Mechanosensitivity of Na_v1.5 sodium channels is regulated by specific β -subunits

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Mechanically active organs such as the heart, skeletal muscles, and the gastrointestinal tract contain complex neuronal networks that generate and coordinate contraction and relaxation of these organs. In addition to the generation of movement, contractile organs can also recognize and respond to mechanical stimuli via mechanoelectrical feedback. The molecular targets that sense mechanical force and translate it into electrical signals are ion channels located in the excitable membranes of neurons and muscle cells. Among them are included specialized mechano-gated channels as well as ion channels with distinct primary gating stimuli, whose functions are also modulated by mechanical stress as it occurs during cellular stretch and compression. Voltage-gated sodium (Na_v) channels belong to the latter group. These channels are essential elements for the electrical communication of excitable cells. They initiate and shape action potentials by permitting influx of Na⁺ ions into cells in response to small membrane depolarizations. Na_v channels are macromolecular protein complexes composed of a large pore-forming α -subunit and one or more smaller β -subunits with regulatory functions [4]. The family of human Na_v channels consists of nine α -subunits (Na_v1.1–1.9) and four Na_v β -subunits (β 1–4), which all possess tissue-specific expression patterns [3, 5]. Mechanomodulation of α -subunit Na_v1.5 is of particular interest because this channel contributes to action potential generation in cardiac myocytes and smooth muscle cells of the gut where it is inherently exposed to mechanical load [2, 7]. Although the mechanosensitivity of Na_v1.5 α -subunits is well established [1, 6], it has not been demonstrated yet if

and how associated β -subunits can modulate the channel's response to mechanical stimuli.

In this issue, Maroni et al. show that β 1- and β 3-subunits differentially modulate the response of Na_v1.5 to mechanical stimulation. In their paper entitled “ β 1 and β 3 subunits amplify mechanosensitivity of the cardiac voltage-gated sodium channel Na_v1.5,” the authors describe whole-cell patch-clamp recordings on human embryonic kidney (HEK) cells expressing Na_v1.5 α -subunits either alone or in combination with β 1 or β 3, and expose the cells to shear stress generated by a standardized perfusion system. Using this approach, they confirmed that mechanical stress accelerates activation and inactivation of Na_v1.5 and demonstrate that only the presence of β 3 but not β 1 enhances the mechano-induced acceleration of channel activation and inactivation. Previous work has revealed that mechanical stress stabilizes inactivated states of Na_v1.5 by shifting the channel voltage-dependence of steady-state inactivation to more hyperpolarized potentials [1]. Maroni et al. analyze this effect in absence and presence of β 1- or β 3-subunits and show that particularly, β 3 increases the shear stress-triggered hyperpolarizing shift of channel inactivation, thus effectively increasing the voltage window in which mechanomodulation of Na_v1.5 channels occurs.

The reported findings strengthen the hypothesis that modulation of Na_v1.5 channel activity is part of the mechanoelectrical feedback in heart and gut tissue, and suggest that Na_v1.5-dependent mechanoelectrical feedback depends strongly on the type of β -subunit present in Na_v1.5 channel complexes.

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