Effects of CCK Basket Cell Inhibition on Place Cell Firing in the Hippocampus

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Abstract

CCK connections to pyramidal cells exhibit an interesting phenomena termed "Depolarization-Induced Suppression of Inhibition (DSI)." During DSI, depolarization of the pyramidal cell (PC) releases cannabinoids that bind to the CB1 receptor on CCK cells. This initiates a molecular cascade in the CCK basket cell that results in decreased release of GABA onto the pyramidal cell. Thus, when a pyramidal cell is excited, the perisomatic inhibition from CCK cells is reduced and the pyramidal cell is capable of becoming even more excited. Since CA1 pyramidal cells often act as place cells, it seems likely that DSI would play a role in place cell behavior. Here, DSI is modeled in a Hodgkin-Huxley neuron microcircuit and its spike timing relative to theta is quantified. Using this model, we are able to show that the CCK-PC connections contribute to phase precession in CA1 pyramidal cells.

1 Introduction

The mechanistic underpinnings of hippocampal place cells have been extensively studied since they were first discovered by John O'Keefe and John Dostrovsky in 1971. These spatially responsive pyramidal neurons encode a specific location within an animal's environment and preferentially fire when the animal traverses that space. Although there are many aspects of place cells that are computationally intriguing, one particularly interesting feature is their marked phase precession relative to underlying theta oscillations. The theta oscillation is an 8-12 Hz. frequency oscillation that occurs in the hippocampus and in other areas of the brain. As an animal crosses a place field, the place cell encoding that area will begin to fire. As the animal continues to cross the place field, the place cell will fire at a slightly faster frequency than theta, resulting in bouts of firing that precess with respect to the underlying theta frequency (Figure 1). Although many models have attempted to explain this phenomenon, to date nobody has experimentally demonstrated how phase precession occurs. In this project, I propose a novel model incorporating CCK basket cells, a subtype of interneuron that synapses on the perisomatic region of CA1 pyramidal cells.

CCK basket cells are the only perisomatically-targeting interneurons that express CB1 (cannabinoid receptor type1) receptors. Importantly, CB1 receptors are involved in DSI (depolarization-induced suppression of inhibition) an aspect of the microcircuit that seems likely to contribute to phase precession. DSI describes a process whereby a pyramidal cell is depolarized and, subsequently, releases cannabinoids near the soma. These cannabinoids can bind to the CB1 receptors on CCK basket cells where they initiate a cascade resulting a decrease in GABA release onto the pyramidal cell. This feedback circuit results in increased excitability of the CCK basket cell. As the CCK basket cell becomes less inhibited, it becomes easier for the CCK basket cell to fire meaning that it can fire earlier during the theta cycle. Thus, this phenomenon seems likely to allow for phase precession.
2 Methods

2.1 CA1 Microcircuit

In this model (Figure 2), the CCK basket cell synapses onto the CA1 pyramidal cell and releases GABA, effectively inhibiting the pyramidal cell. The pyramidal cell also synapses recurrently on the CCK basket cell, releasing cannabinoids. The net effect of this cannabinoid release is to inhibit the CCK basket cell. However, this inhibition is mediated by an intrinsic molecular cascade that takes much longer than a traditional, GABAergic, inhibitory synapse. Both the CCK basket cell and the pyramidal cell receive subthreshold sinusoidal oscillatory input delivered at 8 Hz, a frequency matching that of endogenous theta oscillations. To begin with, the only input to either cell is the subthreshold oscillatory input. At t = 100 msec, the CCK cell receives a constant 6 \( \mu \text{A/cm}^2 \) input thus inhibiting the pyramidal cell. At t = 200 msec, the pyramidal cell receives a constant 2 \( \mu \text{A/cm}^2 \) input. This input is just enough to allow the pyramidal cell to fire during the peaks of the theta oscillation but not during the troughs.

2.2 Hodgkin-Huxley Model

For purposes of modeling, both the CCK basket cell and the pyramidal cell follow a Hodgkin-Huxley model. Using this model, the voltage response of each cell is as follows:

\[
\frac{dV_{PC}}{dt} = \frac{1}{C} \left( I_{\text{theta}} + I_{\text{ext,PC}} - I_{\text{CCK to PC}} - I_{Na} - I_K - I_L \right)
\]

\[
\frac{dV_{CCK}}{dt} = \frac{1}{C} \left( I_{\text{theta}} + I_{\text{ext,PC}} - I_{\text{PCToCCK}} - I_{Na} - I_K - I_L \right)
\]
where the currents are given by:

\[ I_{\text{theta}} = 2 \sin \left( \frac{16\pi}{1000} \right) + 2 \]

\[ I_{\text{CCKtoPC}} = g_{GABA} r (V_{\text{post}} - E_C) \]

\[ I_{\text{PtoCCK}} = g_{CB1} r (V_{\text{post}} - E_C) \]

\[ I_{Na} = g_{Na} m^3 h (V - E_{Na}) \]

\[ I_K = g_K n^4 (V - E_K) \]

\[ I_L = g_L (V - E_L) \]

Rate equations are defined below:

\[ \frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(m) \]

\[ \frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(n) \]

\[ \frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(h) \]

\[ \frac{dr_{GABA}}{dt} = \alpha_{r_{GABA}}(T)(1 - r) - \beta_r(r) \]

\[ \frac{dr_{CB1}}{dt} = \alpha_{r_{CB1}}(T)(1 - r) - \beta_r(r) \]

And the rate functions are as follows:

Figure 2: CA1 Microcircuit. Inhibitory synapses exist between the pyramidal cell and the CCK basket cell. Both cells receive subthreshold sinusoidal input mimicking hippocampal theta oscillation. At \( t = 0 \) msec, the CCK cell also receives a 6 \( \mu \)A/cm\(^2\) input. At \( t = 100 \) msec, the pyramidal cell receives a 2 \( \mu \)A/cm\(^2\) input.
\[ \alpha_m = \frac{0.1(V+45)}{1-e^{-(V+45)/10}}; \quad \beta_m = 4e^{-2(V+70)/18} \]

\[ \alpha_h = 0.07e^{-(V+70)/20}; \quad \beta_h = \frac{1}{1+e^{-(V+40)/10}} \]

\[ \alpha_n = \frac{0.01(V+60)}{1-e^{-(V+60)/10}}; \quad \beta_n = 0.125e^{-(V+70)/80} \]

\[ T = \frac{T_{max}}{1 + e^{-(V_{pre}-V_p)/K_p}} \]

The constants within these equations are as follows:

\[ C_m = 1 \ \mu F \ cm^{-2} \]

\[ E_{Na} = 50 \ mV; \quad g_{Na} = 120 \ \text{mS/cm}^2 \]

\[ E_K = -80 \ mV; \quad g_K = 36.0 \ \text{mS/cm}^2 \]

\[ E_L = -60 \ mV; \quad g_L = 0.30 \ \text{mS/cm}^2 \]

\[ T_{max} = 1.5 \ mM \]

\[ K_p = 5 \ mV; \quad V_p = 7 \ mV \]

2.3 Phase Precession

To determine the phase of each neuronal spike relative to the underlying oscillation, the sinusoid was binned into cycles. For each cycle, the spikes within that time bin were analyzed to determine

Figure 3: Voltage Response. As the sinusoidal input to the pyramidal cell approaches the peak, the pyramidal cell begins to spike, thus turning off the CCK basket cell. As the theta oscillation decreases, approaching the trough of the oscillation, the pyramidal cell ceases its spiking and the CCK basket cell begins firing again.
if they passed a threshold of 0 mV. For each spike in the cycle that crossed this threshold, the phase of the spike relative to the sinusoidal cycle was obtained. Comparison of these phases for each cycle can then be used to determine whether spiking precesses across cycles.

3 Results and Discussion

3.1 Voltage Response of Cells

Using the circuit model described above the voltage response of the CCK basket cell and the pyramidal cell were obtained (Figure 3). As the underlying sinusoidal oscillation approaches its peak, the increased current to the pyramidal cell pushes it to spike. Spiking in the pyramidal cell results in decreased spiking of the CCK basket cell due to the DSI response. As the oscillation to the pyramidal cell approaches the trough, the pyramidal cell ceases to spike and, subsequently, the CCK cell is able to spike.

Figure 4: Phase Precession without DSI. If the CCK to pyramidal cell synapse is removed the phase precession of the pyramidal cell is minimal. However, if we compare the first spike of each burst (highlighted in red) we do still see a slight negative trend. This suggests that pyramidal cells modulated by theta activity will still exhibit theta precession even without any inhibitory inputs.

Figure 5: Phase Precession with DSI. DSI mediated by the CCK basket cells exacerbates the effects on phase precession of the pyramidal cell. Comparison of the first spike within each burst (highlighted in red) demonstrates a negative slope in phase.
3.2 Phase Precession of the Pyramidal Cell

Using the method described previously, the phase of each spike within each cycle was calculated. To begin with, the inhibition from the CCK cell was removed to examine whether a pyramidal cell receiving simple feed-forward inhibition (such as that delivered by parvalbumin+ interneurons) would display phase precession. Interestingly, when we do this we see very subtle phase precession suggesting that DSI via the CCK cells is not required for phase precession (Figure 4). When the inhibition from the CCK cell to the pyramidal cell is added into the model, we see an exacerbated phase precession response. That is, the slope of the phase across spike number declines much more steeply (Figure 5). Given these results, it seems that the CCK basket cells, while not required for phase precession, greatly contribute to this phenomena.

3.3 Effects of Changing the Reverse Kinetics of the CB1 Synapse

One aspect of the CA1 microcircuit that is not well understood is how long the cannabinoid-mediated suppression of GABA to take effect in the CCK basket cell, we chose here to investigate several different values of beta. Low values of beta reflect a longer reverse duration of the reverse kinetics of the CB1 channel. Small values of beta produce stronger effects in phase precession suggesting that this feature of DSI is a crucial component of the observed effects on pyramidal cell phase precession behavior.

Figure 6: Effects of beta on phase precession. Since it is not well known how long it takes for the cannabinoid-mediated suppression of GABA to take effect in the CCK basket cell, we chose here to investigate several different values of beta. Low values of beta reflect a longer reverse duration of the reverse kinetics of the CB1 channel. Small values of beta produce stronger effects in phase precession suggesting that this feature of DSI is a crucial component of the observed effects on pyramidal cell phase precession behavior.
4 Conclusion

In this study, we modeled a portion of the CA1 microcircuit using the Hodgkin-Huxley equations. For this model, the synaptic connections between the pyramidal neuron and the CCK basket cell mimicked DSI, thus allowing for a window of increased excitation in the pyramidal cell. Using this model, we were able to demonstrate, as hypothesized, that CCK basket cells in this microcircuit play a role in the phase precession of the pyramidal cell relative to theta. Interestingly, eliminating DSI from the circuit by removing the synaptic connection between the CCK basket cell and the pyramidal cell did not completely eliminate phase precession. Thus, it seems possible that simple feed-forward inhibition to the pyramidal cells may mediate phase precession. Nevertheless, introduction of DSI via the CCK basket cell does exacerbate the phase precession of the pyramidal cell.

5 Future Work

CCK basket cells are one of two perisomatically-targeting interneurons in CA1 of the hippocampus, the other subtype being parvalbumin (PV) positive. Interestingly, PV interneurons receive inhibitory input from the CCK basket cells. In the current model, we only include the CCK basket cells. Future work will need to incorporate PV interneurons to fully understand how the local inhibitory network modulates the CA1 pyramidal cells. Furthermore, in this paper, the CCK basket cells are modeled as being non-accommodating. In reality, these cells are highly accommodating and this may have implications for the phase precession behavior of the pyramidal cells.

Phase precession is just one feature of hippocampal CA1 place cells. It seems likely that the CCK basket cells would also play a role in other features of the pyramidal cells. For instance, perhaps these neurons shape the spatial tuning of the place fields of these neurons. Additional models should investigate these behaviors to obtain an overarching view on how place cell behavior is determined by the local inhibitory network.

References

