JGP Journal of General Physiology

EDITORIAL

Excitation–Contraction Coupling

# Excitation–contraction coupling in cardiac, skeletal, and smooth muscle

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The term "excitation–contraction (EC) coupling" was introduced by Alexander Sandow (Sandow, 1952) as "the entire sequence of reactions—excitation, inward acting link, and activation of contraction"—in skeletal muscle. It is evidence of Sandow's foresight that 70 years later, a large community of researchers still recognizes EC coupling as its field. EC coupling now includes all muscles and has spawned like-named franchises for secretion, transcription, and other "couplings." Not only is EC coupling still key to understanding the normal physiology of muscle, but it is widely accepted that alterations of EC coupling underlie a wide spectrum of conditions including muscle fatigue (Allen et al., 2008), congenital myopathy (Jungbluth et al., 2018), hypertension (Koide et al., 2021), and heart failure (Dibb et al., 2022).

Although Sandow coined the term, interest in EC coupling can be traced back over two centuries. The history begins in Bologna, then in the Papal States, when Luigi Galvani started the field of bioelectricity in the 1780s with the first demonstration of EC coupling. More than a century later, the story moves to Pavia where Emilio Veratti (Veratti, 1902) applied the techniques of his mentor Camillo Golgi to demonstrate the presence of transverse tubules (see Franzini-Armstrong, 2018 for an account). The adventure then relocates to London, where A.V. Hill ruled out diffusion as a mechanism for the propagation of excitation inside muscle (Hill, 1948)—thus providing significance to the structures described by Veratti. This line of research reached another landmark with the demonstration by Hodgkin and Horowicz (1960) that in skeletal muscle it is membrane depolarization which links excitation to release of $Ca^{2+}$ from the sarcoplasmic reticulum (SR), as subsequently shown by the involvement of charge movement in the membrane (Schneider and Chandler, 1973). In contrast, in cardiac muscle, calcium release from the SR is activated by an influx of calcium (calcium-induced calcium release; Barcenas-Ruiz and Wier, 1987; Cannell et al., 1987). Finally, the richness of roles that evolution has provided for the link between the SR and surface membrane is illustrated in vascular smooth muscle, where localized calcium release from the SR activates potassium channels, thereby promoting relaxation (Nelson et al., 1995). In cardiac muscle, the extrusion of this calcium through the electrogenic Na/Ca exchanger modulates the action potential, feeding back on excitation, but is also causally involved in cardiac arrhythmias (Sipido et al., 2006).

A reason for the persistence of the interest in EC coupling, and the expansion of its formulation to other areas of cell function, was also previewed in the concluding statement of Sandow's remarkable article: "We therefore suggest that, in the living muscle, activation of the contractile material (in the sense of Hill) may be attributed to the enzymatic activation of the myosin-ATPase system by Ca++" (Sandow, 1952). As proposed (and made abundantly clear in the cover illustration by Werner Melzer), calcium is the common link that runs through these fields. The present *JGP* special issue samples current research in the EC coupling field as it is now understood in the three major types of muscle. The number, scientific quality, and broad variety of the contributions contained in this issue reflects the continued vibrancy of the field, as indicated by the combined enthusiastic response of researchers to the journal's appeal.

While celebrating advances in the field, it is also appropriate to note the deaths over the last year of two of the pioneering giants of the EC coupling field who were both born in 1937. Alex Fabiato pioneered our understanding of calcium-induced calcium release in cardiac muscle (Fabiato, 1983, 1985). Gerhard Meissner has provided us with so much of what is now known about the structure, function, and regulation of the ryanodine receptor (RyR; Lai et al., 1988; Meissner, 1994).

In addition to the papers in this special issue, *JGP* has recently published many other insights in this area. This includes work on the link between the $Ca^{2+}$ channel and activation of $Ca^{2+}$ release from the SR in skeletal muscle (Savalli et al., 2021; Wu et al., 2021), measurement of localized changes of $Ca^{2+}$ concentration

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This work is part of a special issue on excitation–contraction coupling.

(Sanchez et al., 2021), as well as the effects of disease on the transverse tubular network (Romer et al., 2021). Another developing area in skeletal muscle concerns the mechanisms by which $Ca^{2+}$ enters the cell to compensate for that which is pumped out during activation (Michelucci et al., 2020; Uwera et al., 2020; Jaque-Fernández et al., 2021; Meizoso-Huesca and Launikonis, 2021). In cardiac muscle, in addition to considering the relationship between EC coupling and contractile force (Mijailovich et al., 2021), a considerable amount of the published work links alterations in EC coupling to the development of arrhythmias (Cely-Ortiz et al., 2020; Ahern et al., 2021; Angelini et al., 2021; Dries et al., 2021; Millet et al., 2021; Moise et al., 2021), as well as the relationship between myofilament proteins, EC coupling, and arrhythmias (Greenberg and Tardiff, 2021; Tobacman and Cammarato, 2021).

Finally, the cohesion and strong sense of identity of the EC coupling community has been fostered and maintained for many decades by scientific meetings. The interruptions in research interactions and community caused by the COVID-19 pandemic inspired the *JGP* editors to attempt to fill this void by organizing a virtual symposium and this special issue. The specifics of the Symposium, including videos of some of the platform presentations (http://physiol.gy/3QATs8H) and poster abstracts, have been published alongside the issue. The rich expanse of this special issue is in good measure a consequence of the success of the Symposium. We are grateful to all the colleagues who contributed to this (listed in supplemental text).

## References


Ahern, B.M., A. Sebastian, B.M. Levitan, J. Goh, D.A. Andres, and J. Satin. 2021. L-type channel inactivation balances the increased peak calcium current due to absence of Rad in cardiomyocytes. *J. Gen. Physiol.* 153: e202012854. https://doi.org/10.1085/jgp.202012854

Allen, D.G., G.D. Lamb, and H. Westerblad. 2008. Impaired calcium release during fatigue. *J. Appl. Physiol.* 104:296–305. https://doi.org/10.1152/japplphysiol.00908.2007

Angelini, M., A. Pezhouman, N. Savalli, M.G. Chang, F. Steccanella, K. Scranton, G. Calmettes, M. Ottolia, A. Pantazis, H.S. Karagueuzian, et al. 2021. Suppression of ventricular arrhythmias by targeting late L-type $Ca^{2+}$ current. *J. Gen. Physiol.* 153:e202012584. https://doi.org/10.1085/jgp.202012584

Barcenas-Ruiz, L., and W.G. Wier. 1987. Voltage dependence of intracellular $[Ca^{2+}]_i$ transients in Guinea pig ventricular myocytes. *Circ. Res.* 61: 148–154. https://doi.org/10.1161/01.res.61.1.148

Cannell, M.B., J.R. Berlin, and W.J. Lederer. 1987. Effect of membrane potential changes on the calcium transient in single rat cardiac muscle cells. *Science.* 238:1419–1423. https://doi.org/10.1126/science.2446391

Cely-Ortiz, A., J.I. Felice, L.A. Díaz-Zegarra, C.A. Valverde, M. Federico, J. Palomeque, X.H.T. Wehrens, E.G. Kranias, E.A. Aiello, E.C. Lascano, et al. 2020. Determinants of $Ca^{2+}$ release restitution: Insights from genetically altered animals and mathematical modeling. *J. Gen. Physiol.* 152:e201912512. https://doi.org/10.1085/jgp.201912512

Dibb, K.M., W.E. Louch, and A.W. Trafford. 2022. Cardiac transverse tubules in physiology and heart failure. *Annu. Rev. Physiol.* 84:229–255. https://doi.org/10.1146/annurev-physiol-061121-040148

Dries, E., I. Bardi, R. Nunez-Toldra, B. Meijlink, and C.M. Terracciano. 2021. CaMKII inhibition reduces arrhythmogenic $Ca^{2+}$ events in subendocardial cryoinjured rat living myocardial slices. *J. Gen. Physiol.* 153: e202012737. https://doi.org/10.1085/jgp.202012737

Fabiato, A. 1983. Calcium-induced release of calcium from the cardiac sarcoplasmic reticulum. *Am. J. Physiol.* 245:C1–C14. https://doi.org/10.1152/ajpcell.1983.245.1.C1

Fabiato, A. 1985. Time and calcium dependence of activation and inactivation of calcium-induced release of calcium from the sarcoplasmic reticulum of a skinned canine cardiac Purkinje cell. *J. Gen. Physiol.* 85:247–289. https://doi.org/10.1085/jgp.85.2.247

Franzini-Armstrong, C. 2018. The relationship between form and function throughout the history of excitation–contraction coupling. *J. Gen. Physiol.* 150:189–210. https://doi.org/10.1085/jgp.201711889

Greenberg, M.J., and J.C. Tardiff. 2021. Complexity in genetic cardiomyopathies and new approaches for mechanism-based precision medicine. *J. Gen. Physiol.* 153:e202012662. https://doi.org/10.1085/jgp.202012662

Hill, A.V. 1948. On the time required for diffusion and its relation to processes in muscle. *Proc. R. Soc. B: Biol. Sci.* 135:446–453. https://doi.org/10.1098/rspb.1948.0022

Hodgkin, A.L., and P. Horowicz. 1960. Potassium contractures in single muscle fibres. *J. Physiol.* 153:386–403. https://doi.org/10.1113/jphysiol.1960.sp006541

Jaque-Fernández, F., G. Jorquera, J. Troc-Gajardo, F. Pietri-Rouxel, C. Gentil, S. Buvinic, B. Allard, E. Jaimovich, V. Jacquemond, and M. Casas. 2021. Pannexin-1 and CaV1.1 show reciprocal interaction during excitation–contraction and excitation–transcription coupling in skeletal muscle. *J. Gen. Physiol.* 153:e202012635. https://doi.org/10.1085/jgp.202012635

Jungbluth, H., S. Treves, F. Zorzato, A. Sarkozy, J. Ochala, C. Sewry, R. Phadke, M. Gautel, and F. Muntoni. 2018. Congenital myopathies: Disorders of excitation–contraction coupling and muscle contraction. *Nat. Rev. Neurol.* 14:151–167. https://doi.org/10.1038/nrneurol.2017.191

Koide, M., O.F. Harraz, F. Dabertrand, T.A. Longden, H.R. Ferris, G.C. Wellman, D.C. Hill-Eubanks, A.S. Greenstein, and M.T. Nelson. 2021. Differential restoration of functional hyperemia by antihypertensive drug classes in hypertension-related cerebral small vessel disease. *J. Clin. Invest.* 131:149029. https://doi.org/10.1172/jci149029

Lai, F.A., H.P. Erickson, E. Rousseau, Q.Y. Liu, and G. Meissner. 1988. Purification and reconstitution of the calcium release channel from skeletal muscle. *Nature.* 331:315–319. https://doi.org/10.1038/331315a0

Meissner, G. 1994. Ryanodine receptor/$Ca^{2+}$ release channels and their regulation by endogenous effectors. *Annu. Rev. Physiol.* 56:485–508. https://doi.org/10.1146/annurev.ph.56.030194.002413

Meizoso-Huesca, A., and B.S. Launikonis. 2021. The Orai1 inhibitor BTP2 has multiple effects on $Ca^{2+}$ handling in skeletal muscle. *J. Gen. Physiol.* 153: e202012747. https://doi.org/10.1085/jgp.202012747

Michelucci, A., S. Boncompagni, L. Pietrangelo, T. Takano, F. Protasi, and R.T. Dirksen. 2020. Pre-assembled $Ca^{2+}$ entry units and constitutively active $Ca^{2+}$ entry in skeletal muscle of calsequestrin-1 knockout mice. *J. Gen. Physiol.* 152:e202012617. https://doi.org/10.1085/jgp.202012617

Mijailovich, S.M., M. Prodanovic, C. Poggesi, M.A. Geeves, and M. Regnier. 2021. Multiscale modeling of twitch contractions in cardiac trabeculae. *J. Gen. Physiol.* 153:e202012604. https://doi.org/10.1085/jgp.202012604

Millet, J., Y. Aguilar-Sanchez, D. Kornyeyev, M. Bazmi, D. Fainstein, J.A. Copello, and A.L. Escobar. 2021. Thermal modulation of epicardial $Ca^{2+}$ dynamics uncovers molecular mechanisms of $Ca^{2+}$ alternans. *J. Gen. Physiol.* 153:e202012568. https://doi.org/10.1085/jgp.202012568

Moise, N., H.L. Struckman, C. Dagher, R. Veeraraghavan, and S.H. Weinberg. 2021. Intercalated disk nanoscale structure regulates cardiac conduction. *J. Gen. Physiol.* 153:e202112897. https://doi.org/10.1085/jgp.202112897

Nelson, M.T., H. Cheng, M. Rubart, L.F. Santana, A.D. Bonev, H.J. Knot, and W.J. Lederer. 1995. Relaxation of arterial smooth muscle by calcium sparks. *Science.* 270:633–637. https://doi.org/10.1126/science.270.5236.633

Romer, S.H., S. Metzger, K. Peraza, M.C. Wright, D.S. Jobe, L.S. Song, M.M. Rich, B.D. Foy, R.J. Talmadge, and A.A. Voss. 2021. A mouse model of Huntington's disease shows altered ultrastructure of transverse tubules in skeletal muscle fibers. *J. Gen. Physiol.* 153:e202012637. https://doi.org/10.1085/jgp.202012637

Sanchez, C., C. Berthier, Y. Tourneur, L. Monteiro, B. Allard, L. Csernoch, and V. Jacquemond. 2021. Detection of $Ca^{2+}$ transients near ryanodine receptors by targeting fluorescent $Ca^{2+}$ sensors to the triad. *J. Gen. Physiol.* 153:e202012592. https://doi.org/10.1085/jgp.202012592

Sandow, A. 1952. Excitation–contraction coupling in muscular response. *Yale J. Biol. Med.* 25:176–201

Savalli, N., M. Angelini, F. Steccanella, J. Wier, F. Wu, M. Quinonez, M. DiFranco, A. Neely, S.C. Cannon, and R. Olcese. 2021. The distinct role of the four voltage sensors of the skeletal CaV1.1 channel in voltage-dependent activation. *J. Gen. Physiol.* 153:e202112915. https://doi.org/10.1085/jgp.202112915

Schneider, M.F., and W.K. Chandler. 1973. Voltage dependent charge movement of skeletal muscle: A possible step in excitation–contraction coupling. *Nature*. 242:244–246. https://doi.org/10.1038/242244a0

Sipido, K.R., A. Varro, and D. Eisner. 2006. Sodium calcium exchange as a target for antiarrhythmic therapy. *Handb. Exp. Pharmacol.* 159–199. https://doi.org/10.1007/3-540-29715-4_6

Tobacman, L.S., and A. Cammarato. 2021. Cardiomyopathic troponin mutations predominantly occur at its interface with actin and tropomyosin. *J. Gen. Physiol.* 153:e202012815.https://doi.org/10.1085/jgp.202012815

Uwera, F., T. Ammar, C. McRae, L.J. Hayward, and J.M. Renaud. 2020. Lower $Ca^{2+}$ enhances the $K^+$-induced force depression in normal and HyperKPP mouse muscles. *J. Gen. Physiol.* 152:e201912511. https://doi.org/10.1085/jgp.201912511

Veratti, E. 1902. Ricerche sulla fine struttura della fibra muscolare striata. *Mem. R. Ist. Lombardo, Cl. Sc. Mat. Nat.* 19:87–133.

Wu, F., M. Quinonez, and S.C. Cannon. 2021. Gating pore currents occur in CaV1.1 domain III mutants associated with HypoPP. *J. Gen. Physiol.* 153: e202112946. https://doi.org/10.1085/jgp.202112946