

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 changes to 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 Horowitz (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 and 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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(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 myofibrillar 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).

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