracellular matrix; HC = healthy controls; HMGB1 = high mobility group box 1; IE = idiopathic epilepsy; IVDD = intervertebral disc disease; MGBA = microbiota–gut–brain axis; miRNA = micro-RNA; MUO = meningoencephalomyelitis of unknown origin; NLR = neutrophil-to-lymphocyte ratio; OS = oxidative stress; SE = structural epilepsy; SCFA = short chain fatty acids; SRMA = steroid-responsive meningitis-arteritis; TLR4 = Toll-like receptor 4; Tx = treated; vit = vitamins.

Table 2: Summary of metabolic system and pathway alterations in canine idiopathic epilepsy and human epilepsy.

Metabolic system/pathway	Similarities canine – human	Divergence canine - human	Role of system/pathway unclear
Acute phase response	↑ CRP, neutrophil-to-lymphocyte ratio, TNF-α, IL-1β; BBB dysfunction; ↑ xanthurenic acid	—	CRP variability across subtypes and age groups; specific plasma lipid alterations
DAMPs and tissue damage markers	↑ Serum HMGB1 and CNS HSP70	↑ CK-BB CE, but not PWE	—
Innate immune system	Complement involvement in both species	Complement cascade: ↑C3/C4 in CE *vs* ↓C3/C4 in PWE	Functional impact on epileptogenesis
Adaptive immune system	Th17 cells involved and ↑ IL-17	—	Role of coagulation markers (D-dimer); Importance of autoimmune encephalitis unclear
MGBA	Tryptophan–kynurenine pathway alterations; ↓ fecal *Phascolarctobacterium*	Phylogeny of some microbial alterations differs	Peripheral histamine role in humans; alterations of *Prevotella* and *Escherichia-Shigella* in both directions for PWE
Oxidative stress	↑ AOPP	Lipid peroxidation inconsistent; selenium status opposite	ASM influence on oxidative markers
Lipid metabolism	Therapeutic use of MCT diets	Specific lipid metabolites (OEA, 11,12-DHET) detected in dogs, not humans	Impact of ASM on lipid profile
Amino acid metabolism	↑ Blood leucine; lysine acetylation parallels	Blood threonine: ↑ CE *vs* ↓PWE	Timing post-seizure and ASM effects
Protein metabolism	↑ Amyloid-β	Proteomic patterns differ (e.g., ↓ MMP-2 in CE)	Functional role of haptoglobin
Vitamins	↓ Vitamin B6	ASM impact on vitamin B6 more documented in PWE	Optimal dosing and safety margins
Minerals	↑Cu/Zn ratio	Selenium: ↑ CE vs ↓PWE	Clinical relevance of manganese and chromium
Neurotransmission	Serotonin involvement; GABA/glutamate ratio altered	Urinary NE/E ratio changes in CE; ↑ Plasma and CSF NE in PWE	Correlation with comorbidities
Endocannabinoid system	Therapeutic use of CBD	CSF anandamide: ↑ CE *vs* ↓ PWE	CB1 receptor modulation complexity
Post-transcriptional regulation	↑ miR-134 and miR-129 in drug-resistant cases	Limited canine data, mainly pilot studies	Inconsistent alterations for miR-223

Abbreviations: 11,12-DHET = 11,12-dihydroxyeicosatrienoic acid; AOPP = advanced oxidation protein products; ASM = antiseizure medication ; BBB = blood-brain barrier ; C3/4 = complement factor 3/4; CB = cannabinoid ; CBD = cannabidiol ; CE = canine idiopathic epilepsy ; CK-BB = creating kinase – brain isoform; CNS = central nervous system ; CRP = C-reactive protein ; CSF = cerebrospinal fluid ; DAMPs = damage associated molecular patterns ; E = epinephrine ; HMGB1 = high mobility group box 1 ; HSP70 = heat shock protein 70 ; MCT = medium chain triglycerides ; miR = microRNA ; MMP-2 = matrix metallopeptidase 2 ; NE = norepinephrine ; OEA = oleoylethanolamide ; PWE = people with epilepsy ; TNF = tumor necrosis factor.

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