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RESEARCH NEWS

How PKA helps cardiomyocytes Na$_v$igate chronic stress

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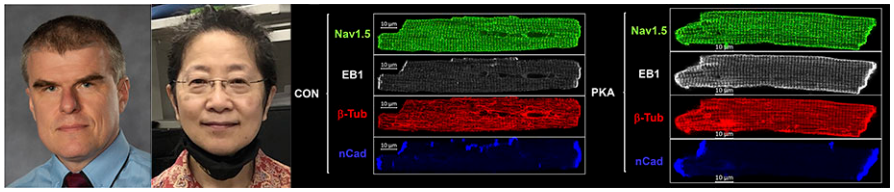
JGP study (Bernas et al. 2024. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.202313436) suggests that, by altering microtubule dynamics, persistent PKA activation promotes the delivery of Na$_v$1.5 channels to intercalated discs.

The voltage-gated sodium channel Na$_v$1.5 is a crucial contributor to cardiac action potentials, helping to propagate impulses at the intercalated discs (ICDs) that connect neighboring cardiomyocytes. In this issue of *JGP*, Bernas et al. (1) reveal that, during chronic stress, prolonged activation of cAMP-dependent protein kinase (PKA) may preserve impulse propagation by enhancing the trafficking of Na$_v$1.5 to ICDs (1).

As part of the acute, "fight or flight" stress response, the activation of PKA downstream of β-adrenergic receptors temporarily increases the amplitude of sodium channel currents (I_{Na}) in cardiomyocytes, while also accelerating current inactivation (2). But the effects of chronic stress and persistent PKA activity on I_{Na}, as might occur during heart failure or aging, for example, are less well understood.

To investigate the effects of persistent PKA activation on Na$_v$1.5, Tytus Bernas, Gea-Ny Tseng, and colleagues at Virginia Commonwealth University treated adult rat ventricular myocytes with a membrane-permeable cAMP analog and the phosphatase inhibitor okadaic acid (1). "After about 15 h of PKA activation, the amplitude of I_{Na} became much higher, even though the total level of Na$_v$1.5 protein stayed the same," Tseng says. "That motivated us to examine whether there was a change in the distribution of the channel."

Indeed, while acute PKA activation had no effect on Na$_v$1.5 localization, prolonged activation stimulated the channel's redistribution from intracellular storage sites (believed to be junctional sarcoplasmic reticulum) to the peripheral surface of cardiomyocytes, including at ICDs. Moreover, chronic PKA activation increased the size and density of Na$_v$1.5 clusters at the cell surface, which, through a mechanism of positive cooperativity, is likely to increase the channels' open probability and boost I_{Na} amplitude (3).



Tytus Bernas (left), Gea-Ny Tseng (right), and colleagues reveal that persistent PKA activation induces a redistribution of Na$_v$1.5 to the lateral surface and ICDs of cardiomyocytes, which may help protect impulse propagation during chronic stress. Compared with a control cell (left), prolonged PKA activation (right) results in the delivery of Na$_v$1.5 (green) to ICDs (blue), via a pathway involving the upregulation of EB1 (white) and a reorganization of the microtubule cytoskeleton (red).

The microtubule-associated protein EB1 helps target Na$_v$1.5 to ICDs (4), and the gene encoding EB1 is regulated by the transcription factor CREB1, a downstream target of PKA. Accordingly, Bernas et al. (1) found that persistent PKA activation increases the expression of EB1 in cardiomyocytes. This, in turn, appears to prompt a reorganization of the cells' cytoskeleton, diminishing the number of stable, interfibrillar microtubules while increasing the number of dynamic, EB1-positive microtubules at the cell surface and ICDs.

Using a variety of experimental approaches, Bernas et al. (1) provide evidence that Na$_v$1.5 interacts with EB1 and β-tubulin inside cells, and that these interactions are enhanced by PKA. These associations likely facilitate the delivery of Na$_v$1.5-containing vesicles to ICDs along microtubule tracks, helping to maintain the propagation of impulses between cells in chronically stressed hearts. "However, we're sure that there are other proteins involved in this pathway as well," Tseng says.

Tseng and colleagues are now investigating other proteins that are upregulated in response to persistent PKA activation and could help to organize Na$_v$1.5's distribution at ICDs. "Indeed, we need to look at the organization of the ICD as a whole," Tseng explains. "It's a complicated, important structure and is really a new frontier in cell biology."

References

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