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Alzheimer's disease and epilepsy: insight from animal models

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Abstract

Alzheimer's disease (AD) and epilepsy are separated in the medical community, but seizures occur in some patients with AD, and AD is a risk factor for epilepsy. Furthermore, memory impairment is common in patients with epilepsy. The relationship between AD and epilepsy remains an important question because ideas for therapeutic approaches could be shared between AD and epilepsy research laboratories if AD and epilepsy were related. Here we focus on one of the many types of epilepsy, temporal lobe epilepsy (TLE), because patients with TLE often exhibit memory impairment, depression and other comorbidities that occur in AD. Moreover, the seizures that occur in patients with AD may be nonconvulsive, which occur in patients with TLE. Here we first compare neuropathology in TLE and AD with an emphasis on the hippocampus, which is central to both AD and TLE research. Then we compare animal models of AD pathology with animal models of TLE. Although many aspects of the comparisons are still controversial, there is one conclusion that we suggest is clear: some animal models of TLE could be used to help address questions in AD research, and some animal models of AD pathology are *bona fide* animal models of epilepsy.

Keywords

amyloid precursor protein; dentate gyrus; hilus; mossy fiber sprouting; neurodegeneration; presenilin-1; seizure; temporal lobe

Background

There have been several excellent reviews comparing the epidemiology, cognitive impairments and pathophysiology in Alzheimer's disease (AD) and epilepsy [1–5]. Here we do not intend to repeat the material in these comprehensive and excellent reviews. Instead, the goal is to provide an additional perspective, that there are similarities between AD and a specific subset of the epilepsies – temporal lobe epilepsy (TLE), based on the clinical neuropathology as reviewed before [1–5] and research using animal models of the diseases. We will devote most attention to the mouse models of AD pathology where seizures have

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been reported [6,7] and common models of acquired TLE where epilepsy is induced by initiating status epilepticus (SE) in adult rodents. We suggest that extensive similarities exist if one considers neurobiological changes other than the classic pathology in AD (i.e., characteristics other than amyloid plaques and neurofibrillary tangles). We also suggest that animal models of TLE are useful in AD research because they provide insight into mechanisms leading to progressive memory dysfunction. Conversely, some of the animal models of AD could be useful in epilepsy research because they are excellent examples of genetic forms of epilepsy.

Before further discussion, it is important to clarify that there are many types of epilepsy, and as mentioned above, the type that will be discussed here is TLE. The reason to focus on TLE is that this type of epilepsy is the subtype where memory impairment is probably most common [8]. AD is also a risk factor for TLE. Traumatic brain injury and stroke are risk factors for AD and also TLE [9,10]. Inflammation, stress and the vascular system are also considered potential contributing factors in both AD and TLE [11–16]. In addition, there are common psychiatric comorbidities in AD and TLE, such as depression [17,18].

Another reason to focus on TLE is that the seizures in TLE are not always convulsive, and nonconvulsive seizures are likely to be the type of seizures that are underestimated in AD because the patient would not necessarily know the seizure occurred. Furthermore, in one of the animal models of AD where seizures have been studied, seizures were nonconvulsive [6]. TLE is also relevant because some patients with AD describe symptoms that are similar to those associated with partial seizures arising from temporal lobe structures, such as transient confusion or sensations. These transient experiences could be similar to the ‘auras’ in patients with TLE, where a transient sensation often occurs immediately before a seizure.

Changing perspectives: from clinical neuropathology to neurobiology

AD is defined clinically by its hallmark pathology (i.e., amyloid plaques and tangles) and the classic symptoms (i.e., memory deficits). By contrast, epilepsy is defined by recurrent spontaneous seizures. These definitions make the two diseases appear to be very different, but upon closer examination of neurobiological mechanisms underlying memory impairment and seizures, the differences do not appear to be as significant.

First, we consider the neurobiological basis of learning and memory. The hippocampus is a useful area of the brain to consider because it is a location where learning and memory has been studied extensively. Based on the work of Hebb [19] and studies of long-term potentiation in area CA1 of hippocampus, coordinated pre- and post-synaptic neuronal activity has emerged as an important part of encoding or learning at the cellular level. *In vivo*, encoding of spatial information by pyramidal cells in the hippocampus is considered to be dependent on precisely timed, coordinated activity as well. Typically this activity occurs in ensembles (subsets) of hippocampal pyramidal cells. The activity of pyramidal cells appears to require precise timing, occurring at specific frequencies, such as theta or gamma rhythm [20–22]. Thus, most would agree that hippocampal-dependent learning requires coordinated activity of ensembles of neurons with temporal precision. Retrieval (one definition of memory) has been suggested to depend on subsequent activity within the same neuronal ensembles that simulates the activity that occurred during encoding, but is ‘offline’, a phenomenon called ‘replay’ [23,24]. As a result, hippocampal-dependent memory would be impaired if coordinated neuronal activity during theta and gamma rhythms were perturbed.

This idea that normal brain function depends on coordinated activity among neuronal ensembles, and impairment occurs when that rhythmic activity is disturbed, is not that far from ideas about the normal control of neuronal excitability and its disruption, which can

lead to seizures. Thus, seizures involve rhythmic discharges of neurons, like the activity of an ensemble of pyramidal cells during encoding, but it is 'excessive' in its synchrony (often termed 'hypersynchronous') compared with normal rhythmic activity. In other words, too many neurons become synchronously active, or they discharge too much, or both. The point here is that memory impairment and seizures both involve an abnormality in the normal rhythmic activity of neurons. The causes of abnormal activity can be quite different, and the type of abnormality may differ, but both can lead to memory impairment and seizures. And both the impairment in memory and seizures can be resolved if normal rhythmic activity is restored.

Thus, the fundamental problems in the brain in AD and epilepsy could indeed have more in common than one might think, even if the clinical definitions are very different. By focusing on the clinical definitions and not the underlying neurobiology, differences in AD and epilepsy are emphasized, and the potential similarities are easily overlooked.

The neuropathology of TLE & AD

Plaques & tangles: not only a characteristic of AD

While it is true that the neuropathology that is considered to define AD (i.e., plaques and tangles), makes AD seem extremely different from TLE, it is important to note that amyloid plaques have been reported in TLE. Mackenzie and Miller studied 101 TLE surgical specimens and found that plaques were present in ten individuals (aged 36–61 years) and plaques positively correlated with age [25]. Autopsy controls exhibited plaques, and they were similar in distribution as the plaques in TLE specimens, but the incidence of plaques was greater in patients with TLE than the normal population.

Thom and colleagues recently reviewed Braak stages in 138 individuals with epilepsy and showed that Braak stages I–VI were present, which is interesting because the Braak staging criteria are based on neurofibrillary tangles [26]. Therefore, patients with epilepsy not only develop plaques, as noted above, but can develop tangles. However, the most advanced Braak stages (V–VI) were rarely reached in individuals with epilepsy. One interpretation of these data is interesting to consider – that some types of seizures may interfere with tangle formation. This idea may seem implausible but it has been shown that seizures can be protective. In rodents, for example, almost every type of experimental seizure induces diverse types of growth factors and protective peptides [27,28]. Some of the same peptides that are induced by seizures are considered to be deficient in AD, and when increased in animals there is reduced neuropathology (e.g., BDNF [29,30]). Therefore, seizures could potentially protect against tangles to a certain extent, as remarkable as that might seem.

Hippocampal sclerosis: not only a characteristic of TLE

In TLE, the hallmark pathology is typically hippocampal sclerosis, also called Ammon's horn sclerosis, which has been known since the early 1800s when it was identified in post-mortem specimens of individuals in insane asylums [31]. The pattern of neuronal loss in hippocampal sclerosis includes substantial neuronal loss in area CA1, CA3 (Ammon's horn), and the hilus (also known as CA4 or the endfolium), but the dentate gyrus granule cells and area CA2 pyramidal cells are typically more resistant [31]. The term mesial temporal sclerosis (MTS) has been widely used because there is also neuronal loss in the parahippocampal region in TLE (e.g., the entorhinal cortex). MTS is often discussed as if it were a defining feature of TLE and therefore unique to TLE, but it is not. Some patients with TLE do not exhibit hippocampal sclerosis, and hippocampal sclerosis is observed in some normal-aged individuals [32] and patients with frontotemporal lobe dementia [32,33].

Progressive pathology or symptom severity

If one looks beyond plaques and tangles, and MTS, there are similarities in the neuropathology of AD and TLE. For example, one similarity is that both AD and TLE involve progression, or increasing severity with time. In AD, this is well known, and may seem unnecessary to point out. More and more plaque accumulates with age. Cognitive impairments become increasingly severe with age. (However, the ages when impairments are detected are not necessarily the same ages when plaque accumulation is detected [34]). In TLE, it may seem that the onset of epilepsy is sudden, because the first seizure often occurs after years of relatively normal neurologic function. However, the changes in the brain that cause the first seizure may start many years before it. Several investigators have suggested that seizures can make epilepsy become progressively more severe with age, by causing neurodegeneration [35]. Therefore, epileptogenesis and chronic epilepsy may involve gradual changes instead of sudden changes. The idea that a gradual emergence of epilepsy occurs in TLE has recently gathered more support because of detailed recordings from animals with epilepsy [36] or studies of epileptic rat hippocampus in brain slices [37–39]. For example, after SE in rats, it had been assumed that animals suddenly become epileptic after a prolonged period where epilepsy was absent but somehow developing in silence. Continuous video-EEG monitoring showed that electrographic activity gradually increases in severity and continues to do so after the first convulsive seizure [38]. Moreover, indices of seizure susceptibility continue to become more severe after the first convulsive seizure even when studied *ex vivo*. For example, sensitivity of hippocampal area CA3 to elevated concentrations of extracellular potassium increases when slices are made from epileptic rats at longer and longer intervals after the first convulsive seizure [37].

Although it can be argued that both AD and TLE are progressive, there is a potentially significant difference between these two diseases in what is considered to be the initial stage (Figure 1). In TLE, the initial precipitating event is considered to be severe and sudden, such as birth trauma, febrile seizures, neonatal hypoxia or head injury. In AD, a sudden initial event is not considered to be particularly relevant. Instead, a gradual accumulation of A β emerges, although there is some evidence for periods of rapid accumulation of A β [40]. The pathophysiology may develop faster in some patient populations compared with others, but progressive neurodegeneration is not considered to begin with a sudden insult or injury, in general. We suggest that this sudden and severe onset in TLE and more gradual onset in AD could be an important distinguishing factor, because it would probably induce a different cascade of progressive pathophysiology, and possibly explain lifelong seizures in TLE but not in AD (Figure 1). In addition, the precipitating factor in TLE may occur very early in childhood, although this is not always true. By contrast, AD is only a disease of older individuals.

Septohippocampal projections

Another example of similarity between AD and TLE is damage to septal projections to the hippocampus. Most of what is known about the septum in TLE is based on animal models, because human data are limited, and most of what is known in AD is from human data, because most animal models of AD pathology lack cholinergic deficits. Therefore, the comparison of TLE to AD is difficult. Nevertheless, it is interesting to note that in the pilocarpine animal model of TLE, the defect in the septum appears primarily to be the GABAergic projection [41], whereas the vulnerable septal neurons in patients with AD appear to be cholinergic primarily [42]. The difference is intriguing because the GABAergic septohippocampal projection innervate the GABAergic interneurons of the hippocampus preferentially [43]. As a result, animals with TLE would be more likely to have a disinhibited hippocampus. This could be a reason why seizures occur in animal models of

TLE, but seizures are not universal in AD – the cholinergic versus GABAergic nature of the defect in the septal projection to hippocampus has extremely different consequences.

Neuronal loss

Another important characteristic of both AD and TLE is loss of the neurons in layers II and III of the entorhinal cortex. These cells give rise to the perforant pathway, a projection from entorhinal cortex to hippocampus. The reduction in entorhinal cortical volume is one of the earliest sites of pathology in AD [44–46], and the entorhinal cortex is one of the most vulnerable areas of the brain to seizures in animal models of TLE [47] or patients with intractable TLE [48,49]. However, upon closer examination, the data from patients with AD suggest that a loss of layer II neurons occurs primarily [45], whereas in TLE there is a reduction in layer III neurons primarily [48,49]. In animal models of TLE, layer III is the layer of the entorhinal cortex where most neurons are lost [47], so the clinical and animal data agree well. In AD, the animal data do not agree as well, with one study indicating preferential layer V loss in the entorhinal cortex of a mouse model of AD [50]. Nevertheless, it appears that a fundamental difference exists in the cell types of the entorhinal cortex that are lost, with primarily a layer II deficit in AD and primarily a layer III deficit in TLE. This difference could have substantial consequences if true: if layer II were primarily lost, the dentate gyrus and area CA3 would be denervated preferentially, and if layer III were primarily lost, area CA1 would lose its perforant path input preferentially. One would predict a greater defect in pattern separation, a function of the dentate gyrus, in AD, and there is evidence for this defect in AD at early stages [51,52]. However, ultimately when the entire parahippocampal/hippocampal network becomes affected, late in AD, these differences might go away.

Late in AD, hippocampal neuronal loss is common, as it is in TLE [53]. One difference appears to be neuronal loss in the hilus. In patients with TLE, this area sustains extensive neuronal loss, sometimes selectively (endfolium sclerosis [54]) but in clinical AD the percentage of neuronal loss in the hilus appears to be less than 15% [53]. This could be an important difference because hilar neurons are thought to regulate dentate gyrus excitability [55–57], which in turn is potentially important if the dentate gyrus is one of the hippocampal subfields that survives best in AD and TLE. The way that hilar neurons influence dentate gyrus granule cells is not completely known, and is complicated because there are numerous cell types in the hilus. However, most evidence accumulated to date suggests that hilar neuron loss leads to an increase in excitability of granule cells, an effect that would facilitate seizure activity [55].

Summary

The clinical neuropathology in AD and TLE appears to be very different if one focuses on plaques and tangles, but upon closer examination even these forms of pathology are not exclusive to AD. Conversely, hippocampal sclerosis, the hallmark of TLE, is not unique to TLE. The available data are useful to review because they suggest reasons why the two diseases could be related in some ways, and also reasons why they differ. For example, differences in pathology within the septal nuclei, entorhinal cortex and hilus could explain why seizures occur in all cases of TLE, but not in all cases of AD. These considerations are useful in epilepsy research because they help identify what might be critical areas to target to improve seizure control and cognitive function. They are useful in AD research because they suggest reasons why some individuals with AD may develop seizures but others do not. For example, perhaps individuals with AD who have seizures sustain more neuronal loss in the hilus, which could occur because several risk factors for AD (e.g., traumatic brain injury or stroke) injure vulnerable hilar cells [56,58].

Animal models of AD & TLE

General similarities between animal models of AD & TLE

In general, animal models of AD and TLE have two features in common. First, AD and TLE seem to be ‘human’ disorders (i.e., they are difficult to simulate in rodents). For example, it is difficult to find plaques and tangles in normal-aged rodents. It is also difficult to induce epilepsy in a very common laboratory mouse, the C57bl6 strain [59].

In addition, AD and TLE animal models share another general theme. The animal models that have been developed are somewhat ‘skewed’ in their representation of the human disease. In AD, the animal models are mostly based on genes that cause familial AD, which represent only a small percentage of cases of AD. For example, mice that have been altered so that they express amyloid precursor protein (APP) with mutations that have been identified in familial forms of AD are extremely common in research, but the familial mutations are rare in AD.

In TLE, the most common animal models are mostly based on insults or injuries that are known risk factors for TLE. For example, it is common to induce SE in adult rodents, which leads to epilepsy for the lifespan of the animal. However, SE in adult life is not considered to be a common cause of TLE. The emphasis on acquired forms of TLE in epilepsy research and genetic models of AD in AD research is important because it could foster the idea that the two diseases are very different.

Animal models of AD

In AD, many familial mutations are known, although each one does not account for a large percentage of patients with AD. Thus, a number of families with AD have been identified where mutations in APP exist. The mutations lead to cleavage of APP by amyloidogenic rather than nonamyloidogenic pathways, and when combined with APP overexpression, A β pathology is robust as early as 6 months of age, young adulthood for a mouse. Multiple mutations and combinations can make pathology develop at even younger ages [60]. The animals develop memory impairments, leading to their popularity as mouse models that simulate AD, despite the fact that neurofibrillary tangles and cholinergic dysfunction do not necessarily occur. However, there are other mouse models that have been developed to evaluate the role of neurofibrillary tangles, also using transgenic methods; several excellent reviews have described genetic animal models of AD in detail [61,62]. Below we discuss two animal models primarily, the so-called hAPP mice (which refers to J9, J20 and ARC48 mice) and APPSwPS1dE9 (also called APdE9) mice, because these animals have seizures [6,7].

Animal models of TLE

Historically, animal models of TLE have focused on acquired TLE because, in the past, acquired TLE has been better defined than genetic forms. In addition, ideas regarding TLE based on neuropathology have had a strong influence on model development: the idea that pathology in acquired TLE involves a pattern of neuronal loss like hippocampal sclerosis, and a precipitating insult or injury leads to TLE after a delay or ‘silent’ (more recently called ‘latent’) period [31,63]. Given that one of the types of precipitating insults that has been suggested to ultimately lead to TLE is SE [64], induction of SE became popular after it was shown that systemic kainic acid injection led to SE in rodents, a pattern of damage resembling MTS, and lifelong spontaneous recurrent limbic seizures [65]. Subsequently it was shown that systemic injection of the muscarinic agonist pilocarpine induces a similar effect as kainic acid (i.e., SE and hippocampal pathology resembling MTS) followed by lifelong limbic seizures [66]. Kainic acid and pilocarpine are now some of the most common

tools used to induce a TLE-like syndrome in rodents, although they have been criticized for initiating too much neuronal damage, and there are many other models [67].

Could some animal models of AD be useful in epilepsy research & vice versa?

Some of the AD transgenic mouse models simulate epilepsy well, and, by the criteria used in epilepsy research, are potentially good animal models of epilepsy, because the criteria are primarily that the animal has spontaneous seizures. Those animal models of AD pathology that exhibit spontaneous seizures are good candidates, such as hAPP and APde9 mice [6,7]. By contrast, a common model of TLE is kindling, but spontaneous seizures are not usually induced. Instead, kindling has been used primarily to study the gradual decrease in seizure threshold in a normal rodent by presenting an initially subthreshold stimulus through an indwelling electrode one or more times per day for weeks. Ultimately a single stimulus evokes a seizure, a dramatic change from the response to the stimulus at the onset of the procedure. It can be argued that kindling is not an ideal model of epilepsy, based on the criterion that an animal model of epilepsy should have spontaneous seizures, however, extensive kindling has been shown to induce a state of spontaneous seizures [66]. Using the same criterion, hAPP and APde9 mice would actually be a better epilepsy model, remarkably enough.

On the other hand, kindling is a potentially excellent model of progressive memory impairment and cholinergic dysfunction. Therefore, it has utility in AD research. One advantage of kindling is that it could allow one to potentially dissociate changes in the brain with progressive memory impairment from changes in the brain caused by the combination of progressive plaque or tau pathology and cognitive dysfunction, which occurs in mouse models of AD. There is very little evidence of neurodegeneration in kindled animals, allowing that variable to be excluded from an analysis of progressive memory impairment.

Kindled rodents have robust memory impairment, and it is remarkable that it may develop after only ten kindling stimulations [68,69]. Sensitivity to memory impairment is one reason to consider kindling to gain insight into memory loss, but it is not the only reason. The site of kindling is interesting to consider because different behavioral impairments occur after kindling, and some of these impairments may reflect what occurs in some patients with AD. When kindling stimulations are delivered to the amygdala, for example, anxiety increases, kindling of the perirhinal cortex causes deficits in the recognition of novel objects, kindling of the hippocampus causes increased locomotor activity as well as impaired spatial memory [70]. Kindling could also be useful to understand how cholinergic deficits affect the brain in AD, because kindling reduces acetylcholine release and therefore cholinergic function [71,72], which has been extensively studied in AD [73].

SE models of TLE & mouse models of AD pathology

Comparison of the kindling model and the AD mouse models is instructive because it shows the utility of TLE models for AD research and AD models for epilepsy research. Now we turn our attention to mouse models of AD pathology where there are spontaneous seizures, and animal models of epilepsy with spontaneous seizures. For the epilepsy models, we consider the animal models where SE is used to initiate epilepsy in adult rodents, because of the wealth of information that has been obtained from these animal studies, especially in the hippocampus. Comparison will be to two mouse models of AD pathology. The first are hAPP mice that are referred to elsewhere as J9, J20 and ARC48 mice; these mice express a mutated form of hAPP. For the J9 and J20 mouse, hAPP is under the control of the PDGF- β -chain promoter. hAPP mutations are those that have been found in a Swedish family with AD (K670N and M671L mutations; APPSw) and family from Indiana with AD (V717F mutations, APPInd). The ARC48 mouse has mutations in APP that were found in Swedish,

Indiana and Artic (E22G mutation) families. These mice are bred on a C57bl6 background or a background that is partly C57bl6 [6]. The other mouse expresses a mutated form of APP and has a deletion in the *presenilin 1* gene. It expresses APP695 with mutations from a Swedish family with AD (K595N, M596L) that is under the control of the mouse prion protein promoter. In addition, there is a deletion at exon 9 in the *presenilin 1* gene. These animals also have a C57bl6 background and are often called APPSwPS1de9; they will be referred to as APde9 hereafter [7]. The SE and AD animal models are compared at the ages when they typically are reported to exhibit spontaneous seizures (i.e., typically >1 month after SE when animals are >2 months of age, or >3 months of age in the hAPP and APde9 mice, respectively) [6,7].

The dentate gyrus is a useful region to evaluate for this comparison because it is considered to be a gate or a filter for cortical input during hippocampal-dependent cognitive tasks and for seizure activity that enters the hippocampus from the entorhinal cortex [74]; a schematic of the normal rodent hippocampus is shown in Figure 2 (for more detail see [75,76]). The dentate gyrus is also implicated in the pathophysiology of AD [4,77] and TLE [78,79]. However, it is acknowledged that the dentate gyrus is only one part of the brain that is involved in AD and TLE, and the comparisons below have limitations in what they can tell us about these complex diseases, which involve multiple brain areas.

It is also important to note that there is more than one SE model and they are not identical, just as there is more than one hAPP or APP-PS1 mouse and they have important differences. Regarding the SE models, there are differences between kainic acid-induced SE and pilocarpine-induced SE, there are differences between rats and mice, investigators use different doses of convulsants, different ages, and may treat SE with anticonvulsants to reduce the severity of SE and sequelae (e.g., the extent of neuronal loss). Regarding APP and APP-PS1 mice, there can be distinct promoters, different mouse strains, and different familial mutations. In SE models, there is variability in the neuropathology that follows SE. This variability is due to many factors that are known, such as age at the time of SE, species, strain, and the use of anticonvulsants, which decreases the severity of SE and reduces morbidity and mortality. In the discussion of SE models below, we mention those characteristics of SE that are similar in rats and mice that have had SE as young adults. For example, it is common to find neuronal loss in the hilus of the dentate gyrus. It is also common to observe mossy fiber sprouting. We do not make absolute statements because there is variability from animal to animal, and within a given animal (described further below). However, there are several characteristics that are common to young adult animals that have had SE, and these are used for discussion. We will focus on the hAPP and APde9 mice that have been shown to have spontaneous seizures [6,7], but also raise studies of other APP or APP-PS1 mice where relevant.

Neuronal loss

In Figure 2, a representation of common sites of neuronal loss and preservation are shown for SE models and hAPP/APde9 mice. The typical pattern of neuronal loss in SE models is similar to MTS: granule cells are relatively resistant and hilar neurons are vulnerable. The preservation of granule cells is not surprising, because granule cells are known to be resistant to insult or injury, such as ischemia, excitotoxicity, or traumatic brain injury [58,80,81]. However, it should be noted that there are exceptions where granule cell loss is observed after SE [82] and in severe sclerosis [31]. Regarding the GABAergic cells located near the granule cells, one of the most common types is the parvalbumin immunoreactive cell, which make a basket-like plexus around granule cells ('basket cells'). The majority of data suggest that they are relatively resistant in SE models and many types of insults or injury [80,81,83]. However, there are discrepancies in the literature: parvalbumin immunoreactive cells have been suggested to decrease in epilepsy models [55] as well as

human AD [84]. There also may be changes specific to neuritic plaques [85]. This may create focal areas of hyperexcitability near plaques, surrounded by areas with lesser excitability [86]. The point is interesting because an epileptic focus is also considered to be an area of hyperexcitability that is often surrounded by an area of inhibited neurons [87,88].

The hilar neurons that are vulnerable in SE models are mainly two types of hilar neurons: the glutamatergic ‘mossy’ cells, and a subset of GABAergic cells that project to the molecular layer where the perforant path terminals are located (Figure 2) [56,58,80,81]. They are called HIPP cells (hilar cell body, axon projection to the terminal zone of the perforant path) [75,89]. The majority of HIPP cells co-express somatostatin and neuropeptide Y (NPY) [90]. Numerous studies suggest that mossy cells and HIPP cells are vulnerable in SE models [91] and in epilepsy models without SE [92].

In contrast to the studies of SE, hilar cell loss does not appear to be substantial in hAPP or APde9 mice [6,7]. However, two studies of an APP-PS1 mouse, not the APde9 mice, have provided evidence for a considerable loss of hilar neurons. One study evaluated calretinin expression in the hilus and the inner molecular layer, reflecting mossy cell bodies and axon terminals, respectively, there was a significant reduction in expression in both locations [84]. There is also a report that a substantial number of HIPP cells are lost in an APP-PS1 mouse model [93]. This result is not consistent with the preservation of NPY-containing hilar neurons in APde9 mice [6], but is consistent with a clinical study showing decreased somatostatin immunoreactive hilar cells in patients with AD [94]. One reason for the different data sets may be related to the complexity of HIPP cells, where expression of somatostatin may be altered but not NPY, and the opposite has also been reported [95]. Furthermore, some cells that express somatostatin may be altered morphologically in AD, but not lost [94], which has also been reported in an SE model (see below).

Taken together, the available evidence suggests that the hilar neuron loss is modest in hAPP and APde9 mice with seizures relative to SE models. This difference is potentially significant because it could explain why more seizures develop in the SE models [55–57]. In other words, hAPP and APde9 mice could have fewer seizures than animals with SE because hAPP and APde9 mice have more hilar cells. Although the function of hilar neurons is a topic of debate, a common interpretation is that hilar neurons keep granule cell excitability normal. If this interpretation is correct, survival of hilar neurons would cause the dentate gyrus to be less excitable, resulting in fewer seizures.

Calbindin expression

Calbindin D28K is a calcium-binding protein that is a robust marker of adult granule cells in rodents and primates (Figure 3). It has been shown by many laboratories that calbindin expression is decreased in granule cells in hAPP and APde9 mice, SE animal models and specimens from patients with AD or TLE [6,7,96–99]. In our analyses of rats that have had SE, and are evaluated at least 4 weeks later, the loss of calbindin occurs in a peculiar pattern – typically clusters or ‘patches’ of granule cells exhibit calbindin downregulation (Figures 3 & 4). This also is apparent in hAPP and APde9 mice [6,7], in other rodents after SE [99,100], as well as post-mortem specimens from patients with AD [101] or TLE [98]. In the hAPP mice, calbindin downregulation occurred in a very specific pattern that we have also found in rats after pilocarpine-induced SE: the outer third or inner third of the layer losing expression exclusively, leading to loss of staining around a robust central area of the cell layer that retains calbindin expression (Figure 4) [7]. This remarkable similarity in calbindin expression of granule cells in hAPP mice and a SE model suggests a functional change that is similar, not only an anatomical one. The change in function may be explained by heightened activity of granule cells that lose calbindin expression because both the hAPP mice and pilocarpine-treated rats had seizures. Moreover, the immediate early gene *c-fos*

stained the areas of the granule cell layer where calbindin expression was weak (Figure 4). Conversely, robust calbindin expression was associated with weak c-fos immunoreactivity (Figure 4). The results suggest, although they do not prove, a similarity in AD and TLE models in granule cell activity.

Mossy fiber sprouting

Mossy fiber sprouting is the formation of new collaterals of granule cell axons, the mossy fibers, which terminate in the inner molecular layer instead of the normal terminal zone (Figures 2 & 5). In patients with intractable TLE, mossy fiber sprouting was first identified using Timm stain as a marker of granule cell axons [102]. It has subsequently been identified in rodents using other markers of granule cell axons in rodents with chronic seizures, such as NPY [82,103]. Although mossy fiber sprouting has been reported in the hAPP and APde9 mice with spontaneous seizures [6,7], it appears to be much less robust than in animals with chronic seizures (Figure 5). However, rodents that have experienced SE treated with anticonvulsants (so it is a milder SE [82]) often exhibit very little mossy fiber sprouting in septal regions of the hippocampus (Figure 5) [82,103], and mossy fiber sprouting in the hAPP and APde9 mice was evaluated in the septal hippocampus [6,7]. Therefore, mossy fiber sprouting in the hAPP and APde9 mice could be underestimated.

In clinical specimens, mossy fiber sprouting has not been noted in AD, but it is common in TLE [78,102]. Therefore, the clinical data would argue that mossy fiber sprouting in AD is weaker than mossy fiber sprouting in TLE, even if the differences in sprouting between the animal models are less clear.

The cells that are targeted by sprouted mossy fibers are important to consider because they influence the net effect of sprouting on the dentate gyrus network. In SE models, there clearly are synapses of sprouted fibers on granule cell dendrites, shown by electron microscopy (EM) [104,105], and this creates increased recurrent excitatory circuits [78,79], but there is also evidence that GABAergic interneurons are innervated by sprouted mossy fiber collaterals [106]. Quantitative EM studies suggest that the majority of the synapses are on granule cells, which would lead to a primarily excitatory effect [105]. In hAPP and APde9 mice, the targets of the sprouted fibers have not been studied in quantitative detail or EM.

GABAergic sprouting

One of the observations made in the hAPP and APde9 mice is that there is sprouting of the NPY-expressing GABAergic neurons of the dentate gyrus [6], the HIPP cells. Importantly, sprouting of HIPP cells into the molecular layer has been recently identified in an SE model where somatostatin-expressing cells were noted to have increased in size [107]. We have also observed hypertrophy of hilar cells, which appear to be GABAergic because of their aspiny processes, and express calbindin (Figures 3 & 4) [99], which is atypical because ordinarily there are few calbindin-expressing hilar cells in our experience, and when they are present they are small in size (Figure 3) [100]. Other experiments using the intrahippocampal kainic acid SE model [108] or the lithium-pilocarpine SE model [109] have shown that markers of dentate GABAergic neurons are elevated in the molecular layer in epileptic rodents, suggesting that GABAergic sprouting is common in SE models. Therefore, sprouting of GABAergic neurons appears to be a common finding in both the SE models and hAPP/APde9 mice, although EM evidence of synapses is often unavailable. There are many other changes in GABAergic inhibition that have been evaluated in epilepsy research, such as changes in GABA receptors of granule cells and K^+-Cl^- co-transporters [110], but thus far there is very little information about alterations in GABA receptors or K^+-Cl^- co-transporters in AD mouse models.

GABAergic sprouting has been suggested to confer a state of hyperinhibition in the hAPP mice [6] and this is similar to some of the perspectives on animal models of TLE [106,111,112]. In both hAPP and APde9 mice and SE models, there appears to be underlying hyperexcitability that presumably leads to intermittent seizures [78,79,111].

We suggest that the major differences between SE models and hAPP or APde9 mice are greater loss of hilar neurons and greater mossy fiber sprouting in the SE models (Figure 6). These differences are potentially important because they can explain why there are more robust seizures in the SE models than the hAPP and APde9 mice. However, more data would be useful. For example, it is unclear at the present time which dentate gyrus cell types are actually lost in the different animal models, and which cell types may simply lose expression of a peptide that is used to identify the cell type normally. EM and electrophysiology would also be useful to determine whether functional synapses are definitely made in pathways that appear to exhibit sprouting using light microscopy.

Summary

There are many similarities in the dentate gyrus when comparing hAPP and APde9 mice and SE models. The similarities support the hypothesis that there are common abnormalities in AD and TLE in the dentate gyrus if one studies characteristics other than plaques and tangles. Based on the information that is available, there are likely to be two main differences – a greater degree of hilar cell loss and greater degree of mossy fiber sprouting in SE animal models compared with hAPP and APde9 mice (Figure 6). In both SE models and hAPP/APde9 mice, there is evidence for ‘hyperinhibition’ that masks underlying hyperexcitability. Therefore, it is remarkable how similar the hAPP/APde9 mice are to the SE models, with respect to the dentate gyrus.

Conclusion

Based on the discussion above, we suggest that there are similarities in the neurobiological mechanisms underlying AD and TLE. However, what is most important is not actually answering ‘yes’ or ‘no’ to the question whether AD and TLE are related. Instead, what is most important is the potential insight that can be gained by careful comparisons of these two diseases. For example, these comparisons can distinguish characteristics of TLE that are potentially relevant to AD but not well known to TLE researchers. We suggest that comparisons between AD and TLE can identify novel opportunities for mechanistic insight and therapeutic strategies.

Future perspective

It may be hard to convince all investigators in AD and epilepsy research that these two diseases have much in common. For those who think there are many characteristics that are shared, there is a lot to do. For example, many mouse models have not been examined with current standards in epilepsy research, such as continuous video EEG monitoring. Do all of the mice have seizures? Are they generated by the same mechanisms? Many circuits that are potentially relevant have not been studied in as much detail as the dentate gyrus. Immunocytochemical studies of epilepsy models rarely use antibodies to A β or tau. Testing drugs that are being developed in AD research using epilepsy models (and *vice versa*) could provide a great deal of important information as well.

For those who remain unconvinced that AD and epilepsy are related, there are opportunities that should not be missed. Electrophysiological tools like EEG analysis, common in epilepsy research, would potentially be valuable in AD research to clarify the reasons for cognitive impairments – usually only behavioral tasks are tested. Are there fast ripples in AD, which

are a potential ‘biomarker’ of the epileptic brain [113]? Sharing expertise will undoubtedly benefit both fields. Similarly, to better understand the rise in epilepsy with aging, a long-standing question in epilepsy research, who better to consult than the large body of researchers who study aged individuals or aged mice all the time. Specific opportunities also exist. For example, epilepsy researchers who puzzle over the inability to induce epilepsy in C57bl6 mice might gain insight from studies of the hAPP mice on a C57bl6 background, because the mice clearly have a type of epilepsy. As the number of people with AD becomes an increasing fraction of the population, and drugs for both AD and epilepsy are often ineffective or incur severe side effects, it makes sense to consider all potential avenues for advances.

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Executive summary

Changing perspectives: from clinical neuropathology to neurobiology

- Clinical definitions make Alzheimer's disease (AD) and temporal lobe epilepsy (TLE) seem different.
- The neurobiology of memory and seizures makes AD and TLE seem similar.

The neuropathology of TLE & AD

- Plaques and tangles are not only a characteristic of AD.
- Hippocampal sclerosis is not only a characteristic of TLE.
- Both AD and TLE are progressive disorders but there is a sudden precipitating event in TLE that does not occur in AD.
- Projections to memory centers like the hippocampus are altered in both AD and TLE.

Animal models of AD & TLE

General similarities between animal models of AD & TLE

- Caution is important when comparing animal models to the clinical condition.
- AD and TLE are 'human' disorders (i.e., there are difficulties reproducing clinical features in rodents).
- AD animal models have been based on familial rather than sporadic AD; for TLE the reverse is true.

Animal models of AD

- This review focuses on two animal models, the hAPP (J9, J20 and ARC48) mouse with two to three mutations in APP (Swedish, Indiana, Arctic), and APdE9 mice with an APP mutation (Swedish) and deletion in presenilin 1 (removal of exon 9).

Animal models of TLE

- This review focuses on animals that have status epilepticus as adults, which induces a state of spontaneous recurrent limbic seizures, a simulation of TLE.

Models of TLE may be useful in AD research & vice-versa

- Animals with memory loss and cholinergic dysfunction but without spontaneous seizures are considered suboptimal in epilepsy research but would be useful in AD research.
- Animals with spontaneous seizures and hippocampal pathology are considered suboptimal for AD research but could be beneficial as animal models of TLE.

Comparisons of AD mouse models & SE models

- Similar neuropathology arises in the dentate gyrus when comparisons are made of hAPP and APdE9 mice with SE models: hilar neuronal loss, reduced calbindin expression, mossy fiber sprouting and GABAergic sprouting.
- Two main differences are a greater degree of hilar cell loss and a greater degree of mossy fiber sprouting in SE animal models.

- The similarities support the hypothesis that there are common abnormalities in AD and TLE in the dentate gyrus if one studies characteristics other than plaques and tangles.
- In both models, there is evidence for 'hyperinhibition' that masks underlying hyperexcitability.

Figure 1. A comparison of common perspectives of the pathophysiology in temporal lobe epilepsy and Alzheimer's disease

(A) Some of the major stages in the sequence of progressive pathophysiology is shown for TLE where there is an early-life precipitating insult, and (B) AD, where A β accumulates gradually and diagnosis typically occurs after 50 years of age. The sequential stages are similar in several ways, including a stage where toxicity and plasticity is likely to be important in both diseases, and increased excitability is potentially a common theme. One major difference is the timeline, because the toxicity and plasticity is likely to occur much earlier in life in TLE, which has implications because of the increased plasticity of the young brain. Another major difference is the sudden and severe nature of the initial stage in TLE, at least for acquired TLE, compared with common conceptions of AD etiology. The sudden, severe and earlier timeline for TLE could be what contributes to the different outcomes in AD and TLE.

A β : Amyloid β ; AD: Alzheimer's disease; APP: Amyloid precursor protein; TLE: Temporal lobe epilepsy.

Figure 2. The normal dentate gyrus and changes in animal models of temporal lobe epilepsy and Alzheimer's disease

(A) The normal dentate gyrus of the rodent and primate is shown. There are three layers, the molecular layer, granule cell layer (containing the major cell type, the granule cells) and hilus. All layers contain various types of GABAergic interneurons, and only two are shown: the PV-immunoreactive basket cell (blue), and the SS/NPY hilar cells (HIPP cells; red) that innervate the outer two-thirds of the molecular layer, the location of the major cortical input from the layer II neurons of the entorhinal cortex. Besides granule cells, there is one other type of glutamatergic cell in the hilus called the mossy cell, which terminates primarily in the inner third of the molecular layer. Axonal projections are usually laminar specific, and shown to the right. (B) In rodent models of TLE where SE is used to induce epilepsy in adulthood, there are many differences in the way the SE is induced, but some common changes in circuitry occur, and these are illustrated schematically. These changes include loss of hilar neurons, including HIPP and mossy cells. There is sprouting of mossy fibers into the inner molecular layer, where granule cells appear to be targeted primarily, although some interneurons are also innervated. Another common finding is sprouting of GABAergic interneurons into the molecular layer. (C) In amyloid precursor protein (APP) or APP-PS1 mouse models of AD pathology, there are differences in APP (or PS1) mutations and promoters to drive expression, as well as background strain, but there are some of the common findings from studies of hAPP and APde9 mice, which are shown schematically. Remarkably, changes are similar to those in (B). Exceptions include relatively more preservation of hilar cells, and less mossy fiber sprouting.

AD: Alzheimer's disease; NPY: Neuropeptide Y; PV: Parvalbumin; SE: Status epilepticus; SS: Somatostatin; TLE: Temporal lobe epilepsy.

Figure 3. Immunoreactivity in the normal dentate gyrus and the dentate gyrus in epileptic rats using an antibody to the calcium-binding protein calbindin D28K

(A) Immunocytochemistry of the normal adult rat dentate gyrus using an antibody to the calcium-binding protein calbindin D28K shows that granule cell bodies in the GCL are stained, including granule cell dendrites in the Mol, granule cell axons (mossy fibers) in the hilus and mossy fibers in area CA3. Calibration = 100 μ m. (B & C) In status epilepticus (SE) models, there are several changes in calbindin immunoreactivity. One that we have found is novel staining of hilar neurons or neurons at the border of the hilus and granule cell layer that have very large somata and thick but aspiny dendrites compared with granule cells (arrows). These neurons may reflect hypertrophied interneurons in SE models, which has recently been reported for somatostatin-immunoreactive hilar cells [107]. Calibration in (C) = 100 μ m. (D) Calbindin immunocytochemistry in the granule cell layer of rats that are epileptic after SE induction show weak expression in the inner and outer third of the layer, and patches of the layer where all granule cells exhibit weak expression. The arrows points to the top and bottom of the granule cell layer which is blue. The patchy labeling of granule cells was shown in hAPP, APde9 and another mouse model of Alzheimer's disease pathology [6,7,101] and in human specimens from Alzheimer's disease and temporal lobe epilepsy [98]. Calibration = 200 μ m. (E) Higher magnification of the area of (D) at the arrows. Arrows indicate the top of the granule cell layer and the base. Calibration in (D) = 100 μ m. Reproduced with permission from [114].

GCL: Granule cell layer; Mol: Molecular layer; SGZ: Subgranular zone.

Figure 4. Inverse relationship between c-fos and calbindin immunoreactivity in the epileptic dentate gyrus of rats

(A & B) The dentate gyrus of a rat that had status epilepticus and developed chronic seizures is shown, stained with an antibody to calbindin and counterstained with cresyl violet. Note that the GCL (blue) is stained for calbindin only in the center of the layer, and there are areas where there is an absence of calbindin in the cell layer (arrows). Arrowheads point to hypertrophied aspiny cells, similar to those in Figure 3. (C & D) An adjacent section to the one in (A) is shown, stained with an antibody to c-fos. Note that where c-fos is expressed in the GCL there is reduced expression of calbindin (arrows) and where c-fos expression is weak (arrowheads), there is strong expression of calbindin. Calibration shown in (A) is 100 μ m for (A) and (C). Calibration is 50 μ m for (B) and (D).

GCL: Granule cell layer; Mol: Molecular layer.

Figure 5. Mossy fiber sprouting in epileptic rodents is not necessarily homogeneous

(A & B) Mossy fibers of an epileptic rat that experienced pilocarpine-induced status epilepticus (SE) are stained with an antibody to neuropeptide Y (NPY). (A) In the septal pole of the hippocampus, a coronal section illustrates NPY staining primarily in the locations where mossy fibers normally terminate, the hilus of the dentate gyrus and stratum lucidum (arrows) of area CA3. (B) In the temporal pole of the same hemisphere, cut in the horizontal plane, there is striking mossy fiber sprouting in the inner Mol (arrows) that appears to be absent in (A). (C) NPY immunoreactivity in a control rat is primarily exhibited by hilar neurons (axons) and their fibers. (D) In an epileptic rodent, where granule cell axons exhibit NPY immunoreactivity, sprouting is typically inferred from the NPY immunoreactivity in the inner Mol (arrows). A section is shown from a rat that experienced pilocarpine-induced SE. (E) In other epileptic rodents that were treated the same way as the animal in (D), and evaluated at similar times after SE, mossy fiber sprouting is more robust. NPY immunoreactivity is greater and the plexus in the inner Mol (arrows) appears to be larger. Therefore, mossy fiber sprouting may not be homogeneous in the septotemporal axis of the same animal or across animals. Similar observations have been reported in other SE models and in surgical specimens from patients with intractable TLE [78].

(A & B) Modified with permission from [82].

GCL: Granule cell layer; IML: Inner molecular layer; Mol: Molecular layer.

Figure 6. Schematic representation of the progressive pathophysiology

A schematic is shown that is based on a comparison of the dentate gyrus of animals that experienced SE and developed a temporal lobe epilepsy-like condition (top; SE model), or hAPP/APde9 mice, which have been shown to exhibit recurrent seizures (bottom, AD model). We suggest that there are two major differences: the sudden time course of the early event in the SE model, and increased neuronal loss in the hilus and increased mossy fiber sprouting in the SE model. If hilar cell loss increases dentate gyrus excitability and mossy fiber sprouting increases recurrent excitation, as has been suggested [54,56,57,79], these differences could account for the increased propensity for seizures in the SE model.

AD: Alzheimer's disease; SE: Status epilepticus.