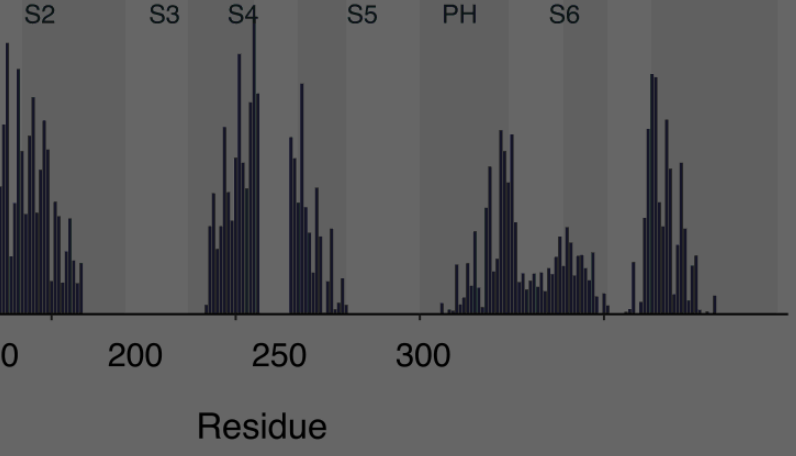

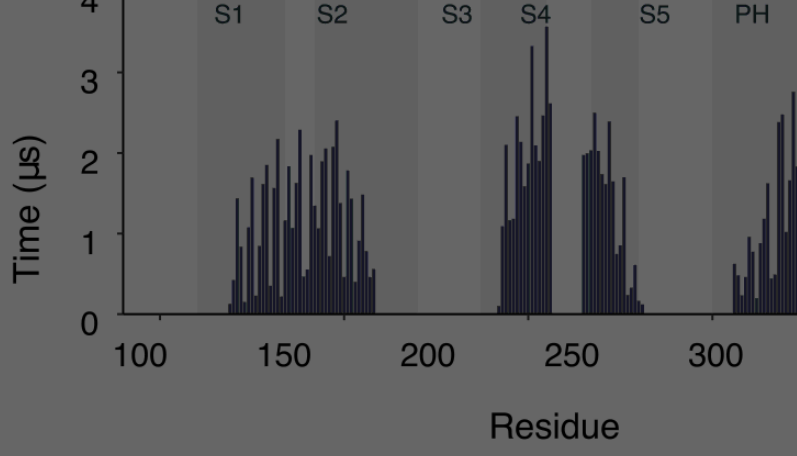

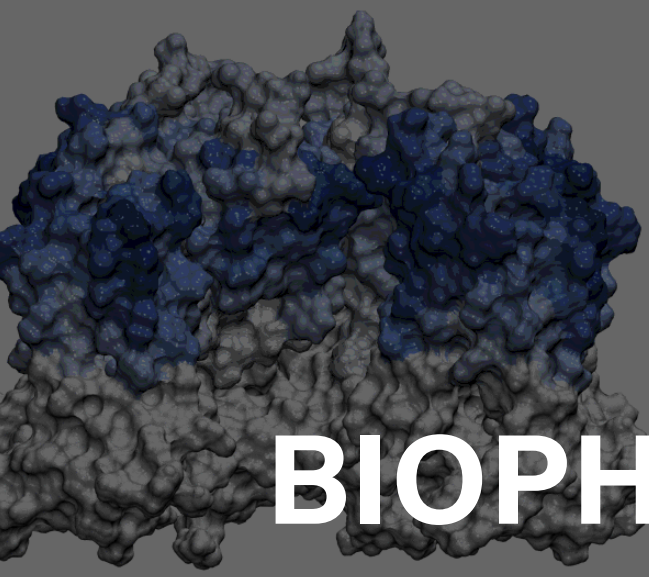

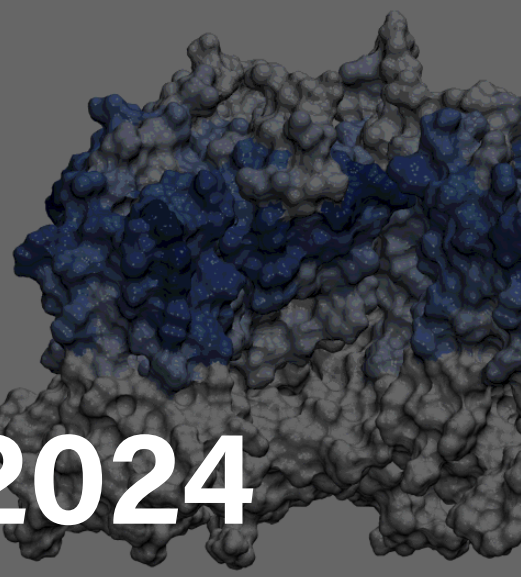

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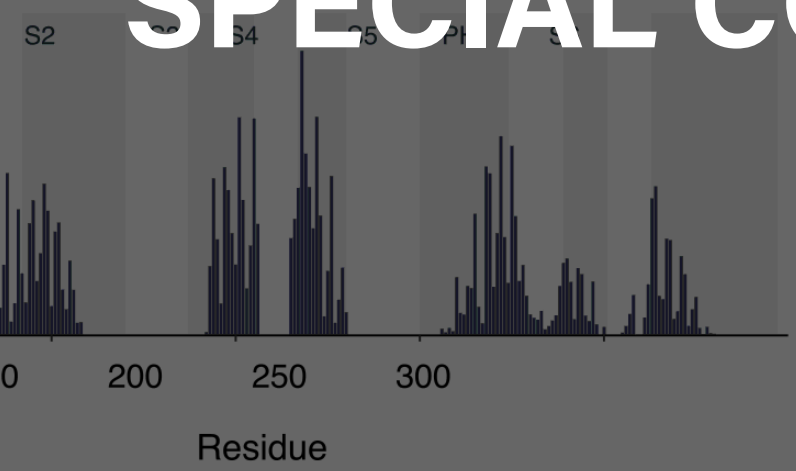

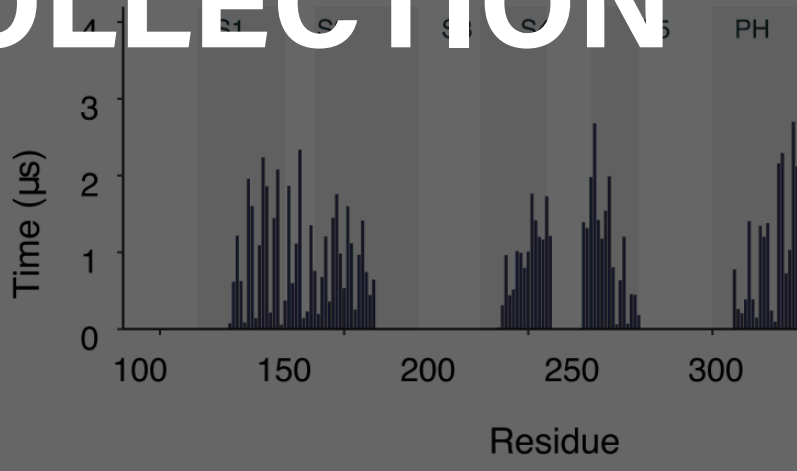

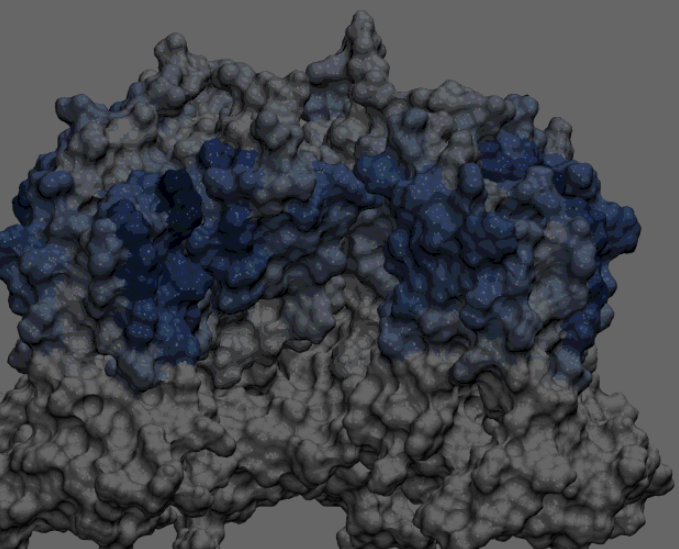

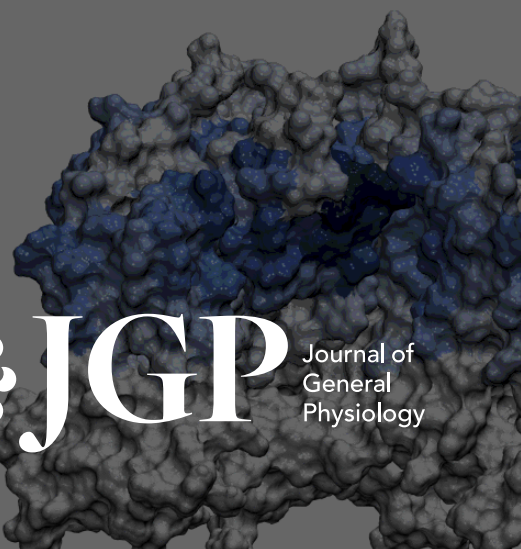

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BIOPHYSICS 2024

Journal of General Physiology (*JGP*) is pleased to present this collection of recent articles that use a range of biophysical approaches to investigate various topics, including analyses of sodium channel variants associated with epilepsy and chronic pain, the binding of fatty acid modulators to ion channels, the structure and function of myosin and other sarcomeric proteins in muscle, and more. If you enjoy this collection, please visit jgp.org to sign up for email alerts and receive the latest articles in your inbox.

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On the cover: Adaptation of figure from Jowais et al. article "Mechanistic understanding of KCNQ1 activating polyunsaturated fatty acid analogs." See page 7.

Rockefeller University Press

EPILEPSY-ASSOCIATED *SCN2A* ($NA_V1.2$) VARIANTS EXHIBIT DIVERSE AND COMPLEX FUNCTIONAL PROPERTIES

Pathogenic variants in voltage-gated sodium (Na_V) channel genes including *SCN2A*, encoding $Na_V1.2$, are discovered frequently in neurodevelopmental disorders with or without epilepsy. *SCN2A* is also a high-confidence risk gene for autism spectrum disorder (ASD) and nonsyndromic intellectual disability (ID). Previous work to determine the functional consequences of *SCN2A* variants yielded a paradigm in which predominantly gain-of-function variants cause neonatal-onset epilepsy, whereas loss-of-function variants are associated with ASD and ID. However, this framework was derived from a limited number of studies conducted under heterogeneous experimental conditions, whereas most disease-associated *SCN2A* variants have not been functionally annotated. We determined the functional properties of *SCN2A* variants using automated patch-clamp recording to demonstrate the validity of this method and to examine whether a binary classification of variant dysfunction is evident in a larger cohort studied under uniform conditions. We studied 28 disease-associated variants and 4 common variants using two alternatively spliced isoforms of $Na_V1.2$ expressed in HEK293T cells. Automated patch-clamp recording provided a valid high throughput method to ascertain detailed functional properties of $Na_V1.2$ variants with concordant findings for variants that were previously studied using manual patch clamp. Many epilepsy-associated variants in our study exhibited complex patterns of gain- and loss-of-functions that are difficult to classify by a simple binary scheme. The higher throughput achievable with automated patch clamp enables study of variants with greater standardization of recording conditions, freedom from operator bias, and enhanced experimental rigor. This approach offers an enhanced ability to discern relationships between channel dysfunction and neurodevelopmental disorders.

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Thompson, C.H., F. Potet, T.V. Abramova, J.-M. DeKeyser, N.F. Ghabra, C.G. Vanoye, J.J. Millichap, and A.L. George, Jr. 2023. Epilepsy-associated *SCN2A* ($Na_V1.2$) variants exhibit diverse and complex functional properties. *J. Gen. Physiol.* 155 (10): e202313375. https://doi.org/10.1085/jgp.202313375

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CHARGE-VOLTAGE CURVES OF SHAKER POTASSIUM CHANNEL ARE NOT HYSTERETIC AT STEADY STATE

Charge-voltage curves of many voltage-gated ion channels exhibit hysteresis, but such curves are also a direct measure of free energy of channel gating and, hence, should be path independent. Here, we identify conditions to measure steady-state charge-voltage (Q-V) curves and show that these are curves are not hysteretic. Charged residues in transmembrane segments of voltage-gated ion channels (VGICs) sense and respond to changes in the electric field. The movement of these gating charges underpins voltage-dependent activation and is also a direct metric of the net free-energy of channel activation. However, for most voltage-gated ion channels, the Q-V curves appear to be dependent on initial conditions. For instance, Q-V curves of Shaker potassium channel obtained by hyperpolarizing from 0 mV is left-shifted compared to those obtained by depolarizing from a holding potential of −80 mV. This hysteresis in Q-V curves is a common feature of channels in the VGIC superfamily and raises profound questions about channel energetics because the net free-energy of channel gating is a state function and should be path independent. Due to technical limitations, conventional gating current protocols are limited to test pulse durations of <500 ms, which raises the possibility that the dependence of Q-V on initial conditions reflects a lack of equilibration. Others have suggested that the hysteresis is fundamental thermodynamic property of VGICs and reflects energy dissipation due to measurements under non-equilibrium conditions inherent to rapid voltage jumps (Villalba-Galea. 2017. *Channels*. https://doi.org/10.1080/19336950.2016.1243190). Using an improved gating current and voltage-clamp fluorometry protocols, we show that the gating hysteresis arising from different initial conditions in Shaker potassium channel is eliminated with ultra-long (18–25-s) test pulses. Our study identifies a modified gating current recording protocol to obtain steady-state Q-V curves of a VGIC. Above all, these findings demonstrate that the gating hysteresis in Shaker channel is a kinetic phenomenon rather than a true thermodynamic property of the channel and the Q-V curve is a true measure of the net-free energy of channel gating.

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THE BIOPHYSICAL PROPERTIES OF TRIC-A AND TRIC-B AND THEIR INTERACTIONS WITH RYR2

Trimeric intracellular cation channels (TRIC-A and TRIC-B) are thought to provide counter-ion currents to enable charge equilibration across the sarco/endoplasmic reticulum (SR) and nuclear membranes. However, there is also evidence that TRIC-A may interact directly with ryanodine receptor type 1 (RyR1) and 2 (RyR2) to alter RyR channel gating. It is therefore possible that the reverse is also true, where the presence of RyR channels is necessary for fully functional TRIC channels. We therefore coexpressed mouse TRIC-A or TRIC-B with mouse RyR2 in HEK293 cells to examine if after incorporating membrane vesicles from these cells into bilayers, the presence of TRIC affects RyR2 function, and to characterize the permeability and gating properties of the TRIC channels. Importantly, we used no purification techniques or detergents to minimize damage to TRIC and RyR2 proteins. We found that both TRIC-A and TRIC-B altered the gating behavior of RyR2 and its response to cytosolic Ca^{2+} but that TRIC-A exhibited a greater ability to stimulate the opening of RyR2. Fusing membrane vesicles containing TRIC-A or TRIC-B into bilayers caused the appearance of rapidly gating current fluctuations of multiple amplitudes. The reversal potentials of bilayers fused with high numbers of vesicles containing TRIC-A or TRIC-B revealed both Cl^- and K^+ fluxes, suggesting that TRIC channels are relatively non-selective ion channels. Our results indicate that the physiological roles of TRIC-A and TRIC-B may include direct, complementary regulation of RyR2 gating in addition to the provision of counter-ion currents of both cations and anions.

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MULTISCALE MOLECULAR DYNAMICS SIMULATIONS PREDICT ARACHIDONIC ACID BINDING SITES IN HUMAN ASIC1A AND ASIC3 TRANSMEMBRANE DOMAINS

Acid-sensing ion channels (ASICs) play important roles in inflammatory pathways by conducting ions across the neuronal membrane in response to proton binding under acidic conditions. Recent studies have shown that ASICs can be modulated by arachidonic acid (AA), and, in the case of the ASIC3 subtype, even activated by AA at physiological pH. However, the mechanism by which these fatty acids act on the channel is still unknown. Here, we have used multiscale molecular dynamics simulations to predict a putative, general binding region of AA to models of the human ASIC protein. We have identified, in agreement with recent studies, residues in the outer leaflet transmembrane region which interact with AA. In addition, despite their similar modulation, we observe subtle differences in the AA interaction pattern between human ASIC1a and human ASIC3, which can be reversed by mutating three key residues at the outer leaflet portion of TM1. We further probed interactions with these residues in hASIC3 using atomistic simulations and identified possible AA coordinating interactions; salt bridge interactions of AA with $R65_{hASIC3}$ and $R68_{hASIC3}$; and AA tail interactions with the $Y58_{hASIC3}$ aromatic ring. We have shown that longer fatty acid tails with more double bonds have increased relative occupancy in this region of the channel, a finding supported by recent functional studies. We further proposed that the modulatory effect of AA on ASIC does not result from changes in local membrane curvature. Rather, we speculate that it may occur through structural changes to the ion channel upon AA binding.

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OPTIMIZATION OF CFTR GATING THROUGH THE EVOLUTION OF ITS EXTRACELLULAR LOOPS

CFTR chloride channel mutations cause the lethal and incurable disease cystic fibrosis (CF). CFTR is activated by phosphorylation, and phosphorylated channels exhibit "bursting" behavior—"bursts" of openings separated by short "flickery" closures and flanked by long "interburst" closures—driven by ATP binding/hydrolysis at two nucleotide-binding domains. The human channel (hCFTR) and the distant zebrafish ortholog (zCFTR) display differences both in their gating properties and structures. In phosphorylated ATP-bound hCFTR, the hR117 side chain, conserved across evolution, forms an H-bond that stabilizes the open state. Lack of that bond in the hR117H mutant causes CF. In the phosphorylated ATP-bound zCFTR structure, that H-bond is not observable. Here, we show that the zR118H mutation does not affect the function of zCFTR. Instead, we identify an H-bond between the zS109 and zS120 side chains of phosphorylated ATP-bound, but not of unphosphorylated apo-, zCFTR. We investigate the role of that interaction using thermodynamic mutant cycles built on gating parameters determined in inside-out patch clamp recordings. We find that zS109 indeed forms an H-bond with zN120 in the flickery closed state, but not in the open or interburst closed states. Although in hCFTR an isoleucine (hI119) replaces the asparagine, mutation hS108A produces a strong hR117H-like phenotype. Since the effects of the latter two mutations are not additive, we conclude that in hCFTR these two positions interact, and the hS108-hR117 and hR117-hE1124 H-bonds cooperate to stabilize the open state. These findings highlight an example of how the gating mechanism was optimized during CFTR molecular evolution.

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Simon, M.A., and L. Csanády. 2023. Optimization of CFTR gating through the evolution of its extracellular loops. *J. Gen. Physiol.* 155 (4): e202213264. https://doi.org/10.1085/jgp.202213264

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COOPERATIVITY OF MYOSIN II MOTORS IN THE NON-REGULATED AND REGULATED THIN FILAMENTS INVESTIGATED WITH HIGH-SPEED AFM

Skeletal myosins II are non-processive molecular motors that work in ensembles to produce muscle contraction while binding to the actin filament. Although the molecular properties of myosin II are well known, there is still debate about the collective work of the motors: is there cooperativity between myosin motors while binding to the actin filaments? In this study, we use high-speed AFM to evaluate this issue. We observed that the initial binding of small arrays of myosin heads to the non-regulated actin filaments did not affect the cooperative probability of subsequent bindings and did not lead to an increase in the fractional occupancy of the actin binding sites. These results suggest that myosin motors are independent force generators when connected in small arrays and that the binding of one myosin does not alter the kinetics of other myosins. In contrast, the probability of binding of myosin heads to regulated thin filaments under activating conditions (at high Ca^{2+} concentration in the presence of 2 μM ATP) was increased with the initial binding of one myosin, leading to a larger occupancy of available binding sites at the next half-helical pitch of the filament. The result suggests that myosin cooperativity is observed over five pseudo-repeats and defined by the activation status of the thin filaments.

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Matusovsky, O.S., A. Månsson, and D.E. Rassier. 2023. Cooperativity of myosin II motors in the non-regulated and regulated thin filaments investigated with high-speed AFM. *J. Gen. Physiol.* 155 (3): e202213190. https://doi.org/10.1085/jgp.202213190

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LONGITUDINAL DIFFUSION BARRIERS IMPOSED BY MYOFILAMENTS AND MITOCHONDRIA IN MURINE CARDIAC MYOCYTES

Using optical and electrical methods, we document that diffusion in the cytoplasm of BL6 murine cardiomyocytes becomes restricted >20-fold as molecular weight increases from 30 to 2,000, roughly as expected for pores with porin channel dimensions. Bodipy-FL ATP diffuses >40-fold slower than in free water at 25°C. From several fluorophores analyzed, bound fluorophore fractions range from 0.1 for a 2 kD FITC-labeled polyethylene glycol to 0.93 for sulforhodamine. Unbound fluorophores diffuse at 0.5–8 × 10^{-7} cm^2/s (5–80 μm^2/s). Analysis of Na/K pump and veratridine-modified Na channel currents suggests that Na diffusion is nearly unrestricted at 35°C (time constant for equilibration with the pipette tip, ∼20 s). Using multiple strategies, we estimate that at 35°C, ATP diffuses four to eight times slower than in free water. To address whether restrictions are caused more by protein or membrane networks, we verified first that a protein gel, 10 g% gelatin, restricts diffusion with strong dependence on molecular weight. Solute diffusion in membrane-extracted cardiac myofilaments, confined laterally by suction into large-diameter pipette tips, is less restricted than in intact myocytes. Notably, myofilaments extracted similarly from skeletal (diaphragm) myocytes are less restrictive. Solute diffusion in myocytes with sarcolemma permeabilized by β-escin (80 µM) is similar to diffusion in intact myocytes. Restrictions are strain-dependent, being twofold greater in BL6 myocytes than in CD1/J6/129svJ myocytes. Furthermore, longitudinal diffusion is 2.5-fold more restricted in CD1/J6/129svJ myocytes lacking the mitochondrial porin, VDAC1, than in WT CD1/J6/129svJ myocytes. Thus, mitochondria networks restrict long-range diffusion while presumably optimizing nucleotide transfer between myofilaments and mitochondria. We project that diffusion restrictions imposed by both myofilaments and the outer mitochondrial membrane are important determinants of total free cytoplasmic AMP and ADP (∼10 µM). However, the capacity of diffusion to deliver ATP to myofilaments remains ∼100-fold greater than ATP consumption.

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MECHANISTIC UNDERSTANDING OF KCNQ1 ACTIVATING POLYUNSATURATED FATTY ACID ANALOGS

The KCNQ1 channel is important for the repolarization phase of the cardiac action potential. Loss of function mutations in KCNQ1 can cause long QT syndrome (LQTS), which can lead to cardiac arrythmia and even sudden cardiac death. We have previously shown that polyunsaturated fatty acids (PUFAs) and PUFA analogs can activate the cardiac KCNQ1 channel, making them potential therapeutics for the treatment of LQTS. PUFAs bind to KCNQ1 at two different binding sites: one at the voltage sensor (Site I) and one at the pore (Site II). PUFA interaction at Site I shifts the voltage dependence of the channel to the left, while interaction at Site II increases maximal conductance. The PUFA analogs, linoleic–glycine and linoleic–tyrosine, are more effective than linoleic acid at Site I, but less effective at Site II. Using both simulations and experiments, we find that the larger head groups of linoleic–glycine and linoleic–tyrosine interact with more residues than the smaller linoleic acid at Site I. We propose that this will stabilize the negatively charged PUFA head group in a position to better interact electrostatically with the positive charges in the voltage sensor. In contrast, the larger head groups of linoleic–glycine and linoleic–tyrosine compared with linoleic acid prevent a close fit of these PUFA analogs in Site II, which is more confined. In addition, we identify several KCNQ1 residues as critical PUFA-analog binding residues, thereby providing molecular models of specific interactions between PUFA analogs and KCNQ1. These interactions will aid in future drug development based on PUFA–KCNQ1 channel interactions.

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STRUCTURAL BASIS FOR SEVERE PAIN CAUSED BY MUTATIONS IN THE VOLTAGE SENSORS OF SODIUM CHANNEL $NA_V1.7$

Voltage-gated sodium channels in peripheral nerves conduct nociceptive signals from nerve endings to the spinal cord. Mutations in voltage-gated sodium channel $Na_V1.7$ are responsible for a number of severe inherited pain syndromes, including inherited erythromelalgia (IEM). Here, we describe the negative shifts in the voltage dependence of activation in the bacterial sodium channel Na_VAb as a result of the incorporation of four different IEM mutations in the voltage sensor, which recapitulate the gain-of-function effects observed with these mutations in human $Na_V1.7$. Crystal structures of Na_VAb with these IEM mutations revealed that a mutation in the S1 segment of the voltage sensor facilitated the outward movement of S4 gating charges by widening the pathway for gating charge translocation. In contrast, mutations in the S4 segments modified hydrophobic interactions with surrounding amino acid side chains or membrane phospholipids that would enhance the outward movement of the gating charges. These results provide key structural insights into the mechanisms by which these IEM mutations in the voltage sensors can facilitate outward movements of the gating charges in the S4 segment and cause hyperexcitability and severe pain in IEM. Our work gives new insights into IEM pathogenesis at the near-atomic level and provides a molecular model for mutation-specific therapy of this debilitating disease.

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MYOSIN AND TROPOMYOSIN–TROPONIN COMPLEMENTARILY REGULATE THERMAL ACTIVATION OF MUSCLES

Contraction of striated muscles is initiated by an increase in cytosolic Ca^{2+} concentration, which is regulated by tropomyosin and troponin acting on actin filaments at the sarcomere level. Namely, Ca^{2+} binding to troponin C shifts the "on–off" equilibrium of the thin filament state toward the "on" state, promoting actomyosin interaction; likewise, an increase in temperature to within the body temperature range shifts the equilibrium to the "on" state, even in the absence of Ca^{2+}. Here, we investigated the temperature dependence of sarcomere shortening along isolated fast skeletal myofibrils using optical heating microscopy. Rapid heating (25 to 41.5°C) within 2 s induced reversible sarcomere shortening in relaxing solution. Further, we investigated the temperature dependence of the sliding velocity of reconstituted fast skeletal or cardiac thin filaments on fast skeletal or β-cardiac myosin in an in vitro motility assay within the body temperature range. We found that (a) with fast skeletal thin filaments on fast skeletal myosin, the temperature dependence was comparable to that obtained for sarcomere shortening in fast skeletal myofibrils (Q_{10} ~8), (b) both types of thin filaments started to slide at lower temperatures on fast skeletal myosin than on β-cardiac myosin, and (c) cardiac thin filaments slid at lower temperatures compared with fast skeletal thin filaments on either type of myosin. Therefore, the mammalian striated muscle may be fine-tuned to contract efficiently via complementary regulation of myosin and tropomyosin–troponin within the body temperature range, depending on the physiological demands of various circumstances.

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MYOSIN-BINDING PROTEIN C STABILIZES, BUT IS NOT THE SOLE DETERMINANT OF SRX MYOSIN IN CARDIAC MUSCLE

The myosin super-relaxed (SRX) state is central to striated muscle metabolic and functional regulation. In skeletal muscle, SRX myosin are predominantly colocalized with myosin-binding protein C (MyBP-C) in the sarcomere C-zone. To define how cardiac MyBP-C (cMyBP-C) and its specific domains contribute to stabilizing the SRX state in cardiac muscle, we took advantage of transgenic cMyBP-C null mice and those expressing cMyBP-C with a 271-residue N-terminal truncation. Utilizing super-resolution microscopy, we determined the lifetime and subsarcomeric location of individual fluorescent-ATP turnover events within isolated cardiac myofibrils. The proportion of SRX myosin demonstrated a gradient along the half-thick filament, highest in the P- and C-zones (72 ± 9% and 71 ± 6%, respectively) and lower in the D-zone (45 ± 10%), which lies farther from the sarcomere center and lacks cMyBP-C, suggesting a possible role for cMyBP-C in stabilizing the SRX. However, myofibrils from cMyBP-C null mice demonstrated an ∼40% SRX reduction, not only within the now cMyBP-C-free C-zone (49 ± 9% SRX), but also within the D-zone (22 ± 5% SRX). These data suggest that the influence of cMyBP-C on the SRX state is not limited to the C-zone but extends along the thick filament. Interestingly, myofibrils with N-terminal truncated cMyBP-C had an SRX content and spatial gradient similar to the cMyBP-C null, indicating that the N-terminus of cMyBP-C is necessary for cMyBP-C's role in enhancing the SRX gradient along the entire thick filament. Given that SRX myosin exist as a gradient along the thick filament that is highest in the C-zone, even in the absence of cMyBP-C or its N-terminus, an inherent bias must exist in the structure of the thick filament to stabilize the SRX state.

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Hiroko Takeuchi, PhD
Associate Professor, Osaka University

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