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Modeling study of the synaptic competition induced by NMDA receptor-mediated regulation of spike-timing-dependent plasticity

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Abstract: The competition among synapses is required for the Hebbian learning to develop functional synaptic circuits. Recent theoretical studies have shown that spike-timing-dependent plasticity (STDP) can yield the competition when the magnitude of LTP and LTD in the STDP curve is almost equal, although the physiological mechanism that elicits this balance is not understood. In this study, we examine the effects of Ca^{2+}-dependent desensitization of NMDA receptors (NMDARs) on the regulation of the STDP learning rule and show that it can suppress the LTP induction more than the LTD induction, decreasing the LTP/LTD ratio. We also examine how the Ca^{2+}-dependent desensitization of NMDARs and the developmental increase in the desensitization property can regulate the synaptic competition when a neuron receives two groups of synaptic inputs with mutually independent input correlations. The results show that the NMDAR-dependent modification of the STDP curve can be considered as a physiological mechanism that contributes to the stable synaptic circuit formation through robust synaptic competition.

Keywords: Synaptic competition, NMDA receptor, Development, Neuroscience.

I. INTRODUCTION

The Hebbian learning has been believed to contribute to the development of functional neural circuits and widely used in early neural network studies ([1-3]). Under this plasticity rule, synapses are increased based on the correlations between the firing rates of pre- and postsynaptic cells such that the synapses between the neurons that fire together are strengthened. However, simple correlation-based rules lead to instability by the positive feedback, since the synaptic modification that strengthens the inputs effective for driving the postsynaptic neuron leads to further increase in the effectiveness of the inputs for eliciting the postsynaptic discharge [4, 5]. A solution to overcome this problem is to take into account the competition between synapses such that when some synapses are potentiated, others are depressed. Actually, many neural network models have introduced a constraint that conserves or limits the total synaptic strength over a postsynaptic cell [6, 7], although the biological mechanism that elicits the constraint in Hebbian learning is not clear.

A recent theoretical study [8] has proposed an entirely different mechanism for inducing the competition based on the experimental finding that the synaptic modification depends on the precise timing of pre- and postsynaptic spikes, which is termed as spike-timing-dependent plasticity (STDP). In this STDP, long-term potentiation (LTP) of synapses occurs if a presynaptic spike precedes a postsynaptic spike by < 100ms. On the other hand, a presynaptic spike that follows a postsynaptic spike produces long-term depression (LTD) of synapses (see [9] for a review). Groups of synapses that are frequently activated before the postsynaptic spike and are effective at generating postsynaptic discharges are potentiated by STDP, while synapses from other inputs that are activated slightly after the postsynaptic firing and therefore does not contribute to it are depressed; this leads to the strong competition among different synapses over controlling the firing of a given postsynaptic cell [8]. However, the STDP-mediated competition requires another constraint, different from that for the rate-based learning; the areas under the STDP curve in the LTP and LTD portions must be approximately balanced. Otherwise, all synaptic inputs are potentiated when LTP surpasses LTD, while all inputs are depressed when LTD dominates over LTP. An adaptive STDP model by Tegner and Kepecs [10] has shown that the feedback control of the ratio of the magnitude of LTP to that of LTD in the STDP curve can produce the approximate balance in LTP and LTD, which leads to the competition among synapses and stabilizes the postsynaptic activity under correlated inputs. However, it is not yet understood how the relative magnitude of LTP and LTD in the STDP learning can be dynamically modified depending on the postsynaptic activity.

Therefore, in this study, we examine the physiological mechanism that induces the change in the ratio of

LTP and LTD in STDP and elicits the synaptic competition robustly. We use a biophysical two-compartmental neuron model including Ca^{2+}-dependent plasticity [11] and show that the Ca^{2+}-dependent desensitization of NMDA receptors (NMDARs) can reduce the LTP/LTD ratio, which contributes to the induction of strong competition among different groups of synapses.

II. Methods

1. Simulation for the STDP experiment

We have constructed a two-compartmental model of a cortical pyramidal neuron containing a somatic and a dendritic compartment. Both compartments have voltage-dependent I_{Na} and I_K currents, while the dendritic compartment also contains the AHP current I_{AHP}. The active currents are described by the Hodgkin-Huxley-type equations, the parameters of which have been modified from those for the pyramidal neuron model [12]. The dendritic compartment receives synaptic inputs composed of AMPA receptor (AMPAR)- and NMDAR-mediated excitatory currents and GABA receptor (GABAR)-mediated inhibitory currents.

Additionally, we considered the calcium dynamics in a spine, which has the same membrane potential as that of the dendrite. The calcium dynamics is described as the first-order kinetics, and the calcium entry is mediated by NMDARs and voltage-gated Ca^{2+} channels (VGCCs). In order to reproduce the experiment of STDP, we calculated the time course of Ca^{2+} transient $\Delta[Ca(t)]$ induced by the pre- and postsynaptic spike pair, and then applied the Ca^{2+}-dependent plasticity model [11]:

$$\Delta w = f_P(\Delta[Ca]_p) + f_D(\Delta[Ca]_p) \cdot f_V(T - \hat{T}(\Delta[Ca]_p)). \quad (1)$$

Here, Δw denotes the amount of synaptic weight change; $\Delta[Ca]_p$, the peak calcium level induced by each pre- and postsynaptic spike pair; and T, the time interval at which the Ca^{2+} concentration is above a threshold. f_P and f_D are functions that determine the amount of LTP and LTD, respectively, depending on the Ca^{2+} peak level. f_v is the Heaviside step function that blocks LTD induction when T is smaller than $\hat{T}$. The temporal threshold $\hat{T}$ increases with the Ca^{2+} peak level. This model is based on the hypothesis of Ca^{2+}-dependent plasticity that states that higher Ca^{2+} levels elicit LTP, while sufficiently long duration of medium levels of Ca^{2+} elevation is required for the stable induction of LTD [13, 14].

2. Simulation for the synaptic weight dynamics

In the simulation for the dynamics of synaptic weight modification, the model neuron receives random inputs from 4000 excitatory and 800 inhibitory synapses with the average input rate of 3Hz. We divided the excitatory synapses into two groups with the same number and introduced independent correlations of equal magnitude into each of them by the method given by [15].

Experimental findings suggest that the accumulation of intracellular Ca^{2+} elicits the desensitization of NMDARs, which decreases both the decay time constant and the peak conductance of NMDAR currents [16, 17]. Since the average presynaptic rate does not alter in our model, the determinant of the degree of desensitization is the postsynaptic firing rate, which linearly increases the accumulated Ca^{2+} concentration through VGCCs. Therefore, we assume that the NMDAR decay time constant τ_N and its peak conductance g_N decrease as a function of the postsynaptic firing rate f_{post}. Furthermore, there exists evidence that the developmental change in the NMDAR subunit composition decreases the decay time constant, while it increases the degree of desensitization [16, 18]. Therefore, we model the Ca^{2+}-dependent inactivation of NMDARs as follows:

$$\tau_N = \tau_0 - a\gamma - b\gamma f_{post} \quad (2)$$

$$g_N = g_0 - c\gamma f_{post}. \quad (3)$$

Here, the parameter γ ($0 \le \gamma \le 1$) represents the developmental condition, where $\gamma = 0$ and 1 correspond to immature and mature neurons, respectively; and a, b, and c are positive parameters.

In order to calculate the change in the synaptic weight w for each pre- and postsynaptic spike pair with the interspike interval (ISI) $\Delta t = t_{post} - t_{pre}$, we constructed a 4-dimensional STDP map, represented as $\Delta w(\Delta t, \tau_N, g_N)$, in advance from the simulation of the STDP experiment. For each spike pair, we used different values of τ_N and g_N derived from Eqs. (2) and (3) and obtained the amount of Δw from the STDP map. The additive model was used for the weight update and the peak AMPAR conductance of each synapse was modified in proportion to the value of the synaptic weight.

III. Results

1. Simulation for the STDP experiment

We performed simulations of the pairing protocol to reproduce the experiment of STDP (Fig. 1). Figure 1a

shows the Ca^{2+} peak value as a function of ISIs for different pairs of NMDAR decay time constant and the peak conductance. The figure indicates that the Ca^{2+} increase is reduced for all ISIs by the decrease in either the NMDAR decay time or the peak conductance. However, the decrease in the Ca^{2+} peak level is much larger for the positive ISIs than negative ISIs. Therefore, the synaptic weight change obtained by using the Ca^{2+}-dependent plasticity model (Eq. (1)) also decreases more significantly in positive ISIs (Fig. 1b). Therefore, if we define the areas of the STDP curve under the LTP and LTD portions to be S_+ and S_-, respectively, then the ratio S_+/S_- decreases with the reduction in both NMDAR decay time constant and the peak conductance (Fig. 1c). The result here is attributable to the fact that the spike-evoked Ca^{2+} transient in the pre-post timing is very sensitive to the decay time course of NMDAR currents [11].

2. Simulation for the synaptic weight dynamics

Next, we examined the effects of the activity-dependent Ca^{2+}-dependent desensitization of NMDARs on the competition among synapses, in cases where the neuron receives random inputs from two groups of synapses with mutually independent correlations. We first consider the case of $\gamma = 1$, which corresponds to mature neurons. In this case, the desensitization of NMDARs, which decreases both the decay time and the peak conductance (Eqs. (2) and (3)), also decreases the S_+/S_- ratio (Fig. 1b). Therefore, higher postsynaptic activity decreases the S_+/S_- ratio, while lower activity increases it. This activity-dependent regulation of the STDP learning leads to the dynamic balance in the overall effects of LTP and LTD, stabilizing the S_+/S_- ratio around a value of ~0.9, similar to [10]. In the presence of this approximate balance in LTP and LTD, STDP forces two groups of synapses to compete with each other. Therefore, at the steady state, one group of synapses converges to the upper limit, while the other group is pushed towards zero (Fig. 2a). We also performed the same simulations with changing the parameter for the developmental condition γ to explore how the developmental change in the NMDAR subunit composition affects the competition property of STDP (Fig. 2b). For smaller γ, the activity-dependent regulation of STDP is suppressed, so that the decay time and the peak conductance of NMDAR currents tends to increase. Since this change functions to increase the S_+/S_- ratio, the amount of average synaptic weights increase (Fig. 2b, dotted line) and the difference in the average synaptic weights of two groups diminishes (Fig. 2b, solid line). When γ becomes less than 0.4, the competitive property of STDP disappears and all synapses converge to values near the upper limit. These results suggest that the change in the desensitization properties of NMDARs can modulate the synaptic competition.

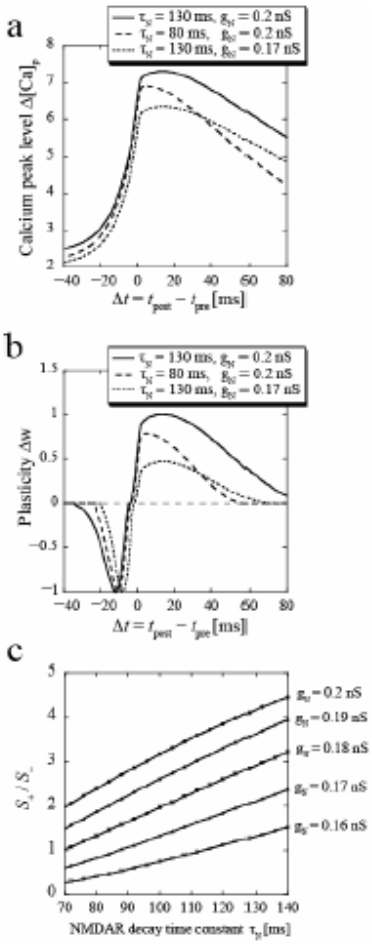

Fig. 1. (a) and (b) The changes in the Ca^{2+} peak level $\Delta[Ca]_p$ (a) and the plasticity Δw (b) for different pairs of the NMDAR decay time constant τ_N and the peak conductance g_N. (c)The relationship between the S+/S- ratio and τ_N for various values of g_N.

IV. Conclusions

In this study, we have studied the physiological mechanism that regulates the LTP/LTD ratio in STDP learning and induces the competition among synapses. Our results suggest that the Ca^{2+}-dependent desensitization of NMDARs primarily suppresses the induction of the pre-post timing LTP and reduces the LTP/LTD ratio. When

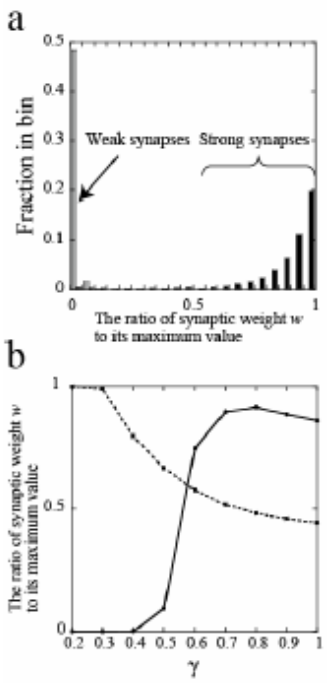

Fig. 2. (a) The steady-state weight distributions for two groups of synapses, denoted by black and gray bars, when $\gamma = 1$. (b) The changes in the average weight of all synapses (dotted line) and the difference between the average weights of two groups of synapses (solid line) for different values of γ.

the Ca^{2+}-dependent desensitization is sufficiently strong, the desensitization induced by the accumulation of VGCC-mediated Ca^{2+} influx can provide the activity-dependent regulation of the STDP learning, which acts to keep the balance in the overall effects of LTP and LTD and introduce robust synaptic competition. Furthermore, the developmental change in the desensitization properties of NMDARs may control the strength of synaptic competition. In immature neurons, weaker desensitization strengthens all presynaptic inputs, while the developmental enhancement of the desensitization induces the strong competition at later stages. Therefore, the developmental change in the NMDAR subunit expression may be a physiological mechanism that regulates the level of competition, depending on the developmental stages.

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