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Model of carbachol-induced gamma-frequency oscillations in hippocampus☆

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Abstract

Recent experiments in hippocampus show that a cholinergic drive can induce gamma-frequency oscillations. At present, it is unclear what is the specific role of interneurons in producing these oscillations. Here we compare two possible mechanisms that can generate this type of rhythmogenesis in the hippocampus: (i) Recurrent excitatory, non-NMDA, coupling between pyramidal neurons in combination with fast feed-forward inhibition, versus (ii) pyramidal neurons stochastically entrained to the rhythm of interneurons that are synchronized by mutual inhibition.

Keywords: Gamma-oscillations; Cholinergic agonist; Hippocampus; Interneurons

1. Introduction

Rhythmogenesis in the hippocampus has recently attracted significant attention (see for example Ref. [11]). Rhythmogenesis is, for example, clinically important because it is involved in elliptogenesis in the hippocampus. In addition, synchronization

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is purported to be a substrate for binding and information processing [10]. The CA3 area of the hippocampus contains different types of inhibitory GABAergic interneurons, as well as excitatory glutamatergic pyramidal neurons. The pyramidal cells have recurrent excitatory connections among themselves, and also excite local interneurons. The interneurons in turn project divergently to a large number of pyramidal neurons. The role played by the two main neurotransmitters, GABA and glutamate, in producing synchronization has been delineated by pharmacological manipulation of in vitro slices (e.g. Ref. [11]).

It is well known that EEG contains many different frequency components, including delta (0.5–2 Hz), theta (4–12 Hz), and gamma (40–100 Hz). In hippocampus the same frequency range of oscillations can be measured in vivo using extracellular and intracellular electrodes (see for a review Ref. [2]).The hippocampus is innervated by subcortical structures. These projections can change the balance between excitation and inhibition, and can thus affect rhythmogenesis. Here we consider the cholinergic projection from the medial septum/diagonal band. The activity of this projection can be mimicked by in vitro application of the muscarinic receptor agonist Carbachol (CCH). Carbachol can induce theta-frequency-range rhythmic population oscillations in the hippocampus [5]. Recent experimental studies show that Carbachol induces gamma-frequency-range oscillation in hippocampal slices [4]. Fellous and Sejnowski also studied the effect of Carbachol on oscillations in hippocampal slices [3]. For increasing concentrations of CCH these authors observed transitions from incoherent activity, to delta-frequency-range oscillations (CCH-δ), and from delta to theta-frequency-range oscillations (CCH-θ). In addition, gamma-frequency-range oscillations (CCH-γ) can occur alone or in combination with CCH-θ and CCH-δ. The origin of these oscillations, in particular CCH-γ, is not yet fully understood. CCH *increases* the excitability of interneurons and pyramidal cells (and also reduces accommodation), but *decreases* excitatory synaptic coupling (see Overview of Methods). The net result of these antagonistic effects is hard to intuit. We have therefore started a detailed investigation of rhythmogenesis in the hippocampus for different relative strengths of the inhibitory and excitatory couplings. Here we report our preliminary results. Our aim is to find a physiologically realistic and consistent explanation of the Carbachol-concentration-dependent occurrence of CCH-δ, θ, and γ. Presently, we can account for the experimental results by Fisahn et al. [4], and Fellous and Sejnowski [3] in *multiple* ways, by using biophysically plausible manipulations of the parameters. Further experiments are therefore still needed to determine what is the actual mechanism by which the synchronization is obtained. Our simulations provide predictions for possible experimental measurements that can delineate the different synchronization mechanisms that we propose here. In the experimental preparation there is always synaptic noise, a distribution of initial states of the neurons, heterogeneity in the intrinsic properties of the neurons, heterogeneity in the drive (provided by the CCH concentration), and stochastic variations in the number of active synapses per neuron. The theoretical mechanisms proposed here must therefore be robust against these disturbances, and this will provide additional constraints on the model parameters and possible mechanisms.

2. Overview of methods

We have studied the effect of different Carbachol (CCH) concentrations on the dynamics of a model hippocampal slice. To account for the effect of Carbachol we have both varied the intrinsic properties of pyramidal cells and interneurons, as well as the network properties. Pinsky and Rinzel [9] (PR) introduced an appropriate reduced two compartmental version of a full CA3 pyramidal neuron model by Traub and coworkers (e.g. Ref. [11]). Here we have reduced the Calcium conductance (to prevent bursting); we have also, in a concentration-dependent manner, reduced the conductance of the Calcium-dependent hyperpolarizing current I_{AHP}, and increased the constant dendritic driving current I_{dendr} [7,8]. Depolarization can induce subthreshold membrane potential oscillations in hippocampal pyramidal cells [6]. We have therefore added an intrinsic theta frequency oscillator consisting of a sodium and potassium current. For our interneurons we use a model introduced by Wang and Buzsaki [12]. The excitatory effects of Carbachol on interneurons are simulated by an increased constant driving current in the soma.

The network properties are determined by the value of the strength of the synaptic coupling g_{x-y} and the (average) number of synapses n_{x-y} made on a neuron, where $x-y$ can be either one of the two AMPA-type synapses (the kinetics are as in Ref. [9]): the recurrent excitations between pyramidal cells (e–e) or the excitatory synapses made by pyramidal cells onto the interneurons (e–i); or either one of the two GABA_A-type synapses (kinetics as in Ref. [12]): the mutual inhibition between interneurons (i–i) and the inhibitory drive from interneurons onto pyramidal cells (i–e). The main effect of carbachol is to reduce the synaptic coupling strength.

In our numerical simulations we generate voltage traces, and determine the spike times of each neuron. The spike times are then plotted in a rastergram. We have also determined the time-dependent firing rate of the network as the number of action potentials in a 1 ms bin. The details of computational implementation and analysis will be reported elsewhere.

3. Summary of results

For each of the different frequency ranges mentioned above we will first describe the experimental results of Fellous and Sejnowski [3], and then briefly summarize our corresponding simulation results.

3.1. *Incoherent activity* ($CCH < 4$ μM)

For low concentrations of CCH the excitability of pyramidal neurons is increased, and they are spontaneously active. In experimental voltage measurements, a clear subthreshold theta oscillation is observed, with sparse spikes riding on top of the oscillations. The field potential is incoherent, suggesting that the discharge is not synchronized. In our model neuron, depolarization induces subthreshold theta oscillations. Spikes are generated once in a while under the influence of noise. The

low-average firing rate prevents the neurons in the network from synchronizing by way of the recurrent excitatory coupling.

3.2. *Delta-frequency-range activity* ($CCH = 4–13$ μM)

Sudden, large amplitude population events are present in the field potential for moderate concentrations of CCH. They occur at frequencies of approximately 0.5–2 Hz. The oscillatory state is intermittent, as it starts and it ends at random times. Only AMPA receptors are required for this oscillation. GABA does not influence the occurrence of these oscillation in a significant way. The size of the AHP conductance is reduced between 20–80% for the CCH concentrations of 4–13 μM [7]. We have found two regimes, namely weak (δ-I) and strong excitatory coupling (δ-II), for which the oscillations occur in our model. However, we find that δ-I is not robust against heterogeneity. In δ-II the network alternates between the high (the delta event in the field potential) and low (or sustained) activity state. In the sustained activity state a few spontaneously active neurons fire incoherently. When enough neurons fire in a short enough time interval, a critical level is reached. The activity can then quickly propagate through the network. After a number of action potentials the activity terminates. During the course of the many action potentials in the delta event the Calcium-dependent AHP accumulates and may lead to a refractory state. (It is also possible that a slowly inactivating persistent sodium, or a slowly activating potassium current is responsible for termination [1], possibly in combination with synaptic depression.) This AHP may also prevent subthreshold theta-frequency oscillations from being activated. The possible frequency range is determined by the length of the refractory period of the neuron. The quantitative details also depend on whether or not single neurons burst during CCH-δ.

3.3. *Theta-frequency-range oscillations* ($CCH = 13–40$ μM)

The population of pyramidal neurons oscillates at frequencies between 4–12 Hz with individual neurons spiking only once in a few theta cycles (typically 3–5). These oscillations start and stop intermittently. GABAergic inhibition is not required for these oscillations. Oscillations in a wide frequency range, including CCH-θ, are obtained using fast feed forward inhibition and an increased constant current drive. Here we propose a more plausible mechanism, namely that the Carbachol-induced depolarization activates the subthreshold intrinsic theta-frequency-range oscillator. The much higher average firing rate can now induce synchronized oscillations. The underlying frequency is determined by the intrinsic oscillator and depends to a lesser extent on the driving current. Instead the pyramidal cells will fire at more cycles for an increased driving current. This is consistent with experiment. The importance of the excitatory drive is corroborated by the experimental result that blocking NMDA-receptors turns CCH-θ into CCH-δ. This mechanism explains how a higher firing rate, weaker synaptic coupling, and reduced AHP may make the CCH-δ unstable, and instead may lead to CCH-θ.

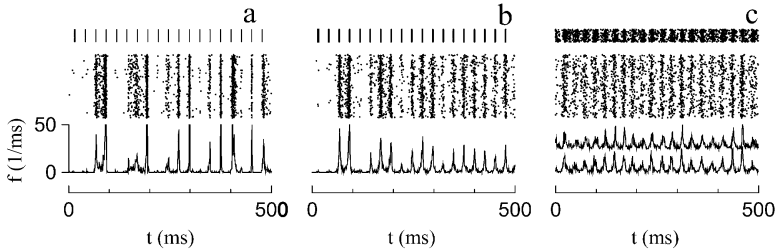

Fig. 1. Illustration of (a, b) γ-I and (c) γ-II. In each panel from top to bottom, rastergram of interneurons, rastergram and firing rate of pyramidal cells. In (c) we also plot the firing rate of the interneurons (curve translated by 25 units). There are 500 pyramidal cells, and 100 interneurons. The interneurons are driven by (a) a tonic current, (b) a tonic current with Gaussian noise, and (c) by the EPSPs of pyramidal cells.

3.4. *Gamma-frequency-range oscillations* ($CCH = 4$–40 μM)

CCH-γ is observed during CCH-δ and CCH-θ, and also by itself [4]. $GABA_A$ ergic synapses are required for the CCH-γ. The time constant of inhibition determines the frequency of the CCH-γ [4]. Electrophysiological recordings suggest that the number of neurons participating in CCH-γ is less than the number participating in CCH-δ and CCH-θ. This yields support to the possibility that CCH-γ are generated by a separate circuit that can be either activated by the increased activity during CCH-δ and CCH-θ, or by CCH-induced increases in the spontaneous firing rate. We find two mechanisms to generate CCH-γ (see Fig. 1). Tonically active and synchronized networks of interneurons (γ-I) may pattern the discharge of excitable pyramidal cells. Networks of inhibitory neurons are capable of synchronizing in the gamma-frequency range [11,12]. The inhibited pyramidal cells may be above threshold and possibly they phase-lock to the inhibitory drive, or they may need synaptic noise to escape from inhibition. Our work suggests that in the latter case the synchronized gamma-oscillations are more robust against disturbances such as heterogeneity and recurrent excitation. Another mechanism operates via feedforward inhibition (γ-II). The discharge of pyramidal cells recruits interneurons which in turn terminate the pyramidal discharge until the pyramidal cells are disinhibited again. A sufficient amount of mutual inhibition has to be present to synchronize the interneurons. The pyramidal neurons will not synchronize without synchronized interneurons. A more detailed description of these and other results will be presented elsewhere.

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