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

Koki Yamashita, Shoji Tanaka[1]

Department of Electrical and Electronics Engineering, Sophia University

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

Abstract

Our continuing studies have sought to simulate circuit properties of the mesocortical dopaminergic system. This article describes a reduced model which elucidates the essential nature of dopaminergic modulation in the prefrontal cortex (PFC). Simulating a delayed-response task, we observed that the delay-period activity of the model neurons follows an inverted-U-shaped curve according to the increase in the dopamine level. Subsequent analysis showed that the inverted-U-shaped activation of the model PFC neurons derives from a supercritical pitchfork bifurcation, the formation of which requires synergism between the modulation of the pyramidal-interneuron connection and that of the interneuron's excitability.

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

1. Introduction

Dopamine (DA) plays a critical role in modulating the activity of prefrontal cortex (PFC) neurons, which encode working memory information via their sustained firing patterns [1,2,3,4,5,9]. An important feature of DAergic modulation in the PFC is that the activation level of the neurons follows an inverted-U-shaped curve according to DA D1 receptor stimulation, as experimental studies have shown [5,8,13]. That is, working memory activity of the PFC neuron population was impaired when PFC DA levels were either below or above the optimal range. Although certainty of this feature of DAergic modulation in the PFC has been growing, no theory has been established to explain mechanisms that engender the inverted-U-shape property. We have sought to develop simulative models to investigate mechanisms of DAergic modulation in the PFC [12, 14, 15]. Our previous simulation with a model PFC network that contains DAergic effects on each neuron has yielded an inverted-U-shaped pattern of activation as a network effect of D1 receptor activation [14,15]. However, the previous model network is too computationally expensive to investigate analytically the

[1]Corresponding author. Tel: +81-3-3238-3331, fax: +81-3-3238-3321. *E-mail address: tanaka-s@sophia.ac.jp*

way in which DA modulation is characterized by the inverted-U-shape property. For that reason, the present study constructs a simpler PFC model network. Using this model, we analyze essential dynamics of DAergic modulation of the prefrontal cortical sustained activity.

2. Model

2.1 Neuron model and circuit architecture

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 the constraints imposed by this objective. It has been reported that DA application influences not only excitatory pyramidal cell, but also inhibitory interneurons in the PFC [6,8,10,11,16]. Therefore, our model consists of both pyramidal cell (x_p) and interneuron (x_n). The state equations of the model neurons are given as the following equations:

$$\frac{dx_p(t)}{dt} = -\frac{1}{\tau_p}x_p(t) + \tilde{W}_{pp}f(t,x_p) - W_{np}f(t,x_n) + I_{input}(t), \quad (1)$$

$$\frac{dx_n(t)}{dt} = -\frac{1}{\tilde{\tau}_n}x_n(t) + \tilde{W}_{pn}f(t,x_p), \quad (2)$$

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

$$f(t,x) = \frac{2x_{max}}{1+exp[-Gx(t-\Delta t)]} - x_{max}, \quad (3)$$

where Δt is the transmission and synaptic delay. The term $f(t,x_p)$ in Eq. (1) indicates a recurrent excitation, which enables the neurons to exhibit sustained activity.

/ Table 1 /

2.2 Effects of dopamine

Goldman-Rakic et al. [5,8] have suggested that the inverted-U-shaped modulation by DA is attributable to modulation of the efficacy of glutamatergic transmission. This suggestion is compatible with the finding that D1 receptor activation mediates the increase in the NMDA EPSCs in PFC neurons [11]. This study and our previous study support the suggestion that D1 activation induces an increase in the NMDA EPSCs. That activation is necessary for the inverted-U-shaped modulation of PFC neurons, whereas DAergic modulation of non-NMDA component seems to

contribute to the scenario of inactivation of PFC neurons in supranormal DA conditions [14]. Here we reduce the DAergic modulation of glutamatergic transmission to its simplest form, thereby allowing an analytical approach. That is, this DAergic modulation is expressed as the replacement of excitatory connection strength: $\tilde{W}_{pp} = r_1(Z)W_{pp}$; and $\tilde{W}_{pn} = r_1(Z)W_{pn}$; where $r_1(Z) = aZ + b$. In these equations, Z represents the DA level.

DA modulates not only excitatory, but also inhibitory, transmission [6,11,16]. Gorelova et al. [6] have suggested that DA increases the intrinsic excitability of inhibitory interneurons by suppressing a voltage-independent '*leak*' K^+ current. This suppression is reflected in the reduction of the whole cell slope conductance. Consequently, it can be inferred that DA lengthens the time constant of PFC neurons because the reduction of a leak conductance corresponds to the increase in the time constant of the present model neurons. This DAergic modulation is expressed as follows: $\tilde{\tau}_n = r_2(Z)\tau_n$, where $r_2(Z) = cZ + d$.

3. Dopaminergic modulation of delay-period activity

When DA levels are lower than the optimum (Z<1), increasing the DA level potentiates the delay-period activity of the model neurons (Figs. 1A and 1B). However, the delay-period activity is attenuated by supraoptimal increases of the DA level (Z>1) (Figs. 1A and 1B). These results indicate the existence of an inverted-U-shaped relationship between the DA level and the tonic activities of the model neurons. Using a phase plane analysis [7], we observed that the increase in the DA level shifts the intersection between the x_p nullcline and x_n nullcline, thereby providing the inverted-U shape's locus of the equilibrium point as the DA level increases. It is also noteworthy that the equilibrium point that forms the inverted-U shape is a stable node (Figs. 1C–1E) [7].

/ Fig. 1 /

4. Equilibrium points

The equilibrium points are obtained from

$$F(x_p, Z) \equiv \tau_p r_1(Z) W_{pp} f(x_p) - \tau_p W_{np} f[r_1(Z) r_2(Z) \tau_n W_{pn} f(x_p)] - x_p = 0. \quad (4)$$

Considering $F(x_p, Z)$ as a function of x_p ($F[x_p; Z]$), we obtain two equilibrium points at most, as shown in Fig. 2A. The increase in the DA level within the suboptimal range provides a rightward shift of the higher equilibrium point on the x_p-axis. Conversely, the increase in the DA level to one greater than the optimum point produces a leftward shift of

the equilibrium point. However, such an increase or decrease in the DA level does not influence the location of the lower equilibrium point (the origin). When $F(x_p, Z)$ is regarded as a function of Z ($F[Z; x_p]$), the equation $F[Z; x_p] = 0$ has solutions in both suboptimal and supraoptimal ranges, where $x_p = 0.5$ (Fig. 2B). The function is influenced linearly by the DA-induced increase in the recurrent connection (Fig. 2B, $p_1[Z; x_p]$). On the other hand, the DA-induced facilitation in the pyramidal-interneuron connection and the increase in the time constant of the interneuron cooperates to generate nonlinear dependency between $F(x_p, Z)$ and the DA level (Fig. 2B, $p_2[Z; x_p]$), which contains the sigmoidal function of Z^2. The model PFC network consequently generates equilibrium points both in the suboptimal and in the supraoptimal DA range (Fig. 2B).

As we put the set of solutions of $F[Z; x_p] = 0$ on the $x_p - Z$ plane, we obtain a bifurcation diagram as shown in Fig. 2C. The diagram indicates a supercritical pitchfork bifurcation [7]. For $Z < 0.195$ or $Z > 1.802$, there is a unique equilibrium point at the origin. Calculating the Jacobian matrix shows that the origin is a stable node. On the other hand, there are three equilibrium points for $0.195 < Z < 1.802$. In this situation, Jacobian calculations show that the origin is a saddle and the other two equilibria are stable nodes. Therefore, as the DA level crosses one bifurcation point $Z = 0.195$, the stable node at the origin bifurcates into a saddle and engenders two stable nodes. Conversely, as Z crosses another bifurcation point $Z = 1.802$, the saddle at the origin collides with the stable nodes and bifurcates into a stable node at the origin. This bifurcation pattern shows an inverted-U-shaped activation of the pyramidal neuron according to the increase in the DA level, which is compatible with the observation regarding Fig. 1A. Either the lack of DA effects on the recurrent excitation (Fig. 2C1), the pyramidal-interneuron connection (Fig. 2C2), or the time constant of the interneuron (Fig. 2C3) obstructs generation of the inverted-U-shaped bifurcation.

/ Fig. 2 /

5. Discussion

This study examined the influence of particular parameters on cortical neuronal activities. Results that are described herein provide theoretical evidence of the mechanisms for the inverted-U-shape property in addition to computational findings of our previous studies [12,14,15]. Analyzing the qualitative behavior of the model PFC network suggests the possibility that the symmetrical property of the inverted-U-shaped curve can be explained by a local bifurcation, as characterized by the pitchfork bifurcation in the resultant bifurcation diagram (Fig. 2C). 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. More specifically, the rising phase is attributable to the facilitated excitatory connections. On the other hand,

the falling phase is derived from the potentiated interneurons' activities according to the results shown in Figs. 2C1–2C3. Therefore, our present model explains the dynamics of the inverted-U shape of neuronal activity that is induced by DA. Nevertheless, it is important to understand DAergic modulation from a behavioral viewpoint. Regarding cognitive modulation by DA, Tanaka [12] has suggested that DA plays major roles in various operations of spatial working memory.

In conclusion, our results suggest that slight quantitative changes in parameters that are modulated by DA engender a large qualitative difference in the PFC circuitry. Thereby, they provide the inverted-U shape of activation of PFC neurons via D1 receptor activation. The present study has addressed qualitative aspects of the DA-induced inverted-U-shaped modulation, but further quantitative studies are required to reveal the entire property of DAergic modulation of neuronal activity in the PFC from both experimental and computational points of view.

Acknowledgements

This work was supported by a Grant-in-Aid for Japan Society for the Promotion of Science Fellows to K. Y. (#15·02170), and Grants-in-Aid for Scientific Research on Priority Areas to S. T. (#14017083, #15016096, and #15500218) from the Ministry of Education, Science, and Technology, Japan.

Author biosketch

Koki Yamashita

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

Shoji Tanaka

received his B.E., M.E., and Ph.D. from Nagoya University, Japan. He is a Professor of 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) The pyramidal neuron shows persistent activity in response to the phasic input ($t = 1$ s). The amplitude of the persistent activity follows an inverted-U-shaped curve according to the increase in the DA level. (B) Similar activity profiles are found for the interneuron. (C) Result of a phase plane analysis in the case of a suboptimal DA level ($Z = 0.25$). The curve (a) is a trajectory that corresponds to that shown in panels A and B. There is a stable node characterized as an intersection of nullclines (white box). (D) Result of the phase plane analysis for the optimal DA level ($Z = 1.0$). (E) Result of the phase plane analysis for a supraoptimal DA level ($Z = 1.75$).

Fig. 2. (A) Superimposition of a function obtained by solving for x_p in the simultaneous equations $\dot{x}_p = 0$ and $\dot{x}_n = 0$, which represent nullclines, in the case of $Z = 0.5$ (a), $Z = 1.0$ (b), and $Z = 1.5$ (c). The function is given as $F(x_p, Z) = p_1(x_p, Z) + p_2(x_p, Z) + p_3(x_p, Z)$, where $p_1(x_p, Z) = \tau_p r_1(Z) W_{pp} f(x_p)$; $p_2(x_p, Z) = -\tau_p W_{np} f[r_1(Z) r_2(Z) \tau_n W_{pn} f(x_p)]$; and $p_3(x_p, Z) = -x_p$ (see also Eq. (4)). The x_p-intercepts correspond to the equilibrium points. The location of the higher equilibrium point depends on the DA level. (B) Graphical representation of the function $F(x_p, Z)$ as a function of Z ($F[Z, x_p]$). x_p is fixed at 0.5. Note that $F[Z, x_p]$ has Z-intercepts at both suboptimal and supraoptimal levels. (C) A bifurcation diagram indicating a pitchfork bifurcation. The bifurcation pattern is consistent with the observation in Fig. 1A. The model neurons do not show the inverted-U-shaped activation when DA has no effects on W_{pp} (C1), W_{pn} (C2), or τ_n (C3). The optimal DA level is fixed at $Z = 1$.

Table 1. Model parameters.

Symbol	Description	Defined value
τ_p	Time constant of the excitatory neuron	20.00 [ms]
τ_n	Time constant of the inhibitory neuron	6.80 [ms]
Δt	Transmission and synaptic delay	5.00 [ms]
W_{pp}	Connectivity strength from x_p to x_p	1.11 [a.u.]
W_{pn}	Connectivity strength from x_p to x_n	3.84 [a.u.]
W_{np}	Connectivity strength from x_n to x_p	0.27 [a.u.]
x_{MAX}	Maximum value of the activation function	10.00 [a.u.]
G	Steepness in the output function of the PFC neurons	0.3 [a.u.]
a	Coefficient in the equation of DA effect on W_{pp} (or W_{pn})	0.12 [a.u.]
b	Coefficient in the equation of DA effect on W_{pp} (or W_{pn})	0.68 [a.u.]
c	Coefficient in the equation of DA effect on τ_n	0.24 [a.u.]
d	Coefficient in the equation of DA effect on τ_n	0.26 [a.u.]

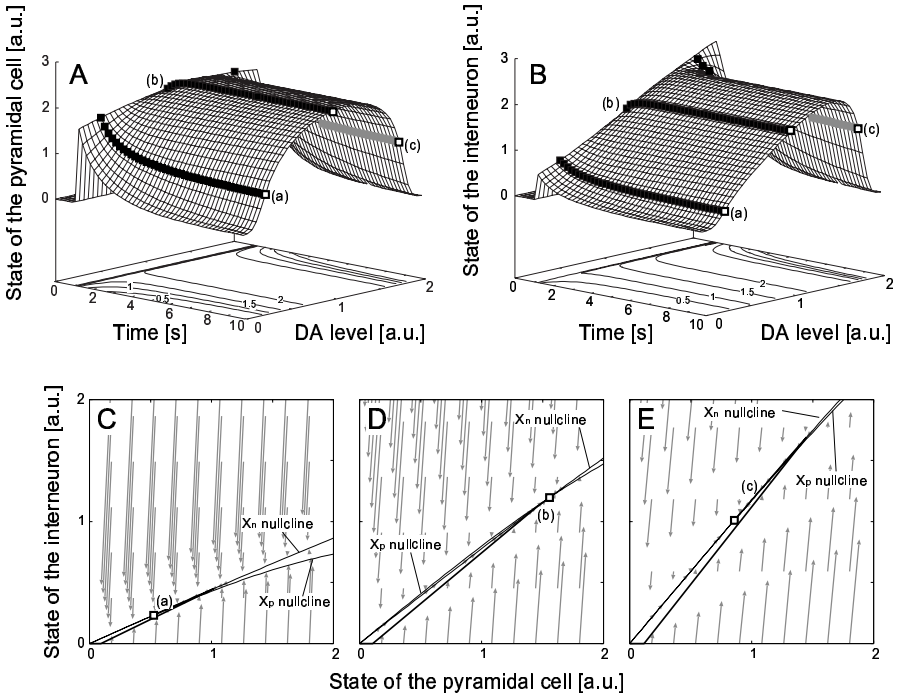

Figure 1. Yamashita and Tanaka

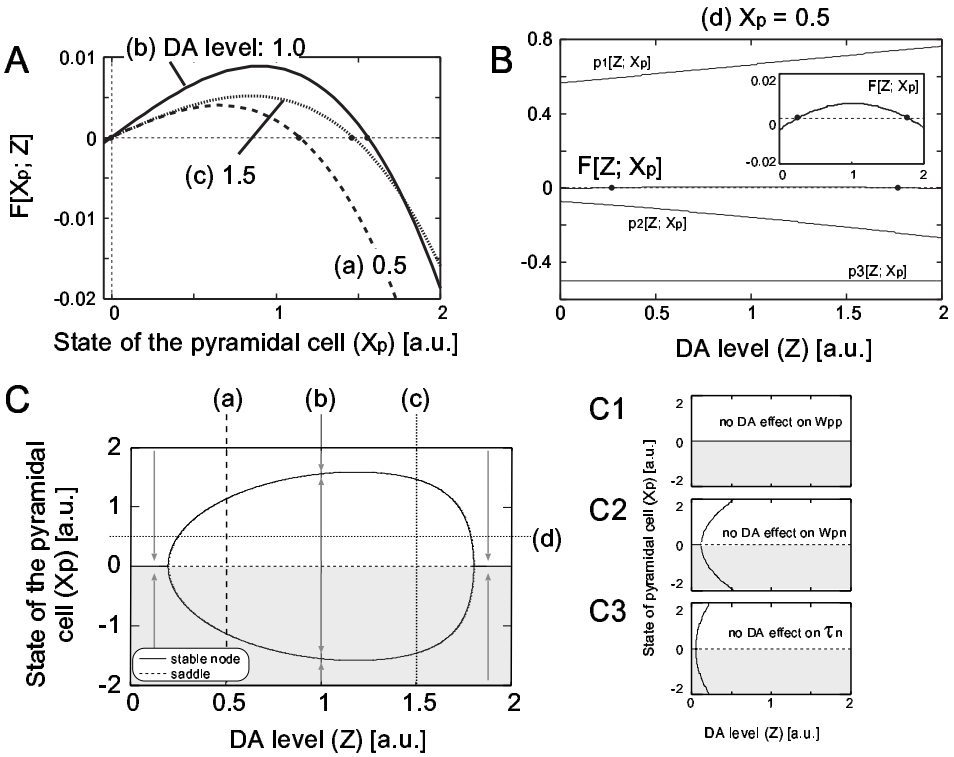

Figure 2. Yamashita and Tanaka