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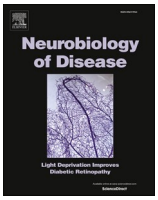

The gut microbiome and adult hippocampal neurogenesis: A new focal point for epilepsy?

Sebastian Dohm-Hansen [a,b,1], Francisco Donoso [a,b,1], Paul J. Lucassen [d,e], Gerard Clarke [a,c,*,2], Yvonne M. Nolan [a,b,2]

[a] APC Microbiome Ireland, University College Cork, Cork, Ireland
[b] Department of Anatomy & Neuroscience, University College Cork, Cork, Ireland
[c] Department of Psychiatry & Neurobehavioural Science, University College Cork, Cork, Ireland
[d] Swammerdam Institute for Life Sciences, Brain Plasticity Group, University of Amsterdam, the Netherlands
[e] The Center for Urban Mental Health of the University of Amsterdam, Amsterdam, the Netherlands

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ABSTRACT

Temporal lobe epilepsy (TLE) is a neurological disorder affecting millions of people worldwide and currently represents the most common form of focal epilepsy. Thus, the search for aetiological and pathophysiological parameters of TLE is ongoing.

Preclinical work and *post-mortem* human studies suggest adult hippocampal neurogenesis as a potentially relevant factor in TLE pathogenesis. Although progress has been made in elucidating the molecular links between TLE and hippocampal neurogenesis, recent evidence suggests that additional peripheral mediators may be involved.

The microbiota-gut-brain axis mediates bidirectional communication between the gut and the brain and could comprise a link between neurogenesis and TLE. In this review, we discuss emerging evidence highlighting a potential role for the gut microbiome in connecting TLE pathogenesis and hippocampal neurogenesis. We focus in particular on mechanisms associated with neuronal excitability, neuroinflammation and gut microbial metabolites. As the evidence does not yet support a direct link between gut microbiota-regulated hippocampal neurogenesis and TLE aetiology or pathophysiology, future studies are needed to establish whether current findings comprise circumstantial links or a potentially novel avenue for clinically relevant research.

1. Introduction

Epilepsy is a chronic neurological condition characterized by recurrent seizures, often provoked by an earlier insult in the central nervous system (CNS) (Beghi, 2020). Over 65 million people suffer from epilepsy worldwide, making it a leading neurological cause of loss in quality of life (Johnson, 2019). Temporal lobe epilepsy (TLE) is one of the most common types and is divided into two main groups: mesial temporal epilepsy and lateral epilepsy (Bartolomei et al., 1999; Pascual, 2007; Tatum, 2012). Although TLE has been scientifically investigated since the beginning of the 20th century (Gross, 1992), its aetiology remains poorly understood. Despite the variable factors associated with its development and onset, important advances have been made in elucidating the underlying mechanisms (Manford, 2017). In the last decade, both preclinical and clinical evidence has pointed to the gut microbiome as a possible moderator of epileptic seizures as well as a possible novel therapeutic target (Dahlin and Prast-Nielsen, 2019; De Caro et al., 2019; Lum et al., 2020; Wu et al., 2016; Yue et al., 2021).

The gut microbiota comprises the trillions of microorganisms inhabiting the gastrointestinal tract and represents an important component in the bidirectional communication between the brain and the gut, currently referred to as the "microbiota-gut-brain axis" (MGBA) (Cryan et al., 2019). The MGBA has been linked to several psychiatric diseases and neurological disorders, including depression (Cruz-Pereira et al., 2020; Du et al., 2020), autism spectrum disorder (Srikantha and Mohajeri, 2019), Alzheimer's disease (Kowalski and Mulak, 2019),

* Corresponding author at: Department of Psychiatry & Neurobehavioural Science/APC Microbiome Ireland, University College Cork, Cork, Ireland.
E-mail address: g.clarke@ucc.ie (G. Clarke).
[1] Joint first authors
[2] Joint last authors

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Parkinson's disease (Mulak and Bonaz, 2015), and recently also epilepsy (Yue et al., 2021).

Accumulating evidence also indicates a possible role for adult hippocampal neurogenesis (AHN) as a process that may not only be involved in the initiation of seizures in TLE (Chen et al., 2020; Cho et al., 2015) but also might be impacted as a consequence of epilepsy (Andres-Mach et al., 2011). Although AHN is modulated by changes in the gut microbiome (Cavallucci et al., 2020; Cruz-Pereira et al., 2020; Ogbonnaya et al., 2015), it currently remains unclear to what extent gut microbiome-AHN interactions are relevant in the context of epilepsy and seizures. For instance, some factors that are associated with TLE pathophysiology are known to be modulated by the MGBA and to also impact AHN, including neuronal excitability (Iori et al., 2016) and neuroinflammation (Sharma et al., 2019).

Here, we aim to provide a review of the current state of the preclinical and clinical literature investigating specific gut microbiota-associated factors that could be relevant for TLE, the possible role of AHN as a modulatory process in TLE pathogenesis, and to discuss the implications of the gut microbiome in potential AHN-TLE interactions. To this end, we conducted PubMed searches using the following search terms: (epilepsy OR epileptogenesis OR TLE) AND gut microbiota; gut microbiota AND (neurogenesis OR hippocampal neurogenesis OR AHN); gut microbiota AND neuronal excitability; gut microbiota AND synaptic signalling; gut microbiota AND (inflammation OR neuroinflammation); neurogenesis AND epilepsy; hippocampal neurogenesis AND temporal lobe epilepsy; epilepsy AND neuronal excitability; epilepsy AND synaptic signalling; epilepsy AND (inflammation OR neuroinflammation).

We start by highlighting the physiological changes that occur in the temporal lobe after an epileptic event, particularly in the hippocampus. Then, the relevance of physiological and aberrant AHN to TLE pathophysiology and aetiology is discussed, mainly through pre-clinical literature. Subsequently, we focus on the potential of the gut microbiome to interact directly, or indirectly, with relevant hippocampal regions (Tang et al., 2021), and to thereby modulate TLE through different mechanisms (Ding et al., 2021). We further present current evidence for the microbiome and neuronal excitability as potential features of TLE (Hammer et al., 2019). Finally, the possible roles of neuroinflammation and AHN (Kohman and Rhodes, 2013) in TLE induction are discussed within the framework of the MGBA (Gershen et al., 2015; Rana and Musto, 2018).

2. Temporal lobe epilepsy: the hippocampus and adult neurogenesis

Seizures are characterized by uncontrolled and excessive electrical discharges in the CNS. A common focus for seizures is the temporal lobe (Pascual, 2007), which is involved in sensory input processing, episodic memory, and language comprehension (Smith and Kosslyn, 2019). Indeed, TLE is a form of epilepsy that can originate in one or several areas of the temporal lobe (Tramoni-Negre et al., 2017). When the epileptic focus originates in the medial structures of the temporal lobe, like the hippocampus, entorhinal cortex, amygdala or parahippocampal gyrus, it is defined as mesial TLE (Tatum, 2012). On the other hand, when the epileptic event occurs in the temporal neocortex, including the temporal-occipital and temporal-parietal junctions, temporal circumvolutions, and the associative sensorial areas for hearing, visual, and language functions, it is defined as lateral or neocortical TLE (Michelucci et al., 2009).

Lesions or insults in the temporal lobe are identified as one of the most common causes of epileptic seizures (Chong et al., 2018). For example, sclerosis of the hippocampus is strongly associated with pharmaco-resistant epilepsy (Tai et al., 2018; Thom, 2014), but there are other pathologies that precede TLE development, including ganglioglioma and malformations of cortical development, as well as infectious, vascular and traumatic lesions (Slegers and Blumcke, 2020; Tubi et al., 2019; Vezzani et al., 2016). The hippocampus, located within the temporal lobe and involved in cognition and memory (Sweatt, 2004), can be critically affected by recurrent seizure episodes, resulting in sustained damage throughout life, as demonstrated in pre-clinical and clinical studies (Janz et al., 2022; Kälviäinen et al., 1998). For example, significant structural changes have been reported in the hippocampus in rat models of epilepsy, including selective and extensive hippocampal neuronal loss in the CA1 and CA3 regions (Biagini et al., 2005; Ouardouz and Carmant, 2012; Tyler et al., 2012). In a preclinical study, kainic acid-induced TLE in rats caused substantial changes in the hippocampus, including loss of GABAergic interneurons expressing parvalbumin and neuropeptide Y, reduced neurogenic (doublecortin-positive) cells, hypertrophied astrocytes, activated microglia, and sprouting of mossy fibres in the hippocampus (Upadhya et al., 2019) and related regions (Qiao et al., 2013; Tolner et al., 2007; Ketelaars et al., 2004). These neuroanatomical changes were accompanied by impairments in cognition, as measured in hippocampal-dependent behavioural tests such as the object location test, novel object recognition test, and the pattern separation test (Upadhya et al., 2019). In another pre-clinical investigation using kainic acid to induce epilepsy in rats, cognitive decline as observed in the novel object recognition test and the Y-maze test of spatial memory was reported, suggesting impaired hippocampal function (Carron et al., 2019). Moreover, seizure-induced hippocampal damage is correlated with a loss of cognitive performance in both rat models of epilepsy and human subjects with TLE (Shetty, 2014; Vascouto et al., 2020).

Subjects with TLE also have demonstrated severe alterations in hippocampus-dependent cognitive performance. A clinical study evaluating 100 patients with TLE revealed that neuronal loss affected all hippocampal subfields, including CA1, CA4 (hilus) and the dentate gyrus, or predominant cell loss in CA4 and partially affecting CA3 and the dentate gyrus in 63 of the subjects, who also presented with significantly reduced declarative memory capacities (Coras et al., 2014). In contrast, patients with CA1 predominant cell loss did not show declarative memory impairment and were indistinguishable from patients without any hippocampal cell loss. Finally, a recent study found that TLE patients displayed poorer performance in a putatively dentate gyrus-dependent memory task compared to healthy controls (Madar et al., 2021).

2.1. Adult hippocampal neurogenesis

The adult mammalian hippocampus harbours a neurogenic niche within the dentate gyrus that continues to produce principal neurons (granule cells, GCs) throughout life. Briefly summarized, neural stem cells (NSCs) ("type 1" or "radial glia-like" cells) in the dentate subgranular zone give rise to neural progenitor cells ("type 2" or "transit-amplifying progenitor" cells) that undergo proliferative expansion and apoptotic selection before generating radially migrating neuroblasts ("type 3" cells), which subsequently differentiate into mature GCs (Kempermann et al., 2004; Pilz et al., 2018; Sierra et al., 2010; Sun et al., 2015). These newly generated neurons lastingly and functionally integrate within the dentate gyrus network (Kempermann et al., 2003; van Praag et al., 2002), where they contribute to hippocampal memory formation (Clelland et al., 2009; Danielson et al., 2016; Nakashiba et al., 2012; Niibori et al., 2012), regulation of the stress response (Anacker et al., 2018; Snyder et al., 2011), and possibly mediate some of the effects of antidepressants (Santarelli et al., 2003; Surget et al., 2011). The birth and survival rates of the new-born neurons are influenced by several hormonal and environmental factors, age and diseases (Lucassen et al., 2015; Kozareva et al., 2019; Terreros-Roncal et al., 2021). Additionally, a role for the gut microbiome in regulating AHN is receiving increasing empirical support (e.g. Mohle et al., 2016; Ogbonnaya et al., 2015; Wei et al., 2021) and will be discussed in a dedicated section below.

AHN appears to be particularly relevant for one of the main mnemonic functions of the dentate gyrus, pattern separation (Clelland et al.,

2009), the capacity to encode and store distinct memories of spatio-temporally similar events with minimal interference. This is thought to be mediated by decorrelation of upstream entorhinal inputs to facilitate orthogonal storage of similar memory traces in the downstream CA3 (Leutgeb et al., 2007; Neunuebel and Knierim, 2014). Indeed, ablating AHN in mice impairs discriminative fear conditioning of similar contexts and increases the overlap of associated CA3 engrams (Niibori et al., 2012), while boosting AHN has the opposite behavioural effect (Sahay et al., 2011).

AHN may also be important for the normal homeostatic (Snyder et al., 2011) and antidepressant-mediated (Surget et al., 2011; Tartt et al., 2022) recovery of glucocorticoid levels and behaviour after chronic stress (Lucassen et al., 2013), potentially via ventral hippocampal projections to the hypothalamus and extended amygdala (Gergues et al., 2020). Accordingly, manipulating the levels of AHN in the murine ventral dentate gyrus alters depressive-like behaviour in response to social defeat stress (Anacker et al., 2018).

In humans, the presence of AHN has been demonstrated in *post-mortem* brains using bromodeoxyuridine (BrdU) labelling (Eriksson et al., 1998), radiocarbon dating (Spalding et al., 2013), and immunohistochemical markers of neurogenesis (Boldrini et al., 2018; Knoth et al., 2010; Moreno-Jimenez et al., 2019; Moreno-Jimenez et al., 2021; Terreros-Roncal et al., 2021; Tobin et al., 2019; see Lucassen et al., 2020b for an overview). Progenitor cells with neural potential have also been isolated from resected hippocampal tissue from epilepsy patients (Roy et al., 2000). Interestingly, histochemical studies of resected hippocampi have suggested an increase in putative neural progenitor cells in adult (Crespel et al., 2005) and paediatric (Blumcke et al., 2001) cases of TLE. Others have noted a decrease in putative immature GCs compared to non-epileptic cases (Seki et al., 2019) or autopsy controls (Mathern et al., 2002), while some have failed to find meaningful differences (Fahrner et al., 2007; Liu et al., 2008).

As a caveat, human histochemical studies of AHN have been subject to debate concerning methodological issues over the last years (Kempermann et al., 2018; Lucassen et al., 2020a; Lucassen et al., 2020b; Paredes et al., 2018; Tartt et al., 2018). However, there exists a rich literature of rodent studies that has established mechanistic and, potentially, aetiological links between seizures and aberrant AHN, which will be reviewed in the following sections. We will also describe the current state of research supporting a role for the gut microbiome in regulating AHN, and finally, we highlight future opportunities for studying the relevance of this possible relationship between the gut microbiome and AHN in the context of TLE, which has yet to be formally investigated.

2.2. The effects of seizures on adult hippocampal neurogenesis

Early studies of resected and *post-mortem* tissue from epileptic patients revealed gross morphological changes to the hippocampus, including dispersion of the GC layer (Houser, 1990), aberrant mossy fibre projections (“sprouting”) to the dentate inner molecular layer (Gorter et al., 2001; Sutula et al., 1989), and ectopic hilar migration of GCs (Mathern et al., 1994). A seminal study by Parent et al. (1997) sought to elucidate the contribution of postnatally generated GCs to these phenomena. Using a rat model of status epilepticus, the authors demonstrated that pharmacologic induction of convulsive seizures by the muscarinic agonist pilocarpine was associated with increased cellular proliferation (BrdU labelling) and net neurogenesis (double-labelling of BrdU and postmitotic neuronal marker Tuj1) in the adult subgranular zone. Moreover, these putative seizure-induced GCs displayed patterns of ectopic migration and mossy fibre sprouting similar to those observed in the hippocampus of humans. The very same year, Bengzon et al. (1997) similarly showed an increase in cells double-labelled for BrdU and postmitotic neuronal nuclear marker NeuN in the rat subgranular zone after both kainic acid-induced seizures and kindling (i.e. repetitive electrical stimulation of the hippocampus to produce spontaneous recurrent seizures). A follow-up study by Parent et al. (2006) confirmed the identity of the ectopic neurons observed in pilocarpine-treated rats and human epileptic post-mortem tissue by positive immunostaining against the GC fate-specification marker Prox1 (Iwano et al., 2012).

The increase in proliferation observed after pharmacologically induced seizures in rodents has been shown to involve type-1 NSCs, type-2b progenitors, and type-3 neuroblasts (Bielefeld et al., 2019; Huttmann et al., 2003; Jessberger et al., 2005; Steiner et al., 2008). For instance, kainic acid treatment in mice recruits quiescent NSCs into the cell cycle and causes expansion of the NSC pool (Lugert et al., 2010), possibly mediated via glutamatergic AMPA receptors located on NSC radial processes (Renzel et al., 2013; Shtaya et al., 2018). This is in line with the well-established coupling of NSC maintenance, activation and cell fate, progenitor survival, and net neurogenesis to local network activity (Bao et al., 2017; Deisseroth et al., 2004; Song et al., 2013; Song et al., 2012; Uemura et al., 2021; Yeh et al., 2018). However, the seizure-associated rise in new-born cell numbers is transient (Nakagawa et al., 2000) and does not necessarily result in a net increase of the GC population (Mohapel et al., 2004). This may partly be due to compensatory mechanisms, such as adaptation in the rate of apoptotic selection (Ekdahl et al., 2001) and microglia-mediated elimination of new-born cells (Luo et al., 2016), which help to ensure population homeostasis.

Compared to acute seizures, chronically recurrent seizures are associated with compromised AHN in the long-term (Hattiangady et al., 2004; Kralic et al., 2005). In animal models, neuronal cell death is mostly induced by the initial status epilepticus and not by subsequent repeated, spontaneously occurring seizures (Gorter et al., 2003). Also, a different sensitivity, or responsivity, may exist for different subsets of new-born cells (Bielefeld et al., 2014) where a low seizure intensity has been proposed to only stimulate neurogenesis to a 'physiological plasticity' level, without many pathological consequences. In contrast, a high initial seizure intensity could induce a specific subset of altered and/or ectopically located new GCs to emerge, with different electrophysiological properties, that could initiate hyper-excitatory recurrent networks, which in turn, could contribute to chronic epilepsy (Bielefeld et al., 2014).

An elegant study by Sierra et al. (2015) helped to elucidate the possible cause of the decline in AHN in the long term. Using genetic lineage tracing of mouse NSCs and intrahippocampal infusions of kainic acid, the authors showed that both convulsive and non-convulsive seizures ultimately deplete the NSC population in an activation- and division-dependent manner, leading to lower levels of net neurogenesis. Indeed, depletion of NSCs is fundamentally tied to their division history (Encinas et al., 2011). Additionally, recurrent convulsive seizures caused NSCs to become hypertrophic and switch to symmetric gliogenic divisions, generating reactive astrocytes. Sasaki-Takahashi et al. (2020) demonstrated similar aberrant morphology and astrocytic differentiation of NSCs as a function of seizure severity in a pilocarpine model of epilepsy.

However, even non-convulsive seizures have been shown to produce hypertrophic (so-called “reactive”) NSCs (Bielefeld et al., 2019). Interestingly, this fate switch was recently suggested to be regulated by an NSC piwi RNA pathway (Gasperini et al., 2021). In light of the known importance of NSC quiescence (i.e. reversible cell cycle arrest) for maintaining both the NSC pool and net neurogenesis throughout the lifespan (Harris et al., 2021; Urban et al., 2016; Schouten et al., 2020), excessive activation of NSCs due to recurrent seizures would be expected to lead to neurogenic exhaustion in the long-term. Indeed, Fu et al. (2019) tracked the development of recurrent seizures in an Alzheimer’s disease mouse model (APP) over 14 months and found an initial increase in NSC divisions and neurogenesis with the onset of seizures, but NSCs eventually began depleting, and neurogenesis decayed to levels below age-matched control mice. Most recently, Ammothumkandy et al. (2022) corroborated some of the abovementioned findings in surgically resected hippocampal tissue from adult mesial TLE patients. They

demonstrated an exponential decline of putative immature granule neurons (i.e. cells immunopositive for doublecortin, DCX, and PROX1) as a function of disease duration and a complete lack of such cells in dentate subsections with inter ictal-like activity, as assessed by multi-electrode array recordings. Interestingly, patient dentate sections contained DCX immunopositive astroglia, which were not present in post-mortem tissue from age- and sex-matched controls, and primary hippocampal cell cultures from patients preferentially generated astroglial (as opposed to neuronal) cells upon 6-week differentiation. In summary, while acute seizures temporarily boost neurogenesis through NSC activation, chronic seizures could exhaust long-term neurogenesis through NSC pool depletion and/or by triggering a switch toward a gliogenic fate.

2.3. Role of adult-born granule cells in dentate excitability and epileptogenesis

GCs display particularly sparse activity and connectivity patterns, which underlie the mnemonic computations carried out by the dentate gyrus (Marr, 1971; O'Reilly and McClelland, 1994). This sparseness is largely due to a uniquely high abundance of lateral inhibition motifs in the dentate circuit, mediated by local parvalbumin$^+$ inhibitory interneurons (Espinoza et al., 2018). The same properties also appear to impose a limiting function on their excitatory input, allowing the dentate to potentially act as a "gate" against spreading epileptiform activity (Heinemann et al., 1992; Lothman et al., 1992). Indeed, optogenetic inhibition of GCs during ictal activity can prevent behavioural seizure progression in mice, while activation of GCs alone can be sufficient to induce seizures (Krook-Magnuson et al., 2015). Importantly, adult-born GCs take 8 weeks to fully integrate into this inhibitory circuitry in mice, while feedforward excitation and inhibition of downstream CA3 is detectable within 4 weeks (Restivo et al., 2015; Temprana et al., 2015). As a result of the maturational delay in perisomatic inhibition by local parvalbumin$^+$ interneurons, 4-6-week-old GCs are mainly limited by excitatory drive and, therefore, uniquely excitable and likely to be recruited by afferent activity (Groisman et al., 2020; Marin-Burgin et al., 2012). Interestingly, optogenetic activation of 6-7-week-old GCs still drives feedback inhibition onto mature GCs via local inhibitory neurons (Drew et al., 2016), potentially allowing for a unique contribution to overall DG excitability. Indeed, pharmacogenetic stimulation of AHN in mice reduces evoked responses to excitatory stimulation in the GC layer, seemingly via an increased drive onto hilar interneurons, while x-ray ablation of neurogenesis has a smaller but opposite effect (Ikrar et al., 2013). Similarly, the bidirectional effects of environmental enrichment and ageing on neurogenesis moderate the aforementioned inhibitory drive onto mature GCs (Drew et al., 2016). The window of high feedforward inhibition and hyperexcitability in 6-7-week-old GCs could be due to faster maturation of efferent synaptic transmission to parvalbumin$^+$ interneurons compared to inhibitory afferents (Groisman et al., 2020). As dentate gyrus interneurons have been suggested to act as local gamma-rhythm generators (Pernia-Andrade and Jonas, 2014), such dynamics could account for the observed change in gamma-frequency burst amplitude throughout the dentate gyrus of neurogenesis-ablated mice (Lacefield et al., 2012).

As a correlate to the above in humans, Reagh et al. (2018) found that age-related dentate/CA3 hyperactivity predicted poor mnemonic discrimination as assessed by the "mnemonic similarity task" (MST). The MST requires participants to correctly reject highly visually similar lures from previously studied targets (Stark et al., 2019), which is thought to reflect dentate pattern separation (Bakker et al., 2008). In a prior study, administration of the anticonvulsant levetiracetam to reduce hippocampal hyperactivity had improved performance on the same task in a cognitively impaired cohort (Bakker et al., 2012). Interestingly, patients with TLE display impaired mnemonic discrimination compared to healthy controls, as assessed by the MST (Lalani et al., 2021; Madar et al., 2021) and similar tasks (Poch et al., 2020; Reyes et al., 2018). It is important to stress, however, that mnemonic discrimination as a behavioural output – be it in animals or humans – does not necessarily imply pattern separation, a network- and ensemble-level computation (Santoro, 2013). Madar et al. (2021) recently addressed this interpretational gap in a mouse model of epilepsy. Kainic acid-treated mice not only performed worse than controls on an object location discrimination task, but the authors also demonstrated impaired GC decorrelation of perforant path stimuli in hippocampal slice preparations from the same mice.

Taken together, the evidence from rodent studies suggests a role for adult neurogenesis in maintaining the dentate gate, which could allow it to modulate hippocampal seizures and epileptiform activity. Jain et al. (2019) investigated this possibility by pharmacogenetic augmentation or ablation of ongoing neurogenesis prior to pilocarpine-induced status epilepticus in adult mice. Animals with reduced neurogenesis displayed more severe and longer seizures, characterized by increased epileptiform activity, and greater hilar neurodegeneration than in intact animals. Interestingly, augmentation of neurogenesis that was timed to accumulate $\leq$6-week-old GCs, had an opposite and ameliorating effect, corroborating their role in maintaining the dentate 'gate'. A previous study found a similar effect of pharmacogenetic ablation of neurogenesis on kainic acid-induced status epilepticus (Iyengar et al., 2015), while Hattiangady et al. (2020) demonstrated a reduction in spontaneous recurrent seizures in adult rats through grafting of embryonic hippocampal neural stem and progenitor cells. However, this could not be attributed solely to increases in AHN, as the treatment may have had other, possibly salutary effects, such as rescuing the loss of GABAergic neurons. Most recently, Lentini et al. (2021) ameliorated chronic seizures in mice treated with intrahippocampal kainate by direct *in vivo* reprogramming of glia to GABAergic interneurons. Intriguingly, these induced neurons integrated functionally within the dentate network and established inhibitory synapses onto GCs, further supporting the pathophysiological relevance of the dentate gate and its lateral inhibition motifs. Thus, in rodents, the level of AHN appears to moderate epileptiform activity, potentially exerting a protective effect.

Conversely, pilocarpine-induced epilepsy in mice is accompanied by aberrant forms of neurogenesis that correlate with increased seizure severity and frequency (Hester and Danzer, 2013). Some GCs migrate ectopically to the hilus, or even CA3, and establish recurrent excitatory synapses with mossy fibres (Pierce et al., 2005; Scharfman et al., 2000). Compared to normotopic GCs, these cells are hyperexcitable and display abnormal epileptiform synchrony (Althaus et al., 2019; Kron et al., 2010; Scharfman et al., 2000). Additionally, seizure-induced GCs may sprout hilar basal dendrites or mossy fibre collaterals projecting to the inner molecular layer, which further contribute to recurrent excitatory activity through functional synaptic integration within the dentate network (Althaus et al., 2016; Jessberger et al., 2007; Kron et al., 2010; Ribak et al., 2000). These recurrently connected GCs have been predicted to form "hubs" that could destabilize the dentate network and drive epileptogenesis (Morgan and Soltesz, 2008). Supporting this, Sparks et al. (2020) used *in vivo* calcium imaging of mature and adult-born GCs (5-6 weeks old) to model their differential contributions to interictal epileptiform discharges in adult mice treated with intrahippocampal kainic acid. It was found that ensembles active during such discharges were preferentially composed of adult-born GCs, though individual cell recruitment appeared stochastic. This is line with previous work showing that interictal epileptiform activity randomly recruits spatially localized GC assemblies (Feldt Muldoon et al., 2013). Most recently, Hadjiabadi et al. (2021) found that adult-born GCs could be overrepresented among epileptic "superhubs", cells predicted to exert a disproportionate influence on the progression of seizures through abundant feedforward excitation motifs. Thus, ablating such aberrant GCs might ameliorate hippocampal seizures. Indeed, chemogenetic ablation of GCs born in the weeks before and after pharmacologically induced epilepsy reduces seizure frequency in mice (Cho et al., 2015; Hosford et al., 2016; Hosford et al., 2017). However, ablation does not

entirely eliminate seizures and may even exacerbate their duration (Hosford et al., 2016). Barring methodological reasons (e.g. off-target astrocyte ablation), a reason for this may be the heterogeneity of integration within recurrent circuits among peri-insult-generated GCs (Murphy et al., 2011). Indeed, some cells have been shown to display reduced, rather than increased, excitability (Jakubs et al., 2006). In the study by Ammothumkandy et al. (2022), even though there was evidence of ectopically migrated immature granule neurons in TLE dentate tissue, these cells were immunonegative for the immediate early genes c-fos and Arc, suggesting they were not recently active; conversely, DCX immunopositive astroglia did express the same markers. Importantly, GC age at the time of insult has significant effects on its subsequent aberrant characteristics, with less differentiated cells being more susceptible (Kron et al., 2010).

Recent chemogenetic approaches that allow reversible manipulation of peri-insult-generated GCs have begun to elucidate this latter issue. Zhou et al. (2019) leveraged retrograde trans-synaptic tracing to show that GCs born 7 days before, or 3 days after pilocarpine administration, but not 3 weeks before or 2 weeks after, receive aberrant excitatory input from cortical areas, CA3 pyramidal cells (so-called "back-projections"), and other dentate GCs. Notably, chemogenetic activation or silencing of GCs born 3 days post-insult was sufficient to ameliorate or exacerbate epileptiform activity and seizures, respectively. Using a similar approach, Lybrand et al. (2021) recently corroborated these findings and provided a mechanistic explanation. The authors demonstrated that chemogenetic activation of $\leq$2-week-old GCs alone was sufficient to induce ectopic migration and spontaneous seizures, while silencing adult-born GCs after pilocarpine treatment ameliorated subsequent seizures and reversed aberrant GC afferents. In line with the known importance of depolarizing GABA for proper synaptic integration (Ge et al., 2006) and migration (Koyama et al., 2012) of early-stage GCs, the activity dependence of aberrant neurogenesis was further demonstrated to be mediated by $GABA_A$-receptor-dependent Ca^{2+} signalling. In conclusion, similar to the circuit-based mechanisms mediating the effects of seizures on proliferation, epilepsy appears to be associated with aberrant neurogenesis in an activity-dependent manner during a critical stage of GC maturation in rodents.

3. The gut microbiome as a possible modulator of adult hippocampal neurogenesis, excitability and temporal lobe epilepsy

Epileptic episodes are associated with diverse physiological changes, such as neuronal excitability (Verhoog et al., 2020), neuroinflammation (Gershen et al., 2015; Rana and Musto, 2018), and altered neurogenesis (Jessberger and Parent, 2015). Each of these neurobiological processes have been reported to be sensitive to, and partly mediated by, the MGBA through different signalling pathways, including the production of microbial-derived neuroactive compounds or metabolites (e.g., neurotransmitters, amino acids, and short-chain fatty acids) (Wall et al., 2014). In the following sections, we will review the evidence linking the gut microbiome with neuronal excitability and inflammation and elaborate on the potential of the gut microbiome to modulate AHN through circulating metabolites and neuroimmune interactions, and how this could ultimately be relevant for TLE.

3.1. The gut microbiota as a modulator of excitability and synaptic signalling

Although there is lack of direct evidence linking the gut microbiome with TLE, the MGBA could play a role in modulating seizure initiation and activity via microbial signals to the hippocampus (Avoli et al., 2016; Goldberg and Coulter, 2013; Pan et al., 2008). Indeed, microbiota deficiency is associated with hippocampal structural and functional alterations, such as decreased dendritic length and spines, and abnormal levels of plasticity biomarkers, including brain-derived neurotrophic factor, serotonin, and nerve growth factor-inducible protein A (Vuong et al., 2017).

Impaired synaptosomal transport of GABA and glutamate, which is crucial to terminate neurotransmission by rapidly removing extracellular transmitters, has also been implicated in the mechanisms underlying epileptogenesis in the temporal lobe (Hoogland et al., 2004). Notably, there is evidence demonstrating a role for the gut microbiome in the modulation of both GABAergic and glutamatergic signalling in the hippocampus (Mazzoli and Pessione, 2016). For example, chronic treatment with *Lactobacillus rhamnosus* (JB-1) in mice is associated with increased GABA(Aα2) and reduced GABA(B1b) receptor expression in the hippocampus compared to control-fed mice (Bravo et al., 2011). A follow-up experiment demonstrated that *Lactobacillus rhamnosus* (JB-1) treatment in mice correlated with increased hippocampal GABA and glutamate as measured by *in vivo* magnetic resonance spectroscopy (Janik et al., 2016). Studies have also reported that commensal bacteria, including several lactic-acid bacteria cultured and isolated from the human intestine (e.g., strains belonging to *Lactobacillus*, *Lactococcus*, and *Streptococcus* genera) and *Bifidobacterium* (Barrett et al., 2012; Siragusa et al., 2007) release GABA/glutamate. The abundance of GABA-modulating bacteria in the gut has been negatively correlated with depression (Strandwitz et al., 2019), suggesting a potential impact of lactic-acid bacteria on brain function via the MGBA. Nevertheless, although microbial modulation of hippocampal GABA and glutamate signalling could be a possible mechanism associated with the pathology of TLE, the functional implications of these observations remain unclear. Future research in TLE may consider the examination of gut-brain pathways to elucidate the role of the MGBA in TLE pathogenesis.

One of the most prominent features of the epileptic brain, is the uncontrolled and excessive neuronal activity in TLE patients (Saniya et al., 2017). The abnormalities in hippocampal excitability associated with epilepsy have been extensively reviewed (Navidhamidi et al., 2017), and the failure of homeostatic mechanisms to restore neuronal firing rates to control levels is still considered the main factor responsible for the hippocampus becoming hyper- or hypo-excitable. A role for the gut microbiome in the regulation of neuronal excitability has tentatively been demonstrated in the enteric nervous system (ENS). Germ-free (GF) mice (raised to control their exposure to viral, bacterial or parasitic agents, and therefore with no microorganisms living in or on them) displayed decreased excitability in myenteric after-hyperpolarization neurons, as measured by a lower resting membrane potential when compared to specific pathogen-free (SPF) control mice (McVey Neufeld et al., 2013). Interestingly, the probiotic *Lactobacillus reuteri* produced a significant increase of excitability in the number of action potentials per depolarising pulse, accompanied by an opening of calcium-dependent potassium channels in a subset of ENS neurons in the colon of Sprague-Dawley rats (Kunze et al., 2009).

The gut microbiome may also be involved in the development of excitatory synapses in the CNS, with implications for neuronal plasticity. *Ex vivo* hippocampal slice electrophysiological recordings revealed that although GF mice displayed normal basal synaptic excitability compared to conventional mice, a significant decrease was observed in long-term potentiation in GF mice, as detected by field excitatory postsynaptic potential (fEPSP) measures (Darch et al., 2021). Ceftriaxone treatment (a β-lactam antibiotic) has shown therapeutic potential by attenuating the exacerbated hippocampal fEPSP slope and population spike amplitude in the okadaic acid model of Alzheimer's disease in the rat and by improving short- and long term memory assessed by alternating behaviour and passive avoidance tasks (Hamidi et al., 2019). It is worth noting that ceftriaxone has been associated with mechanisms linked to the excitatory amino acid transporter-2 expression and glutamate uptake in primary human astrocytes (Lee et al., 2008), so it remains unclear whether ceftriaxone effects *in vivo* are mediated by its antibiotic properties.

These results suggest that significant alterations in the gut microbiome, or the complete absence of gut microbes in the case of GF

animals, are associated with changes in neuronal excitability in both the ENS and the CNS. Nevertheless, it is important to note that all the aforementioned studies involve *in vivo* and in *vitro* work derived from rodent experiments, and thus, it is not yet clear how these findings will translate to the human condition. Furthermore, the findings described above are merely associational, and mechanistic studies are thus be needed to clarify the causal relationships.

3.2. The gut microbiota as a modulator of neuroinflammation

Neuroinflammation, defined as inflammatory processes occurring in nervous tissue, is considered an important element in the pathogenesis of epilepsy (Pracucci et al., 2021). Indeed, the initiation of seizures has been associated with an increased and often persistent inflammatory state in the microenvironment of neural tissue, along with functional changes and subtle neuronal damage, both in rodent models and the human brain (Aronica et al., 2007, 2010; Holtman et al., 2013; Alyu and Dikmen, 2017). The relationship between the gut microbiome and (neuro)inflammation has been extensively reviewed in recent years (Fung et al., 2017; Thaiss et al., 2016; Wang et al., 2020), and the MGBA has been proposed to be an important component in the regulation of the intensity and duration of the immune response in the periphery and the brain. For instance, a role for microbial-derived metabolites (i.e. short-chain fatty acids, SCFA) in modulating the innate immune response has been previously demonstrated (Li et al., 2018; Vinolo et al., 2011; Yao et al., 2020). Some molecular mechanisms associated with the immunomodulatory potential of SCFA include the binding and regulation of free fatty acid receptors (Yao et al., 2020). An *in vitro* investigation revealed that the SCFA butyrate activated the free fatty acid receptor 3 (FFAR3, a GPCR member activated by SCFAs) to down-regulate the expression of pro-inflammatory markers inducible nitric oxide synthase (iNOS), tumour necrosis factor (TNF), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6) in RAW264.7 macrophage-like cells (Ohira et al., 2013). It was further demonstrated that butyrate can reduce inflammation via inhibition of histone deacetylases (HDAC). Moreover, both butyrate and the HDAC inhibitor Trichostatin A significantly decreased the levels of nitric oxide, IL-6, and IL-12p40 secreted by primary bone marrow-derived macrophages (Chang et al., 2014).

It has been hypothesized that SCFAs could also act directly in brain cells, including microglia and astrocytes, by acting on G protein-coupled receptors (GPCR) or as HDAC inhibitors, with subsequent effects on immune pathways (Dalile et al., 2019; Stilling et al., 2016). As mentioned above, FFAR3 can modulate the expression of inflammatory markers and has been detected in the sympathetic ganglia, suggesting possible implications for sympathetic nerve regulation (Kimura et al., 2011). In BV2 microglial cells, sodium butyrate was shown to inhibit the histone modification histone 3-lysine 9-acetylation (H3K9ac), altering the expression of pro-inflammatory genes (Patnala et al., 2017). Furthermore, SCFAs can cross the blood-brain barrier via the systemic circulation and then target microglia to regulate their maturation and function (Wang et al., 2018). As was at least shown in an *in vitro* investigation using rat primary microglial cultures, butyrate counteracted the lipopolysaccharide-induced pro-inflammatory response in microglial cells by reducing the protein expression of IL-6, TNF-α, and nitric oxide (Huuskonen et al., 2004). Whether this also occurs in the brain and whether the mechanisms associated with butyrate actions are mediated by activation of specific receptors at physiological concentrations awaits future studies.

The gut microbiome has also been shown to communicate with the brain via the vagus nerve (Bonaz et al., 2018; Fülling et al., 2019) and through hormonal regulation (Cussotto et al., 2018; Martin et al., 2019), which may have implications for the regulation of neuroinflammation, and indeed, modulation of microglia function appears to be another target of gut microbiota signals. GF mice displayed global microglial deficits, including altered cell proportions and an immature phenotype, which lead to an impaired innate immune and metabolic responses (Erny et al., 2015; Erny et al., 2021). Depletion of intestinal bacteria using broad-spectrum antibiotics was associated with increased microglial cell volume, segment number, and branch points when compared to microglia analysed in SPF mice (Erny et al., 2015). Future investigation is required to clarify the role of those pathways in triggering or modulating inflammatory processes in the brain, and the potential links between these mechanisms with seizure activity.

3.3. The gut microbiota as a modulator of adult hippocampal neurogenesis

In a seminal study, Ogbonnaya et al. (2015) found that GF mice displayed increased neurogenesis in the adult subgranular zone, as assessed by BrdU and NeuN labelling. Interestingly, this also held true for GF mice that were subsequently housed under non-sterile conditions post-weaning, an effect which the authors attribute to developmental programming. Indeed, later-life differences in gene expression between GF mice and their SPF counterparts have been shown to be reversible by gut microbiota reconstitution during critical developmental windows (Diaz Heijtz et al., 2011). As an example, the endocrine response (e.g. circulating corticosterone levels) to acute restraint stress is elevated in adult GF mice but is partly rescued by faecal microbiota transplant (FMT) from SPF mice if done before the second postnatal month (Sudo et al., 2004). This is relevant considering the possible role of AHN in moderating both the endocrine and behavioural responses to stress (Anacker et al., 2018; Snyder et al., 2011) and that of glucocorticoids in both maintaining (Schouten et al., 2020) and decreasing (Anacker et al., 2013) AHN in a concentration- and receptor-dependent manner. Notably, probiotic treatment with the genera *Lactobacillus* and *Bifidobacterium* has been shown to suppress plasma corticosterone levels and prevent reduction of AHN in mice subjected to chronic water avoidance stress (Ait-Belgnaoui et al., 2014).

Two recent studies from the same group explored the effects of FMT from donor mice exposed to a chronic unpredictable mild stress paradigm to antibiotic-treated recipient mice. In both studies, FMT was found to phenocopy the depressive-like behavioural (e.g. immobility time in forced swim and tail suspension tests) and anti-neurogenic effects of stress in recipients, and this was mediated by changes in the biosynthesis of serotonin (Siopi et al., 2020) and endocannabinoids (Chevalier et al., 2020), in line with the known modulatory role of the gut microbiome in host tryptophan (Clarke et al., 2013) and fatty acid metabolism (Kishino et al., 2013). Importantly, the pro-neurogenic effect of fluoxetine was limited by the serotonin precursor 5-hydroxytryptophan in FMT recipient mice (Siopi et al., 2020). In the study by Chevalier et al. (2020), the neurogenic and behavioural effects of FMT were dependent on central CB1 cannabinoid receptors. Indeed, cannabinoids can stimulate net AHN in adult rats via CB1 activation, which also confers antidepressant effects (Jiang et al., 2005).

More recent support for the relevance of microbial metabolism comes from Wei et al. (2021), who used mono-colonisation of mice with *Escherichia coli* tryptophanase mutants to demonstrate that the metabolite indole stimulates AHN by promoting progenitor cell cycle exit and neuronal maturation via the aryl hydrocarbon receptor. Another canonical example of gut microbiota-derived metabolites is that of the SCFAs. Kundu et al. (2019) showed that FMT from healthy 2-year-old donor mice to GF 5-6-week-old recipient mice was enriched in butyrate-producing bacterial strains, which likely led to a butyrate-induced increase in brain-derived neurotrophic factor and AHN. Indeed, butyrate is known to stimulate neural progenitor proliferation *in vitro* (Yang et al., 2020) and AHN *in vivo* (Val-Laillet et al., 2018). Taken together, these results support a role for gut microbiota-mediated metabolism (e.g. tryptophan, SCFAs) in regulating AHN, at least in rodents.

Another way in which the gut microbiome might modulate neurogenesis is via the host immune system. Mohle et al. (2016) used a

cocktail of broad-spectrum antibiotics to ablate the gut microbiome in adult female mice and found that this was associated with reduced progenitor proliferation and survival of new-born granule neurons, but the decrease was rescued by voluntary wheel-running or a probiotic treatment consisting mainly of the genera *Lactobacillus* and *Bifidobacterium*. Importantly, all of these effects appeared to be partly mediated by brain Ly6C^{hi} monocytes, as supported by genetic or antibody-based ablation and adoptive transfer of this particular subset.

Diet is increasingly appreciated to shape human and animal gut microbiota composition and function (Claesson et al., 2012; Muegge et al., 2011), and reciprocally, the microbiome moderates metabolic and inflammatory responses to diet (Asnicar et al., 2021; Maslowski et al., 2009). It was recently found that hypoxia and a ketogenic diet synergistically induce cognitive decline and reduce AHN in adult mice in a T cell-mediated mechanism brought about by an enrichment in the bacterial genus *Bilophila* (Olson et al., 2021). Indeed, diet had previously been associated with altered gut microbiota composition and levels of AHN in pigs but without elucidating any mediating mechanisms (Val-Laillet et al., 2017). The gut microbiome is also known to modulate the function and inflammatory phenotype of microglia (Erny et al., 2021; Erny et al., 2015; Lynch et al., 2021) and astrocytes (Sanmarco et al., 2021) through complex neuroimmune signalling and with the SCFA acetate implicated in driving microglial function and metabolism (Erny et al., 2021). This is pertinent considering the role of these cell types in regulating hippocampal NSC proliferation (Asrican et al., 2020), apoptotic selection of neuroblasts (Sierra et al., 2010), and synaptic integration of adult-born granule neurons (Sultan et al., 2015). For example, co-administering a probiotic cocktail, consisting mainly of strains from *Lactobacillus* and *Bifidobacterium* species, in mice treated with lipopolysaccharide maintained hippocampal microglia in a resting ramified state and reduced pro-inflammatory cytokine levels, which was paralleled by increased NSC and neuroblast proliferation, while preventing decline of the overall neural stem- and progenitor cell pool (Petrella et al., 2021). Indeed, activated microglia are known to mediate the effect of lipopolysaccharide-induced neuroinflammation on AHN (Ekdahl et al., 2003; Monje et al., 2003). Gastrointestinal inflammation itself can lastingly change gut microbiota composition (e.g. butyrate-producing bacteria) and AHN in mice (Salvo et al., 2020). For example, experimental inflammatory bowel disease is associated with microglial activation and has been shown to impede radial migration and functional integration of new-born granule neurons (Gampierakis et al., 2021). Canonical inflammatory cytokines can induce p21-mediated cell cycle arrest in hippocampal neural progenitors (Zonis et al., 2013). It is, therefore, interesting to note that FMT from the 5xFAD Alzheimer's disease model to antibiotic-treated recipient mice is associated with increased levels of pro-inflammatory cytokines and microglia coverage in the hippocampus, with concurrent reductions in progenitor proliferation and increased numbers of p21^{+} cells (Kim et al., 2021). Finally, even drug treatments could potentially convey some of their neurogenic effects via the gut microbiome. As an example, the pro-neurogenic effects of the antidiabetic drug metformin could be partly phenocopied by FMT from treated to untreated obese mice, and this was also paralleled by a decrease in hippocampal microglia density (Clarke, 2021; Ma et al., 2021). Taken together, the above studies point to neuroimmune interactions as another possible way for the gut microbiome to regulate rodent AHN.

As a caveat, many of the studies cited in this section have involved adult male animals only, which could bias the findings. For instance, it has been shown that gut microbiota depletion (both germ-free and antibiotics-treated mice) alters the microglial transcriptome and chromatin landscape differentially in males and females in an age-dependent manner (Thion et al., 2018), which might translate to downstream functional differences. This may be relevant in light of the recent observation that male and female GF mice display different age-related decay dynamics of AHN (Scott et al., 2020). In general, most studies cited above that observe or manipulate AHN alone or in conjunction with the gut microbiome involve young (i.e. often <2-month-old) male mice, with few exceptions (e.g. pigs and rats). This confines the generalizability of many of the findings to a narrow window of postnatal life and one sex. Thus, future studies should consider the potential effect of sex and age as moderating variables. Additionally, given the above-mentioned debates regarding the extent of AHN in humans across the lifespan (Kempermann et al., 2018; Lucassen et al., 2020a; Lucassen et al., 2020b; Paredes et al., 2018; Tartt et al., 2018), it is difficult to determine to what extent the cited rodent studies, which form the bulk of the evidence, translate to the human condition, especially when age and sex are considered. Indeed, studying AHN *in vivo* in humans is practically difficult, and researchers most often have to rely on *post-mortem* tissue, which comes with its own set of experimental caveats and necessarily limits the degree to which cause and consequence can be disentangled (e.g. regarding the link between aberrant AHN and epileptogenesis in TLE). Thus, while the mechanistic link between AHN and TLE, as opposed to the gut microbiome and TLE, may be stronger based on the state of the current literature, further studies are still needed to determine its clinical relevance to human TLE aetiology and pathophysiology.

To the authors' best knowledge, no studies to date have attempted to directly link gut microbiota-mediated regulation of AHN to TLE, epileptogenesis, epileptiform activity, or seizures. However, given the significant body of literature supporting a moderating role for AHN in hippocampal excitability and seizures, this possible link may be warranted as a future avenue of research. In particular, two principal routes of gut-brain communication appear relevant for the dentate neurogenic niche: circulating metabolites and neuroimmune interactions. For instance, in the study by Siopi et al. (2020), the pro-neurogenic effect of fluoxetine was limited by gut microbiota-derived tryptophan metabolites. Given the increased lifetime prevalence of mood disorders and depression (Tellez-Zenteno et al., 2007) and impaired mnemonic discrimination (Lalani et al., 2021; Madar et al., 2021) in TLE patients, exploring whether gut microbiota composition alters the response to antidepressant treatment via AHN could have clinical relevance (e.g. for possible adjuvant treatments). Based on rodent studies, some behavioural (David et al., 2009) and endocrine (Surget et al., 2011, but see Lucassen et al., 2013 for relevant commentary) responses to fluoxetine could partly be mediated by AHN, one of which may be improved mnemonic discrimination. Indeed, at least one study has been proposed to investigate the effect of fluoxetine treatment on mnemonic discrimination in TLE patients (Drew et al., 2019). In the study by Chevalier et al. (2020), the pro-neurogenic effects of FMT were dependent on central CB1 cannabinoid receptors. Critically, the induction of proliferation and neurogenesis by kainic acid treatment, both *in vitro* and *in vivo* in mice (i.e. as a model for epilepsy), has previously been shown to be dependent on CB1 (Aguado et al., 2007).

Concerning the relevance of neuroimmune interactions, it was recently shown that 3D cultures of epileptic human hippocampal tissue (including neural precursor cells, microglia, astrocytes, and endothelial cells) retained an inherently inflammatory microenvironment that suppressed neuronal differentiation when compared to standard 2D culturing conditions (Zaben et al., 2021). This might serve a compensatory role, as suggested by work in mice, where pro-inflammatory microglia have been found to prevent aberrant neurogenesis and, thus, further exacerbation of seizures (Matsuda et al., 2015).

Given the examples cited above of the gut microbiota (Erny et al., 2021; Erny et al., 2015) and probiotics (Petrella et al., 2021) impacting microglia phenotype and inflammatory response, it is at least conceivable that gut microbiome composition could moderate glial shaping of (aberrant) AHN. As a caveat, while neuroinflammation can increase dentate network excitability, it is important to stress that inflammation alone is not sufficient to induce epileptiform activity (Jakubs et al., 2008). While these links are still speculative and largely based on associational findings, the many open questions leave much room for further study. In the future, it will therefore be important to establish

clear mechanistic links (i.e. cellular mediators, signalling pathways, specific microbial species) whereby the gut microbiome could modulate hippocampal excitability via AHN (see Gheorghe et al., 2021 for a recent discussion on methodological considerations for establishing causality in microbiome research). It will be particularly crucial to ascertain whether gut microbiota-mediated regulation of AHN is sufficient to alter hippocampal excitability or trigger *de novo* epileptogenesis or whether such moderation is contingent on already present seizure activity.

4. Conclusion and future perspective

In the present review, we attempted to cover the current state of the literature investigating the possible relevance of AHN, the gut microbiome, and their interaction in TLE. Specifically, we elaborated on the leading-edge science supporting the connection of hippocampal neurogenesis and TLE. We also highlighted MGBA-mediated mechanisms that may possibly be involved in moderating the pathophysiological mechanisms of TLE and with the capacity to impact neurogenesis. Indeed, recent data demonstrate a plausible role for the gut microbiome in modulating neuronal excitability and neuroinflammation. Important targets of gut microbial signalling may include control of neurotransmitter biosynthesis, regulation of microglia function, and modulation of hippocampal neurogenesis. Thus, the gut microbiome could be a new moderating factor in the link between (aberrant) neurogenesis and TLE.

One avenue of research that could hold possible therapeutic relevance is that of the ketogenic diet, which has been investigated since the 1920's for its ability to ameliorate symptoms of epilepsy (de Sampaio, 2016; Ułamek-Kozioł et al., 2019). The ketogenic diet consists in a significant reduction of carbohydrate consumption, where the total caloric intake is predominantly from fat and protein (Dhamija et al., 2013). Nonetheless, the mechanisms whereby the ketogenic diet exerts its beneficial effects remain unclear, but some may be mediated via an altered gut microbiome composition (Fan et al., 2019). For instance, a clinical investigation showed that the ketogenic diet influences the taxonomic and functional composition of the gut microbiota in children with severe epilepsy (Lindefeldt et al., 2019). In a mouse model of spontaneous seizures, the diet not only altered gut microbiota composition, but it also altered brain neurotransmitter levels, which correlated with reduced seizure frequency (Olson et al., 2018). Additionally, it has also been associated with altered microglial morphology and function in the dentate gyrus (Gzielo et al., 2019) and lower hippocampal pro-inflammatory cytokine levels in response to systemic lipopolysaccharide-induced inflammation (Dupuis et al., 2015). Given the abovementioned gut microbiome-immune-mediated effect of the ketogenic diet on AHN (at least in combination with hypoxia; Olson et al., 2021), and the potential role of inflammation in modulating aberrant AHN and seizure susceptibility (Matsuda et al., 2015; Zaben et al., 2021), it will be useful to elucidate whether these observations are merely incidental or whether they constitute a possibly novel link in the pathophysiological chain of epilepsy.

Currently, any conclusions about the relevance of the MGBA for AHN and TLE are limited by the associational nature of most studies cited above, and future studies should therefore focus on establishing causal and mechanistic links. Although animal work has provided valuable information about microbiome-related mechanisms with possible implications for epileptogenesis, results must be interpreted with caution. For instance, preclinical investigations are likely to carry reproducibility issues between different laboratories and animal suppliers, and a degree of bias in the literature overall is likely due to the preferential use of young male rodents. Since most of the cited studies were carried out in animals, future research must also consider a broader integration with human clinical studies to appropriately address the association of the MGBA with neuronal excitability, neuroinflammation, and hippocampal neurogenesis in the context of TLE. Future research could hold the promise of novel biomarkers (e.g. gut microbiome signatures of drug treatment response) or adjuvant therapeutics (e.g. pre-/probiotics, ketogenic diet), but careful attention will have to be paid to reporting standards and experimental design in order to maximize clinical translatability (Mirzayi et al., 2021; Secombe et al., 2021). With these caveats in mind, the cross-talk between the gut microbiome and AHN could represent a new and possibly fruitful avenue of inquiry to better understand TLE.

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