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State-dependent alteration of dopamine and glutamate transmission in the prefrontal cortex by psychostimulants

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Abstract

In spite of accumulating evidence for dopaminergic contribution to cognitive functions, the mechanism how cortical dopamine (DA) level is controlled is still obscure. To investigate the mechanisms of intracortical DA level control, this article investigates the dynamics of the prefronto-mesoprefrontal system under the influence of DA. The fundamental assumption of this model is closed-loop circuitry between the prefrontal cortex (PFC) and midbrain DA nuclei. This study suggests that the system forms a regulator with peculiar characteristics. These characteristics would be responsible for differential responses to psychostimulants and may be critically relevant to negative symptoms and cognitive deficits in schizophrenia.

Keywords: Persistent activity; Pharmacology; Prefrontal cortex; Schizophrenia; Working memory

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1. Introduction

Dopamine (DA) has been suggested to play critical roles in cognitive functions [3]. In spite of accumulating evidence for dopaminergic contribution to cognitive functions, however, the mechanism how cortical DA level is controlled is still obscure. Recently, Tanaka [16] showed computationally that slight changing in DA level in the prefrontal cortex (PFC) can make the cortical circuit dynamics flexible enough to perform several different operations of spatial working memory. This is accomplished by changing the ratio of the NMDA conductance to the non-NMDA conductance of PFC neurons due to the activation of DA D1 receptors. The regulation of DA level in the PFC would thus be critical to the control of cognitive functions.

During delay periods in working memory tasks, no external input is given. Then the brain processes *internally* the relevant cognitive information. In this 'internal mode', intracortical DA level would be regulated by the cortical control of the activity of the midbrain DA neurons. Neuroanatomical studies suggest that the PFC and the midbrain DA nuclei form a closed-loop system [12,17]. In accordance with this notion, this laboratory has recently developed a closed-loop circuit model of the prefronto-mesoprefrontal system [18]. Using this model with minor modifications, this article investigates how extracellular DA level in the PFC is regulated in the 'internal mode'. The computer simulation shows that this system forms a regulator for the regulation of extracellular DA level in the PFC. The analysis, however, suggests that the dynamics of this regulator is somewhat peculiar. It has a stable hyperdopaminergic state but an unstable hypodopaminergic state. With this characteristics, the system would respond to externally given drugs in a complex manner. It is, therefore, interesting to see how psychostimulants (such as amphetamine, methamphetamine, cocaine, and methylphenidate) affect the synaptic transmission throughout the system.

2. Model

Circuitry of the model

In rats, the PFC projects to the ventral tegmental area (VTA) dopaminergic neurons [13]. The dopaminergic neurons in the VTA, in turn, send axons to the PFC. The PFC-VTA, therefore, forms a closed-loop system. In monkeys as well, the PFC and the midbrain DA nuclei form a closed-loop system, but the anatomical connectivity with the dorsolateral PFC has not been

well-established. The tracing studies by Williams and Goldman-Rakic [17] revealed that the DA neurons innervating the macaque PFC as a whole distribute across all three of the mesencephalic DA cell groups, A10, A9, and A8 (i.e., the VTA, substantia nigra, and the retrorubral area, respectively). Our model consists of the PFC and the midbrain DA nuclei. The latter is simplified to be a unit as a whole without discriminating a nucleus from the others.

Midbrain DA unit

The activity of the DA unit, u, depends on the feedback input from the PFC deep layer neurons, I_{PFC}:

$$\tau \frac{du}{dt} = I_{PFC} - u \tag{1}$$

where τ = 10 ms is the time constant of the DA unit. The DA level in the PFC is then given by

$$\tau_{DA} \frac{dy}{dt} = f_{DA}[u(t)] - y, \qquad f_{DA}(u) = \frac{1}{1 + \exp\left(-\frac{u - u_0}{0.05}\right)} \tag{2}$$

where τ_{DA} = 100 ms is the time constant of the DA release.

The action of psychostimulants is mimicked by changing the value of the parameter, u_0. Decreasing in u_0 causes an increase in DA level in the PFC. This is not a comprehensive description but an essential aspect of the actions of psychostimulants because they enhance extracellular DA level by facilitating the release and inhibiting reuptake [4]. In the following, therefore, we call the drug that causes this action just ‘the psychostimulant’.

The D1 receptors are activated according to the following functional relationship:

$$z_{D1}(t) = \gamma_{D1} f_R[y(t)], \qquad f_R(y) = \frac{1}{1 + \exp\left(-\frac{y - 0.4}{0.1}\right)} \tag{3}$$

where γ_{D1} determines the strength of the response of the D1 receptors (γ_{D1} > 1 for up-regulation).

Prefrontal cortex

The PFC of this model contains 2160 pyramidal cells and 720 inhibitory interneurons. The dynamics of these neurons are described by the leaky integrate-and-fire model. The details and

the circuitry of this model of the PFC are identical to [16] and the fundamental circuit properties for spatial working memory processing have been discussed in [14-15]. These are not redescribed here, but see Fig. 1A. Dopaminergic modulation is also described in the same way with [16]. But, unlike the previous model [16], the DA level in the PFC in this model is regulated autonomously because of the closed-loop circuitry. The effects of the alteration in the DA level on the conductance electrical properties are assumed here to be given by

$$g_s[V,t;z_{DA}(t)] = g_s(V,t;0)(1+\alpha_s \cdot z_{D1}), \quad s = \text{AMPA, NMDA, K(Ca), Leak} \tag{4}$$

$$E_{Nap}[z_{DA}(t)] = E_{Nap}[0] + \beta_E \cdot z_{DA}(t) \tag{5}$$

where V is the membrane potential, $z_{DA}(t)$ is the D1 receptor activity, E_{Nap} is the reversal potential of the persistent sodium channels ($E_{Nap}[0]$ = 50 mV), α_s = -0.2 (for g_{AMPA}), +0.5 (for g_{NMDA}), -0.4 (for $g_{K(Ca)}$ and g_{leak}), and $\beta_E = -1.0$. The modulation of the leak conductance, described above, is assumed only for the interneurons [6].

/ Fig. 1 /

3. Results

Fundamental dynamics of the closed-loop regulator

When the DA level is low, the cortical circuit is not driven enough due to the insufficient glutamate transmission [5,9]. An increase in the DA level enhances the activity of the cortical circuit in this regime. When the DA level is too high, however, the network activity of the PFC is suppressed by the excessive activation of inhibitory interneurons in the cortex. This reduces the glutamatergic input to the DA neurons, then reduces the intracortical DA release. The DA level in the cortex is thus regulated at the optimum level in normal conditions. The dynamics is rather stable in the hyperdopaminergic state. When the DA level is slightly decreased from the optimum, on the contrary, insufficient feedback from the PFC to the midbrain decreases the DA release further, resulting in a hypodopaminergic state.

Influences of 'the psychostimulants'

The D1 receptors were either up- or down-regulated beforehand in this series of simulation (Fig. 1B). The simulation started at t = 0 ms. Then the psychostimulant was applied (whose action is mimicked by changing the value of u_0 from 0.2 to 0.1) at t = 1000 ms. After t = 0 ms, the neurons in both the PFC and midbrain DA nuclei raise their activities gradually to reach a steady state (t > 500 ms) (Figs. 2 and 3). This simulation shows that up-regulation of D1 receptors generally decreases DA release in the PFC. Then the PFC tends to become hypodopaminergic. In contrast, down-regulation of D1 receptors generally increases DA release in the PFC, which makes the PFC hyperdopaminergic. Local application of the psychostimulant into the PFC changes the activities after t = 1000 ms. When D1 receptors were down-regulated (Fig. 2), the system was in a low-D1 receptor activation and high-DA release state. DA release increased greatly after the application of the psychostimulant at t = 1000 ms. The firing rates of the pyramidal cells in the PFC, however, did not change significantly. As a result, the psychostimulant increased DA release but not glutamte release. When D1 receptors were up-regulated (Fig. 3), the system was in a high-D1 receptor activation and low-DA release state. DA release did not change even after the application of the psychostimulant at t = 1000 ms in this case. Instead, the glutamate release decreases significantly due to the decrease in the firing rates of the pyramidal cells in the PFC.

/ Fig. 2 / / Fig. 3 /

4. Discussion and Conclusion

Whether D1 receptors are down-regulated or up-regulated in drug-free or drug-naive schizophrenic brains is in debate. The D1 receptor availability has been measured using SCH13390 [7,10] and NNC112 [1]. The results are surprisingly different: the D1 receptor availability was increased [1], decreased [10], or unchanged [7]. This simulation suggests that the change in the release of DA and glutamate depends on the state of the system (Table). The mechanisms are explained as follows: When D1 receptors are down-regulated, DA release in the PFC increases by increasing the glutamate transmission in the PFC. But the increase in DA level in the PFC enhances the intracortical inhibition. Then the glutamate release is suppressed by inhibiting the pyramidal cells. Therefore, the activity of the PFC neurons slightly decreases and the net glutamate transmission does not increase. The up-regulated state is already hyper-activity

of the D1 receptors, in which intracortical inhibition is strong. Further increase in glutamate transmission by increasing DA release yields very strong intracortical inhibition. The activity of the PFC is highly suppressed and net glutamate transmission decreases. This causes a decrease in DA release, which cancels the increasing action of the psychostimulant. Consequently, the DA release does not increase. It is remarkable that the application of the psychostimulant decreases the glutamate level when the D1 receptors are up-regulated. The interaction between the DA system and the glutamate system is to be studied from a viewpoint of etiology of schizophrenia [2,8,11].

In conclusion, this study suggests that the PFC and the midbrain DA nuclei forms a novel regulator with peculiar characteristics. This regulator would work in the 'internal mode' in which no external input is given. These characteristics may be critically relevant to negative symptoms and cognitive deficits in schizophrenia.

Table

	D1 receptors	
	Down-regulated	Up-regulated
DA release	High	Low
D1 receptor activation	Low	High
PFC neuron activity	Rather high	Rather low
Effects of psychostimulants	DA release increased	DA release unchanged
	Glutamate release unchanged	Glutamate release decreased

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Author biosketch

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Figure legends

Fig. 1. A: The fundamental architecture of this model is the closed-loop circuitry between the PFC and the midbrain DA nuclei. The ocrtex has three layers. Only the pyramidal cells in the deep layer send axons to the midbrain dopaminergic neurons. The dopaminergic neurons innervate the pyramidal cells and the interneurons in the PFC. The activation of D1 receptors by DA affects the excitatory synaptic transmission through the AMPA and the NMDA receptors, persistent sodium channels, calcium-dependent potassium channels, and the leak conductance of the interneurons. **B:** The activation curves of the D1 receptors in up-regulated (a: $\gamma_{D1} = 2.0$) and normal or down-regulated (b: $\gamma_{D1} = 1.0$) states.

Fig. 2. The dynamics of the model prefronto-mesoprefrontal system with down-regulated D1 receptors in the PFC. The psychostimulant was applied at t = 1000 ms. **A:** DA neuron activity (dashed line), DA release (solid line), and D1 receptor activation (dot-dashed line). **B:** The population average firing rate of the pyramidal cells in the superficial layer of the PFC (solid line) and glutamate release from the pyramidal cells in the deep layer of the PFC (dashed line). **C:** The population average firing rate of the pyramidal cells in the superficial layer of the PFC versus the DA release in the PFC. **D:** The DA release in the PFC versus the glutamate release from the pyramidal cells in the deep layer of the PFC.

Fig. 3. The dynamics of the model prefronto-mesoprefrontal system with up-regulated D1 receptors in the PFC. The psychostimulant was applied at t = 1000 ms. **A, B, C, D:** See the legend of Fig. 2.

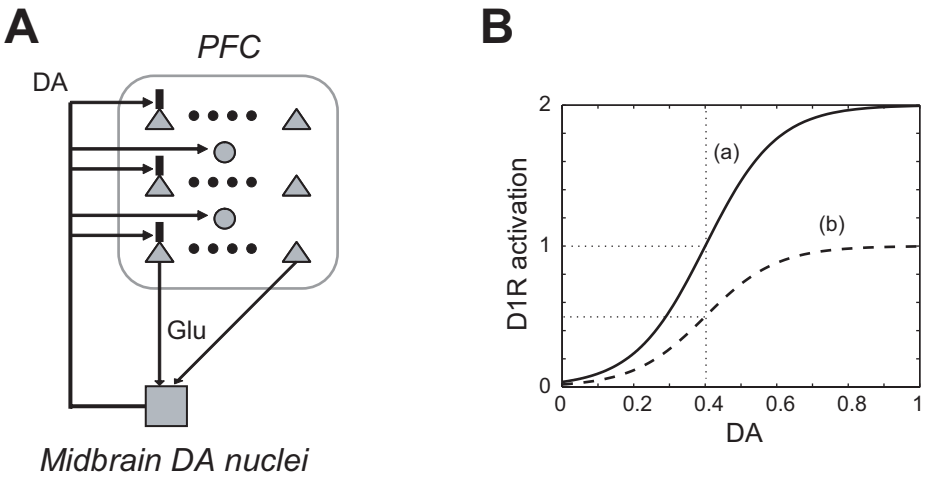
A
PFC
DA
Glu
Midbrain DA nuclei
B
D1R activation
DA
(a)
(b)
0
1
2
0
0.2
0.4
0.6
0.8
1

Fig. 1. Tanaka

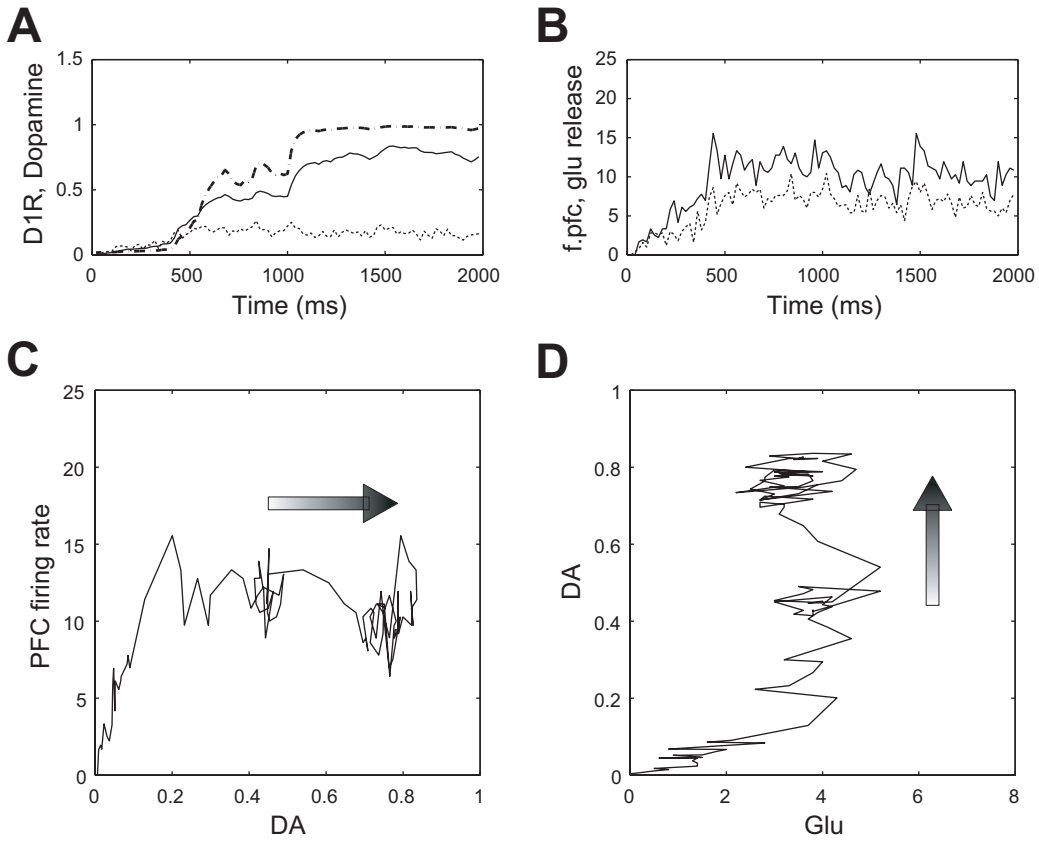
A
D1R, Dopamine
1.5
1
0.5
0
0
500
1000
1500
2000
Time (ms)
B
f.pfc, glu release
25
20
15
10
5
0
0
500
1000
1500
2000
Time (ms)
C
PFC firing rate
25
20
15
10
5
0
0
0.2
0.4
0.6
0.8
1
DA
D
DA
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
Glu

Fig. 2. Tanaka

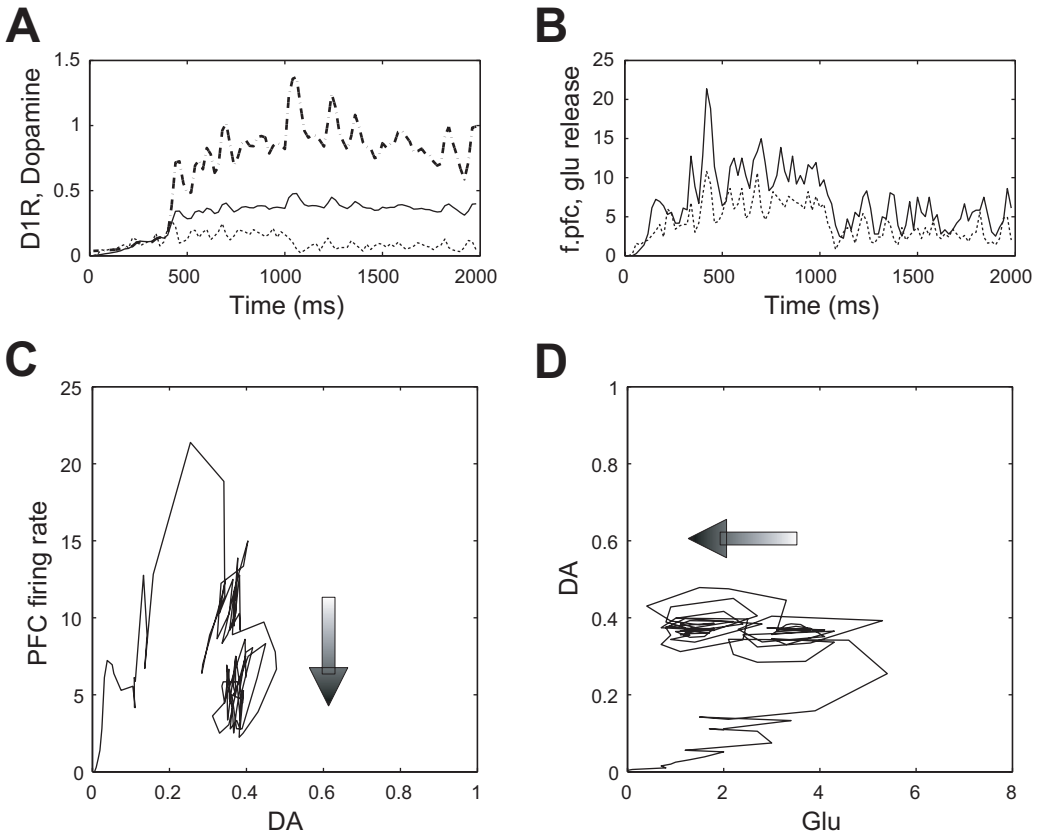
A
D1R, Dopamine
Time (ms)
B
f.pfc, glu release
Time (ms)
C
PFC firing rate
DA
D
DA
Glu

Fig. 3. Tanaka