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Bifurcation Analysis of Nociceptive Neurons

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Abstract: As known, modification of specified slow sodium channels (Na1,8) in the membrane of nociceptive neurons is the basis of the pain perception by the human brain. The work is devoted to determination of parameters of the channels most sensitive to perceiving the painful signals. Using the bifurcation analysis of the model system describing the impulse activity of the membrane of mammalian nociceptive neuron we partition the parameter planes into the regions corresponding to stable and unstable periodic solutions. The left boundary of the region corresponds to subcritical Hopf bifurcation and emergence of the rough excitation in the form of large amplitude oscillations. The right boundary relates to supercritical Hopf bifurcation and appearance of the smooth excitation in the form of small large amplitude. Integrating inside the region of stable solutions we obtain the relationship between the parameter and frequency values. Bifurcation parameters such as the effective charge transfer of the activation gating system of the sodium channels and the maximal conductance of the channels play the main role in increasing the frequency and, hence, in transformation of the unpainful stimulus into the painful one. The results explain ionic mechanisms of action of analgesic drugs having high selectivity to $Na_V1,8$ channels independently of the primary target of action.
Keywords Hopf bifurcation, Membrane model, Sodium channels, Nociceptive neuron.

1. Introduction

It is known that in response to injury of nervous system nociceptive neurons can become hyper-excitable and generate spontaneous impulse activity of unusual frequency [1]. Perception of painful feeling is connected with activation of peripheral nociceptors recording painful signals and transmitting them by afferent nerve fibers to nociceptive neurons soma of which are in spinal ganglia. Low frequency of nerve impulses carries information about adequate tactile action and rise of the frequency for amplification of signal testifies about possible injury [2]. Slow sodium $Na_V1,8$ channels are considered significant in generation of painful feeling since the enhancement of synthesis and functional activity of these channels is related to hyper-excitability of nociceptive neurons and high frequency neurophatic pain [3, 4]. The failure in the synthesis of the channels causes the reduce of neurophatic pain [5]. Modulation of activity of the channels by mediators of inflammation can lead to pathological state such as hyperalgesia (an increase of painful sensitivity) [6]. Hyperalgesia is removed by agents descending impulse activity of $Na_V1,8$ channels [7].That is why these

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agents are believed as the analgesic highly selective drugs [2].The aim of the work is to answer the question: what parameters of the slow sodium $Na_V1,8$ channels do maximal influence on pain signaling transduction?To answer the question it is necessary 1) to study relations between these parameters, an applied external stimulus and a type of stable solution of the model system describing the impulse activity of the nociceptive neuron;2) to clarify what parameters do determine the possibility of the nociceptive neuron to generate spontaneously a signal of a painful range frequency?

2. The model

We have used the space-clamped Hodgkin-Huxley type model:

$$
\begin{aligned}
&c_m \frac{dE}{dt} = I - g_{Naf} m^3 h(E - E_{Na}) - g_K n^4 (E - E_K) - \\
&g_L (E - E_L) - g_{Nas} m_s^3 h_s (E - E_{Na}), \\
&\frac{dm}{dt} = \alpha_m(E)(1-m) - \beta_m(E)m, \\
&\frac{dh}{dt} = \alpha_h(E)(1-h) - \beta_h(E)h, \\
&\frac{dn}{dt} = \alpha_n(E)(1-n) - \beta_n(E)n, \\
&\frac{dm_S}{dt} = \alpha_{m_S}(E)(1-m_S) - \beta_{m_s}(E)m_S, \\
&\frac{dh_S}{dt} = \alpha_{h_S}(E)(1-h_S) - \beta_{h_s}(E)h_S,
\end{aligned}
\qquad (1)
$$

where E is the membrane potential, the variables m, h, n, m_s, h_s represent the probabilities of activation and inactivation of fast sodium, potassium and slow sodium channels, respectively.

The constants c_m=20 pF, g_{Naf} =40 nS, g_K = 20 nS, g_L = 5 nS, E_{Na} =55 mV, E_K= - 85 mV, E_L= -70 mV are the membrane capacitance, the maximal conductance of the fast sodium, potassium and leakage ions channels and the reversal potentials for Na^+, K^+ and leakage ions.

The voltage-dependent expressions

$$
\alpha_m(E) = \frac{0.115(1+e^{(E+70)/10})}{1+e^{(E+40)/42)}}, \qquad \beta_m(E) = 0.015(1+e^{(E+25)/8}),
$$

$$
\alpha_h(E) = 0.012(1+e^{-(E+43)/10}), \qquad \beta_h(E) = \frac{1.32}{1+0.2e^{(E+10)/7)}},
$$

$$
\alpha_n(E) = \frac{0.006(E+45)}{1-e^{-(E+45)/12)}}, \qquad \beta_n(E) = 0.13e^{-(E+45)/30}),
$$

$$\alpha_{m_S}(E) = e^{k_1(E+G)+d_1}, \qquad \beta_{m_S}(E) = e^{k_2(E+G)+d_2},$$

$$\alpha_{h_S}(E) = 0.0015e^{-(E+4)/30}), \qquad \beta_{h_S}(E) = \frac{0.01}{1+0.2e^{-(E+10)/7)}}$$

describe rates of transfer of the activation and inactivation gating structures of ionic channels between the closed and open states.

According to the Boltzmann's principle for the channel with the two-state open-closed structure the ratio of the number of open channels (N_0) to the number of closed channels (N_C) is determined by

$$\frac{N_O}{N_C} = \frac{m_S}{1-m_S} = e^{Z_{eff}\bar{e}(E-\overline{E})/kT},$$

where Z_{eff} is the effective charge of the activation gating structure (in electron units) coupled with conformational change of the gating structure during the ion transfer through the membrane, k is the Boltzmann's constant, T is the absolute temperature, $\bar{e}$ is the electron charge, $\overline{E}$ is the membrane potential such that N_0=N_C.

Then at $E = \overline{E}$ for the activation gating structure of the slow sodium channels one can write $\alpha_{m_S} = \beta_{m_S}$, whence it follows that the effective charge value of the activation gating structure can be gained as

$$Z_{eff} = \frac{kT}{\bar{e}}(k_1 + k_2).$$

3. Partition of the model parameter space into regions of qualitatively different solutions

To obtain relationship between the type of stable solution of the system, its parameters and an applied external stimulus it is sufficient to find points belonging to the boundary partitioning the parameter space of the model system into the regions of the qualitatively different types of stable solutions (steady states and stable periodic oscillations). For constructing the boundary the method of bifurcation analysis is applied.

On the I axis there are at least 3 bifurcation points (I_0<I_1<I_2) [8]. For I<I_0 and I>I_1 there is a one-to-one correspondence between the type of steady state (unstable or stable) and the presence or absence of a stable periodic solution. For $I \le I_0$ and $I \ge I_2$ the steady state is stable and a limit cycle does not exist.

While the bifurcation parameter I increases in interval (I_0<$I \le I_1$) the steady state is stable and a stable and unstable periodic solutions coexist appearing via fold limit cycle bifurcation. The unstable periodic solution shrinks down to the rest state and makes it lose stability via subcritical Andronov-Hopf bifurcation.

Therefore, for $I>I_1$ the stable periodic oscillations of large amplitude exist both with decreasing and increasing I value. But for $I_0<I\leq I_1$ the stable limit cycle of large amplitude is exhibited only with decreasing I

Since for the Hodgkin-Huxley type system $I_0\approx I_1$ for all the physiologically possible parameter values [9], the value of I_1 can be used as an approximate value of I_0. That is why the task of finding the boundary of qualitatively different types of stable solutions can be reduced to the more simple numerical task of constructing the boundary of various steady states (stable and unstable).

We write system (1) in the form

$$\frac{dx}{dt} = F(x, p, I), \qquad (2)$$

where $x=(E, m, h, n, m_S, h_S)$ is a vector of the phase coordinates,
$p=(g_{NaS}, k_1, k_2)$ is a vector of parameters which can be considered as bifurcation ones.

The method for determining the boundary points of the region of stable periodic solutions is reduced to the sequence of operations:

1) finding the equilibrium state of system (2) as a unique solution $x_0(p, I)$ of the equation

$$F(x, p, I)=0,$$

2) calculating the eigenvalues $\{\lambda_i(p,I)\}_1^6$ of the Jacobian matrix

$$J(p,I) = \left(\left.\frac{\partial F_i}{\partial x_j}\right|_{x=x_{0(p,I)}}, \quad i,j=1,...,6 \right),$$

3) finding the parameter values satisfying the Hopf bifurcation, namely, arising of a pair of purely imaginary eigenvalues

$$\lambda_1 = i\omega, \quad \lambda_2 = -i\omega, \quad \lambda_3 < 0, \quad \lambda_4 < 0, \quad \lambda_5 < 0, \quad \lambda_6 < 0 .$$

To determine values $I_1(p)$ and $I_2(p)$ at which maximal real part $(\lambda_m(p,I))$ becomes equal to zero the following algorithm is used.

1) The interval $[I_0, I_K]$ of possible values is discretized with k consecutive subintervals of length Δ.

In the case of existence even though one solution $I_1(p)$ of equation

$$\lambda_m(p,I) = 0 ,$$

the i - subinterval involving the solution, is determined by the consecutive search beginning from the left side of the interval. The value of this solution is determined by linear interpolation.

2) The value of I_2 (p) is calculated in the interval [i*Δ, I_K] by the method of bisection followed by linear interpolation.

The numerical solution of system (1) inside the obtained region of stable periodic solutions is found by a fourth-order Runge-Kutta method with a modified variable step size and Gear algorithm. The frequency of the periodic solution is calculated by the time values corresponding to local maxima.

4. Results and discussion

To elucidate the role of slow sodium channels in generation of the painful stimulus the maximal conductance of the slow sodium channels (g_{NaS}), the effective charge transfer of the activation gating system of the channels (Z_{eff}) and the shift (G) of the activation curve along the membrane potential axis have been used as variable parameters.

The family of the plane sections of the boundary partitioning the parameter space (g_{NaS}, Z_{eff}, I) into the regions of stable and unstable steady states are given in Fig.1 a, b.

Inside the each found region the steady state is unstable and there is a stable limit cycle corresponding to stable periodic solution.

Stain-stepping effect of the left boundary of the region is related to features of arising limit cycles on the left and right sides of the boundary. The left boundary of the region corresponds to subcritical Hopf bifurcation and emergence of the rough excitation in the form of large amplitude oscillations. The right boundary relates to supercritical Hopf bifurcation and appearance of the smooth excitation in the form of small large amplitude.

As is seen, if g_{NaS} =0, periodic oscillations are absent at any stimulus value.

The minimal value of g_{NaS} such that the oscillations emerge is equal to 14,9 nS at the stimulus – 142,5 pA and the value grows when Z_{eff} increases.

When the effective charge is less than $5\bar{e}$ the periodic oscillations arise only by hyperpolarizing stimulus (I<0 pA).

With increasing Z_{eff} the steady periodic solutions region extends significantly and shifts in direction of depolarizing stimulus (I>0 pA).

Integrating inside the constructed regions we obtain the relationship between the model parameter and frequency values. The examples of steady periodic solutions are represented in Fig.2 and Fig.3.

The periodic oscillations emerging on the left boundary of the region have large amplitude and small frequency. When moving inside the region from left to right an amplification of the external stimulus tends to change in amplitude and frequency of the nociceptive neuron. In other words, for the constant maximal conductance of the slow sodium channels and effective charge transfer of the activation gating system an enhancement of the external stimulus leads to the increase of the frequency of periodic oscillations and then their disruption.

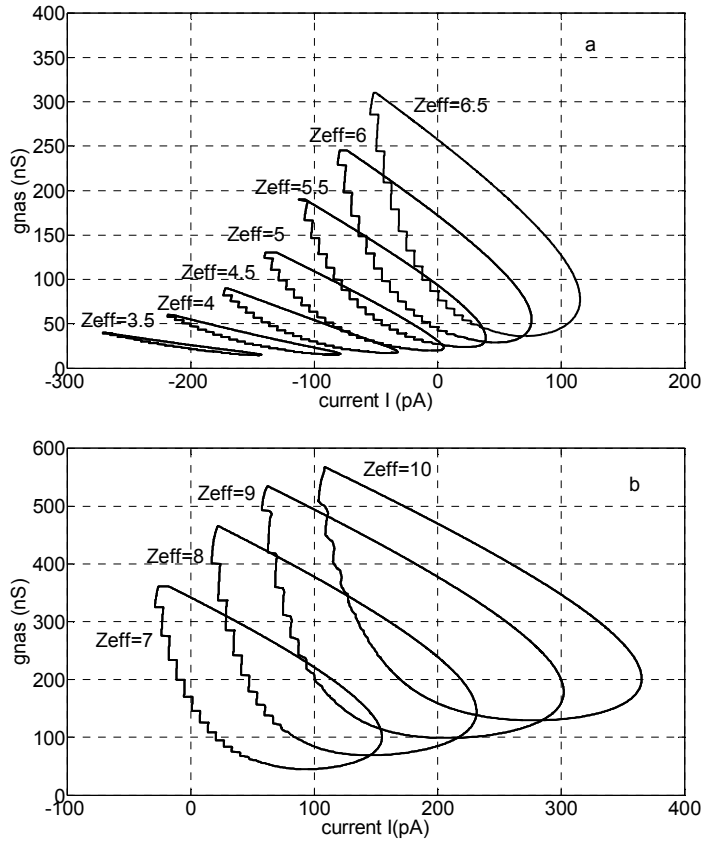

Fig. 1. The examples of the plane sections of the boundary partitioning the parameter space (g_{NaS}, Z_{eff}, I) into the regions of stable and unstable steady states. Each section is constructed with 800 points on the (g_{NaS}, I) plane corresponding to 700 net values of the parameter g_{NaS} .Values G=10 mV, $\{Z_{eff}\}_1^{11} = \{3.5\bar{e}, 4\bar{e}, 4.5\bar{e}, 5\bar{e}, 5.5\bar{e}, 6\bar{e}, 6.5\bar{e}, 7\bar{e}, 8\bar{e}, 9\bar{e}, 10\bar{e}\}$.

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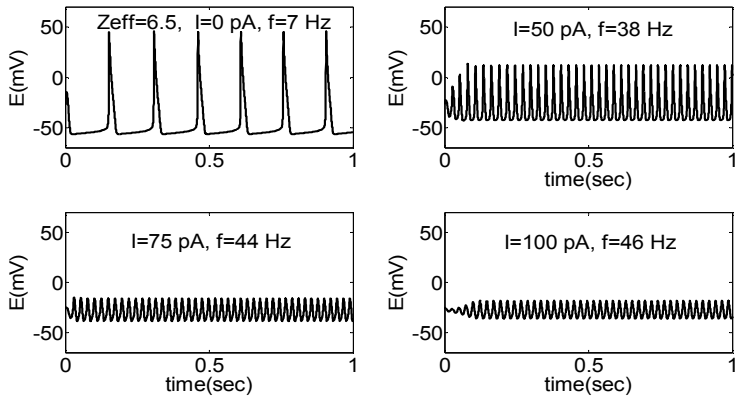

Fig. 2. The examples of steady solutions for $Z_{eff} = 6.5\bar{e}$, $g_{NaS} = 100nS$ and various values of stimulus.

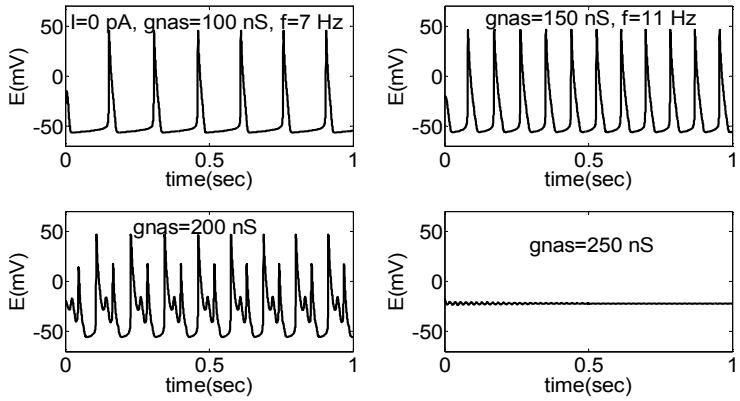

Fig.3. The examples of steady solutions $Z_{eff} = 6.5\bar{e}$, $I = 0$ and different values of g_{NaS}.

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When moving inside the region from bottom to top a growth of the maximal conductance of the slow sodium channels for the constant stimulus value results in increase of the frequency, period doubling and also failure of periodic oscillations (Fig.3).

Thus, both factors, namely, decrease of effective charge transfer of the activation gating system of the slow sodium channels for the constant maximal conductance of the channels and decrease of the maximal conductance of the slow sodium channels for the constant stimulus decline the frequency of impulse activity. Since an increase in the frequency of impulse activity of nociceptive neurons is related to the emergence of neuropathic pain, our findings indicate the direction of looking for chemical agents possessing analgesic properties.

3. Conclusion

The form of the constructed regions demonstrates that ability of each parameter to be bifurcation one significantly depends on the other parameter values. Thus, the conclusions about bifurcation properties of the system parameters are determined by the investigated point in the parameter space.

The character of changes in the system solutions and in the frequency of periodic solutions can be used in searching of chemical agents aimed for selective removal of neuropathic pain.

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