Circuit property of the cortico-mesocortical system

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Abstract

We analyzed an interaction between the prefrontal cortex (PFC) and the ventral tegmental area (VTA) via computer simulation. Our previous study (Yamashita and Tanaka 2002) shows an inverted-U shaped concentration-dependent effect of dopamine (DA) on the delay-period activity, which has been reported in experiment (Goldman-Rakic 2000). We here propose a circuit model of the cortico-mesocortical system. It seems reasonable to conclude that VTA dopaminergic neurons play a role in stabilizing the delay-period activity in the PFC. Furthermore, we discuss modulatory inputs to the VTA. We suggest that these inputs could control the cortico-mesocortical system.

Keywords: Dopamine; Mesocortical; Prefrontal cortex; Ventral tegmental area; Working memory

1 Introduction

Dopamine has been known as a neuromodulator and is relevant to specific behavioral contexts (White 1996). The importance of dopamine cannot be overemphasized in working memory processes. Recently Williams and Goldman-Rakic showed that dopamine modulates the memory fields of PFC neurons (Williams and Goldman-Rakic 1995). In their study, an inverted-U shaped modulation of the memory fields deserves careful attention (Goldman-Rakic 2000; Yamashita and Tanaka 2002). To know the dopaminergic modulation of spatial working memory, it is necessary to understand a circuit property of the cortico-mesocortical system. The VTA has been reported to have connections with reward activity (Schultz et al. 1993, 1997). However, their roles for spatial working memory is still controversial. We have already developed a computational model of the PFC circuit that incorporates the dopaminer-

gic effects (Tanaka 2002; Yamashita and Tanaka 2002). We here analyze an interaction between the PFC and VTA by computer simulation of our model.

2 Model

The neurons are described by a leaky integrate-and-fire neuron model (Tanaka 2001, 2002; Tanaka and Yoshida 2001; Yamashita and Tanaka 2002). Model neurons possess the ion conductances which are AMPA, NMDA, $GABA_A$, persistent sodium, calcium-dependent potassium. As effects of dopamine on these conductances, our model includes the following four effects; suppression of AMPA channeled ion current, enhancement of NMDA channeled ion current, enhancement of persistent sodium current, and suppression of calcium dependent potassium current (Tanaka 2002; Yamashita and Tanaka 2002). The network contains 1320 neurons, which are 1080 pyramidal cells and 240 inhibitory interneurons. Each neuron's connectivity profile is described by the Gaussian function. The PFC network consists of 3 layers, which are the superficial layer, the intermediate layer, and the deep layer. The neurons in the intermediate layer receive sensory inputs. The VTA dopaminergic neurons are driven by the projection of the PFC deep layer pyramidal neurons and send output to the PFC neurons to release dopamine. That is, a closed-loop circuit between the PFC and the VTA. The activation level of the VTA was represented by the equation including the firing rate of the PFC neurons. DA release level is described by the sigmoid function of this level. We simulated an occulomotor delayed response task.

3 Results

In our simulation, the PFC neurons showed well-tuned delay-period activity. The VTA activation level was enhanced by firing of the PFC pyramidal neurons, then DA was released in the PFC. While dispersed firing came from much lower or higher DA release, such extreme DA release reflected in suppressed firing rate of PFC neurons.

In the delay-period activity, DA release was stabilized at a higher level than the optimal level in the inverted-U curve developed in our model (Yamashita and Tanaka 2002). With these issues in mind, we examined a relationship between the VTA and DA release. This was described by the sigmoid function.

In this function, leftward or rightward shift refers DA release that is to be facilitated or suppressed in the VTA. In the case of the leftward shift, much DA was released at first, but it decreased later soon. With an extensive rightward shift, DA release was inhibited because of an insensitivity to the VTA activation.

This study is also devoted to an investigation of modulatory inputs to the VTA. These inputs differ from the projection of the PFC neurons. When the VTA neurons receive an excitatory step input, there was a phasic excitation at the first of the stimulation. However, not only the VTA activation but also firing rates of the PFC neurons decreased soon after the stimulation. And then, the case of inhibitory inputs was quite contrary to the excitatory inputs, that is to say, suppression when the inhibitory input was injected and ascent at the end of the stimulation. As a consequence, after those inputs were withdrawn, DA release level varied intensely with the exception of the inhibitory input injected. In most cases of inhibitory inputs, the PFC neurons show the sustained activity.

4 Discussion

In this study, there was considerable variation in the delay-period activity in the model PFC. It was also found the feedforward inhibition with higher DA release (Yamashita and Tanaka 2002). As for the stimulation in the VTA, while it was hard to disrupt the delay-period activity during suppression of DA release, the activity of the VTA was decreased when DA release was facilitated. This now raises the suggestion that modulatory inhibitory inputs to the VTA neurons exist not to facilitate DA release extremely.

There are some influence lines of recent investigation deals with the likelihood that cortical afferents to the VTA regulate burst firing of dopaminergic neurons. Moreover stimulation of PFC induces burst firing of VTA neurons (Gariano and Groves 1988; Tong 1995). To stimulate the PFC neurons, a sensory input was send to PFC in our model. At that time, the VTA was well activated, as well as the PFC neurons, then, DA was released in the PFC. This sensory input could be a driving signal for the VTA as well as the PFC.

The existence of a GABAergic pathway from the nucleus accumbens to the VTA was also reported. These projection might terminate on both DA and non-DA neurons (Walaas and Fonnum 1980; Yim and Mogenson 1980). As for the afferents to the VTA developed in our model, whereas the excitatory stimulation which differs from the sensory inputs disrupted memory fields, the

inhibitory inputs did not. The inhibitory afferents might stabilize DA release and the delay-period activity . Furthermore, continuous inhibition synchronized with the sensory input could control DA release level. On the contrary, with the existence of intense inhibition, no memory field was organized and then a cue input was ignored. In this way, these inhibitory modulations are suggested to play important roles in stabilizing working memory processes. Because both the excitatory and the inhibitory afferents to the VTA remain as matters to be discussed, further research would clarify the VTA dopaminergic regulation in working memory.

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