Theta Rhythmopathy as a Cause of Cognitive Disability in TLE

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Memory difficulties are commonly associated with temporal lobe epilepsy (TLE) and cause significant disability. This article reviews the role of altered hippocampal theta oscillations and theta-gamma coupling as potential causes of memory disturbance in temporal lobe epilepsy, dissecting the potential mechanisms underlying these changes in large-scale neuronal synchronization. We discuss development of treatments for cognitive dysfunction directed at restoring theta rhythmicity and future directions for research.

Cognitive dysfunction in TLE

Memory deficits have long been associated with temporal lobe epilepsy (TLE) (1–4). In particular, episodic memory deficits in individuals with TLE are prominent and progressive (3–5). Though seizure control has been correlated with improved cognition, it is clear that anticonvulsants can cause additional memory impairments (6). Possibly due partly to the cognitive deficits associated with it, TLE can be accompanied by setbacks in school and occupational performance (7). Therefore, there is a clear need for finding specific treatments not only for seizures but also for cognitive disability in TLE. Many factors likely contribute to cognitive dysfunction in individuals with TLE. Studies in both humans and animals show that extensive cell death in hippocampal and extrahippocampal structures results in loss and reorganization of circuits essential for encoding of memories (8–10). In addition, interictal epileptiform activity may interfere with encoding or retrieval of information (11, 12).

In this review, we will focus on a potentially treatable cause of cognitive dysfunction: disruption to theta rhythms and theta-related synchronization in the hippocampus.

Hippocampal Theta Rhythm in Rodents

The rodent hippocampal theta rhythm is a 4–12 Hz, large amplitude local field potential oscillation that is prominent during exploration and rapid eye movement (REM) sleep (13–15). While theta-band local field potentials and phase locked firing to the theta rhythm can be recorded in a large number of extrahippocampal structures—including cingulate, perirhinal, entorhinal cortices and amygdala (reviewed in [16])—the medial septum and the supramammillary nucleus (which projects

to the medial septum) have been posited to be theta generators, as lesions to these regions abolishes hippocampal and extrahippocampal theta rhythms (17, 18). The supramammillary nucleus may not by itself generate theta rhythmicity but rather have theta rhythmicity imposed on it by the ventral tegmental nucleus of Gudden (19) and the median raphe (20). Lesions, or pharmacological or optogenetic manipulations that impair the theta rhythm severely degrade spatial and nonspatial learning and memory (16, 21–23), and electrical stimulation at theta frequency can restore behavioral deficits (23). Therefore, theta rhythms and the plasticity mechanisms enabled by these oscillations (24) are critical for hippocampal function; they are not just epiphenomena. Any disease process that alters these oscillations will impact a range of cognitive hippocampal-dependent behaviors. Finally, gamma oscillations (30–120 Hz) are also present in a highly theta phase-specific manner, a phenomenon known as “theta-gamma coupling” or nesting (25–28). Higher frequency gamma (60–120 Hz) is recruited close to the trough of theta (as measured in CA1), while slower gamma (25–50 Hz) occurs at the falling phase of theta (28). Fast and slow gamma oscillations occur not only during different phases of theta but also occur mostly on different theta cycles (28). Therefore, theta and different types of gamma rhythms are precisely organized and timed to transmit different information streams from distinct inputs to the hippocampus.

Hippocampal Theta Rhythms in Humans: Links to Cognition

The theta rhythms recorded from the human mesial temporal regions (including hippocampal regions) have also been shown to be intimately involved with cognition and exploration. One caveat is that most studies with intracranial recordings were made in individuals with epilepsy where theta rhythms are likely to be altered. Despite this issue, movement through virtual and real environments elicits theta rhythms in human hippocampal recordings (29, 30), suggesting that there are similarities between human hippocampal theta

and theta rhythms recorded in rodents and other animals. Single-unit studies in humans show clear phase-locked firing to theta oscillations (31). Furthermore, the slow component of hippocampal theta shows increased power during successful encoding (32). Finally, the extent of entrainment and phase-locking of single units to the theta rhythm can predict whether a memory will be encoded and subsequently recalled (33). These results highlight the importance of theta entrainment to memory formation in humans, suggesting that epilepsy-related changes to theta rhythms in humans with TLE will likely adversely impact cognition.

Theta Rhythmpathy in Models of TLE

A large body of literature demonstrates a substantial decrease in hippocampal theta oscillation power and a small decrease in peak theta frequency in multiple rodent models of TLE (34–42). In addition to loss of power, theta oscillations are less coherent within the hippocampus, with a clear loss of theta coherence demonstrated between regions receiving temporoammonic and perforant path entorhinal inputs, mainly in proximal locations (closer to CA3) (40). This alteration of coherence extends beyond intrahippocampal circuits: the synchronization of theta oscillations between the dentate gyrus of the hippocampus and the entorhinal cortex are also affected with a significant delay of theta activity in entorhinal cortex with respect to the dentate gyrus (43). Therefore, theta dysrhythmias in epilepsy likely involve a number of interconnected limbic circuits and may disrupt transfer and integration of information across different brain structures. In animals that underwent both electrophysiological measurements and behavioral studies, the extent of the decrease in theta power correlates well with the magnitude of cognitive deficits in multiple hippocampal-dependent tasks, including spatial and episodic memory tasks (38, 41). In addition, loss of theta power and coherence is associated with a disruption in theta-gamma coupling in a rat model of TLE. In particular, the degree of loss of low gamma (30–60 Hz) coupling with theta in the stratum radiatum correlates with the degree of cognitive dysfunction (44). This correlation suggests that loss of theta and theta-gamma coupling could potentially play a causal role in memory dysfunction; further, interventions to boost theta power and improve theta-gamma coupling may improve cognition in epilepsy.

This epilepsy-related loss of theta oscillation power, coherence, and theta-gamma coupling will have a unique impact on the firing patterns and synchronization of each hippocampal cell population. For example, there are over 20 GABAergic interneuron subtypes in the hippocampus, innervating distinct dendritic and axonal domains (45). Each interneuron type is recruited to fire at specific phases of theta and gamma oscillations (46–51). This stereotyped sequential firing delivers inhibition to specific cellular axodendritic domains at precise times, ensuring that inhibition is precisely timed to incoming excitatory inputs. To determine how the firing of each precisely identified cell type is altered in epilepsy will require painstaking juxtacellular or whole cell *in vivo* recordings in awake behaving animals with posthoc axodendritic reconstructions and immunocytochemical labeling. So far, this has not been possible in models of epilepsy, though extracellular recordings

from nonidentified interneurons in CA1 of epileptic animals show decreased magnitude of theta phase locking (44). Recordings from posthoc reconstructed parvalbumin-positive basket cells in anesthetized epileptic animals confirm these findings (44).

Altered inhibitory firing will undoubtedly impact the way hippocampal pyramidal neurons respond to theta in epileptic animals. In normal animals, excitatory place cells fire at earlier and earlier phases of theta on successive theta oscillations as the animal goes through a place field (a phenomenon called phase-precession) (52, 53). This property allows each neuronal ensemble to encode the animal's location not only by the rate of firing of each cell but also by the temporal code created by the precise phase of theta when action potentials occur. It also creates compressed sequences of activation of ensembles of neurons within single theta cycles (53). A study of phase precession in a rat model of chronic epilepsy shows that a substantial proportion of CA1 neurons do not show evidence of theta phase-precession, greatly impairing the temporal coding of place and temporal compression of theta sequences (54). Maximum entropy network dynamics analysis techniques demonstrate that this loss of temporal coding is accompanied by increased synchronization of CA1 neurons, which may degrade the information coding capacity of the hippocampal circuits (55). Therefore, loss of theta power, coherence, and inhibitory neuron phase-locking in models of TLE are associated with degraded temporal coding of information by excitatory neurons in the hippocampus.

Theta Rhythmpathy in Models of Epilepsy: Potential Causes

The causes of loss of theta power, coherence, and phase-precession in models of epilepsy are complex and multifactorial. Theta oscillation integrity in the hippocampus depends on intact input from both medial septum (23, 56) and medial entorhinal cortex (57–59). Lesions or transient silencing of either of these structures leads to greatly diminished hippocampal theta power and spatial memory deficits. There is neuronal loss in both structures in models of TLE. Garrido-Sanabria and colleagues (60) have found a near complete loss of GABAergic neurons and a small decrease in glutamatergic neurons (but no changes to cholinergic neuron number) in the medial septum in chronically epileptic rats using the pilocarpine TLE model. Silencing of the same population of GABAergic medial septal neurons in nonepileptic animals greatly diminishes theta oscillations (22). There is also a loss of neurons in the entorhinal cortex (40, 61), with detailed studies showing loss of dorsal layer III medial entorhinal cortex neurons that form the temporoammonic input to the lacunosum moleculare layer in epileptic animals (40) and human TLE (62). This loss, when combined with the expansion of the perforant path, may mediate some of the alterations of theta power and coherence in the hippocampus (40), as well as changes to theta phase-precession (58). Alterations of intrinsic ion channels may also contribute to the loss of theta in epilepsy. Loss of h channels (HCN1/HCN2) in CA1 pyramidal cell dendrites in epileptic animals decreases theta resonance, impairing the dendrite's ability to respond to theta paced synaptic inputs (39). Epilepsy-related synaptic reorganization and changes in synaptic strength

within the hippocampus likely also play a role. For example, electrophysiological and computational studies have shown that decreased synaptic reliability between accommodating interneurons and fast-spiking basket cells in the dentate gyrus decreases theta oscillation power in a detailed computational model of the dentate gyrus (63). Though the role of the loss of other vulnerable cell types has not been systematically studied, it is likely that the loss of excitatory mossy cells in the dentate hilus does *not* play a direct role in the decrease of theta power since selective diphtheria toxin deletion of these neurons in nonepileptic animals *increases* theta power during acute stages and causes no change in theta power during the chronic stage (64).

Further studies with specific deletions of other vulnerable cell types will be needed to understand how the loss of each cell type contributes to the network dynamic alterations observed in epilepsy. Further behavioral work will be needed to understand how these changes in turn contribute to specific cognitive deficits.

Restoring Theta Rhythms to Improve Cognition in Epilepsy

Despite the extensive work on the basic mechanisms of theta dysrhythmia in epilepsy, there have been relatively few studies that have attempted to treat cognitive deficits associated with epilepsy by modulating theta rhythms, though the few studies performed show promise. Electrical stimulation of the medial septum at theta frequency in a rat pilocarpine model of TLE (which shows dramatically reduced theta power) can improve the performance of these animals on the Barnes Maze task, a test of spatial learning and memory (42). This suggests that the damaged medial septum may still maintain enough connections to enable rhythmic and structured theta synchronization of hippocampal networks. Altered theta coherence in epilepsy can also be improved by pharmacological administration of the mGluR III antagonist CPPG, though the effects of this drug on cognitive deficits in epilepsy are not known (40). In humans with epilepsy, stimulation of the entorhinal cortex resets theta rhythms and can enhance spatial memory (65), suggesting that neuromodulatory strategies through deep brain stimulation may in the future be used to improve cognition in epilepsy.

Future Directions

Many questions remain unanswered. How does altered theta rhythmicity and theta-gamma coupling in TLE affect how synapses are strengthened and weakened during encoding and retrieval of information? Do strategies that rescue cognitive dysfunction (as in [66]) improve the recruitment of inhibitory neuron subpopulations to theta and gamma rhythms—or do they bypass the need for these rhythms? The loss of which vulnerable cell populations plays a key role in destroying theta rhythmicity and inducing the cognitive dysfunction? Can some of the new tools now being used in neuroscience (optogenetics [67] and chemogenetics [68]) be translated for use in humans to address memory dysfunction in epilepsy? The development and adoption of new technologies for exploring and manipulating neural network dynamics at a large scale will likely play a key role in answering these questions.

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