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Internal friction as possible key factor governing the thermosensitivity of TRP channels

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The mammalian sensory system is capable of detecting and discriminating thermal stimuli over a broad temperature range from noxious cold ($\leq 8\,^\circ$C) to noxious heat ($\geq 52\,^\circ$C). Accumulated evidence suggests that the principal temperature sensors in the sensory nerve endings of mammals belong to the transient receptor potential (TRP) superfamily of cation channels [1]. What can be a reason for their extraordinary thermosensitivity is still an open question. For example, the simplest two-state (close/open, c/o) channel model can adequately describe the experimental data on the open probability P_o and the voltage value $V_{1/2}$ for the half-maximal activation [2] both for the heat- and cold-activated TRP channels (TRPV1 and TRPM8), however, only with unphysically large changes in standard-state enthalpy and entropy. For this reason, Clapham and Miller [3] suggested that the TRP gating is accompanied by large changes in the molar heat capacity. However, the hypothesis leads to an unexpected conclusion: every TRP channel has to be both heat- and cold-activated. Such symmetry is not confirmed experimentally.

In the Letter we would like to draw attention to the fact that these and other current approaches overlook the effect of the strong temperature sensitivity of the intra-channel conformational dynamics due to a strong temperature dependence of so-called internal friction [4]. The internal friction is an effective "intra-protein" parameter that characterizes interactions between protein atoms, reflects a "roughness" of the energy landscape, accumulates the effects of the projection procedure, and depends on temperature and reaction coordinates. The effect was addressed recently for ryanodine receptors (RyR) in the framework of electron-conformational (EC) model [5]. Assumption of the Arrhenius temperature dependence of internal friction allowed to successfully explain all the temperature effects for the ligand-gated RyRs. The simplest two-state ("toy") EC model [6] starts with a simple effective Hamiltonian for a single ion channel as follows:

$$H_s = -\Delta\hat{\sigma}_z - h\hat{\sigma}_x - pQ + \frac{KQ^2}{2} + aQ\hat{\sigma}_z, \qquad (1)$$

where $\hat{\sigma}_x$ and $\hat{\sigma}_z$ are the Pauli matrices, and the first term describes the bare (i.e., at $Q = 0$) energy splitting of "up" and "down" states. The second term describes a quantum "mixing" effect. The third, linear in Q term in (1), corresponds to the energy of an external conformational stress, described by an effective stress, or pressure parameter p. The fourth term in (1) implies a simple harmonic approximation for the conformational energy, K being the effective "elastic" constant. The last term in (1) describes a linear EC interaction with the coupling parameter a. Conformational variable Q is the dimensionless one, therefore the effective parameters (h, p, K, a) are assigned the energy units. It is worth noting that the Hamiltonian (1) resembles that of a two-level electronic system interacting with a bosonic mode. Two eigenvalues of the Hamiltonian:

$$E_\pm(Q) = \frac{KQ^2}{2} - pQ \pm \frac{1}{2}\sqrt{(\Delta - aQ)^2 + h^2} \qquad (2)$$

define the two branches of the conformational potential (CP), attributed to electronically closed (E_-) and electronically open (E_+) states of the channel. Given $h = 0$ we arrive at two diabatic potentials $E_\pm(Q)$ for electronically closed and open states with two minima separated by an intersection point at $Q = 0$ thus providing the "bistability" conditions. At $h \neq 0$ instead of the two parabolas we arrive at two novel isolated CP branches where instead of the twofold degenerated intersection point we have a high-energy metastable state and low-energy unstable transition state. The dependence of the energy gap $\Delta(Q = 0)$ on the membrane potential V can be approximated as follows: $\Delta = \Delta_0 + k_1 V + \frac{1}{2}k_2 V^2$. The ion channel dynamics includes fast electronic transitions triggered by ligands, tunneling effects and slow conformational dynamics obeying a conventional Langevin equation of motion:

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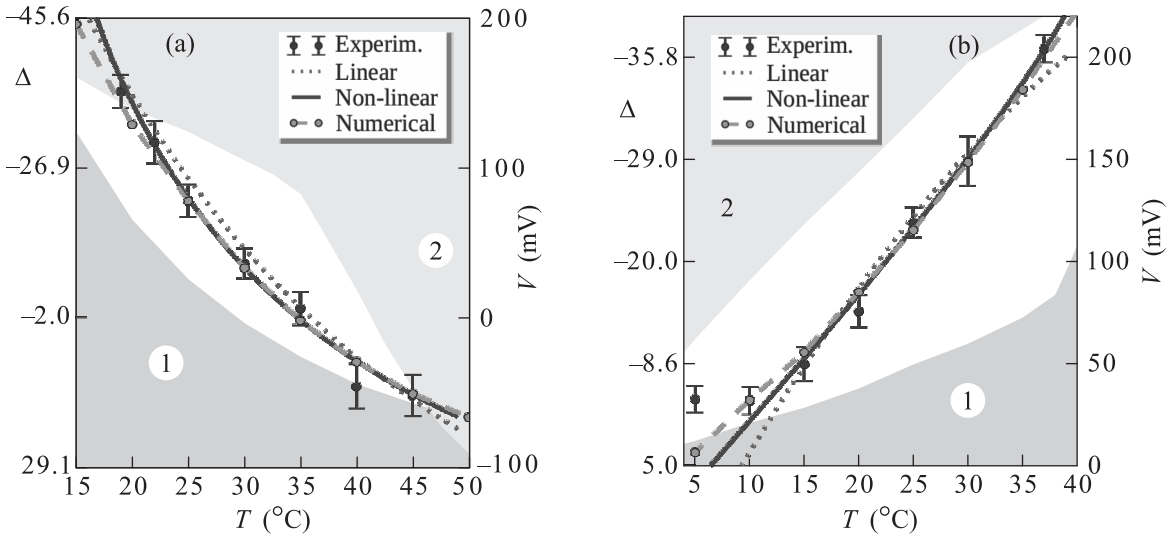

Fig. 1. (Color online) $V_{1/2}$ as a function of temperature for: (a) – TRPV1 channel; (b) – TRPM8 channel [2]. The dotted line corresponds to the linear $\Delta(V)$ dependence; the solid line does to the nonlinear one; the dashed line with dots represents results of numerical solution of Langevin equation (left axis is unrelated to the linear dependence). By filling we have identified the areas where the Kramers equation for escape rate is invalid for open (1) and close (2) states, respectively

$$M\ddot{Q} = -M\frac{\partial}{\partial Q}E(Q) - M\Gamma\dot{Q} + \xi(t), \qquad (3)$$

where M is an effective mass (below M let to be unity), Γ is an internal friction parameter, $\xi(t)$ is the Gaussian-Markovian noise: $\langle\xi(t)\rangle = 0$; $\langle\xi(t)\xi(t')\rangle = 2\gamma k_B T M\delta(t-t')$, where γ is an "external" friction parameter. Hereafter, both Γ and γ are assumed to obey Arrhenius like temperature dependence.

To describe temperature activation of the TRP channels we omit electronic transitions and restrict ourselves by the low-energy CP branch, or double well potential with dynamics which can be analytically described in terms of the Kramers rate theory [7]. The Kramers theory provides expression for rate at which a Brownian particle escapes from a metastable state over a potential barrier. Thus for "c-o" transition

$$k_c = \left(\sqrt{\frac{\Gamma_c^2}{4} + \omega_t^2} - \frac{\Gamma_c}{2}\right)\frac{\omega_c}{2\pi\omega_t}\exp\left(-\frac{\Gamma_c}{\gamma}\frac{\Delta E_c}{k_B T}\right), \quad (4)$$

where Γ_c the internal friction parameter for "close" state, ΔE_c the barrier height, ω_c the angular frequency inside metastable minimum and ω_t is at the transition state.

"Working" parameters of the EC-model for the TRP channels are unknown, so we will rather arbitrarily choose them based on a physically reasonable assumption about the height of barriers ΔE_c and ΔE_o of the order of 1 kcal/mol (≈ 43.3 meV).

Results of the computer simulation based on equation (4) and on the numerical solution of the Langevin equation allowed us to successfully reproduce the experimental voltage dependence of the open probability P_{open} and the temperature dependence of the half-maximal activation voltage $V_{1/2}$ (Fig. 1) [3]. Thus we have shown that the temperature dependence of the internal friction can be a key factor governing the ion channels gating with much smaller energy barriers ≤ 0.1 eV. We argue that the second-order term in $\Delta(V)$ is necessary to accurately describe the TRP channels gating given such a wide range of temperatures. The internal friction mechanism is believed to open novel perspectives for studying the high temperature sensitivity for the TRP as well as for other ion channels.

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