Anxiolytic Drugs and Altered Hippocampal Theta Rhythms: The Quantitative Systems Pharmacological Approach

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Hippocampal Theta Rhythm

Slow, global rhythmic electrical activity of the hippocampus (4-10 Hz)

- associated with gamma frequency
- studied in anesthetized and non-anesthetized rats
- also found in human hippocampal formation

Functional Roles

- Linked to mnemonic processes
- Used for landmark navigation, path integration
- Correlates to anxiety levels
Hippocampal formation generates (top), controls (right), and uses (left, bottom) theta rhythm
Neurological and Psychiatric Disorders as Dynamical Diseases

**Dynamical diseases**

- **Schizophrenia**
  - State changes in attractor structure
  - Pathological attractors

- **Alzheimer’s disease**
  - Storage and recall of memory traces

- **Migraine**
  - Normal
  - Pathological

- **Parkinson’s disease**
  - Fixed point attractor
  - Periodic attractor

- **ADHD**

- **Epilepsy**

- **Anxiety**

- **ADHD**

电力 (μV²/Hz²)

- 100,000
- 10,000
- 1,000
- 0.1

Power (μV²/Hz²)

- 100,000
- 10,000
- 1,000
- 0.1

- 100,000
- 10,000
- 1,000
- 0.1
Neurological and Psychiatric Disorders as Dynamical Diseases

The theory of dynamical diseases emerged from chaos theory.

Dynamical disease occurs due to the impairment of the control system: associated to 'abnormal' dynamics.

- Develop realistic mathematical models and study effects of parameter changes.
- Neurobiological interpretation.
- Integration of molecular, cellular and system neuroscience.
- Therapeutic strategies.
Septohippocampal Rhythm Generation and Pharmacological Control

SEPTOHIPPOCAMPAL SYSTEM

THETA RHYTHM

SKELETON NETWORK

KNOCK-IN, KNOCK-OUT TECHNIQUES

DESENSITIZATION KINETICS

GABA SYNAPSE

RECEPTOR SUBUNITS

ANXIOUS

HAPPY

pyr

i (b)

MS−GABA

i (O−LM) i (S)
Skeleton network of the septo-hippocampal system used to model rhythm generation and control by pharmacological means. The model consists of four cell populations: pyramidal cells of the hippocampal CA1 region (CA1p), stratum oriens interneurons (IO-LM), basket interneurons (IB) and septal GABAergic cells (Isept).

\[ I_{\text{syn}} = \tilde{g}_{\text{syn}} s(V - E_{\text{syn}}), \quad \frac{ds}{dt} = \alpha F(V_{\text{pre}})(1 - s) - \beta s, \]

\[ F(V_{\text{pre}}) = \frac{1}{1 + \exp\left(\frac{V_{\text{pre}} - \Theta_{\text{syn}}}{K}\right)} \]

\[ \leftarrow g_{\text{syn}} \text{ modified to simulate anxiolytics} \]
Septohippocampal Rhythm Generation and Pharmacological Control

Effect of negative allosteric modulator was taken into account by lowering the synaptic conductance at all pathways.

In all neuron populations clustering of spikes occurs at lower synaptic conductance values.

Timing of action potentials tends to have a well defined value.

Theta power in EEG computed from the activity of pyramidal neurons shows a significant increase during simulated administration of the negative allosteric modulator.
Towards a computational/physiological molecular screening and drug discovery

INTEGRATING SYSTEM and MOLECULAR LEVELS

Septohippocampal system

Temporal pattern

Desired temporal pattern

Nontrivial

e.g. theta:

enhanced cognition

anxiogenics

computational & pharmaceutical modulation

interface to further testing
Septohippocampal Rhythm Generation and Pharmacological Control

- Remarkable analogy between Type I (mobile) and Type II (immobile) theta frequency changes in animals
  - linear relationship between frequency and running speed/reticular stimulation
  - linear relationship affected similarly by anxiolytics

- Anxiolytics reduce stimulus-frequency intercept for Type I theta (also atropine resistant), but intercept and/or slope for Type II (also atropine sensitive)

- Reduction of theta frequency in animals has no false positives or negatives in predicting efficacy of human GAD treatment to date
Septohippocampal Rhythm Generation and Pharmacological Control

(McNaughton and Gray, 2000)

The effects of anxiolytic drugs on reticular-elicited (100 Hz stimulation) theta activity. Increasing strength of reticular stimulation produces a linear increase in theta frequency. Compared to pre-drug, anxiolytic drugs (CDP5chlordiazepoxide; DZP5diazepam; ALP5alprazolam; AMY5amylobarbitone) reduced the frequency of theta. Drugs which act to block acetylcholine (ACh), serotonin (5HT), dopamine (DA) or noradrenaline (NA) do not have this effect.
NEW DATA!


Novelty and anxiolytic drugs dissociate two components of hippocampal theta in behaving rats.


- in freely moving rats, there is a broadly linear relationship between hippocampal theta frequency and running speed over the normal range of speeds
- environmental novelty decreases slope, whereas ANXIOLYTIC DRUGS REDUCE INTERCEPT
- Variation in slope predicted changes in spatial representation by CA1 place cells and novelty-responsive behavior
- Variation in intercept predicted anxiety-like behavior.
Septohippocampal Rhythm Generation and Pharmacological Control

a, b: Putative anxiolytic cannabinoid CB1 receptor agonist (O-2545) reduces intercept.
c, d: Environmental novelty reduces its slope. Simultaneous drug and novelty reduces both intercept and slope independently” (Wells et al., 2013)
The Quantitative Systems Approach: Goals

- simulate the effect of stimulating current to nPO on theta frequency
- extend previous model with more realistic septal innervation
- study how chemically diverse anxiolytics modify synaptic parameters and reduce theta frequency (septal GABAergic and glutamatergic synapse modulation → slope reduction?, cholinergic synapse modulation → intercept reduction?)
The Quantitative Systems Approach: Methods

- Simulate effects of varying reticular stimulation on original model
- Implement additional septal innervation to conductance based model of hippocampal CA1 region
- Selectively modify cholinergic, glutamatergic, and GABAergic synaptic conductances and/or dynamics to simulate anxiolytic effects on stimulus-frequency graph

Septohippocampal system modeled as five distinct neuron populations interacting to generate emergent theta rhythm
Power spectra of synthetic EEGs calculated from simulations of varying levels of depolarizing current stimulus to pyramidal cells; shown here are 600 pA (solid line), 625 pA (dashed line), 675 pA (dotted line), and 700 pA (double-dashed line).
Mean frequency of theta band oscillation (3-8 Hz) increases linearly with stimulus (number of simulations run per stimulus, n = 16). Error bars represent standard deviation. Linear regression yields a slope of 0.0193 Hz/pA and intercept -6.91. $R^2 = 0.93$. 
Increase of time constants for synaptically activated GABAergic ion channels by 2 to 3 orders of magnitude in model appears to consistently lower theta frequency for large stimulating currents (compared to line with original constants), but increases variability of frequency for smaller stimulating currents (number of simulations run per stimulus, \( n = 10, 750\tau \)). Error bars represent standard deviation. Linear regression yields a slope of 0.0051 Hz/pA and intercept 1.69. \( R^2 = 0.17 \).
+ synaptic parameters
+ Extrachippocampal and intra hippocampal theta generators: resonance
Collaborators

Colin Lever (Durham University, UK): motivation, data, interpretation

Tibin T. John: simulations (Kalamazoo College, students: will be the first author)

Tamás Kiss: Pfizer, Integrative and Circuit Neuroscience (Boston): general expert :-)