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The onset and closure of critical period plasticity regulated by feedforward inhibition

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ABSTRACT

Synaptic circuits are highly sensitive to sensory experience during a critical period in early development. The maturation of GABA inhibition in the visual cortex is suggested to be required for both the onset and closure of the critical period for ocular dominance (OD) plasticity, although the underlying mechanism is unclear. This study examines a model of a visual cortical cell to investigate the mechanism by which inhibitory pathway regulates OD plasticity, through the competition between the groups of correlated inputs from two eyes. We show that when feedforward inhibition is at a low level, the activity-dependent competition does not arise. In the lack of competition, synaptic dynamics are monostable, which prevents the sensory experience to be embedded into synaptic weights. When the feedforward inhibition becomes greater than a threshold, the competitive interaction segregates the input groups into dominant and recessive ones. In this case, the synaptic dynamics become bistable, which provides the synaptic pattern with the ability to reflect sensory experience, opening the critical period. When the feedforward inhibition is further increased, a strong stability of synaptic patterns makes it difficult to change according to input stimuli. Therefore, it becomes difficult again for the synaptic weights to reflect the information about sensory stimuli, closing the critical period. Our hypothesis suggests that the start and end of critical period plasticity may be explained by the competitive dynamics of synapses, which is modulated by the feedforward inhibition.

1. Introduction

The brain is organized by receiving sensory experience during a restricted critical period [1]. Well-known examples are the effects of modulating visual experience on the developing visual cortex [1]. The deprivation of vision from one eye during a critical period shifts the response of visual cortical cells to favor the inputs from the open eye. In contrast, monocular deprivation (MD) before or after the critical period does not significantly affect the response of the neurons.

Many studies have suggested that the timing of critical period is regulated by the maturation of GABA inhibition [2–7] ([7] for review). When the maturation of inhibition is suppressed by the targeted deletion of an isoform of the GABA synthetic enzyme, glutamic acid decarboxylase (GAD65), the onset of ocular dominance (OD) plasticity is delayed until the inhibition level is pharmacologically recovered [2]. Similarly, OD plasticity can be prematurely induced by pharmacologically enhancing GABA function [3], suggesting the existence of a threshold level of GABA to start visual plasticity. Furthermore, recent experiments have shown that enhanced GABA inhibition not only can trigger the opening of critical period but also contribute to its closure [8–12]. Suppression of GABA through the infusion of an inhibitor of GABA synthesis mercaptopropionic acid, at doses which do not affect the responsiveness of visual cortical cells, can reactivate OD plasticity in the adult rats [9,10]. In addition, exposure to enriched environment or treatment with a serotonin reuptake inhibitor fluoxetine, which reduces intracortical GABA inhibition, can recover plasticity [11,12]. These findings suggest that there may exist two threshold levels of inhibition: a lower threshold above which OD plasticity is expressed and a higher threshold above which the ability of plasticity is suppressed [10].

Several studies using computational models have proposed a role of GABA in regulating the onset of OD plasticity. A recent study [13] suggests that GABA activity preferentially decreases the synaptic efficacy of less coherent inputs, which contributes to inducing an OD shift toward more coherent inputs. A study on subplate circuits [14] also indicates that higher inhibition levels may be necessary to induce an OD shift toward the non-deprived eye during MD. Although these research proposes mechanisms inducing the onset of OD plasticity in response to MD, it appears difficult to extend the same mechanisms to explain the closure of OD plasticity. One possibility is that the closure of critical period may result from a gradual decline in neuronal activity through

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GABA maturation, which will act to prevent long-term potentiation (LTP) and long-term depression (LTD) at cortical synapses [15,16]. However, recent findings suggest that both LTP and LTD occur in the adult visual cortex *in vivo* [17], implying that the suppressive effect of GABA on OD plasticity seems difficult to be simply explained by the reduction in the activity level.

In this study, we examine a simplified model of a visual cortical cell to explain the mechanism by which GABA controls both the onset and closure of the critical period of OD plasticity. In our model, we hypothesized that the level of feedforward inhibition corresponds to the level of GABAergic development. The model neuron receives two groups of excitatory inputs conveying correlated activities, as in a visual cortical cell receiving inputs from two eyes, and feedforward inhibition mediated by GABA. The synaptic weights of the two input groups are modulated by spike-timing-dependent plasticity (STDP) [18,19], where the weight change depends on the precise timing of pre- and postsynaptic spikes. We particularly investigate the synaptic dynamics regulated by competition between the input groups, since many experiments have suggested a key role of activity-dependent competition in OD plasticity [1,20–22]. We show that a higher level of feedforward inhibition induces competition, which generates bistable synaptic pattern. The bistability provides synaptic weights with an ability to reflect sensory experience of MD, opening the critical period. However, a further higher level of feedforward inhibition makes the synaptic patterns too stable to alter according to sensory stimuli, closing the critical period. Our model may be beneficial for understanding the mechanism to regulate the start and end of the critical period, in a unified framework, through competitive dynamics of synapses.

2. Methods

We use a leaky integrate-and-fire (LIF) neuron to model a visual cortical cell [23]. The membrane potential V of the LIF neuron is described as $\tau_m(dV/dt)=g_{leak}(E_{leak}-V)+I$ with $\tau_m=20$ ms, $E_{leak}=-74$ mV, and $g_{leak}=1$ (the values of conductances are measured in units of the leak conductance for all cases) [24]. When the membrane potential arrives at a threshold value of -54 mV, the neuron fires and the membrane potential is reset to -60 mV following the absolutory refractory period of 1 ms. As shown in Fig. 1, the neuron receives 1000 excitatory and 200 inhibitory inputs. To model sensory inputs from two eyes to a visual cortical cell, the excitatory inputs are divided into two groups of equal size [25]. We consider that the excitatory inputs are of AMPA type, while the inhibitory inputs are of GABA type. The conductances for the excitatory and inhibitory inputs are described as $g_{exc}=\overline{g}_{exc}we^{-t/\tau_{exc}}$ and $g_{inh}=\overline{g}_{inh}(e/\tau_{inh})te^{-t/\tau_{inh}}$, respectively, where $\overline{g}_{exc}=0.015$, $\tau_{exc}=5$ ms, $\overline{g}_{inh}=0.005$, and $\tau_{inh}=10$ ms [25]. w denotes the synaptic weight for each excitatory input, which is modified by STDP (see below).

Each group of excitatory inputs are activated by the retinal activities for the corresponding eye (Fig. 1). Inhibitory inputs are activated through pathways originating from excitatory inputs, providing feedforward inhibition, which corresponds to the synaptic connection observed in animal visual cortex [26]. There is evidence that, for sufficiently noisy conditions, as in the in vivo state, the firing probability of a postsynaptic neuron is approximately proportional to the summation of the postsynaptic potentials (PSPs) occurring in the neuron [27,28]. Therefore, we consider that the activation timings of both excitatory and inhibitory inputs are described by non-stationary Poisson processes, the rate of which is determined by the PSPs [29]. With this assumption, the activation rates of the two groups of excitatory inputs ($r_1^{exc}(t)$ and $r_2^{exc}(t)$) and that of inhibitory inputs ($r^{inh}(t)$) are described by the following equations:

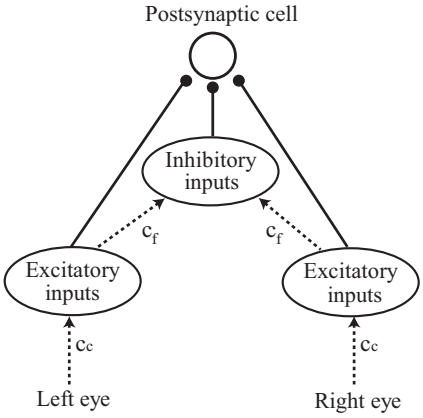

Fig. 1. The model neuron receives inputs from two groups of excitatory (AMPA) inputs and a group of inhibitory (GABA) inputs. Each group of excitatory inputs are driven by the afferent inputs from the corresponding eye. Inhibitory inputs are driven by the activities of excitatory inputs, providing feedforward inhibition. The parameters of c_c and c_f decide the levels of afferent inputs and feedforward inhibition, respectively.

$$r_I^{exc}(t)=c_c\sum_f \varepsilon(t-t_I^f)+r_0^{exc}\ (I=1,2), \tag{1}$$

$$r^{inh}(t)=\frac{c_f}{n_{exc}}\sum_i\sum_f \varepsilon(t-t_{exc,i}^f)+r_0^{inh}. \tag{2}$$

Here, $\varepsilon(t)$ is a function describing the temporal change in PSPs, and $\varepsilon(t)=(t/\tau_e^2)e^{-t/\tau_e}$ with $\tau_e=20$ ms for $t\geq 0$ and $\varepsilon(t)=0$ otherwise. In Eq. (1), t_I^f is the arrival timing of the fth spike to the Ith group of excitatory inputs from retinal ganglion cells, and t_I^f is determined using Poisson spikes with a frequency of $r_{inp}=5$ Hz. The spike arrival timings for the two groups of excitatory inputs are independent, and therefore, the activation of the different groups are uncorrelated to each other. The parameter c_c is to determine the strength of afferent inputs from retinal ganglion cells, and c_c is set to be 0.5 unless otherwise stated. $r_0^{exc}=7.5$ Hz is a component of the activation frequency that corresponds to spontaneous activity. In Eq. (2), $t_{exc,i}^f$ is the fth activation timing of the ith excitatory synapse. Therefore, c_f is a parameter to decide a level of feedforward inhibition, which corresponds to the maturation of GABA inhibition, especially of the developing GABAergic innervation during critical period [30]. n_{exc} $(=500)$ is the number of excitatory inputs within each group, and r_0^{inh} is the frequency corresponding to spontaneous activity for the inhibitory inputs.

It has been suggested that homeostatic regulation may be involved in preserving the overall input activities that drive visual cortical neurons in early development [31]. Therefore, to maintain the activation rate of presynaptic inputs independent of the strength of feedforward connections c_f, the spontaneous activation rate of inhibitory inputs was modified such that $r_0^{inh}=10(1-c_f)$. With this equation, the mean activation rate of inhibitory inputs is kept at 10 Hz.

STDP was assumed to act on all the weights of excitatory inputs. The change in the synaptic weight by STDP, Δw, is described as a function of the interspike interval (ISI), $\Delta t=t_{post}-t_{pre}$, between the pre and postsynaptic activities as follows [24]:

$$\Delta w(\Delta t)=\begin{cases} A_+\exp(-\Delta t/\tau_+) & (\Delta t>0)\\ -A_-\exp(\Delta t/\tau_-) & (\Delta t<0)\\ 0 & (\Delta t=0)\end{cases} \tag{3}$$