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G. 知的所有権の取得状況

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2) 実用新案登録

なし

3) その他

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研究成果の刊行に関する一覧表

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Paper

The hyperpolarization-activated current regulates synchronization of gap-junction coupled dopaminergic neurons in the midbrain

—— A combined approach between computational modeling and electrophysiological recording ——

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To examine the functional role of hyperpolarization-activated and cyclic nucleotide-gated (HCN) current observed in mesencephalic dopaminergic neurons, we constructed a conductance-based model that can mimic the electrical properties obtained in electrophysiological recordings of rat brain slices. In the model, blocking the HCN current resulted in a reduction of spontaneous firing rate and a change in the properties of autonomous pacemaking. In addition, reduced one-dimensional phase equations and their coupled oscillators were analyzed. The analysis indicated that HCN channels can regulate the extent of synchronization of coupled dopaminergic neurons through gap-junction connections. Thus, the HCN current can effectively shape the autonomous and cooperative firing of dopaminergic neurons in the midbrain.

Keywords : conductance-based model, coupled oscillators, electrophysiological recording, phase equation, stability analysis

1. Introduction

Mesencephalic dopaminergic (DA) neurons play a key role in the functions of the basal ganglia including reward-based learning [1], cognition [2], and motor control [3]. Although recent studies have provided significant insights into the properties of many ion channels expressed in DA neurons [4], little attention has been paid to hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels and their roles in neural information processing. Among vertebrate voltage-gated ion channels, HCN channels have two unique properties: (i) they have a reverse voltage dependence that leads to activation upon hyperpolarization; and (ii) voltage-dependent opening of these channels is directly regulated by the binding of cyclic adenosine monophosphate (cAMP) [5]. However, a direct link between HCN channels and superthreshold membrane-voltage phenomena such as firing rate modulation and the synchronization of action potentials among DA cells has not been systematically investigated.

In this study, to understand the functional role of HCN channels systematically, we first constructed a conductance-based Hodgkin–Huxley type DA cell model on the basis of reported results in the literature and data recoded from DA cells in rat midbrain slices. Second, to gain some insight into synchronized phenomena in gap junction-coupled DA neurons, a weak coupled-oscillator phase-equation model of two identical DA neuron pairs was derived after numerically computing the phase resetting curves of regular firing using the conductance-based model. Third, to examine synchronized phenomena among DA cells, a stability analysis of synchronization between coupled oscillators was applied to the model. The results indicated that HCN channels can regulate not only the frequency of firing and subthreshold oscillations in membrane voltage but also the extent of synchronization and desynchronization among DA cells. Hence, the study presented here shed light on to a new functional role in DA cells of the midbrain, using computational and electrophysiological approaches.

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2. Materials and methods

2.1 Electrophysiological recording

At a temperature of 34°C, we recorded membrane voltage from DA neurons in slices of rat midbrain from animals aged 14–16 days. For details of the preparation, solutions, and whole-cell recording technique, see Ref. [6]. All procedures in this study were approved by Osaka University and complied with the NIH Guidelines for Animal Use.

2.2 A conductance-based model

First, the somatic and single-compartment model was represented by the following equations according to the Hodgkin–Huxley type conductance-based scheme [7]. The model includes ion channel currents that are known to exist in the somata of DA cells. The model is based on those reported by Amini et al. [8] and Kuznetsov et al. [9]. However, some terms in the current balance equation such as ATP-pump and Na^+/Ca^{2+}-exchanger mechanisms were omitted for simplicity. Instead, several ion channel current terms were added on the basis of some recent electrophysiological studies described below. In addition, some parameters in the models were modified from data in the recent literature and from the recording carried out in the present study. The current balance equation in a soma is described by

$$C_m \frac{dV}{dt} = -(I_{Na} + I_K + I_A + I_M + I_h + I_{Ca} + I_{SK} + I_L) + I_{app} \quad \cdots\cdots (1)$$

where C_m is the somatic membrane capacitance and V is the somatic membrane potential. The above model includes the transient Na^+ current (I_{Na}), delayed rectifier K^+ current (I_K), A-type K^+ current (I_A), muscarinic-sensitive K^+ current (I_M), hyper-polarization activation current (I_h), leakage current (I_L), Ca^{2+} current (I_{Ca}), Ca^{2+}-activated K^+ or SK current (I_{SK}), and an externally applied current (I_{app}). Furthermore, the Ca^{2+} current has the following four subtypes:

$$I_{Ca} = I_{CaL} + I_{CaN} + I_{CaP} + I_{CaT} \quad \cdots\cdots (2)$$

where I_{CaL}, I_{CaN}, I_{CaP} and I_{CaT} represent L-type, N-type, P-type, and T-type Ca^{2+} currents, respectively, and they are different in their voltage dependency.

Excluding I_{SK}, for an ion channel type j, the current description (I_j) can be written by

$$I_j = g_j m_j^{a_j} n_j^{b_j} (V - E_j) \quad \cdots\cdots (3)$$

where g_j, m_j, n_j and E_j are a maximum conductance, the Hodgkin–Huxley type activation and inactivation gating variables, and the reversal potential of the ion, respectively. Here, a_i and b_j are some non-negative integers. The gating variables are solutions of the following first-order differential equation described by

$$\frac{dz}{dt} = \frac{z_\infty(V) - z}{\tau_z(V)} \quad \cdots\cdots (4)$$

where z is one of the gate variables (i.e., m_j or n_j). In Eq. (4), $z_\infty(V)$ and $\tau_z(V)$ are the voltage-dependent steady-state value and time-constant of the gating variable z at membrane voltage V, respectively.

For simplicity, we characterized the steady-state variable by a sigmoid or Boltzmann-type relationship, and the time constant (in ms) by a Gaussian relationship; they are described in the Appendix. Individual ionic membrane currents were characterized by their fit to published voltage-clamp experimental data, which are available in the literature, or to unpublished data recorded in our experiment. In addition, we used some ion-channel kinetics models from published DA neuron models [8,9]. However, data fitting obtained from voltage-clamp recording is not the only criteria for formulating ionic current descriptions. These descriptions may have to be modified to fit whole-cell membrane potential data in our experiments. These adjustments are justified considering that the voltage-clamp experiments were performed on a particular DA cell of a particular mouse, for example, and there is considerable variation in the waveform of the ionic current response from cell to cell. Therefore, we adjusted the model parameters (specifically, several maximum conductance values of ion channels) to fit the data in our experiment.

Calcium dynamics of the soma is described as

$$\frac{d[Ca^{2+}]_i}{dt} = \frac{2\beta}{\tau z_{Ca} F}\left(-I_{Ca} - z_{Ca} F P_{Ca} [Ca^{2+}]_i\right) \quad \cdots\cdots (5)$$

where $[Ca^{2+}]_i$ is the intracellular Ca^{2+} concentration of the soma and I_{Ca} is the sum of all the calcium currents. Intracellular Ca^{2+} was removed from the cell by an unsaturable pump with maximum rate density P_{Ca}, and the pump was treated as nonelectrogenic. β is the ratio of free to total calcium, τ is the time constant of $[Ca^{2+}]_i$ changes, z_{Ca} is the valence of calcium, and F is Faraday's constant.

2.3 Model parameter selection

In the following section, we describe the kinetics of the ion channels in the above model and parameters in detail. The voltage-dependent activation and/or inactivation curves and time constant used in the model are given in Appendix.

Transient Na^+ current (I_{Na}) and delayed rectifier K^+ current (I_K). The I_{Na} and I_K gating kinetics are the same as those written in Kuznetsov et al. [9]. For The I_{Na} and I_K gating kinetics in the model, the order pairs (a_j, b_j) of the activation and inactivation variables in Eq. (3) are (3, 1) and (4, 0), respectively. However, the voltage-dependency functions of the gate variables and time constants are mimicked by using a sigmoid relationship and by a Gaussian relationship, respectively, as stated previously. The maximum conductance values g_{Na}=120 mS/cm^2 and g_K=0.2 mS/cm^2 and the reversal potential values E_{Na}=55 mV and E_K=−90 mV were used.

Transient outward A-type potassium current (I_A). The 4-aminopyridine (4-AP)–sensitive, or A-type potassium current (I_A), has been observed in DA neurons [10,11]. The A-type potassium current in DA neurons can contribute to spontaneous firing and plays a role in the regulation of action-potential frequency by slowing the recovery of the membrane potential to baseline levels [10,12]. The steady state activation and inactivation characteristics of I_A were determined by fitting published voltage-clamp data [11]. The order pair of the activation and inactivation variables is (3, 1). The maximum conductance value g_A=0.5 mS/cm^2 was used.

Muscarinic-sensitive K^+ current (I_M). The muscarinic-sensitive K^+ current or M-current (I_M) is a voltage-dependent slow delayed rectifier K^+ current and is activated at the subthreshold range of the membrane potential. This current is also known to be Tetraethylammonium chloride (TEA) sensitive and contributes to the regulation of action potential generation and excitability [13]. I_M has been shown to be present in midbrain DA neurons with intracellular voltage-clamp recording in brain slices [14,15]. The order pair of the activation and inactivation variables is (1, 0). The maximum conductance value g_M=15.0 μS/cm^2 was used.

Hyperpolarization-activated cation current (I_h). Doperminergic neurons have a hyperpolarization-activated cation current (I_h) [16,17]. The voltage dependency of steady state activation of I_h was determined by fitting our unpublished data, which was recorded from rat midbrain slices in our voltage-clamp recording experiments. In the I_h model, the voltage dependency of conductance and time constant are similar to the model in Amini et al. [8], although the parameters were different on the basis of the data [16,17] (see also Appendix A). The order pair of the activation and inactivation variables is (1, 0). The reversal potential E_h=−39.0 mV was used. In this analysis, the maximum conductance value g_h=0.135 mS/cm^2 was used as the default value; however, the value was changed in some analyses described in Results to examine the effects of HCN channel expression.

Calcium currents (I_{Ca}). As described previously, the model includes L-, N-, P-, and T-type voltage-dependent calcium currents. For L-, N-, and P-type calcium currents, the voltage dependency of a steady-state of the gate variables and the time constant functions was obtained after fitting the parameters to conductance–voltage (g–V) relationships reported in Durante et al. [18]. Similarly, for the low-threshold T-type Ca^{2+} current, the voltage dependency of a steady state of the gate variables and time constant functions was obtained from results in Kang and Kitai [19]. Our parameters are modifications of those used by Amini et al. [8] because of our g-V function selection. The reversal potential for the calcium currents has been set to a constant 100 mV as used in Kuznetsov et al. [9] (i.e., E_{Ca}=−100 mV). For the L-, N-, P-, and T-types of calcium current, the order pairs of the activation and inactivation variables were (1, 0) (1, 1), (1, 1), and (1, 1), respectively, and the maximum conductance values g_{CaL}=0.15, g_{CaN}=0.0375, g_{CaP}=0.0375, and g_{CaT}=0.02 in mS/cm^2 were used.

Calcium-activated small-conductance potassium current (I_{SK}). DA neurons are known to contain at least two types of calcium-activated potassium currents [20]. The apamin-sensitive, small-conductance (SK) Ca^{2+}-activated K^+ current or slow afterhyperpolarization (AHP) current is included in the model. The SK channel conductance (g_{SK}) was represented as

$$g_{SK}([Ca]_i) = g_{SK}\frac{[Ca]_i^4}{[Ca]_i^4 + K_m^4} \quad \cdots\cdots (6)$$

The conductance model was the same as that reported in Kohler et al. [21]. The conductance depends on the forth power of intracellular calcium concentration ($[Ca^{2+}]_i$) to best represent the known characteristic of the SK channel [21]. The calcium half-activation concentration value K_m has been set to 250 nM [9,22]. The other Ca^{2+}-dependent K^+ current is the big-conductance (BK) or maxi-type channel, which is known to be apamin-insensitive and blocked by TEA. Although the BK channel current is associated with the modulation of excitability because of its role in producing a fast AHP [20], it is less essential for slow underlying oscillations and super-threshold spiking behaviors than the SK channel current. In the present study, therefore, we have excluded the BK current from our model. The maximum conductance value g_{SK}=50.0 μS/cm^2 was used.

Leak current (I_L). The present model includes a nonspecific linear background current without gate variables. This current is the main component of the input resistance of the model. In current-clamp recording, we measured the input resistance of DA neurons using 600-ms hyperpolarizing current pulses with amplitude −10 to −20 pA by holding the potential at −60 mV, and the average input resistance of DA cells was 630 MΩ. The result showed that the conductance value g_L was 12.0 μS/cm^2 by assuming the soma was a cylinder whose diameter and length were 14 μm and 30 μm, respectively. The reversal potential value was set to E_K=−90 mV as used in Kuznetsov et al. [9]. In the current balance Eq. (1), the somatic membrane capacitance C_m=1 μF/cm^2 was used.

Calcium dynamics. The parameters in Eq. (5) were the same those used in the Kuznetsov et al. model [9]: β=0.050, τ=4.0 ms, z_{Ca}=2.0, and P_{Ca}=2,500 μm/s.

Computer simulations were performed using XPPAUT [23] with the stiff method and Matlab Ver. 7.5 (Mathworks, Natick, Massachusetts, U.S.A.) with a nonstiff solver (a build-in function of the Runge–Kutta 4th/5th-order method, ode45). A time step of 50 μs was used in all computer simulations.

2.4 Phase-resetting curves.

DA neurons *in vivo* and *in vitro* show spontaneous periodic activity at the rate of 0.5–4.0 Hz. Generally speaking, the mechanisms underlying such periodic activity of a system can be complex with many hidden variables, and all dynamical variables in such a system thus cannot be directly observed. However, useful information about the dynamics of the system can be gained by studying phase-resetting curves (PRCs) [24], which describe the phase shift of the oscillation in response to a perturbing pulse of variable amplitude at each phase of the oscillation. A perturbation is weak if its effect on the amplitude and intrinsic period is negligible. This approximation is often valid in firing neurons, where a small current pulse delays or advances the next spike (action potential) without changing its shape or average firing frequency. However, to construct precise PRCs, we need to apply short pulse-like stimulation to neurons repetitively at many phase points during one cycle for a long time [25]. As the experimental method usually damages neurons, it is hard to obtain true PRCs in electrophysiological experiments. In contrast, if we have a complete description of periodic oscillations, and if it is written by a set of ordinary differential equations, the PRC is directly calculated using the adjoint method proposed by Williams and Bowtell [26]. Because such a complete description of dynamical variables is impossible in real neurons, therefore, PRCs obtained from the present model can give a reasonable counterpart in DA neurons.

2.5 A coupled oscillator model and its stability analysis

To gain some insight into synchronized phenomena in gap junction-coupled DA neurons, a weakly coupled one-dimensional phase-equation model of two identical DA neurons was constructed. If the neural oscillators have robust limit cycles, the full equations reduce to ones whose interactions are through the differences in the phases of their periodic cycles. Much has been written about such coupled phase-oscillators (see Koppel and Ermentrout [27] and Hoppensteadt and Izhikevich [28] for review). Here, we assume that two identical neural oscillators are reduced to two phase equations as following: for i, j=1 or 2,

$$d\theta_i / dt = \omega_0 + \varepsilon H(\theta_i - \theta_j) \quad (i \neq j), \quad \cdots\cdots (7)$$

where θ_1 and θ_2 are phases in the two limit cycles, ω_0 is the frequency of the uncoupled oscillators, and ε is a small parameter. The interaction function H is T-periodic in the argument and it can be explicitly computed from the original set of Eqs. (1)–(5). Let $\phi = \theta_2 - \theta_1$. Then,

$$H(\phi) = g/T \cdot \int_0^T P(t)[V_0(t+\phi) - V_0(t)]dt, \quad \cdots\cdots (8)$$

where g is the conductance of gap-junction coupling between the cells, T is the period of the original limit cycles, $P(t)$ is the PRC, and V_0 (t) is the membrane voltage of the original limit cycles. In Eq. (8), the conductance g only contributes the function H as a scale factor. In the following, therefore, we consider g=1.0 μS/cm^2. The function of $P(t)$ is the normalized T-periodic solution to the adjoint equation of the present model and numerically computed by the method proposed by Williams and Bowtell [26]. One of the goals of the analysis in this study is to determine the stability of the synchronous, phase-locked, and antiphase-locked solutions, and how it depends on the parameters (specifically, the HCN channel conductance) in the model. It is known that a phase-locked solution ϕ_l is stable if and only if $dH(\phi_l)/d\phi > 0$ [29]. In particular, the synchronous phase-locked solution is stable if and only if $dH(0)/d\phi > 0$. In many neural systems, there exists the possibility of delays at many levels. In particular, there are delays due to axonal and dendritic propagation, and delays encountered when gap-junction coupling was far from the source of the oscillation or the spike initiation zone and must be communicated through dendrites. In the simplest case, a delay effect is described by a phase transition of the interaction function with delay τ: