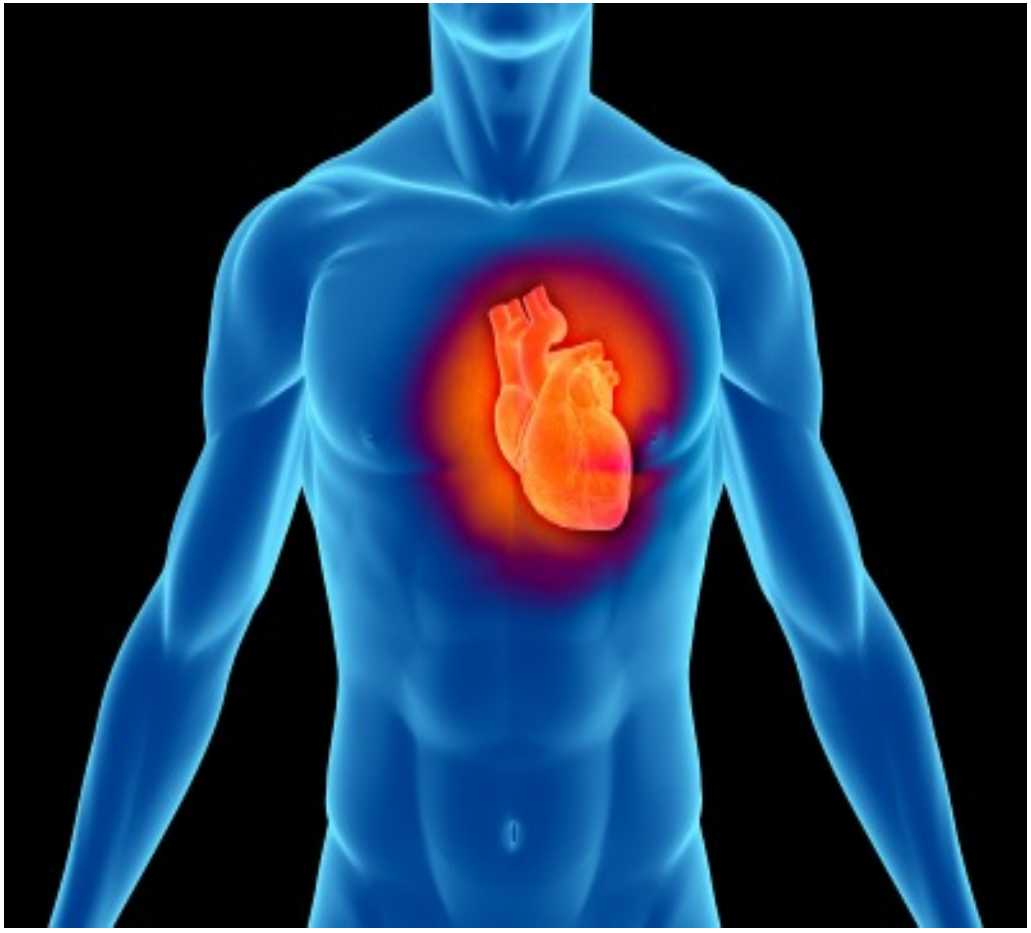
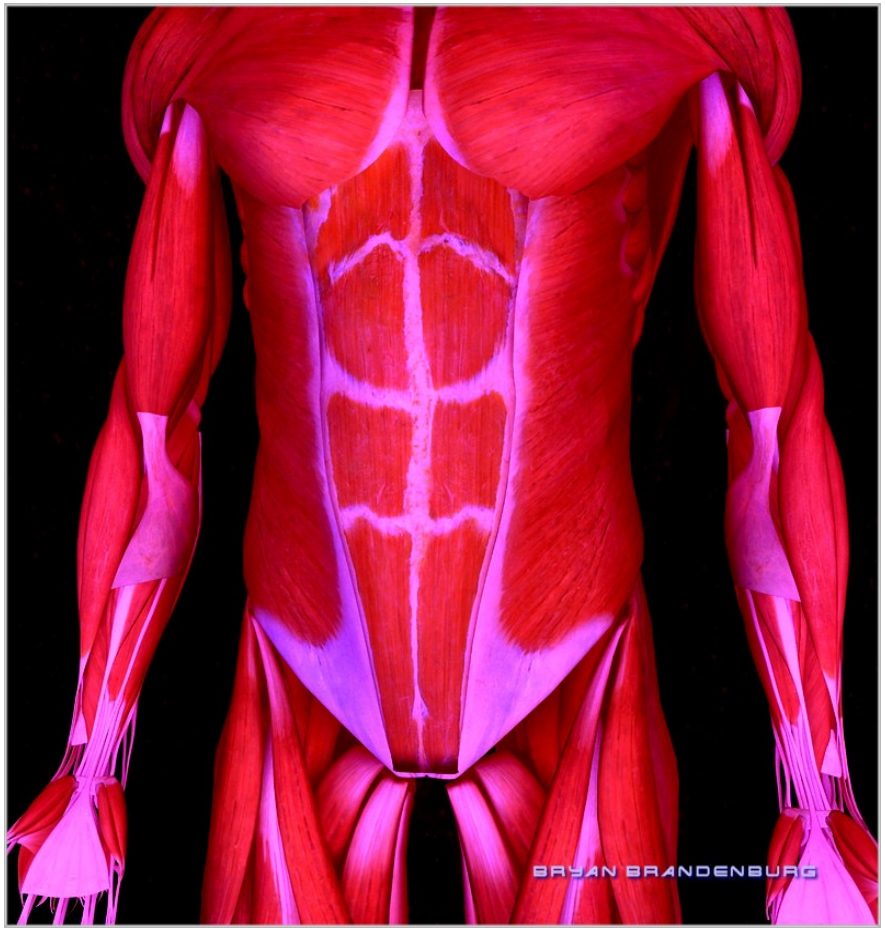
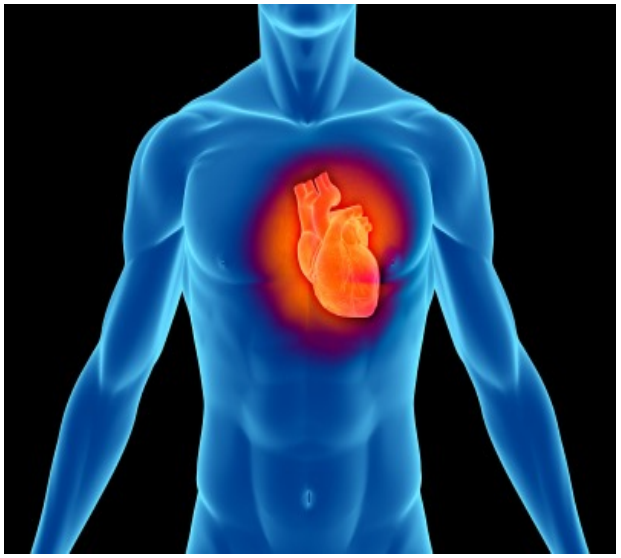
Muscle cells as an extraordinary example of transduction of electrical signals into Ca^{2+} signals

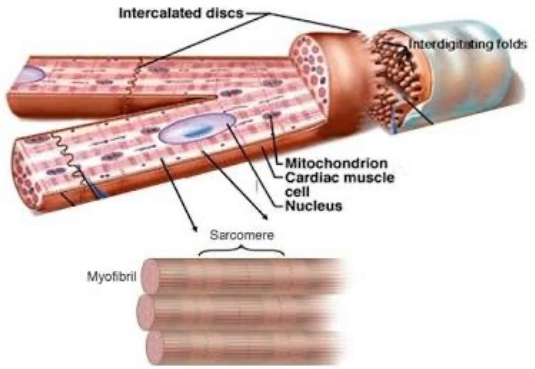




Cardiac muscle: transduction of electrical signals into "global" and "graded" Ca^{2+} signals



1. Synchronous contraction of sarcomeres



2. Graded strength of contraction
   (highest frequency: 180-200 beats/min)

Ultrastructure of cardiac muscle cells: regular distribution of the ON mechanisms

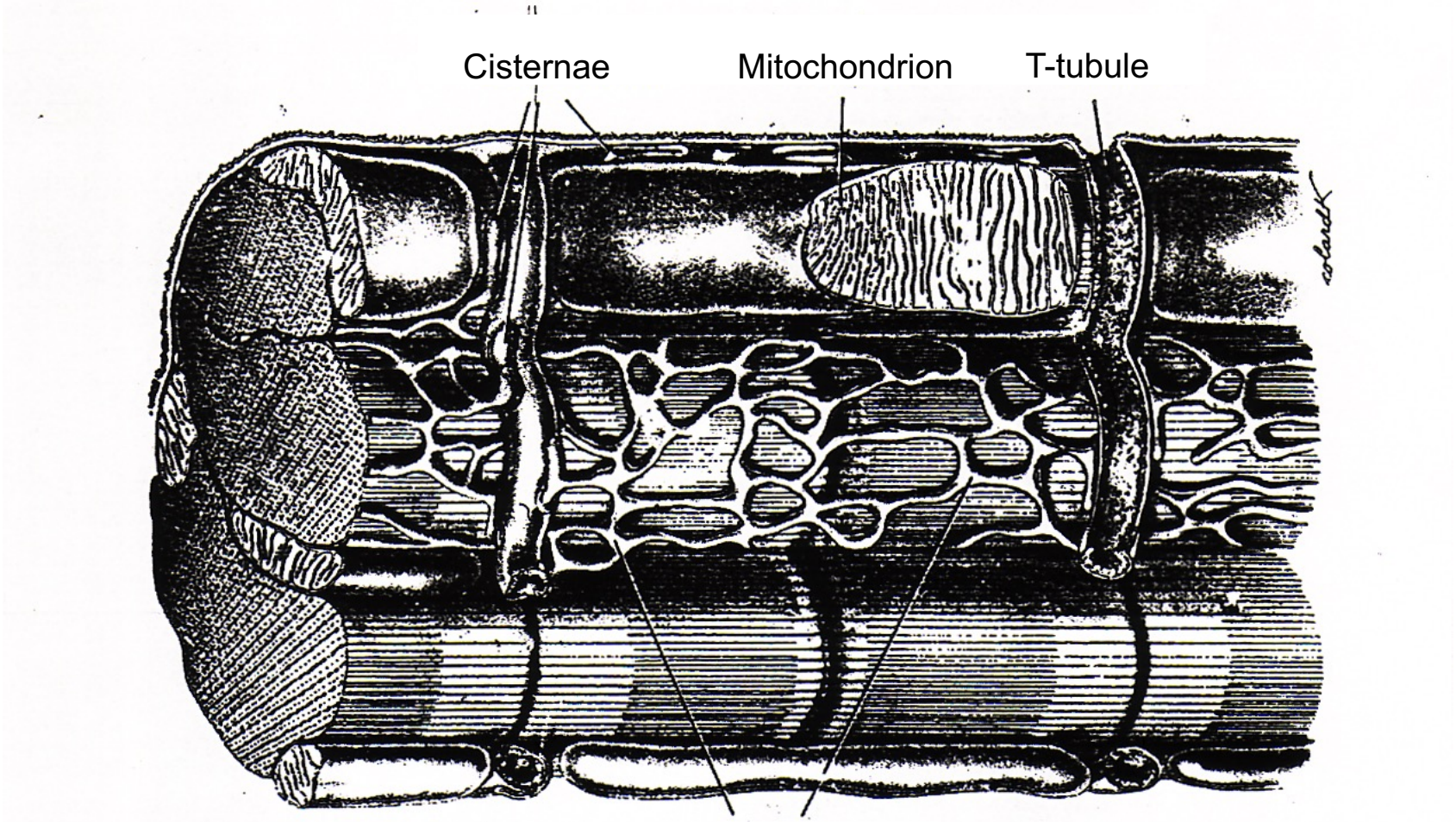


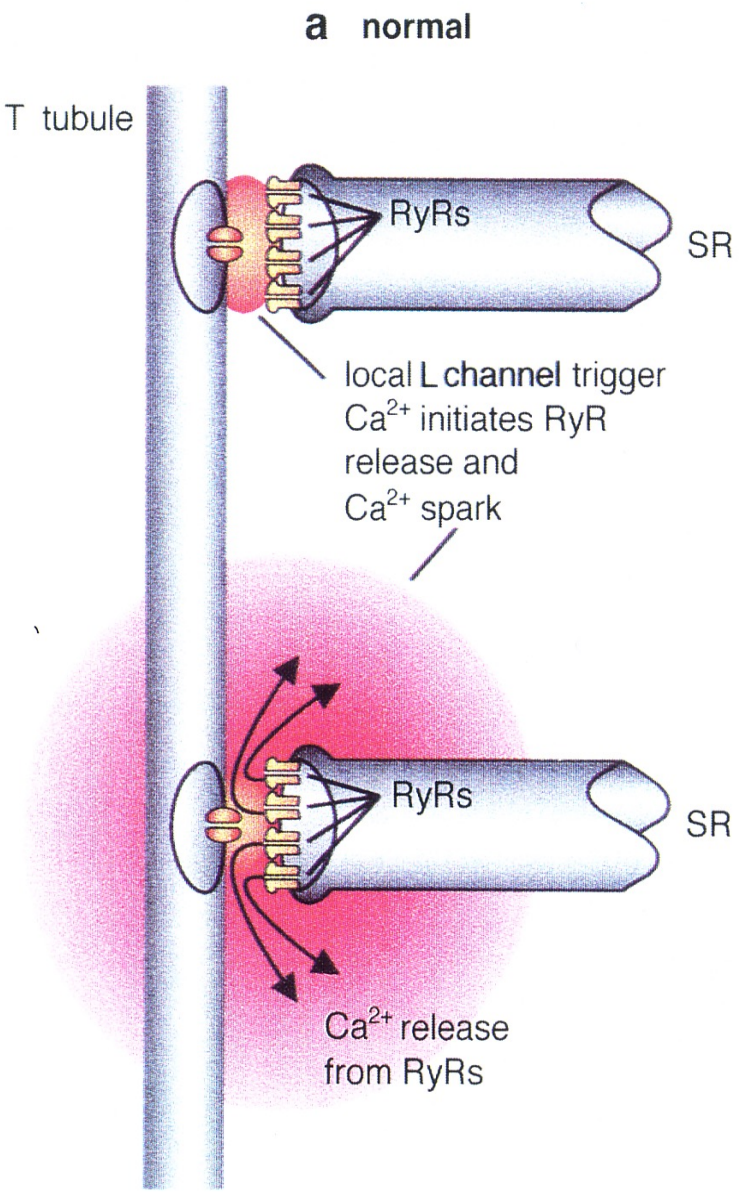
Figura 7.42. *Modello tridimensionale dei sistemi di membrane sarcoplasmatiche del muscolo cardiaco. Il reticolo sarcoplasmatico è organizzato meno complicatamente rispetto al muscolo scheletrico. I tubuli T invece sono ancora più evidenti che nel muscolo scheletrico e le loro membrane sono chiaromente in continuità con il sarcolemma. Si noti che essi sono situati a livello della linea Z.* [Da D. W. Fawcett e N. S. McNutt, 1969.]

The cardiac e-c coupling mechanism

Intracellular stores synchronously amplify the Ca^{2+} signal
(global Ca^{2+} signal)

Larger is the influx of Ca^{2+} larger is the amplification via CICR*
(graded Ca^{2+} signal, sympathetic nervous system control)

(*CICR = Ca^{2+}-induced Ca^{2+} release mechanism)



Uncoupling of voltage-dependent Ca^{2+} channels and Ca^{2+} releasing units

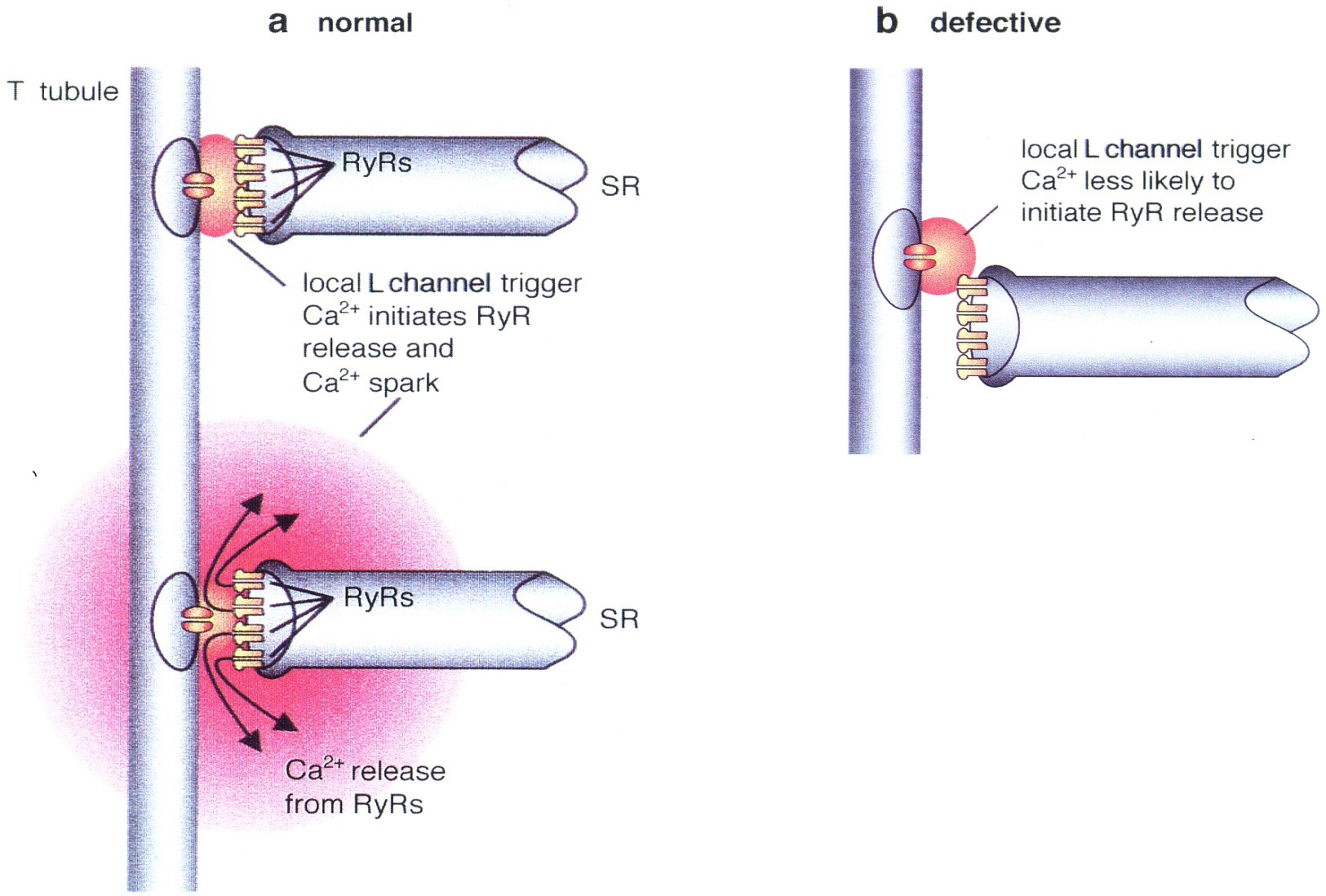
SCIENCE • VOL. 276 • 2 MAY 1997 •

Defective Excitation-Contraction Coupling in Experimental Cardiac Hypertrophy and Heart Failure

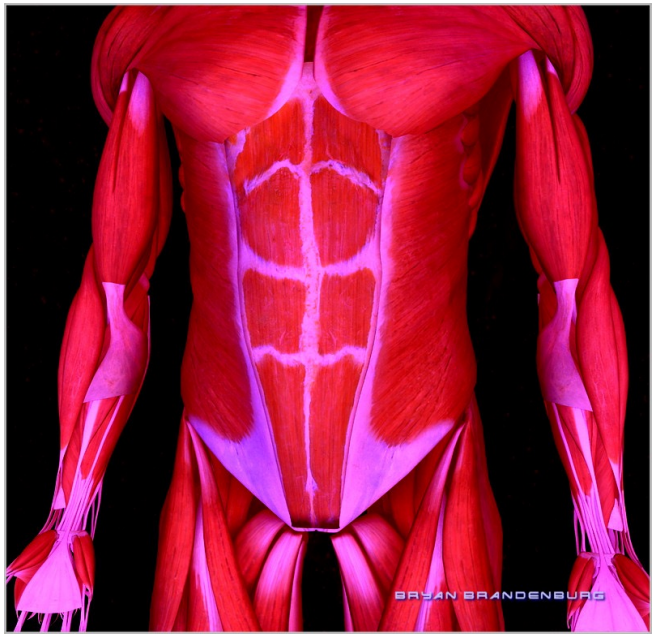
A. M. Gómez, H. H. Valdivia, H. Cheng, Miriam R. Lederer, L. F. Santana, M. B. Cannell, S. A. McCune, R. A. Altschuld, W. J. Lederer*

Cardiac hypertrophy and heart failure caused by high blood pressure were studied in single myocytes taken from hypertensive rats (Dahl SS/Jr) and SH-HF rats in heart failure. Confocal microscopy and patch-clamp methods were used to examine excitation-contraction (EC) coupling, and the relation between the plasma membrane calcium current (I_{Ca}) and evoked calcium release from the sarcoplasmic reticulum (SR), which was visualized as "calcium sparks." The ability of I_{Ca} to trigger calcium release from the SR in both hypertrophied and failing hearts was reduced. Because I_{Ca} density and SR calcium-release channels were normal, the defect appears to reside in a change in the relation between SR calcium-release channels and sarcolemmal calcium channels. β-Adrenergic stimulation largely overcame the defect in hypertrophic but not failing heart cells. Thus, the same defect in EC coupling that develops during hypertrophy may contribute to heart failure when compensatory mechanisms fail.

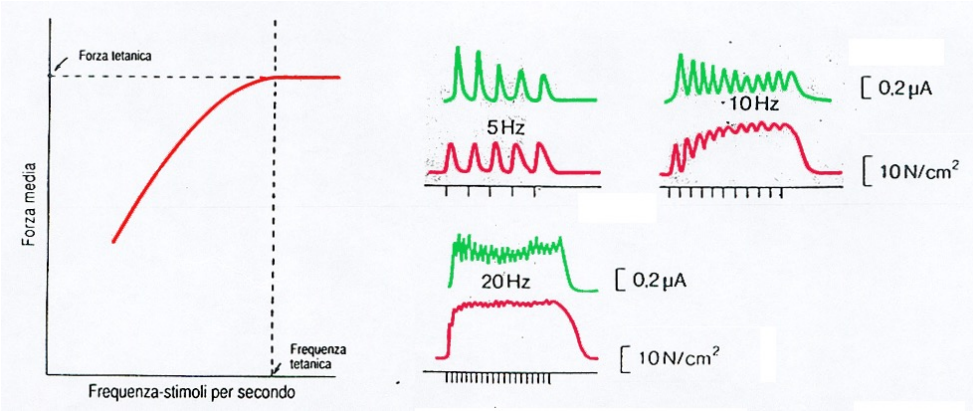
Uncoupling of voltage-dependent Ca^{2+} channels and Ca^{2+} releasing units



Skeletal muscle: rapid transduction of electrical signals into "global" Ca^{2+} signals



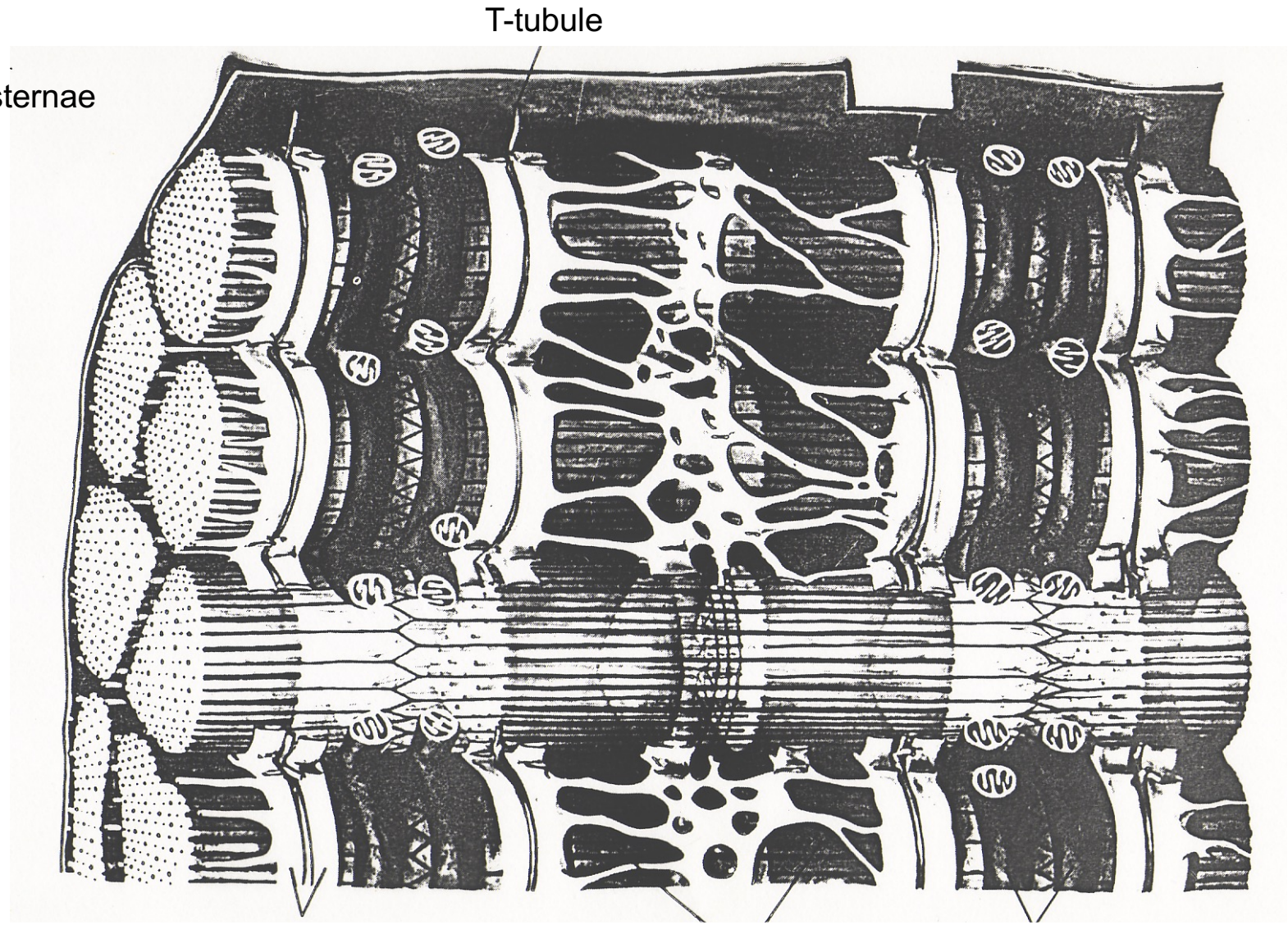
1. High stimulation frequency



2. Synchronous contraction of sarcomeres

Ultrastructure of skeletal muscle cells: widely distributed sarcoplasmic reticulum and triads

Triad:
1 T-tubule
2 Terminal cysternae



Contraction of skeletal muscle cells does not require Ca^{2+} influx

Biochim. Biophys. Acta, 267 (1972) 605–608

Twitches in the presence of ethylene glycol bis(β-aminoethyl ether)-*N,N'*-tetraacetic acid

C.M. ARMSTRONG, F.M BEZANILLA and P. HOROWICZ

SUMMARY

Single muscle fibers continue to twitch for up to 20 min when immersed in ethylene glycol bis(β-aminoethyl ether)-*N,N'*-tetraacetic acid (EGTA) solutions containing less than 10^{-8} M free calcium. Failure of the twitch results from reversible depolarization, which occurs after 15–20 min in EGTA. The results make it clear that external calcium or calcium in the transverse tubules play no essential part in action potential propagation or excitation–contraction coupling.

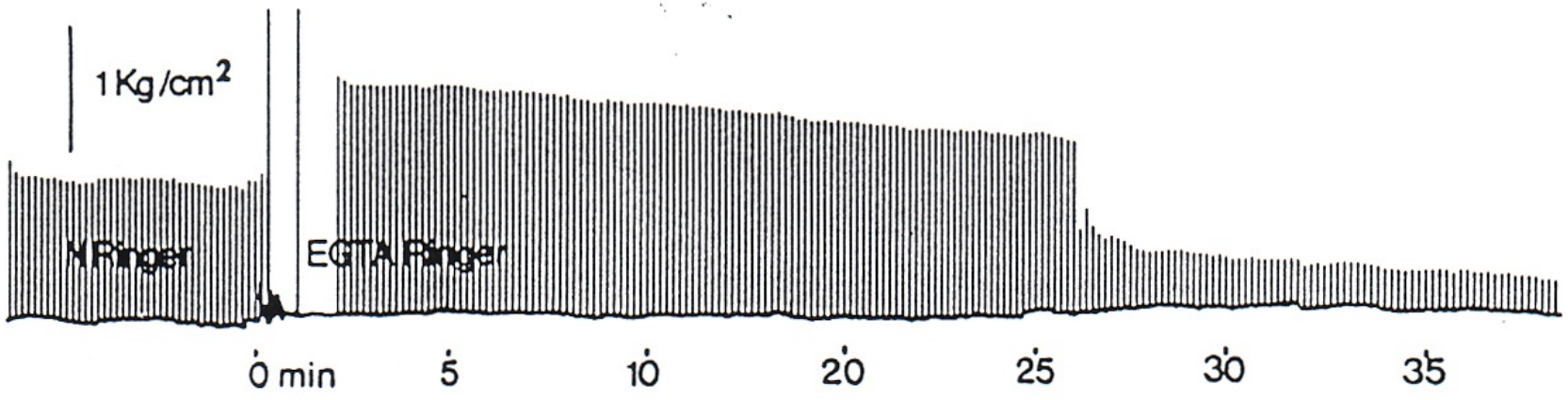
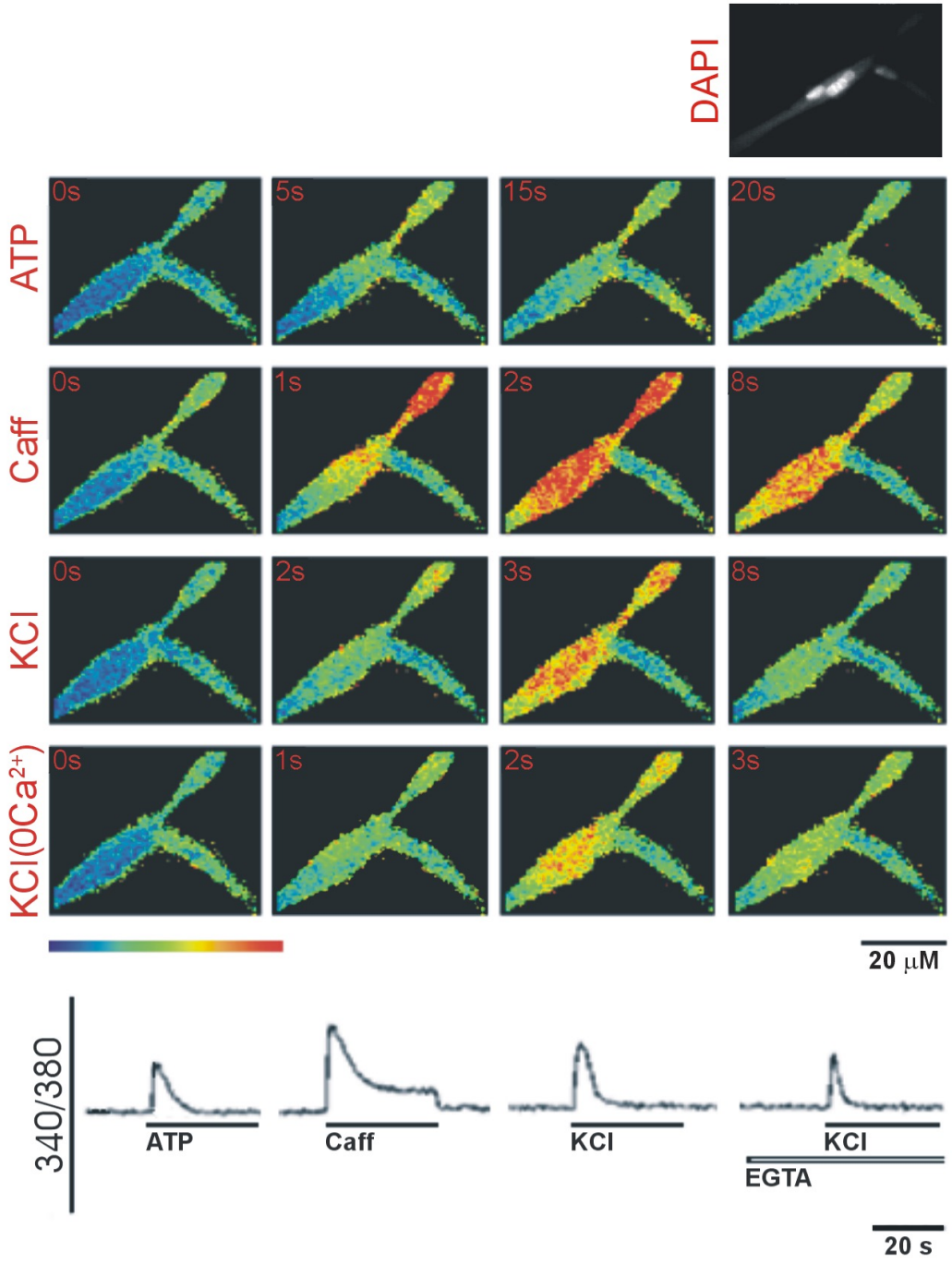


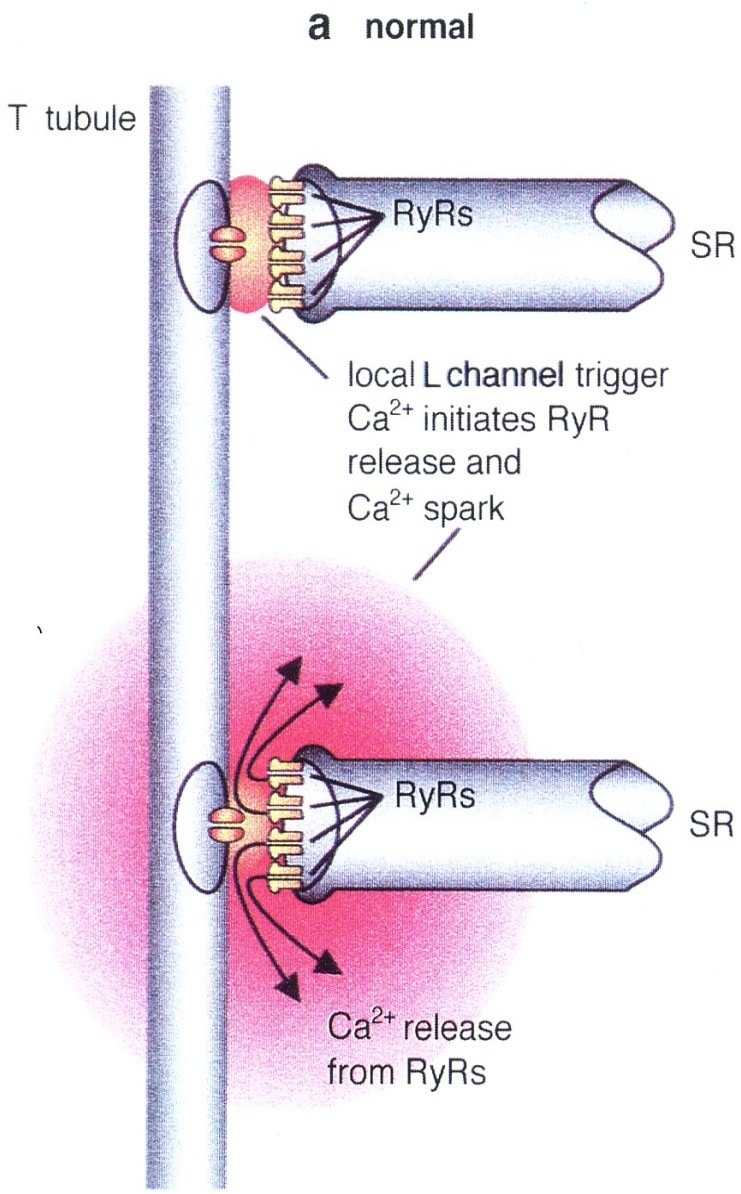
Fig. 1. Twitches in a single fiber on changing from normal Ringer's fluid to one containing 1 mM EGTA and no added calcium. Stimulation frequency, 0.1 Hz.

$[Ca^{2+}]_i$ transients in skeletal muscle cells



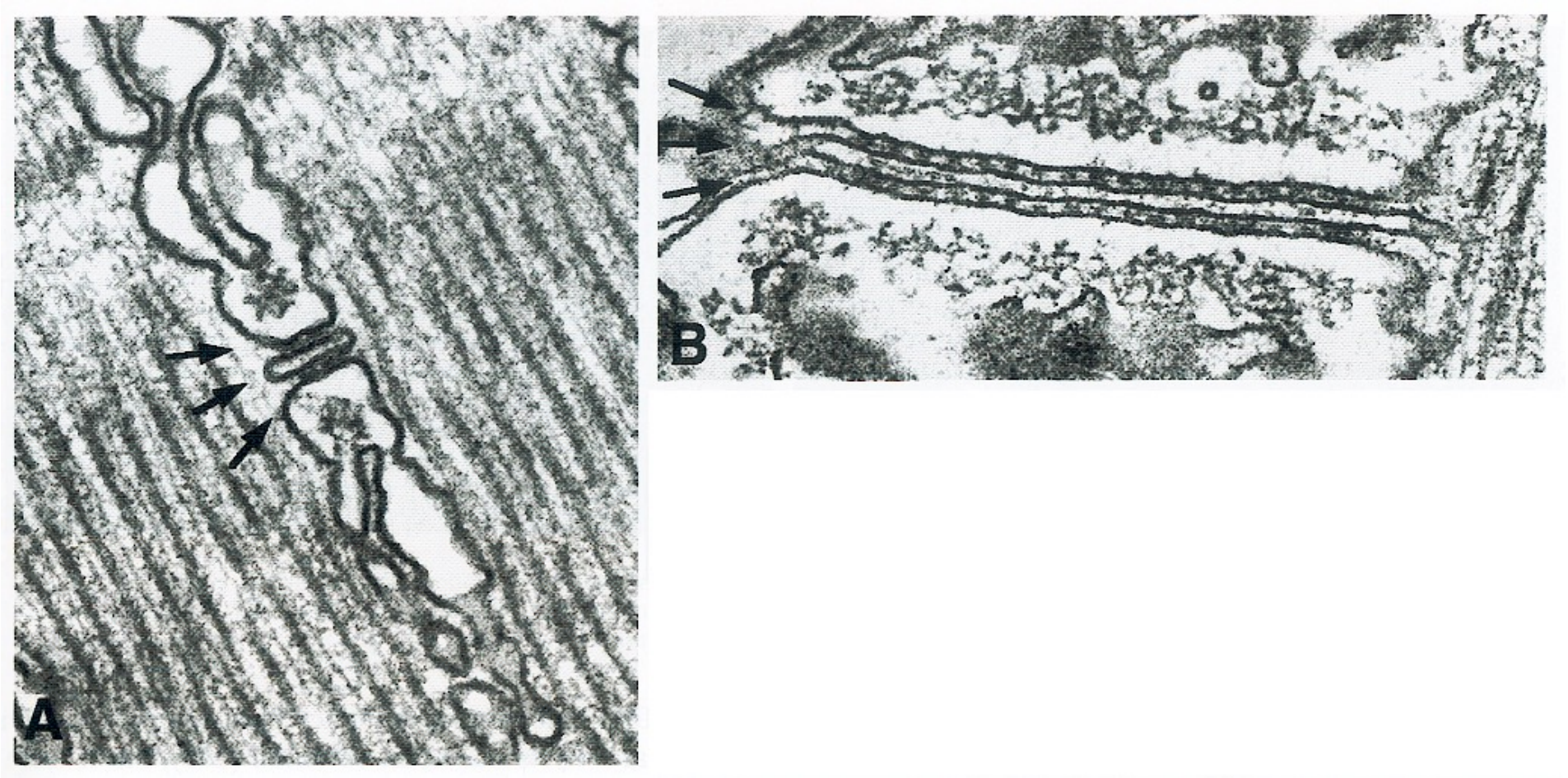
[Lorenzon *et al*. (2002), *Exp. Cell Res*. **278**: 84-91]

The cardiac e-c coupling mechanism requires extracellular Ca^{2+}

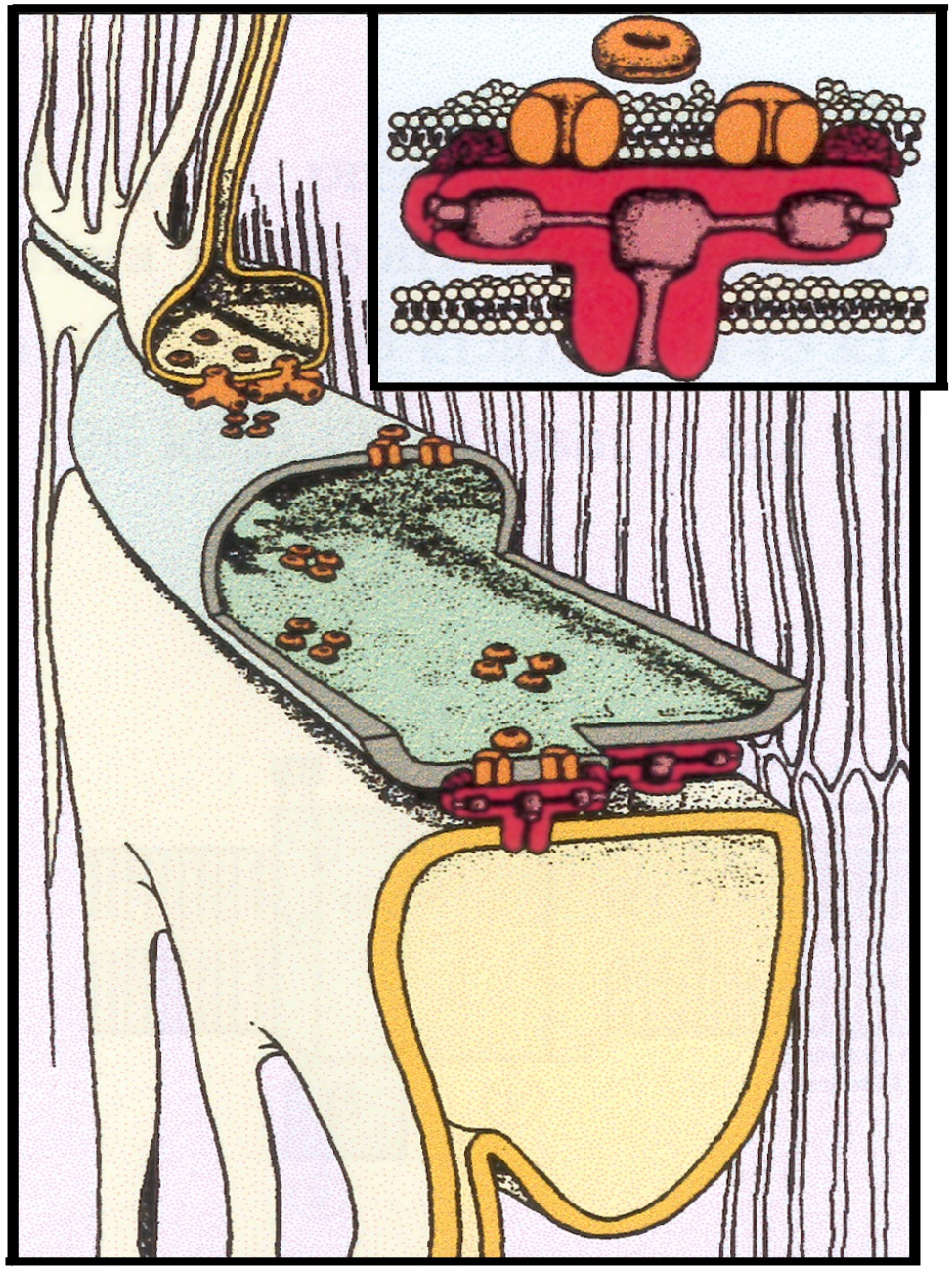


The morphology of triads: the release units

- foot and feet



Feet and triads



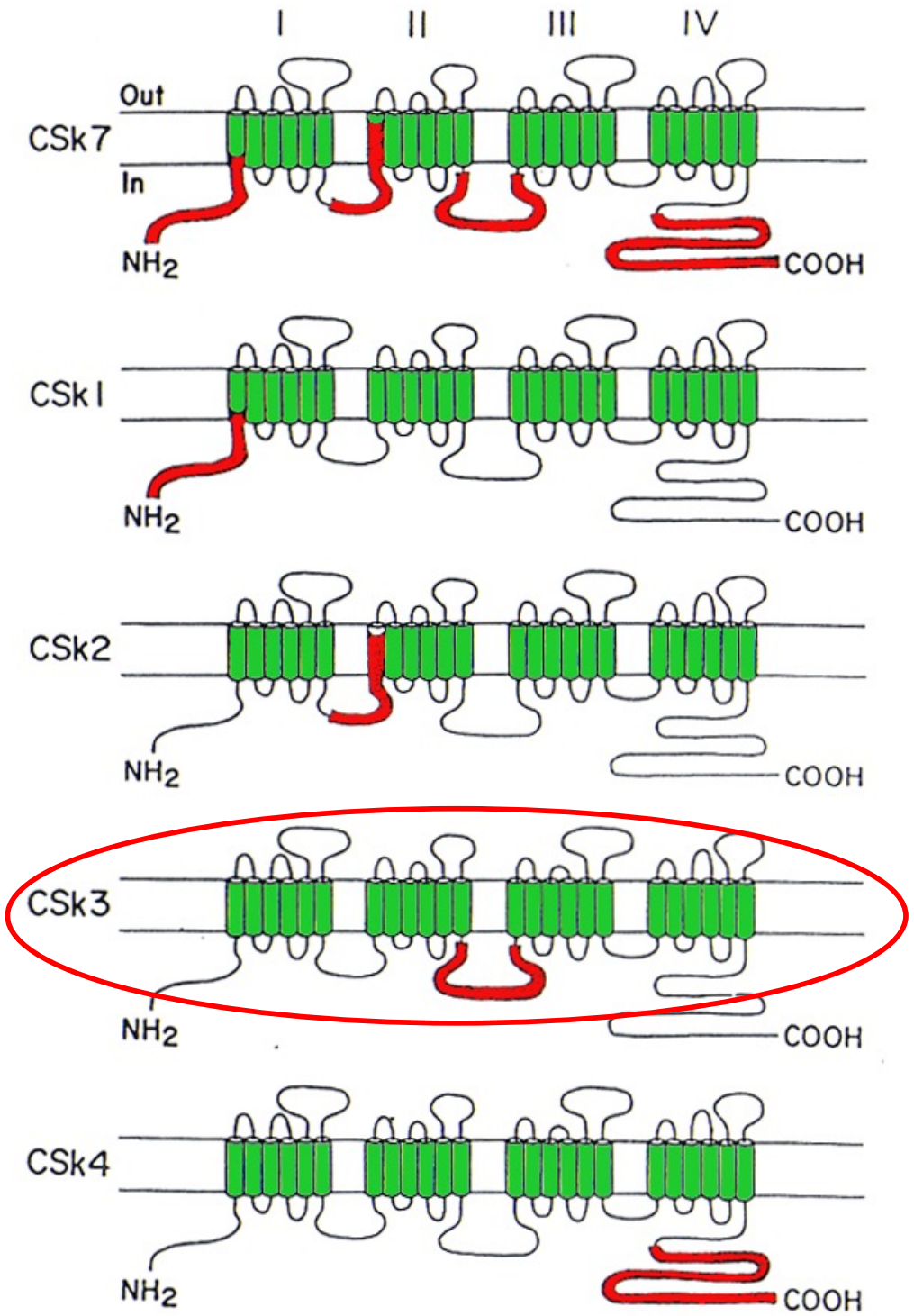
(modificata da Ríos and Pizarro, 1991)

NATURE · VOL 346 · 9 AUGUST 1990

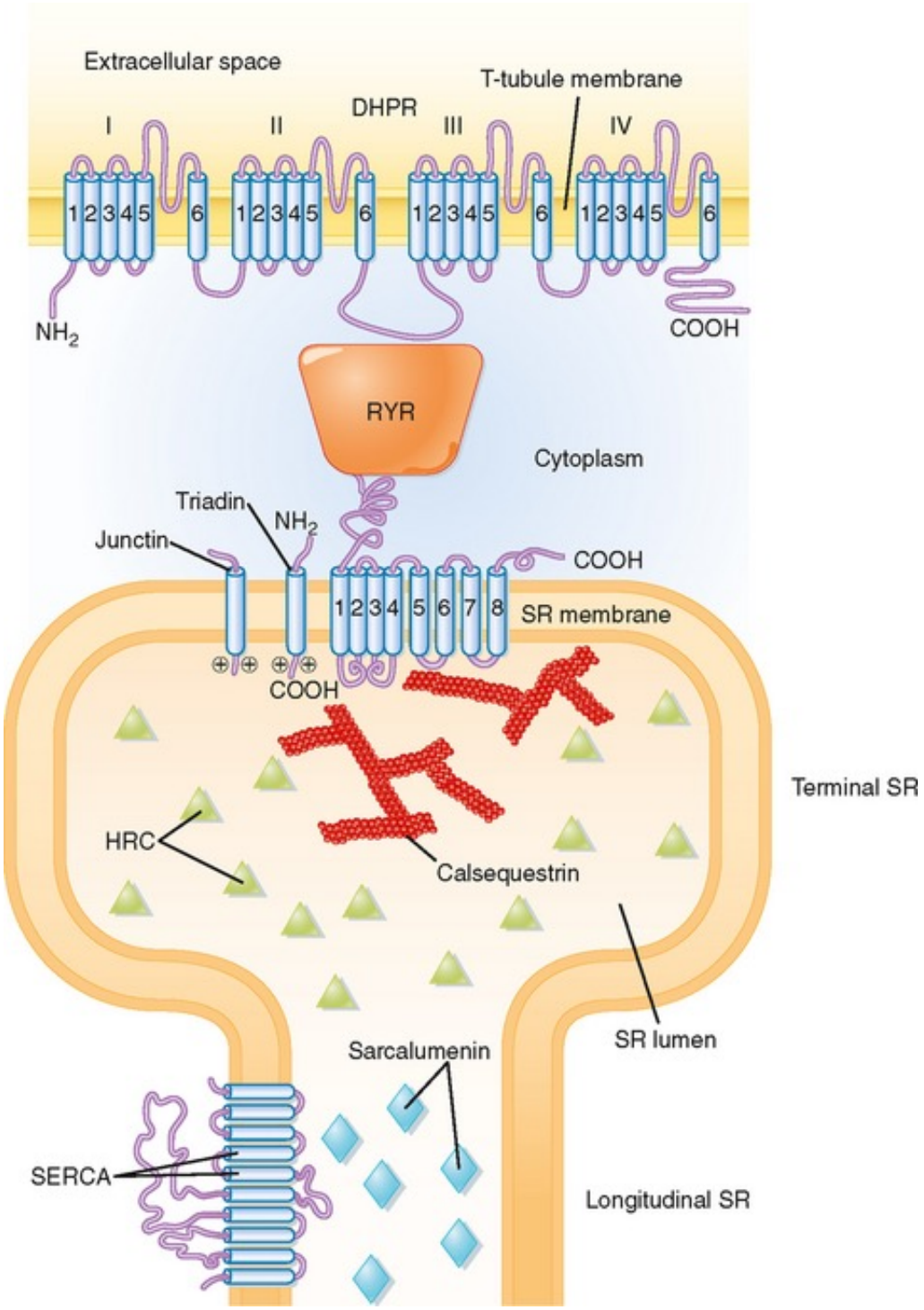
Regions of the skeletal muscle dihydropyridine receptor critical for excitation–contraction coupling

Tsutomu Tanabe*, Kurt G. Beam†‡, Brett A. Adams†, Tetsuhiro Niidome* & Shosaku Numa*‡

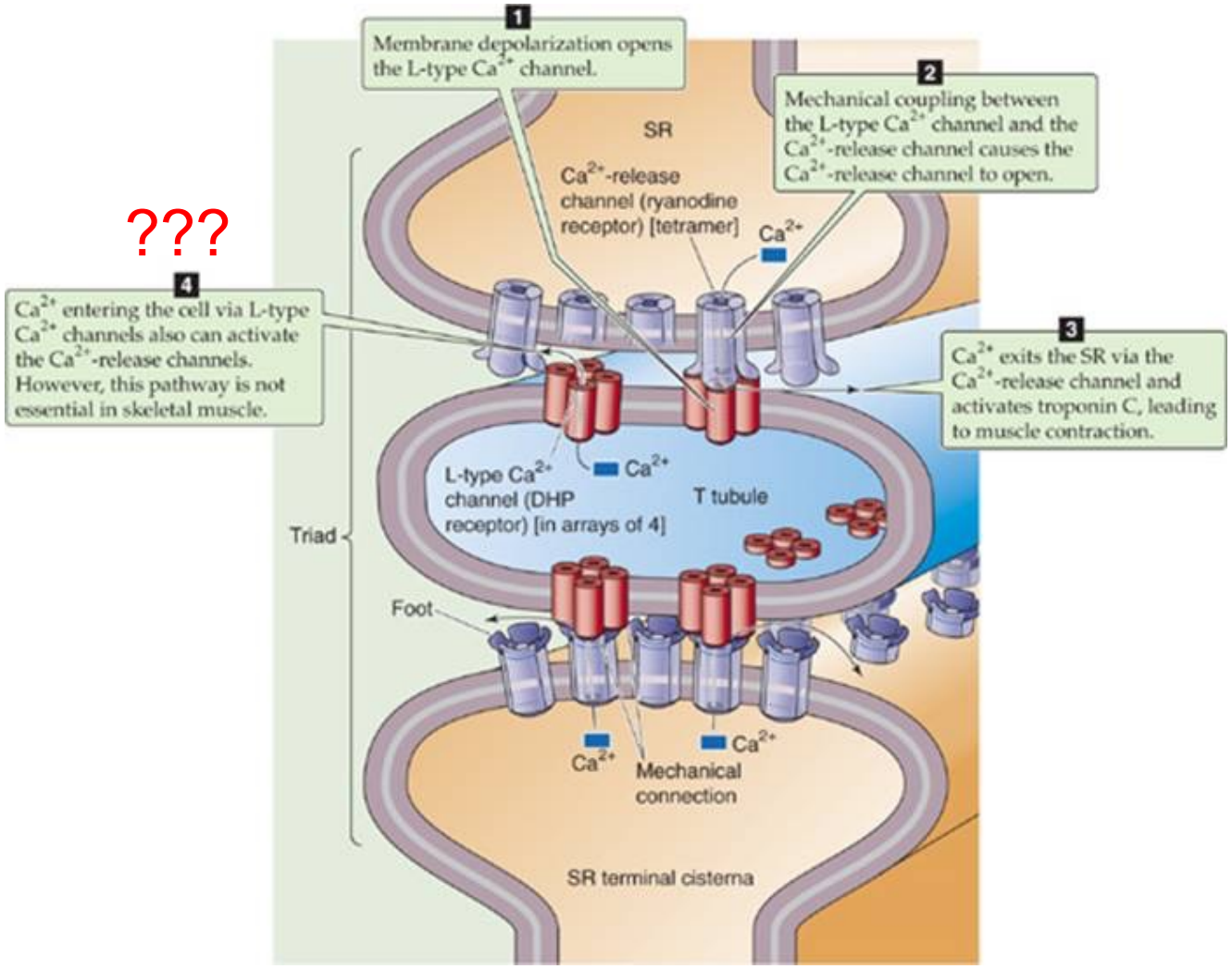
IT is thought that in skeletal muscle excitation–contraction (EC) coupling, the release of Ca^{2+} from the sarcoplasmic reticulum is controlled by the dihydropyridine (DHP) receptor in the transverse tubular membrane, where it serves as the voltage sensor[1–3]. We have shown previously[4] that injection of an expression plasmid carrying the skeletal muscle DHP receptor complementary DNA[3] restores EC coupling and L-type calcium current that are missing in skeletal muscle myotubes from mutant mice with muscular dysgenesis[5–9]. This restored coupling resembles normal skeletal muscle EC coupling[4], which does not require entry of extracellular Ca^{2+} (refs 10, 11). By contrast, injection into dysgenic myotubes of an expression plasmid carrying the cardiac DHP receptor cDNA[12] produces L-type calcium current and cardiac-type EC coupling[13], which does require entry of extracellular Ca^{2+} (refs 14–16). To identify the regions responsible for this important functional difference between the two structurally similar DHP receptors, we have expressed various chimaeric DHP receptor cDNAs in dysgenic myotubes. The results obtained indicate that the putative cytoplasmic region between repeats II and III of the skeletal muscle DHP receptor[3] is an important determinant of skeletal-type EC coupling.



The mechanical link



The skeletal excitation-contraction coupling mechanism



The Ca^{2+} release preceeds the Ca^{2+} influx

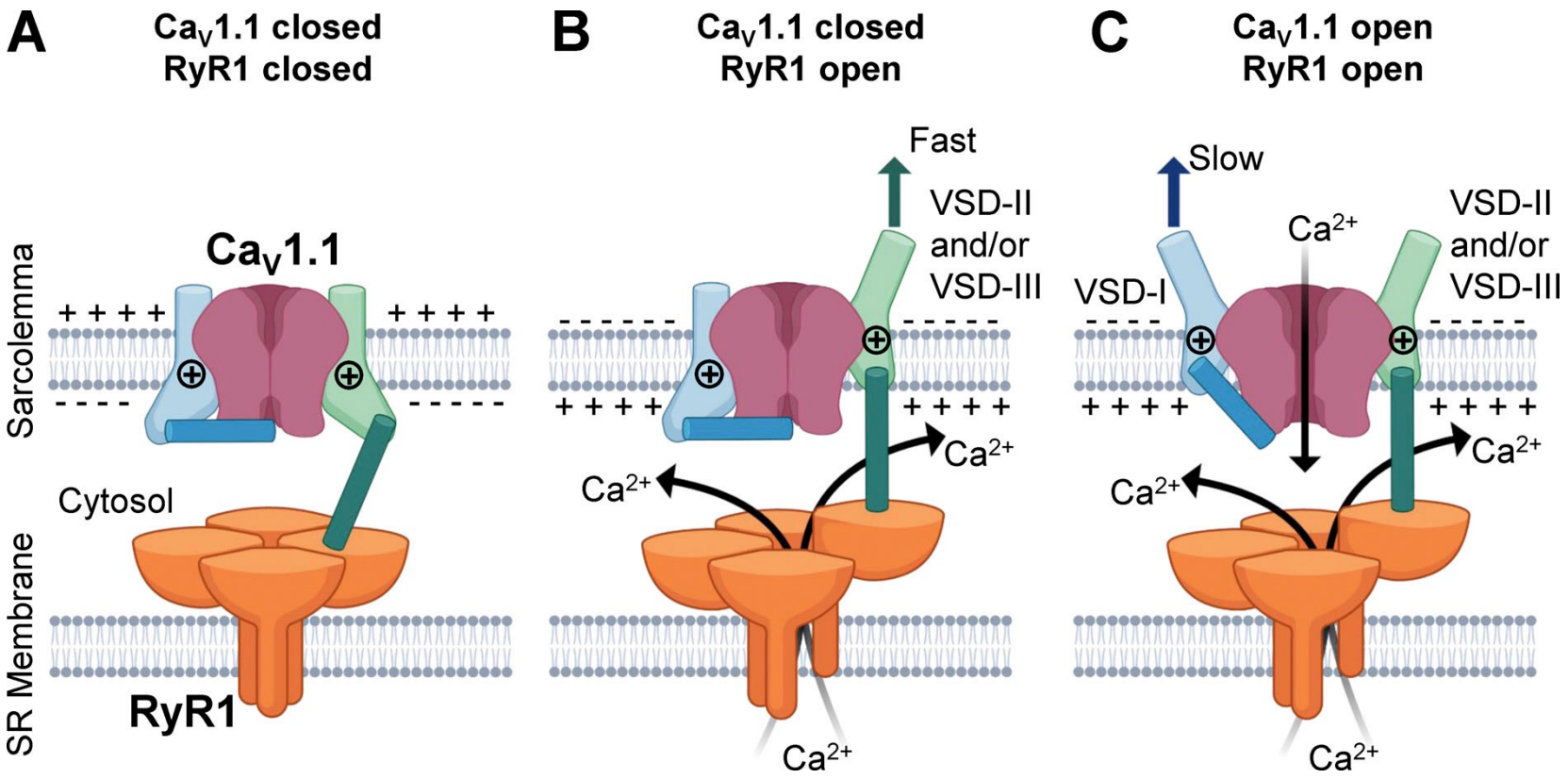


Figure 10. The role of CaV1.1 VSDs: fast and slow VSDs control RYR1 and CaV1.1 activation, respectively. (A) Scheme depicting the main players in the skeletal muscle EC coupling process: RYR1 (orange) is unable to sense depolarizations of the sarcolemma because of its localization in the intracellular SR. RYR1 is in physical contact (directly or via auxiliary proteins) with CaV1.1 channel (red), which is inserted in the sarcolemma and confers voltage dependence to RYR1. At rest, both channels are closed, and the skeletal muscle is relaxed. (B and C) Upon depolarization, the VSDs of CaV1.1 channels (blue and green) rearrange. VSD-II and VSD-III kinetics are compatible with the SR Ca^{2+}-release time course; thus, we propose that their movement mechanically and rapidly propagates to RYR1 (B), allowing for SR Ca^{2+}-release: VSD-II and/or VSD-III constitute the voltage sensor(s) of skeletal muscle contraction. On the other hand, VSD-I (blue) activates with slower kinetics compatible with CaV1.1 opening. Indeed, combining fluorometry, mutagenesis, and mathematical modeling, we demonstrated that VSD-I contributes the most energy to CaV1.1 activation (C). While each homotetrameric RYR1 interacts with four CaV1.1 channels, for clarity, the cartoon only depicts one CaV1.1 interacting with one monomer of RYR1. This scheme was created with http://www.BioRender.com.

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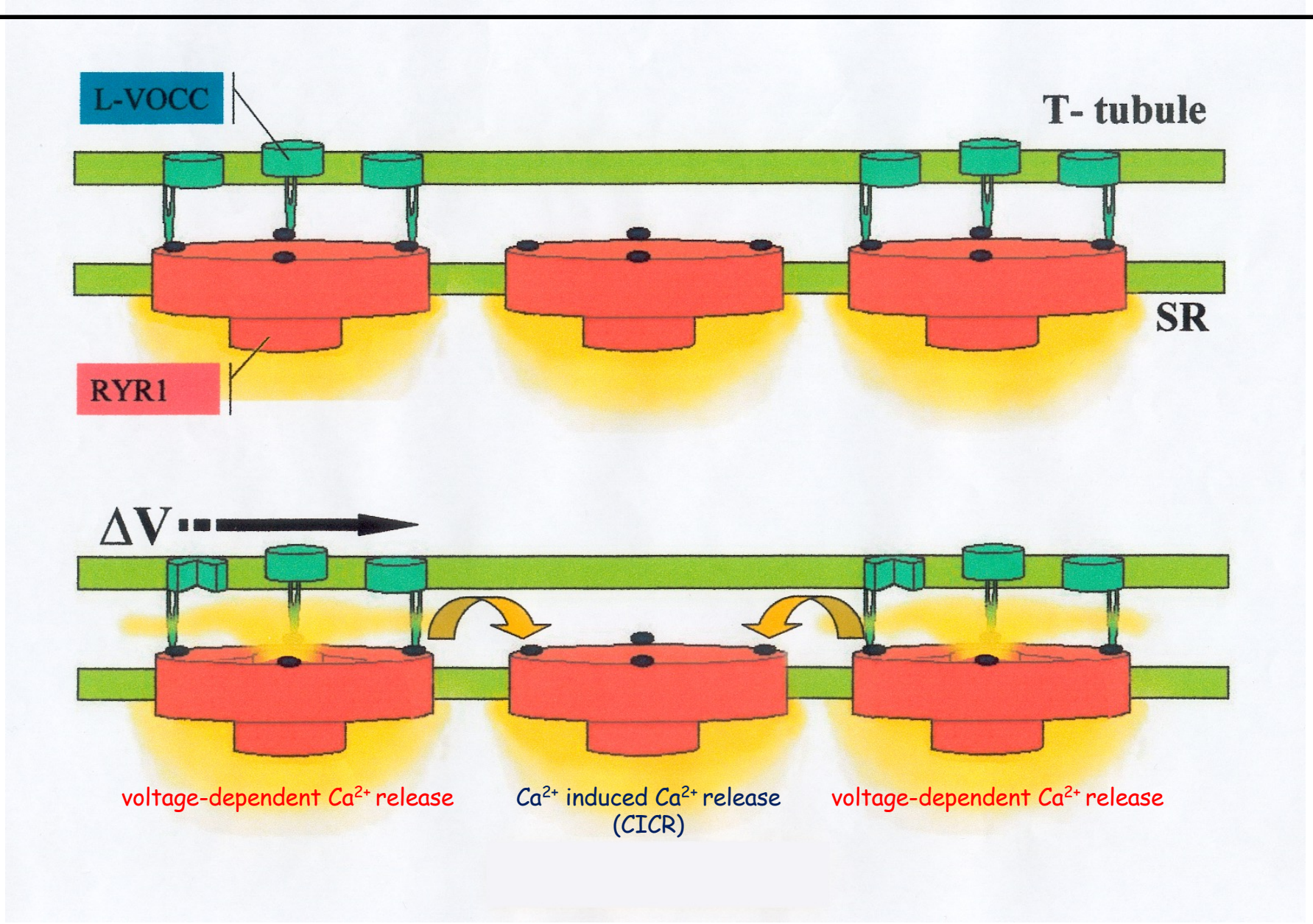
Coupled and uncoupled junctional RyRs



Activation of uncoupled junctional RyRs

- coordinated-gating hypothesis (RyRs are mechanically linked)

Coupled Gating Between Individual Skeletal Muscle Ca^{2+} Release Channels (Ryanodine Receptors)

Steven O. Marx, Karol Ondrias, Andrew R. Marks*

Excitation-contraction coupling in skeletal muscle requires the release of intracellular calcium ions (Ca^{2+}) through ryanodine receptor (RyR1) channels in the sarcoplasmic reticulum. Half of the RyR1 channels are activated by voltage-dependent Ca^{2+} channels in the plasma membrane. In planar lipid bilayers, RyR1 channels exhibited simultaneous openings and closings, termed "coupled gating." Addition of the channel accessory protein FKBP12 induced coupled gating, and removal of FKBP12 uncoupled channels. Coupled gating provides a mechanism by which RyR1 channels that are not associated with voltage-dependent Ca^{2+} channels can be regulated.

7 AUGUST 1998 VOL 281 SCIENCE