Parametric study of dopaminergic neuromodulatory effect in a reduced model of the prefrontal cortex

Koki Yamashita, Shoji Tanaka*

Department of Electrical and Electronics Engineering, Sophia University

7-1 Kioicho, Chiyoda-ku, Tokyo 102-8554, Japan.

Abstract

A reduced model is constructed to explore the essential nature of dopaminergic modulation in the prefrontal cortex. The model network comprises excitatory and inhibitory units. It includes potentiation of the excitatory transmission and prolongation of the time constant of the inhibitory unit as the dopaminergic effect. Results indicate that the tonic activity of the model units shows an inverted U-shape property. Additional parametric analysis has shown that blocking the dopaminergic effects eliminates this property. In conclusion, the reduced model provides a theoretical explanation of the mechanisms for the inverted U-shaped modulation in the prefrontal cortex via D1 receptor activation.

Keywords: Dopamine; Inverted U-shape property; Prefrontal cortex; Working memory

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* Corresponding author

Tel: +81-3-3238-3331, fax: +81-3-3238-3321

E-mail address: tanaka-s@sophia.ac.jp

1. Introduction

Neurons in the prefrontal cortex (PFC) encode working memory information via sustained firing patterns [2,5]. These neurons are considered to form the cellular basis for working memory [3,5]. Dopamine (DA) plays a critical role in modulating the activity of these PFC neurons [1,10,12,14,15]. Single-neuron recording studies have revealed several DAergic effects on the PFC neuron (e.g. [4,7,8,11,16]). Seamans et al. [11] reported that D1/D5 receptor activation selectively enhanced sustained synaptic inputs by increasing the N-methyl-D-aspartate (NMDA) component of excitatory postsynaptic currents (EPSCs), while non-NMDA synaptic current was decreased by D1 agonist application. DA also modulates interneuron activity. In fact, Gorelova et al. [8] have suggested that DA depolarizes inhibitory interneurons by suppressing a voltage-independent '*leak*' K^+ current and an inwardly rectifying K^+ current. This decreases the threshold for spike firing, thereby increasing the neuronal excitability of interneurons in the PFC.

Regarding DAergic effects on a PFC neuron population, it has been suggested that the activation level of the neurons follows an inverted U-shaped curve according to the DA D1 receptor stimulation [6,9,13]. That is, working memory activity was impaired when PFC DA levels were either below or above the optimal range. However, mechanisms of this DAergic modulation in the PFC remain controversial. One way to address this issue is simulating the DAergic modulatory effect to examine whether the DAergic modulation addressed by experimental studies mediates the inverted U-shape property. The present paper reports a computational study of essential effects of D1 receptor activation on PFC neurons during a delayed-response task.

2. Model

The present model is intended to explain mechanisms of DAergic modulatory influence on delay-period activity in the PFC. We produced as simple a model network as possible within constraints imposed by this objective. Figure 1A depicts the resultant network architecture. It has been reported that DA application influences not only excitatory pyramidal cells, but also inhibitory interneurons in the PFC [8,11,16]. Therefore, our model consists of both excitatory (x_p) and

inhibitory (x_n) units. The state equations of the model units are given as the following equations:

$$\frac{dx_p(t)}{dt} = -\frac{1}{\tau_p}x_p(t) + W_{pp}f(t,x_p) - W_{np}f(t,x_n) + W_0\delta(t),\ and \quad (1)$$

$$\frac{dx_n(t)}{dt} = -\frac{1}{\tau_n}x_n(t) + W_{pn}f(t,x_p), \quad (2)$$

where τ_p and τ_n are time constants, and W_{ab} represents the connection strength from a to b; $\delta(t)$ in Eq. (1) corresponds to an external transient input to the PFC neurons during the cue period of a delayed-response task. The activation function in each unit is $f(t,x)$, which is given by:

$$f(t,x) = \frac{1}{2}\left(|x(t-\Delta t)| - |x(t-\Delta t) - x_{MAX}| + x_{MAX}\right). \quad (3)$$

In that equation, Δt is the transmission and synaptic delay. In particular, the term $f(t,x_p)$ in Eq. (1) indicates a recurrent excitation that enables the units to exhibit sustained activity. All parameter definitions are described in Table 1.

/ Fig. 1 /

The DA-induced decrease in non-NMDA EPSCs was not so significant as the increase of NMDA EPSCs via D1 receptor activation [11]. For that reason, the net DAergic effect on the excitatory transmission between the PFC neurons appears to be the facilitation of the excitatory transmission. We model this DAergic effect by increasing W_{pp} and W_{pn}. The DAergic modulatory effects on connectivity strength were assumed to be homogenous. On the other hand, the DA-induced increase in interneuron excitability [8,16] corresponds to prolonging the time constant of the interneuron's activity. The effect of DA on the time constant of the inhibitory unit differed quantitatively from the effects on W_{pp} or W_{pn}. The DAergic modulation was expressed as the replacement of each parameter, as shown in Fig. 1B.

Hypothesis: Herein, we hypothesize that the principal effects of the D1 receptor activation in the PFC that elicit the inverted U-shape property are as follows: (1) enhancement of the excitatory connections between PFC neurons (W_{pp}, W_{pn}); and (2) the increase in the time constant of the interneurons (τ_n) (Fig. 1B).

/ Table /

3. Results

When D1 receptor activation levels were lower than the optimum (Z<1), increasing the DA level potentiated the tonic activities of the model units (Fig. 2). However, the tonic level was attenuated by supraoptimal increases of the DA level (Z>1) (Fig. 2). The results indicate that there is an inverted U-shape relationship between the DA level and the tonic activities of the model units (Figs. 2B,2D). In addition, it is noteworthy that the phasic level of each unit tended to be monotonically potentiated when the DA level increased.

The inverted U-shape property is strongly dependent on quantitative aspects of DAergic effects on excitatory synaptic transmissions (W_{pp} and W_{pn}) and the interneuronal intrinsic property (τ_n). An increase or decrease in the relative effect on τ_n, which was represented by a/b, provided distinct appearances of the inverted U-shape property (Fig. 3A). When the effect on τ_n was weak, the model unit response was potentiated monotonically with increasing DA levels, thereby eliminating the inverted U-shape property.

/ Fig. 2 /

The inverted U-shape feature apparently depends on the contributions of individual DAergic effects. Excitatory inputs were insufficient to activate the model units when the DAergic effect on the recurrent connection strength was blocked (Fig. 3B). On the other hand, blocking the effect on the connectivity, W_{pn}, or the effect on the time constant of the inhibitory unit caused the increase of the units' activities with the DA application (Figs. 3C,3D).

/ Fig. 3 /

4. Discussion

This study examined the influence of particular parameters on cortical neuronal activities. Our results provide theoretical evidence of the mechanisms for the inverted U-shape property in addition to computational findings of our previous studies [12,14,15]. These results indicate that increased excitatory transmission and elevation of the time constant of inhibitory interneurons' activities, the latter of which corresponds to the suppression of a leak current, well explain the DA-induced

inverted U-shape property. In particular, the rising phase is attributable to the facilitated excitatory connections. The falling phase is derived from the potentiated interneurons' activities. In conclusion, (1) insufficient excitatory transmission with the suboptimal DA receptor activation or hyperactivity of the inhibitory interneurons with the supraoptimal DA receptor activation attenuates prefrontal cortical neural activity. Also, (2) decreasing the DAergic effect on potassium channels of inhibitory interneurons eliminates the inverted U-shape characteristic in the prefrontal cortex.

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Author biosketch

Koki Yamashita

has received his B.E. and M.E. from Sophia University, Tokyo. He is a graduate student in the Department of Electrical and Electronics Engineering, Sophia University, and currently studies computational neuroscience and electrical engineering. He is a doctor course researcher of the Japan Society for the Promotion of Science.

Shoji Tanaka

has received his B.E., M.E., and Ph.D. from Nagoya University, Japan. He is a professor at the Department of Electrical and Electronics Engineering, Sophia University. From 1998–1999, he was a visiting scientist at the Section of Neurobiology, Yale University School of Medicine, USA.

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Figure legends

Fig 1. (A) Structure of the model PFC network. The network contains the recurrent connection and the negative feedback connection via the inhibitory unit. The excitatory unit receives an external phasic input. The DA level influences W_{pp}, W_{pn}, and τ_n. (B) DAergic effects on the connectivity strength (W_{pp}, W_{pn}, solid line) and the time constant of the inhibitory unit (τ_n, dotted line). The DAergic modulation on the parameter P was expressed as $\tilde{P} = r(z)P_{original}$. The optimal D1 receptor activation level was fixed at z = 1.

Fig 2. When the DA level increased, both the excitatory (A, B) and inhibitory (C, D) units indicate a biphasic property in their activities. The tonic levels reveal an inverted U-shape feature, whereas phasic activities show a monotonic increase (B, D). The arrows indicate the input onset (t = 200 ms). The phasic and tonic levels were recorded at t = 220 ms and t = 5800 ms, respectively. The optimal DA level was fixed at z = 1 (a = 1.27, b = 4.88).

Fig 3. The parameter a/b, which represents the proportion of the DAergic effects on the inhibitory unit, influences the relationship between the DA level and the excitatory unit activity (A). This activity is represented as the average tonic level of the excitatory unit (400<t<1200). Extremely weak effects on τ_n eliminated the inverted U-shape property. On the other hand, the strong DAergic modulation on the inhibitory unit attenuated the activation level at the optimal DA level. The model units do not show the inverted U-shape property when dopamine has no effect on W_{pp} (B), W_{pn} (C), and τ_n (D) (t = 5800 ms). The optimal DA level was fixed at z = 1.

Table 1. Model parameters.

Symbol	Description	Defined value
τ_p	Time constant of the excitatory unit	20.00 [ms]
τ_n	Time constant of the inhibitory unit	12.00 [ms]
Δt	Transmission and synaptic delay	5.00 [ms]
W_{pp}	Connectivity strength from x_p to x_p	0.75 [a.u.]
W_{pn}	Connectivity strength from x_p to x_n	0.50 [a.u.]
W_{np}	Connectivity strength from x_n to x_p	1.00 [a.u.]
W_0	Amplitude of the external phasic input	1.00 [a.u.]
x_{MAX}	Maximum value of the activation function	10.00 [a.u.]

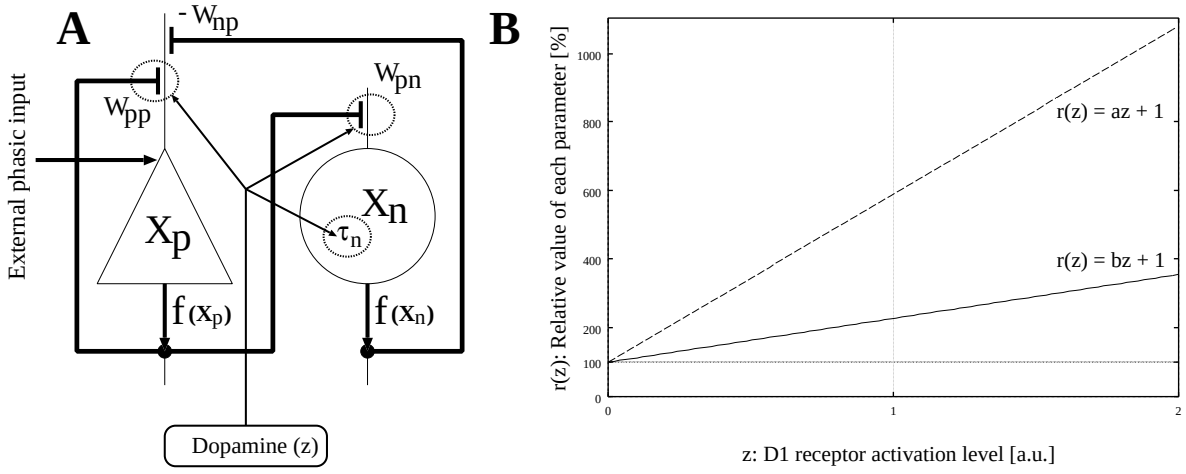

Figure 1 Yamashita and Tanaka

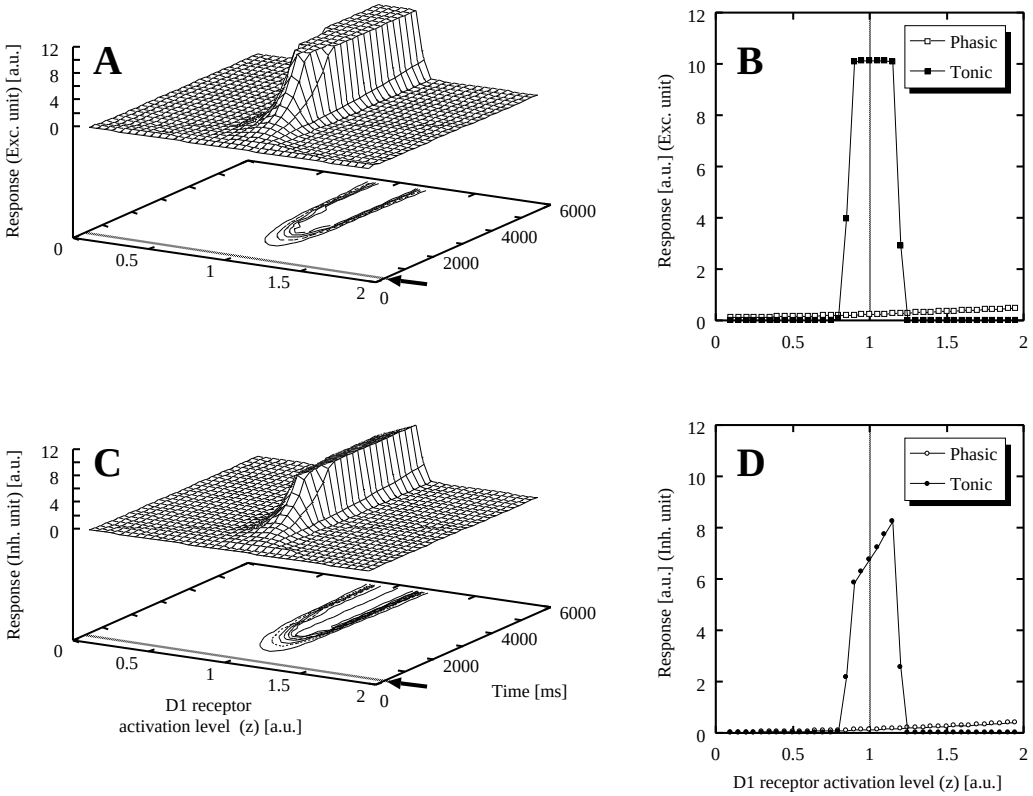

Figure 2 Yamashita and Tanaka

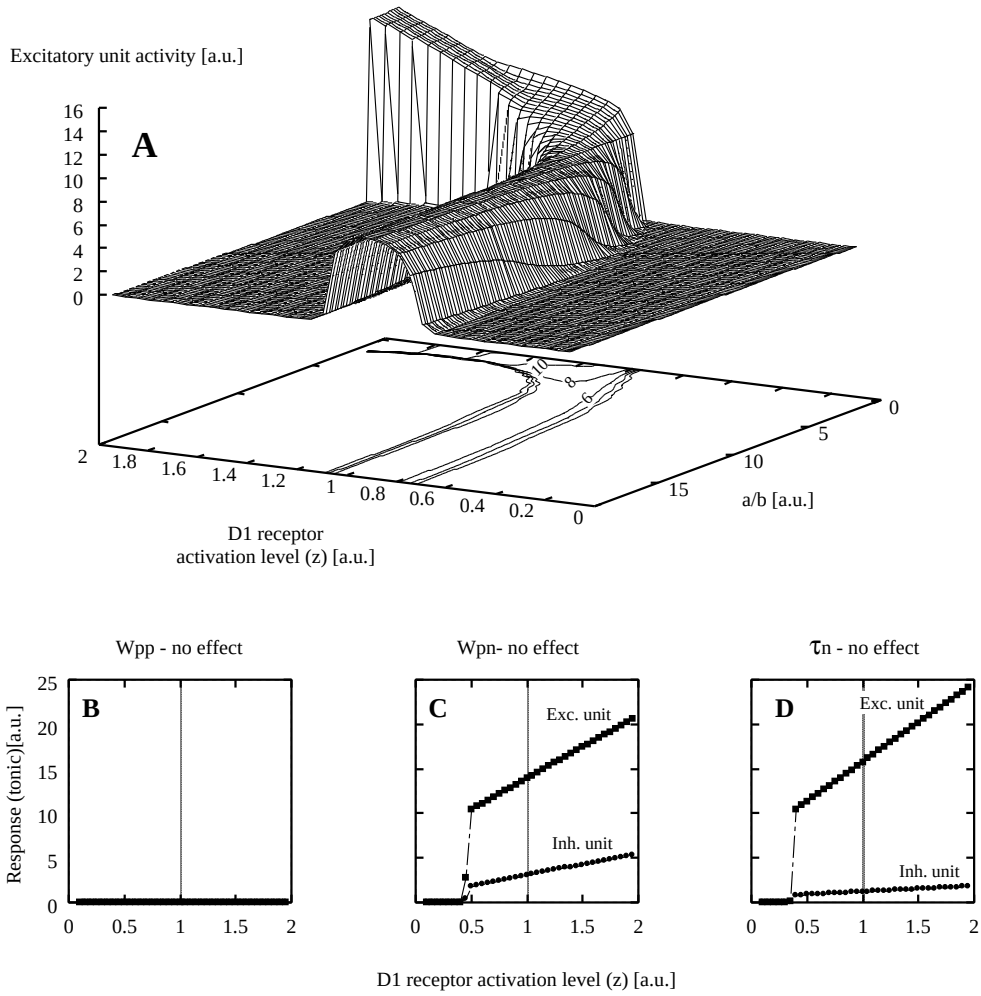

Figure 3 Yamashita and Tanaka