Excerpt of: ”Theta Oscillations in the Hippocampus”, Buzsáki, *Neuron* 33, 325-340 (2002)

Classic model of Theta

- two current generators (forming dipole):
    - from EC (via PP): strong excitatory input to all pyr cells at distal dendrites (most prominent amplitude observed at hippocampal fissure)
    - from septum: 1) cholinergic: slow depolarization of target pyr and int (basket- and chandelier cells) 2) inhibitory GABAergic: onto int
- gradual phase shift of theta waves with depth are brought about by phase-shifted nature of the somatic and dendritic dipoles

Inadequacies

- timing of excitation and experimentally observed spiking behaviour of pyr do not fit to model: highest probability of discharge occurs at positive peak of theta recorded dendritically (model would expect highest discharge rate at peak dendritic depolarization [=CSD sink])
- behavioural modulation of pyr firing phase during theta cannot be explained
- intrinsic neuronal oscillations (pyr) are not implemented into the model
- diversity of interconnections between hipp int-classes is not taken into account
- recurrent circuit of CA3 may function as intrahipp theta generator
- reciprocal anatomical interconnections between MS-DBB, Hipp and EC more complex → model too simple

Pharmacology of Theta

atropine-sensitive Theta:

in anesthetized (urethane) animals muscarinic blockers (such as atropine) eliminate theta completely (urethane attenuates Glu-release from presynaptic vesicles; Moroni et al., 1981)

atropine-resistant Theta:

in awake, nonanesthetized rats: theta not abolished (nor altered in terms of power or frequency) by atropine, even under large doses (though wave shape and depth profiles qualitatively changed)

surgical removal of EC or isolation of EC from its non-hipp afferents (abolishes dipole at hipp. fissure) and render
1) theta atropine-sensitive (despite eliminating the fissure-component of the hipp theta dipole)
2) its depth vs. voltage profile similar to that observed under urethane

Hypotheses derived from these observations:
→ atropine-resistant form of theta is urethane-sensitive AND
→ atropine-resistant component is conveyed by EC-layer II/III afferents

→ **thus:** NMDAR critical for atropine-resistant form of theta
experimental evidence:

- depth vs. voltage profiles under ketamine (NMDAR-blocker) similar to that under urethane
- combination of ketamine, APV or other NMDAR-blocker with atropine eliminates all theta (incl. atropine resistant theta)
- anesthetic doses of urethane or NMDAR-blockers reduce theta frequency (to 2-5 Hz compared to 6-9 Hz in the awake rat)
- candidate targets of NMDAR-Blockers are entorhinal afferent synapses on distal apical dendrites of CA1 pyr (their activation may be brought about by theta phase-locked CA^{2+} potentials; fig. 5)
- EC-input onto CA1 pyr has greater NMDA-component than associational (CA3) input

Hypotheses of action of mAChR / atropine on theta (atropine-sensitive theta)

(precise targets yet unknown)

- bilateral surgical removal of EC (resulting in abolishing PP inputs) leads to patterns of activation compatible to associational/commissural inputs (fig.4); but: septo-hippocampal cholinergic-muscarinic receptors are present in all layers (→ hipp cholinergic receptors are not directly responsible for theta)

- direct excitation of pyr by ACh ?
  M1-R activation at pyr is too slow for generation of theta-associated membrane potential changes (e.g. Cole and Nicoll, 1983) → ACh may simply depolarise pyr and int and/or affect voltage-dependent conductancies (I_M, I_H, I_A)

- possible alternative: tonic cholinergic excitation of int, coupled with their phasic septal GABAergic inhibition which in turn impose rhythmic IPSPs on target principal cells

- involvement of also nicotinic and M2-receptors?
  → pharmacological M1-block only modestly reduces theta amplitude, whereas selective neurotoxin elimination of cholinergic cells in the MS-DBB completely abolishes hipp theta and theta in the EC (Lee et al., 1994)

  → atropine-resistant type of theta is conveyed by EC-input (therefore muscarinic blockers likely do not affect theta generated in the EC)
  → but: lesion of MS-DBB abolishes theta in the EC as well

  ➔ therefore possible, that theta generation in the EC dependent on nicotinic (and/or M2) receptors

Subfield contribution to theta generation (pp. 330/331)

- granule cells:
  - theta waves recorded from outer molecular layer and hilus are phase shifted by appr. 90° (prob. explained by neighbouring dipoles conveyed by excitatory inputs from different parts of the EC)
  - elimination of granule cells by neonatal x-ray irradiation does not affect overall hipp theta (Wishaw et al., 1978)

- CA3 region:
  - directly contributes to CA1 theta (sink in str rad; small magnitude of sink, because only small portion of CA3 cells are active during a given theta cycle)
  - CA3 cells are active on the same phase of theta as CA1 cells
  - Extracellular currents in CA3 smaller than in CA1 during theta:
    - distal dendritic arbor of CA3 pyr smaller compared to that of CA1 pyr
    - CA3 receive perisomatic mossy fiber inputs whose current flows are opposite to that of EC- and recurrent collateral inputs → possibly leads to reduced netto extracellular currents in CA3
    - possibly EC-input to CA1 more prominent than compared to input onto CA3 neurons (not yet shown)
  - CA3 recurrent collateral system can also act as rhythm generator: after surgical removal of EC remaining theta depends on integrity of CA3 and theta in all layers are highly coherent (in the intact brain: coherence of theta waves from *lac-mol* and *rad* is low and powers even inversely correlated; theta waves in CA1 *rad* and inner third of dentate *mol* layer are strongly related – both receive input from associational [CA3] projections)

  → CA3 recurrent collateral network (and possibly hilar mossy cells) form intrahipp. oscillator; it requires cholinergic activation – in absence of EC input, remaining theta is atropine-sensitive

  comment on *in vitro* Theta
  contrary to the *in vivo* phenomenon
  - int not essential for maintenance
  - theta occurs only in brief bursts consisting of limited numbers of cycles
  - magnitude of synchrony is several times larger

- CA1 and dentate only “current generators” – CA3 “rhythm generator”

GABAergic interneuron contribution to theta generation (pp. 331/334)

- hipp int are the exclusive targets for the GABAergic septo-hipp projections (Freund and Antal, 1988)

- hipp int are the only hipp output neurons to MS-DBB neurons (Tóth et al., 1993)

- basket and chandelier cells → perisomatic inhibition of pyr (discharge rhythmically at gamma-frequency on descending phase of theta in pyr layer); leads to periodic "isolation" of somatic and dendritic compartments of pyr at times of maximum somatic inhibition

- Role of $GABA_B$-R in theta? → involvement possible, as approx. 60% of putative basket cells are active during the theta cycle leading to amounts of released GABA sufficient to activate $GABA_B$-R (though amplitude of intrasomatic theta reverses at ~ -70mV implying Cl^- rather than K^+ conductance)

- an unknown subpopulation of int are hypothesized to rhythmically inhibit apical dendrites of pyr and basket cells via "slow $GABA_A$-R" leading to suppression of baskets cell activity and consequently to disinhibition of pyr (Banks et al., 2000)

- O-LM and HIPP (hilar interneuron with perforant path axon projection; Halasy and Somogyi, 1993) innervate the termination zones of entorhinal afferents on pyr and granule cells; they are activated by feedback excitatory local collaterals of CA1-CA3 pyr and granule cells which leads to feedback dendritic inhibition of CA3/CA1 pyr and granule cells, especially of only weakly activated principal cells ("winner-take- all" mechanism) → control EC afferents

- Septally projecting interneurons (Tóth et al., 1993) / Backprojecting interneurons (Gulyás et al., 2001):
  CA1 backprojecting int: receive excitatory input from CA1 pyr and innervate hilar and CA3 located interneurons (Sik et al., 1994);
  septally projecting int: discharge rhythmically during theta → might coordinate discharge of neuronal populations during theta in hipp and septum

- role of int with intrinsic oscillatory properties in the theta frequency band ? (yet unclear anatomical identity [Chapman and Lacaille, 1999]; may project back to MS-DBB or amplify rhythmic inputs from other sources to principal cells or int)

- role of "antitheta" cells ? → reciprocal firing relationship with all other interneuron classes: silent during theta but fire rhythmically at 15-25 Hz in absence of theta; anatomically not yet identified (Buzsáki et al., 1983; Mizumori et al., 1990)

Contribution of intrisic resonance properties (p. 333)

- Layer II stellate cells of EC have been shown to possess voltage-dependent oscillatory properties in theta range

- MS-DBB neurons are especially prone to voltage-dependent subthreshold-oscillations:
  Cholinergic cells: display bursts of APs riding on low-threshold spikes recurring at theta frequency
  GABAergic cells: display non-adapting clusters of spikes interspersed with rhythmic subthreshold membrane–potential oscillations (e.g. Alonso et al., 1996)

- voltage-dependent subthreshold-oscillations have also been described in somata and dendrites of hipp pyr
  → amplification of subthreshold somatic oscillations amplified by high threshold dendritic Ca^{2+}-waves (Fig. 5)?
  → rhythmic activation of NMDA-R ?
  → activation of Ca^{2+}-Chanels at distal apical dendrites by actively backpropagated APs?

- role of voltage-dependent conductancies ? (possibly sequential activation of different voltage-dependent conductancies during theta cycle, as membrane pot. can change considerably)
  → transient K^+ current (I_A) at higher densities in the dendrites
  → density of hyperpolarisation-activated current (I_H) increases over 6-fold from soma to distal dendrites

Timing of action potentials within theta cycle (p. 333-335)

- on average, CA1 pyr discharge on negative phase of the theta cycle (recorded in pyr. Layer)

- variability of phases of individual spikes: (not random!) correlated with behavioural variables (e.g. place cells);
  underlying mechanism: strength of dendritic activation determines timing of firing (→ spike-phase advancement) and number of APs (because of longer suprathreshold depolarization)

- mechanism of systematic AP-shifts possibly involves two oscillators with slightly different frequencies: extrahippocampal (entorhinal) vs. intrahippocampal (CA3) oscillators

  → possibly average field theta primarily determined by EC input and place-related discharge required CA3 input (a faster CA3 theta would then bring about theta cycle spike advancement); CA3 and CA1 pyr discharge on the same phase of theta (Fox et al., 1986)

  → low frequency single spikes (occurring on pyr-layer recorded positive theta phase; Fig. 3c) might result from EC input and might contribute to overall field theta
  (as place fields in EC (layer III) are large [layer III neurons are active over large spatial areas; Barnes et al., 1990], entorhinal input appears to be relatively sustained)

  → cooperation of inputs from CA3 and EC onto CA1 pyr may lead to stronger activation of some neurons and these will discharge earlier in phase

- spike-phase relationship (Fig. 3A) strongly biased as only 3% of pyr (CA1) are active during theta and as majority of spikes are emitted within the place field (majority of neurons contribute to the generation of field theta while the strongly active minority is responsible for the spike-phase relationship)

Hippocampal Plasticity during Theta (pp. 335/336)

- *in vivo*, theta-associated somatic hyperpolarization may provide silent periods for the occurrence of complex spike bursts which backpropagate to dendrites, while depolarizing the dendritic region → induction of synaptic plasticity

→ **two-step process of memory formation:** during theta, repeated pairing of distal dendritic depolarization (via the EC input and CA3 recurrent/Schaffer collaterals to CA3/CA1 projections) may result in synaptic modification; during NON-theta activity without EC inputs (rest and NREM-sleep) these modified pathways give rise to endogenous population patterns (e.g. SPW-R; reactivation of synapses can further strenghten their efficacy)

- repeatedly administrated trains delivered on the negative phase of theta (LFP in *rad*), the previously potentiated pathway becomes depotentiated (Huerta and Lisman, 1993; Höschler et al., 1997)

- important function of theta oscillation may be to assemble and segregate neuronal groups