Cholinergic Regulation of Hippocampal Theta Rhythm

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Cholinergic regulation of hippocampal theta rhythm has been proposed as one of the central mechanisms underlying hippocampal functions including spatial memory encoding. However, cholinergic transmission has been traditionally associated with atropine-sensitive type II hippocampal theta oscillations that occur during alert immobility or in urethane-anesthetized animals. The role of cholinergic regulation of type I theta oscillations in behaving animals is much less clear. Recent studies strongly suggest that both cholinergic muscarinic and nicotinic receptors do actively regulate type I hippocampal theta oscillations and thus provide the cholinergic mechanism for theta-associated hippocampal learning. Septal cholinergic activation can regulate hippocampal circuit and theta expression either through direct septohippocampal cholinergic projections, or through septal glutamatergic and GABAergic neurons, that can precisely entrain hippocampal theta rhythmicity.

Keywords: acetylcholine ; hippocampus ; theta rhythm

1. Introduction

The hippocampus has been widely accepted as the brain region for memory encoding and short-term memory storage. The hippocampus receives major excitatory inputs from entorhinal cortex and sends the major output back to the entorhinal cortex [1][2]. The hippocampus also receives extensive cholinergic and GABAergic inputs from medial septum and diagonal band of Broca (MSDB) [2]. Muscarinic acetylcholine receptor antagonist scopolamine has been long known to impair memory encoding. Accordingly, cholinergic regulation of hippocampal activity has been proposed as a crucial mechanism for memory encoding [3][4]. One featured activity pattern in the hippocampus is theta oscillations. Theta oscillations are large rhythmic fluctuations of the field potential in the hippocampus and many hippocampus-associated brain regions, mostly during active exploration. Due to the observation of phase precession of individual place cell firing relative to the theta phase when the animal is approaching and passing through a place field, theta oscillations have been proposed as a vehicle for encoding the sequence of place cells in spatial memory and potentially the sequence of events in episodic memory [5][6][7][8][9]. Cholinergic transmission is also closely related to theta oscillations [10][11]. Therefore, cholinergic regulation of theta oscillations is of great importance in hippocampal functions especially in memory encoding. However, cholinergic transmission is traditionally more closely linked to the type II theta under urethane anesthesia and alert immobility, which is also called atropine-sensitive theta, since type II theta is eliminated by the muscarinic receptor antagonist atropine (**Table 1**). On the other hand, the type I theta oscillation that occurs during active exploration, which is supposed to be the one involved in memory encoding, is largely atropine resistant (**Table 1**) [11][12]. This makes it difficult to explain the potential cholinergic role in memory encoding through regulation of hippocampal theta oscillation in behaving animals. Recent studies suggest that even though atropine does not eliminate type I theta as it does to type II theta, cholinergic transmission indeed can still actively regulate certain aspects of type I theta oscillations and subsequent behavioral outcomes through both muscarinic and nicotinic receptors [13][14].

Table 1. Comparison of type I and type II theta oscillations.

	Type I Theta	Type II Theta
Occurrence	**Active exploration**	**Urethane anesthesia; alert immobility**
Theta frequency	**6–12 Hz**	**4–9 Hz**
Atropine dependence	**Atropine-resistant**	**Atropine sensitive**
MS-DBB dependence	**Yes**	**Yes**
EC dependence	**Yes**	**No**
NMDAR dependence	**Yes**	**No**

Septal cholinergic and GABAergic inputs to the hippocampus have been traditionally deemed as the pacemakers of theta oscillations, providing rhythmic excitatory and inhibitory hippocampal inputs, respectively [12]. However, recent optogenetic studies suggest that septal cholinergic activity had little direct effect on hippocampal theta rhythm [15][16]. Instead, septal parvalbumin-positive interneurons can directly pace hippocampal theta rhythm [15][17]. Still, it is unlikely that individual septal interneurons pace hippocampal theta. Instead, it is more likely that the interneurons as a population play the pacemaker role as the timing of individual septal neuronal firing is too variable to consistently lead each theta cycle [18]. Even though cholinergic inputs do not directly pace theta rhythm, they can still regulate the intensity and/or the frequency of theta oscillations directly through septohippocampal cholinergic pathway or indirectly through septal local GABAergic and glutamatergic neurons that can precisely pace theta rhythm.

2. MSDB Cholinergic Neuronal Activities Correlate with Theta States

There is strong evidence supporting cholinergic involvement in not only type II theta but also type I theta. Several studies have observed elevated septal cholinergic firing rate or hippocampal acetylcholine (ACh) release during both type I and type II theta dominant behavioral states [3][19][20][21][22][23]. Microdialysis measurements of hippocampal acetylcholine levels in freely moving cats show a significant increase of ACh level during active waking and REM sleep over slow wave sleep baseline or quiet waking [20]. Additional microdialysis studies also found elevated hippocampal ACh levels in freely moving rats during active exploration [22][23]. A recent amperometry study that simultaneously monitored ACh level and local field potential in the dorsal hippocampus also uncovered a clear association between phasic ACh release and induced or spontaneous theta oscillations in urethane-anesthetized rats [19]. A more recent study using optical detection of an acetylcholine sensor fluorescent signal also shows a clear correlation between hippocampal ACh level and theta power in behaving mice [3]. Direct recordings from septal neurons also shows that medial septal cholinergic neuronal activities highly correlate with theta occurrence in freely moving mice [21]. Septal cholinergic neurons are highly active during theta dominant periods, such as active exploration and rapid eye movement (REM) sleep, while they are much less active during non-theta periods such as slow-wave sleep (SWS). However, optogenetic activation of septal cholinergic neurons had little effect on theta oscillations during either non-theta period or theta dominant periods, suggesting that cholinergic activation played a permissive role in theta generation and expression rather than as a driving force. Optogenetic activation of septal cholinergic neurons inhibited sharp wave ripples during slow-wave sleep, which is largely consistent with other studies [15][16]. These studies show that optogenetic activation of septal cholinergic neurons completely blocked sharp wave ripples and robustly enhanced theta oscillations in urethane-anesthetized mice but had less direct effect on type I theta in behaving mice. Yet cholinergic activation suppressed peri-theta events in both anesthetized and behaving mice and thus allowed theta to dominate [16]. Septal cholinergic activation can directly regulate hippocampal theta through elevated hippocampal ACh release and indirectly through the local septal circuit.

3. Cholinergic Regulation of Theta through Direct Septohippocampal Cholinergic Pathway

Both hippocampal muscarinic and nicotinic receptors may contribute to theta regulation [14][15][24][25][26][27][28]. Systemic administration of an α7 nicotinic ACh receptor (nAChR)-selective agonist significantly enhanced brainstem stimulation-induced hippocampal theta power in anaesthetized rats and mice [25][26]. Local hippocampal infusion of either muscarinic or α7 nAChR antagonists reduced peak theta power in freely moving mice, while ipsilateral entorhinal cortical infusion of a cocktail of cholinergic receptor antagonists had little effect on theta power, suggesting that the hippocampus but not entorhinal cortex was the primary target of cholinergic transmission in regulating theta oscillations [14][24]. Furthermore, cholinergic receptor subtype knockout studies suggest that mAChRs expressed in glutamatergic neurons (but not interneurons), and α7 nAChRs expressed in interneurons especially oriens lacunosum moleculare (OLM) interneurons (but not glutamatergic neurons), regulated theta oscillations [14][24]. OLM neurons are a subset of somatostatin-positive interneurons in the CA1 stratum oriens hippocampal layer that primarily target the distal dendrites of pyramidal neurons in stratum lacunosum–moleculare (SLM), overlapping with entorhinal cortical excitatory inputs. OLM neurons may play an important role in theta generation and learning and memory processes [29][30][31][32]. OLM neurons usually have larger α7 nAChR currents than pyramidal neurons and other hippocampal interneurons [14]. α7 nAChR activation on OLM interneurons can directly inhibit EC inputs in SLM but can enhance SC inputs through disinhibition [33]. In addition, α7 nAChR activation on OLM interneurons likely contribute to theta regulation through the disinhibition pathway [14]. Interestingly, direct optogenetic activation of ventral hippocampal OLM neurons can induce type II theta that can be blocked by systemic administration of atropine [34], providing a potential role for OLM neurons to coordinate mAChR and nAChR pathways in regulating theta oscillations. In vitro brain slice studies suggest that mAChR activation may primarily contribute to transient increases of theta power while α7 nAChR activation, together with mAChR activation, may promote synaptic plasticity and prime the network for theta generation by similar stimuli in the future [14]. Therefore, hippocampal

cholinergic transmission may recruit different neuronal subpopulations through different receptor subtypes to regulate different aspects of theta oscillations.

Calcium imaging studies showed that calcium activities in dorsal CA1 pyramidal neurons are high during theta states including active exploration and REM sleep, and low during non-theta states including quiet wakefulness and slow wave sleep. Systemic or local hippocampal administrated mAChR antagonist scopolamine significantly reduced calcium activities in pyramidal neurons [35]. Higher calcium activities associated with theta states may promote synaptic plasticity and memory encoding [4], or place field stabilization [36]. Theta oscillations have been proposed as a mechanism for temporal coding due to phase precession and theta sequences of place cell firing [37][38]. Phase precession refers to the progressively earlier spiking time of a place cell relative to the theta phase when the animal traverses a place field. Accordingly, there can be several place cells firing sequentially in one theta cycle, representing the temporal order of the place fields the animal travels through. Systemic administration of mAChR antagonist scopolamine significantly impairs place cell phase precession [39][40]. Scopolamine significantly reduces the firing frequency of place cells to the same level as local field theta frequency, and thus eliminates the progressive phase precession. As such, the theta phase of individual place cell firing can no longer predict the position the animal travels [40]. Phase precession also depends on intact medial entorhinal cortical inputs to the hippocampus [41]. Scopolamine likely reduces phase precession through disrupting the entorhinal hippocampal interaction. However, theta sequences and place cell assemblies remained intact after the disruption of phase precession by scopolamine [39], suggesting differential mechanisms may underlie phase precession and theta sequence generation. Phase precession also occurred during the first lap on a novel linear track, but theta sequences were absent on the first lap and developed immediately afterwards and were stable once established [42]. Some studies show that place cell sequences formed in a novel spatial experience significantly correlates with spiking events before the novel experience, suggesting the place cell sequences formed during a novel experience result from the interplay of internal drives that likely arise from past experiences and external drives that come from the current novel experience [43][44]. Place cell sequences are more dynamic in the earlier stage and stabilize in the later stage. Taken together, cholinergic transmission may thus promote phase precession and the integration of constantly updated entorhinal cortical inputs during the whole course of an experience, but likely facilitates the formation and stabilization of theta sequences during the early stage of the experience. Once the theta sequences are established, they are no longer sensitive to cholinergic modulation. This is consistent with the general observation that cholinergic transmission is primarily involved in memory encoding but not memory retrieval [45]. It is also consistent with a brain slice study where cholinergic activation promotes synaptic plasticity and theta induction, but once theta was induced and stabilized it was no longer cholinergic sensitive [24].

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