



The role of Ryanodine receptor: calcium homeostasis in cardiac cell

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Korean Heart Rhythm Society COI Disclosure

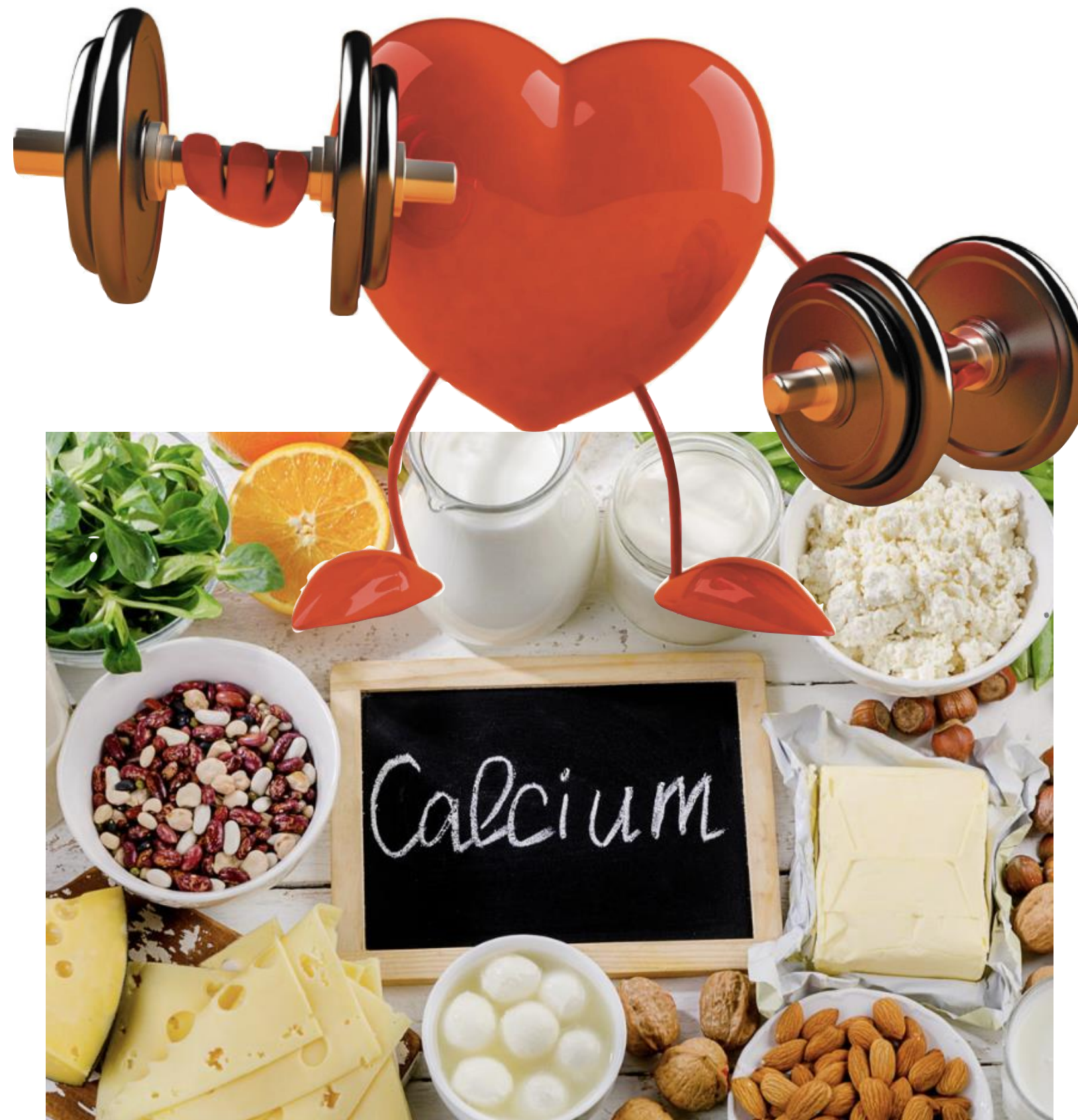
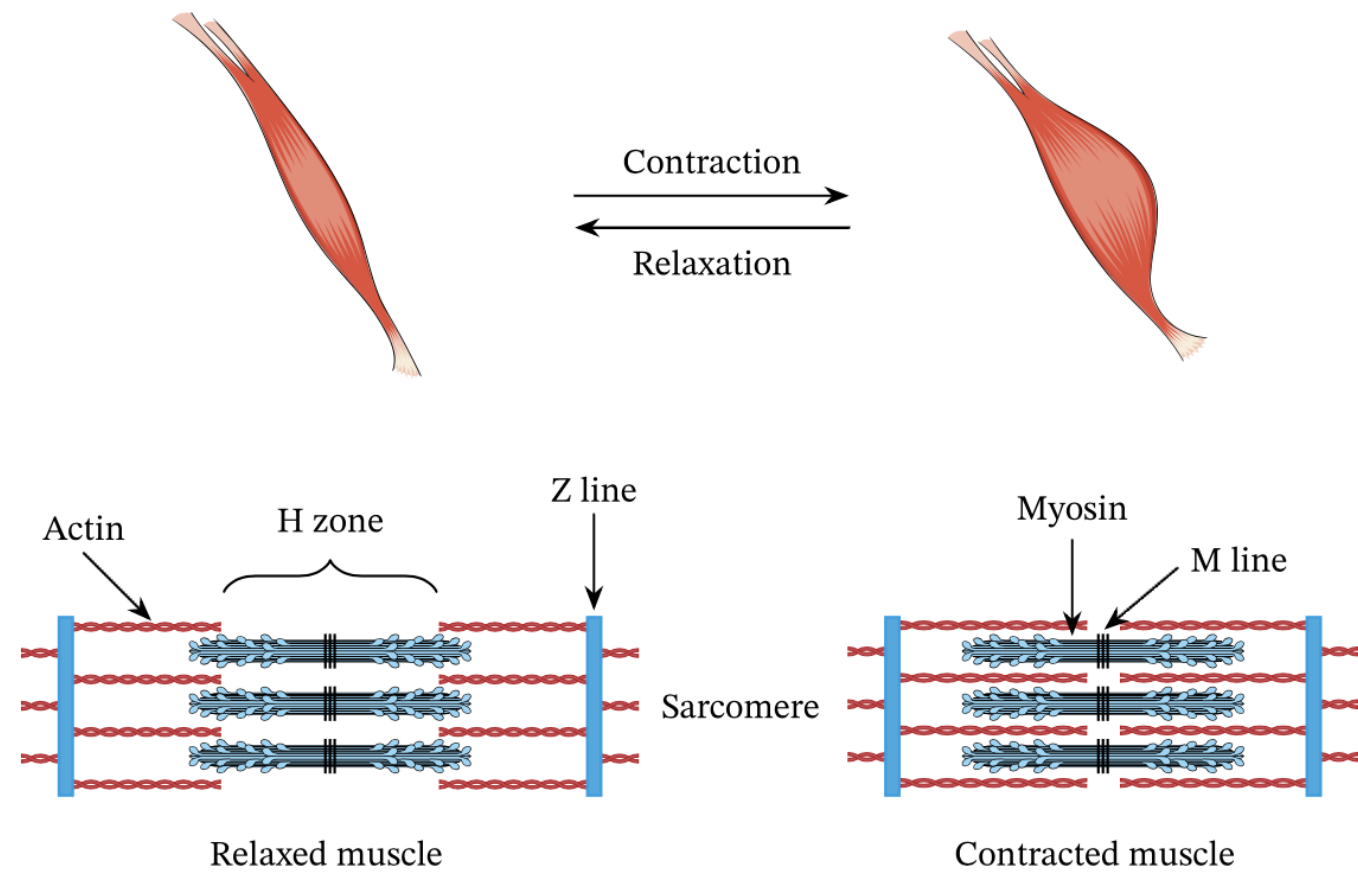
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**The authors have no financial conflicts of interest
to disclose concerning the presentation**

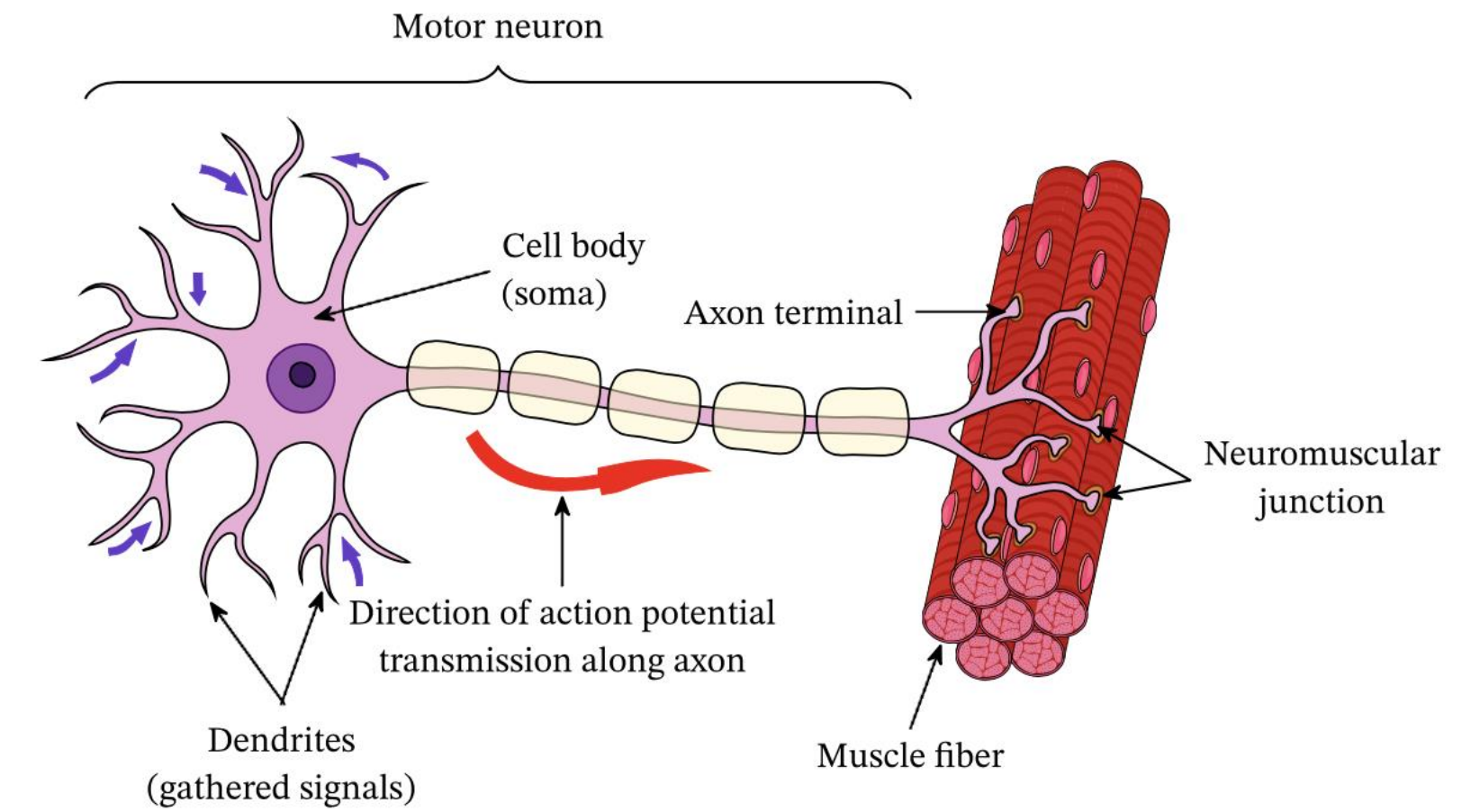


Calcium ion in the cell

Muscle contraction

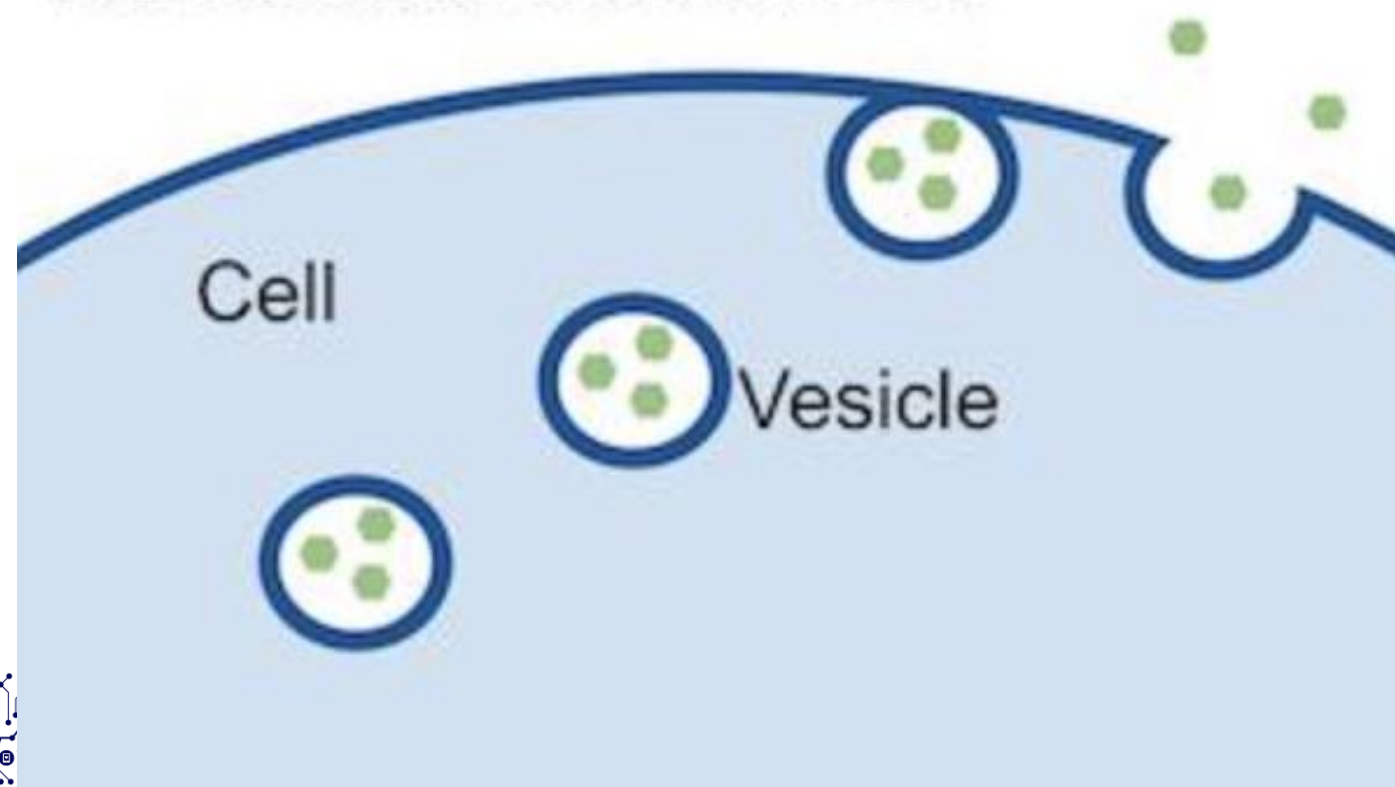


Neuronal activity

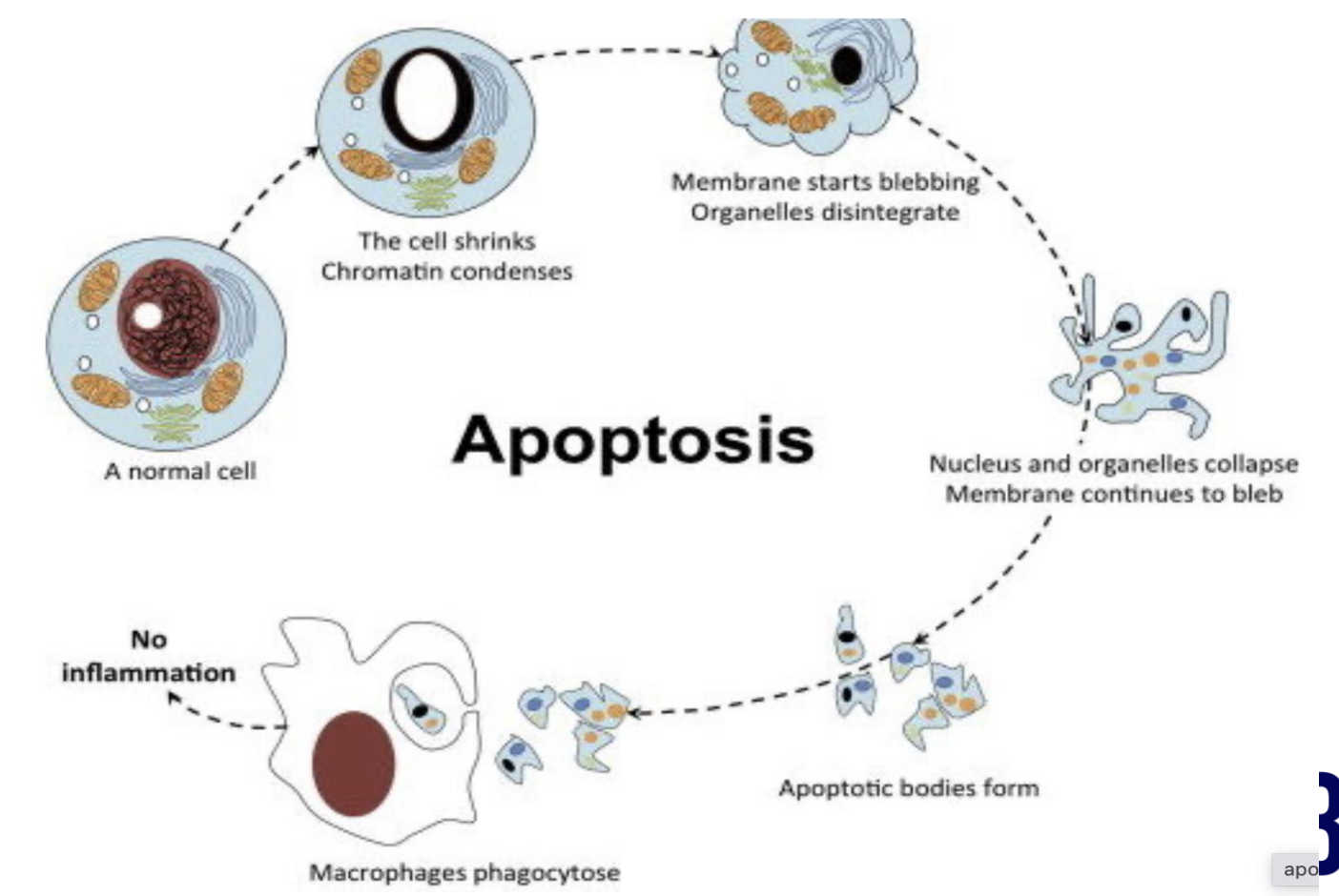


Cellular exocytosis

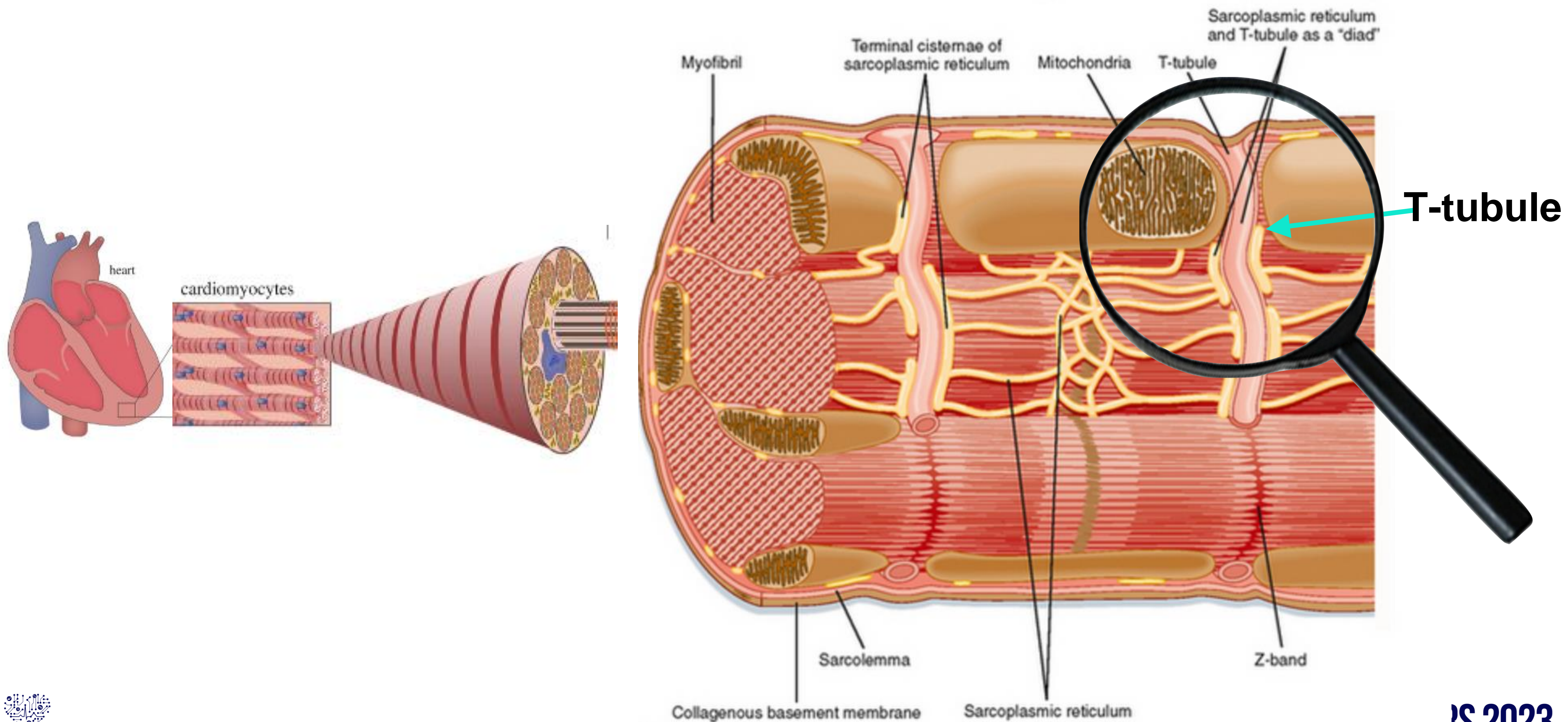
Extracellular environment



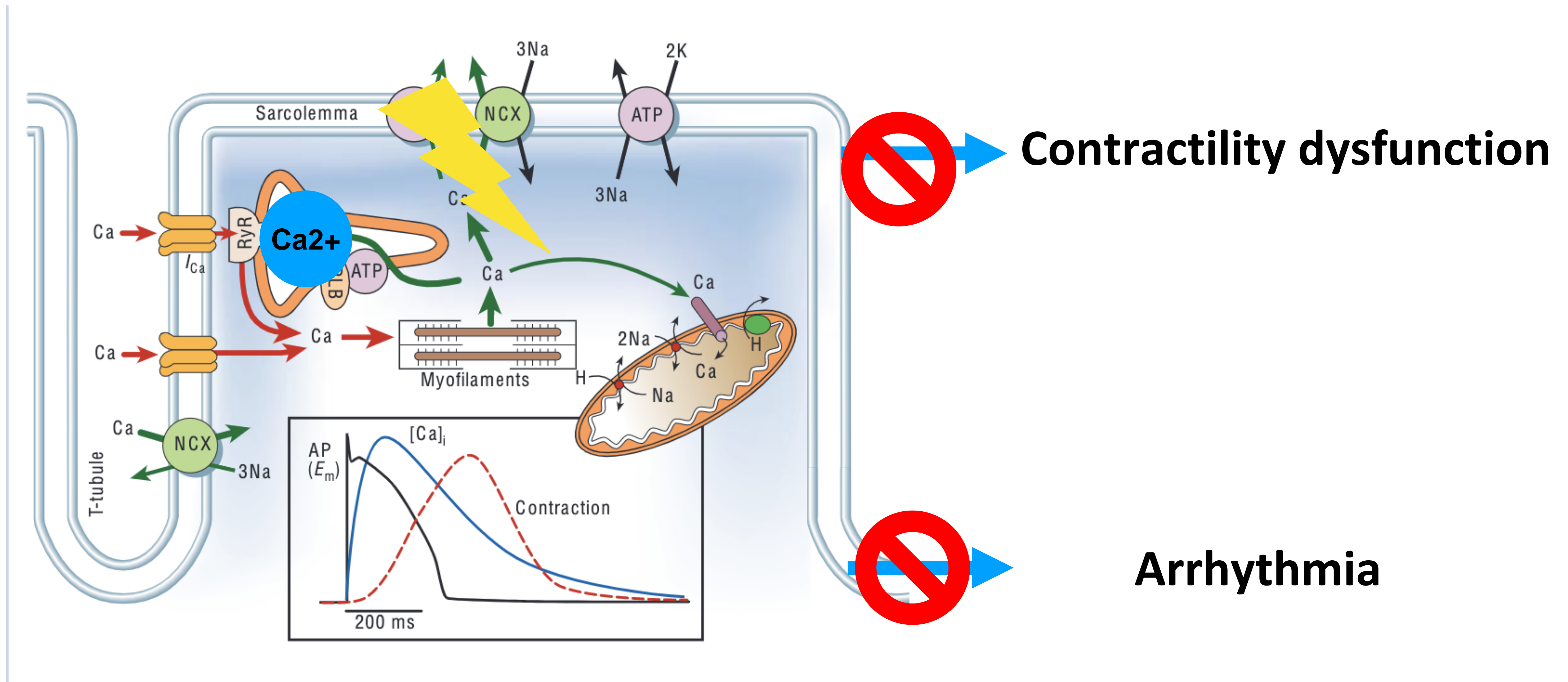
Programmed cell death



Sarcolemma



Excitation-contraction coupling

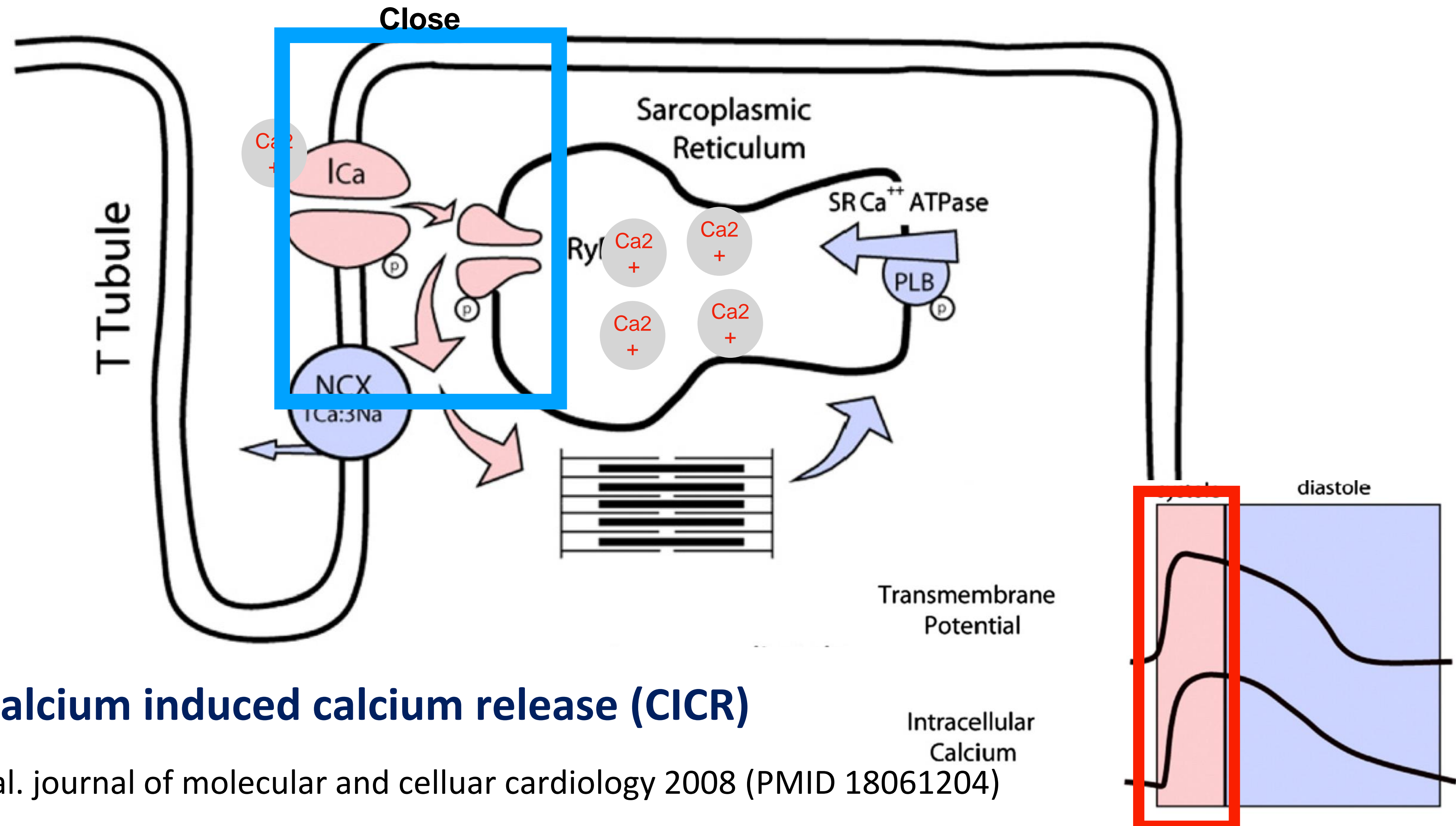


Process from electrical excitation of the myocyte to contraction of the heart



Intracellular calcium signaling in myocyte

Excitation

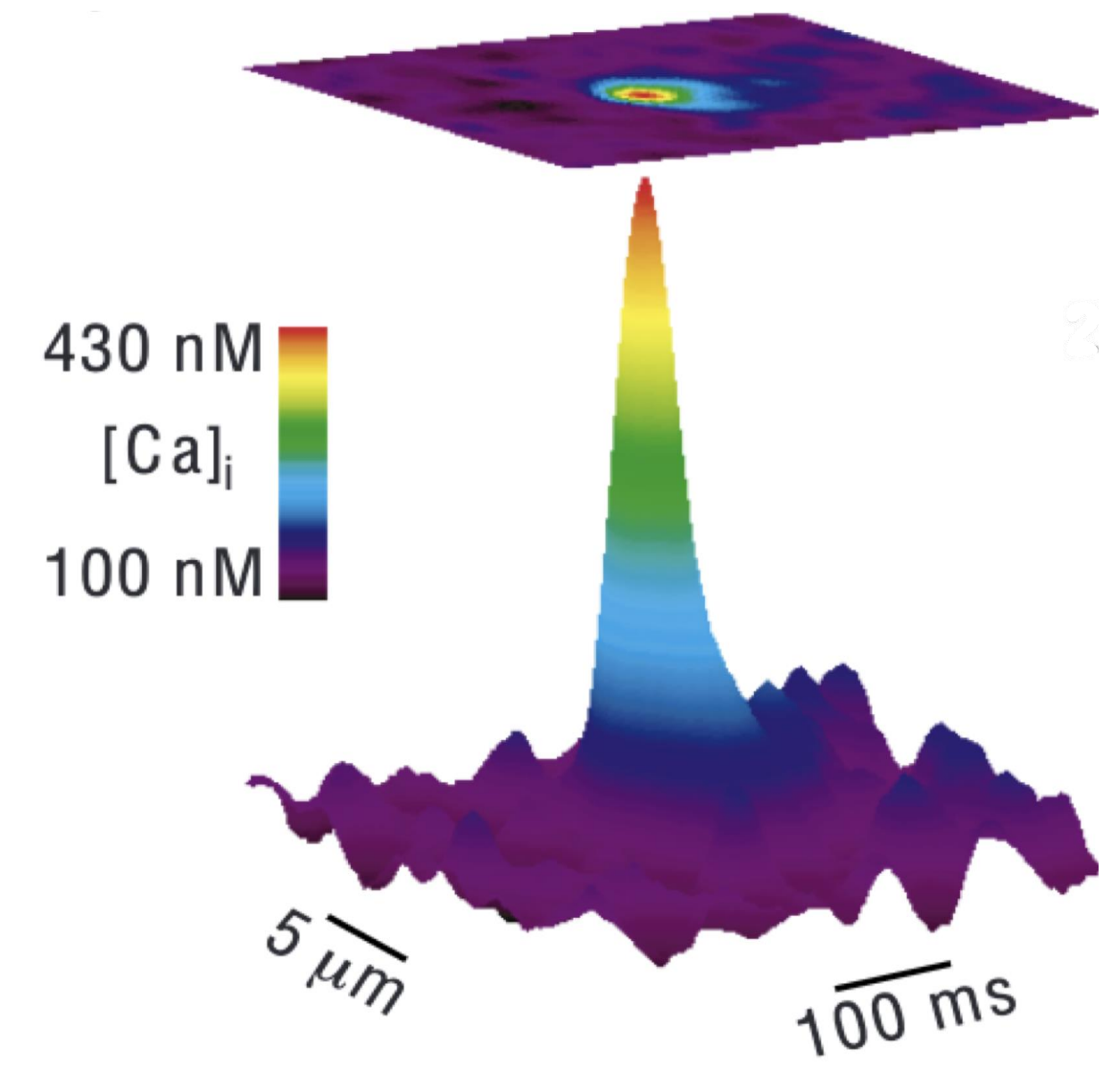
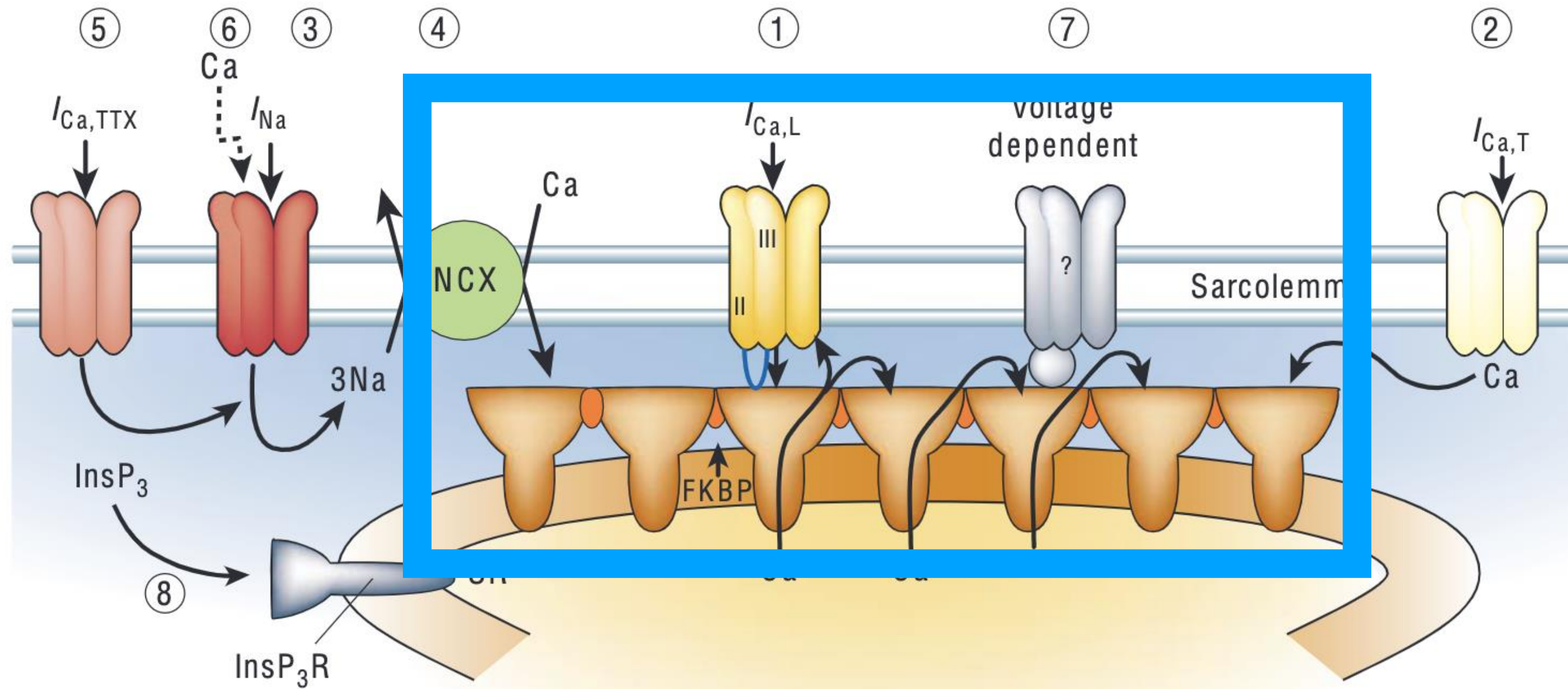


Calcium induced calcium release (CICR)

laurita et al. journal of molecular and cellular cardiology 2008 (PMID 18061204)



Calcium induced calcium release

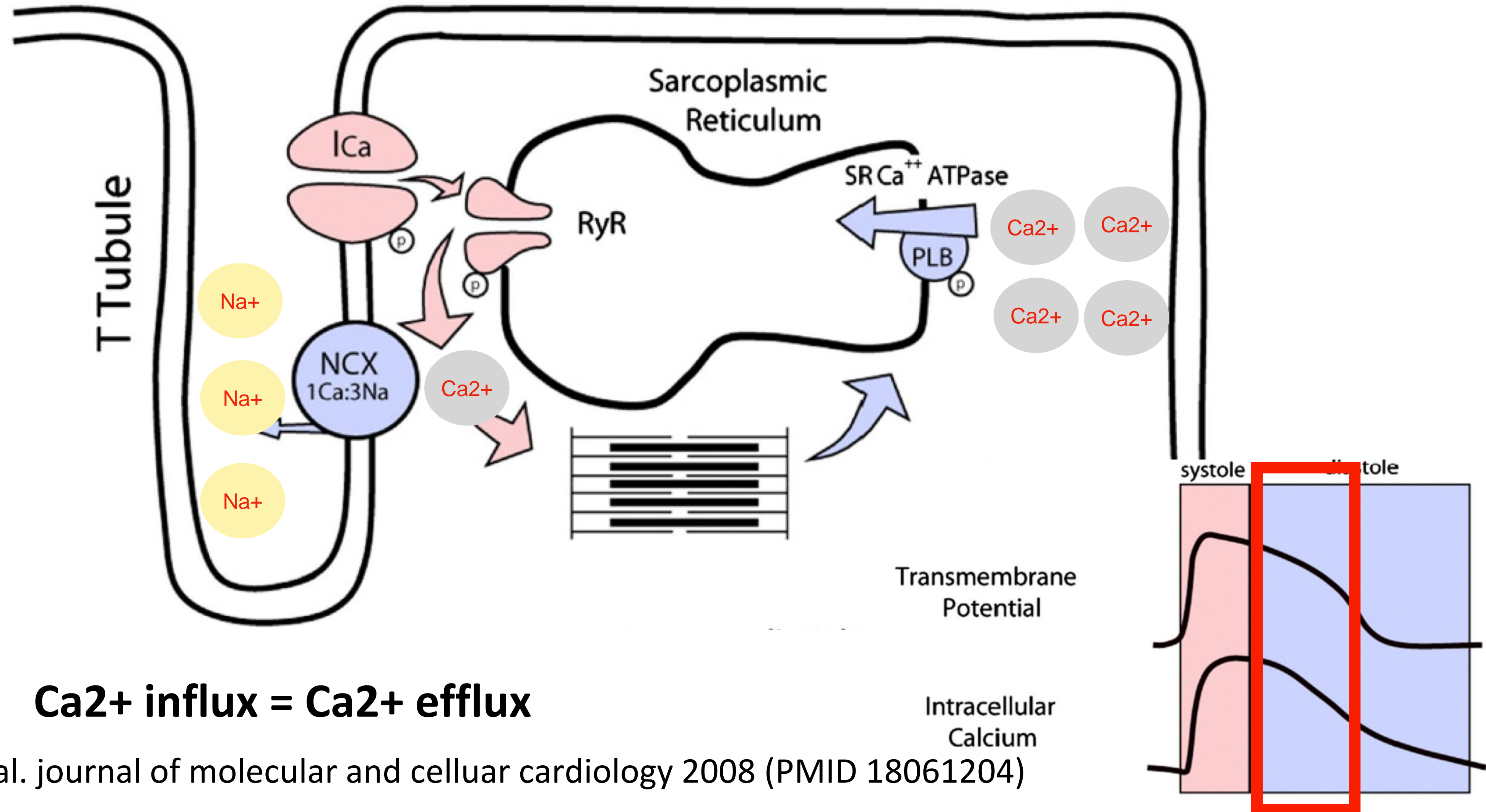


Calcium spark



Intracellular calcium signaling in myocyte

Relaxation

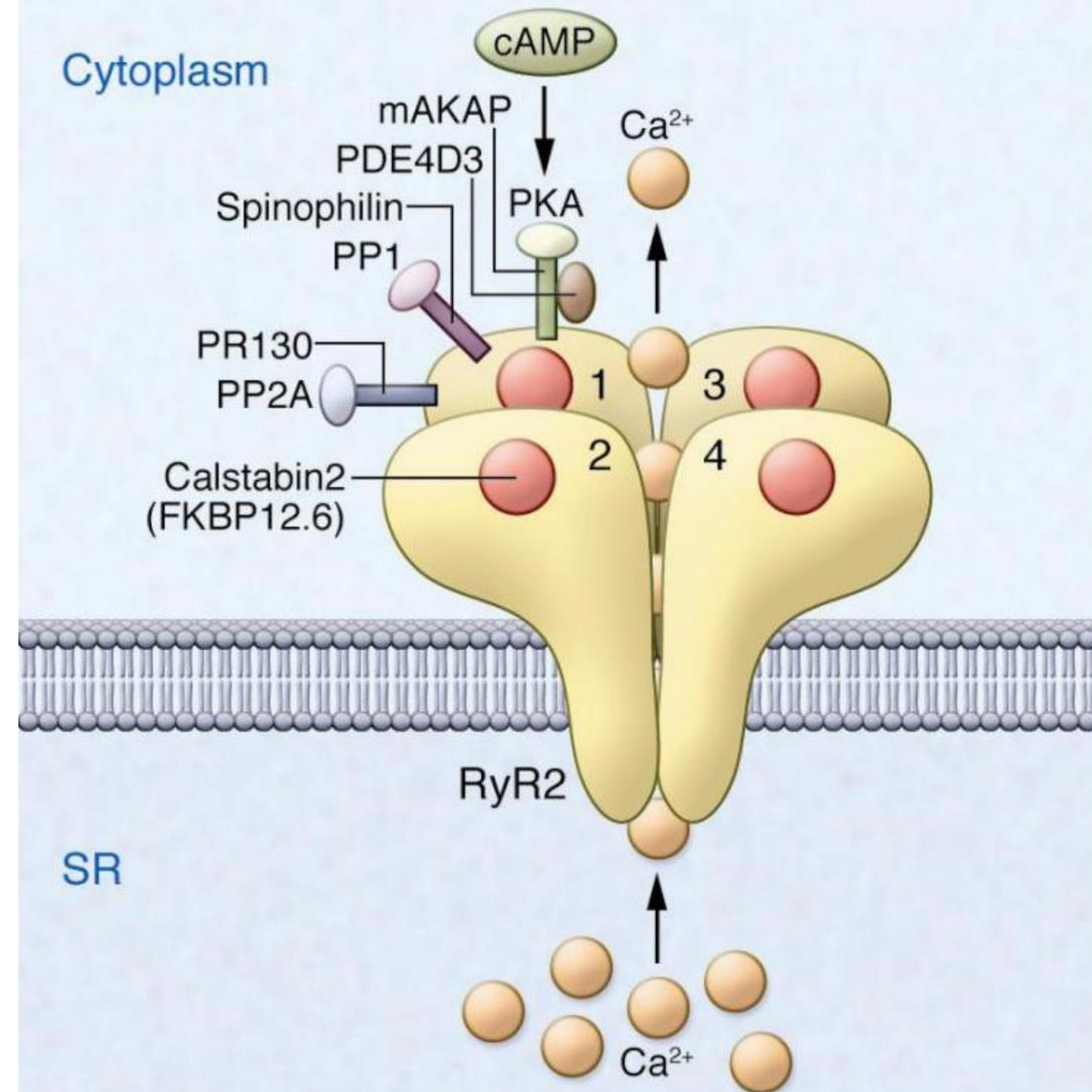


laurita et al. journal of molecular and cellular cardiology 2008 (PMID 18061204)

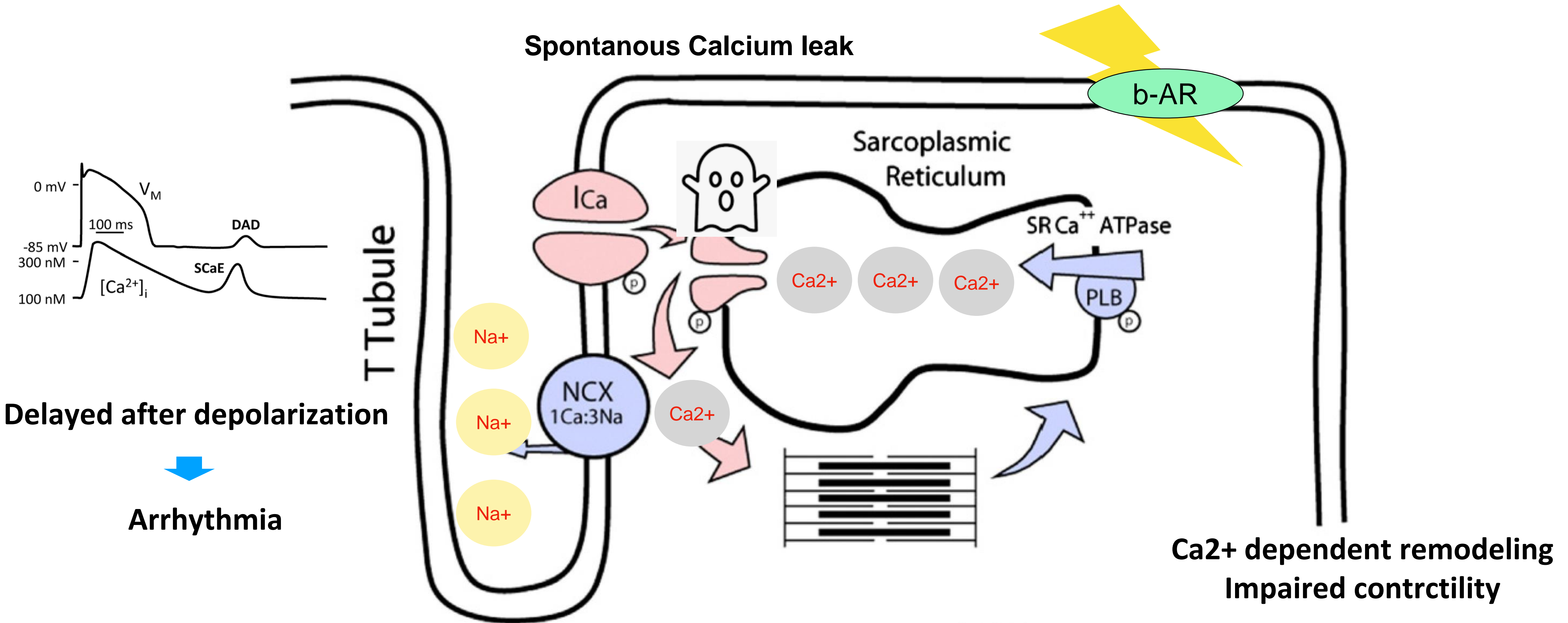
RyR2 receptor

- Largest ion channel, excess of 2MDa tetrameric protein, 4 identical subunits
- Macromolecular complex with cytosolic, SR integral, luminal accessory protein
- Contain binding sites for many different endogenous and exogenous modulator

Orabi et al. Ryanodine Receptor. (2014)



SR calcium leak in diastole



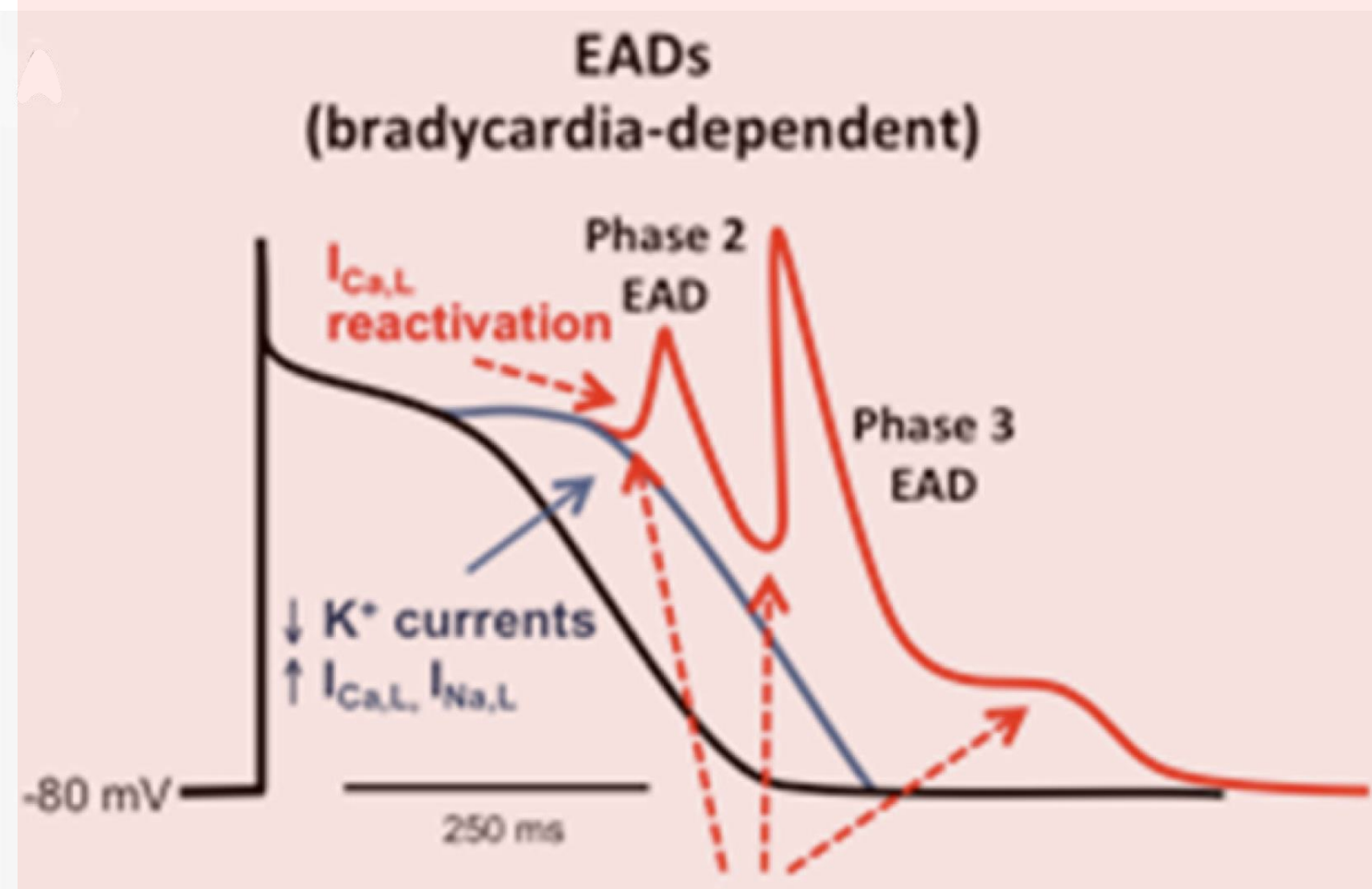
laurita et al. journal of molecular and cellular cardiology 2008 (PMID 18061204)

Taur et al. cardiology in review 2005 (PMID 15831148)

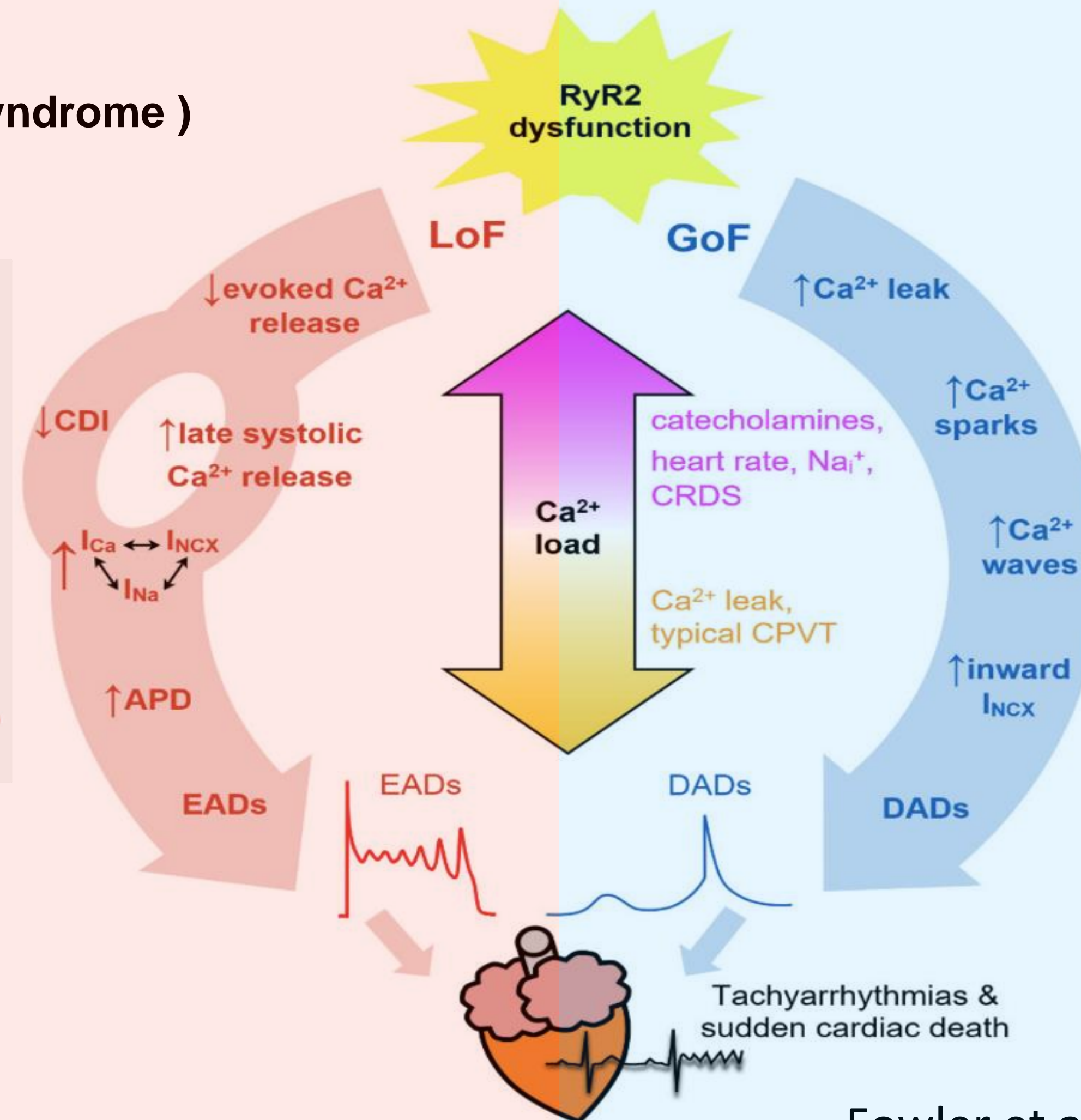
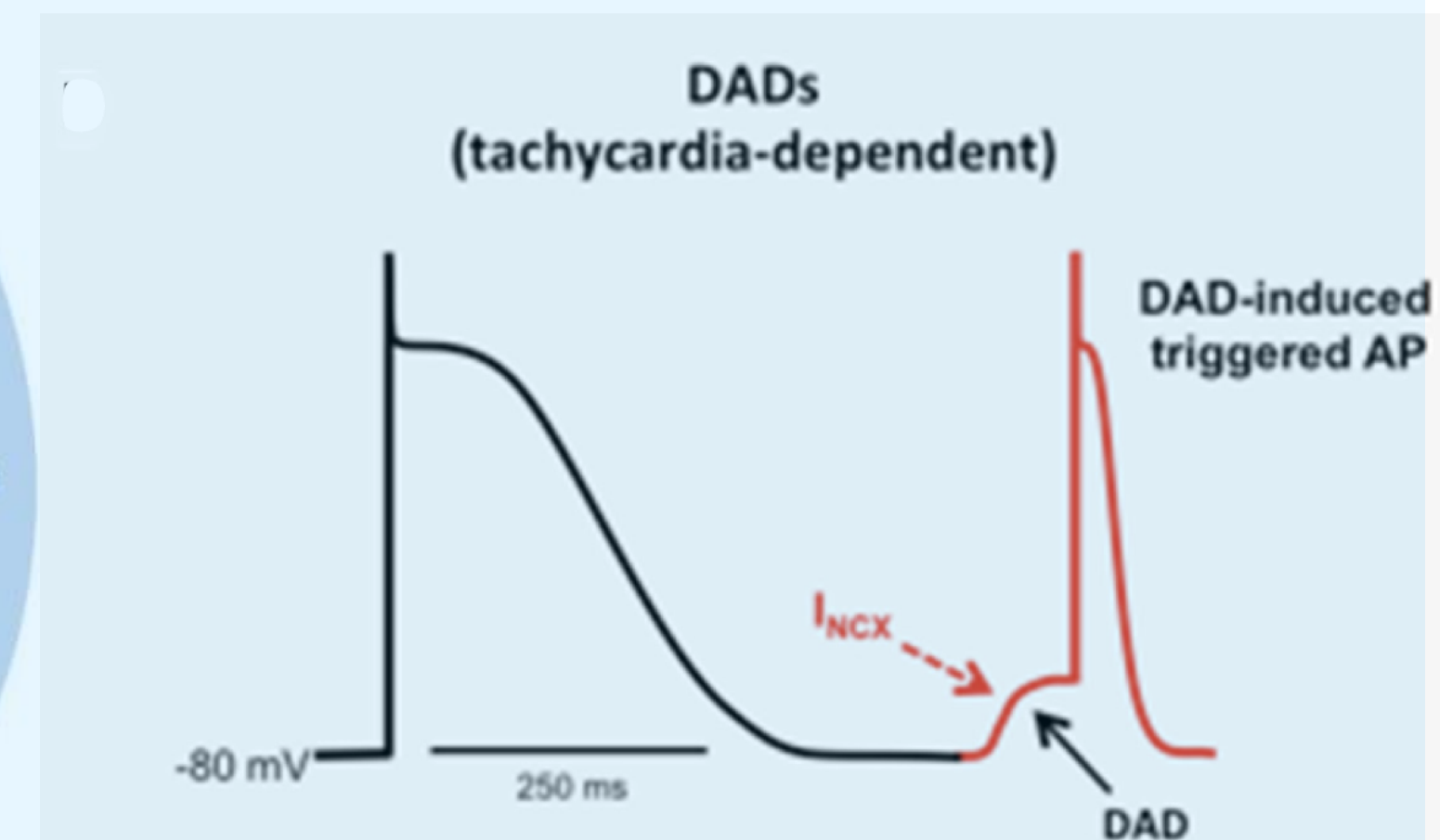


Arrhythmia Mechanism in RyR2 dysfunction

Atypical CPVT
(RyR2 calcium release deficiency syndrome)



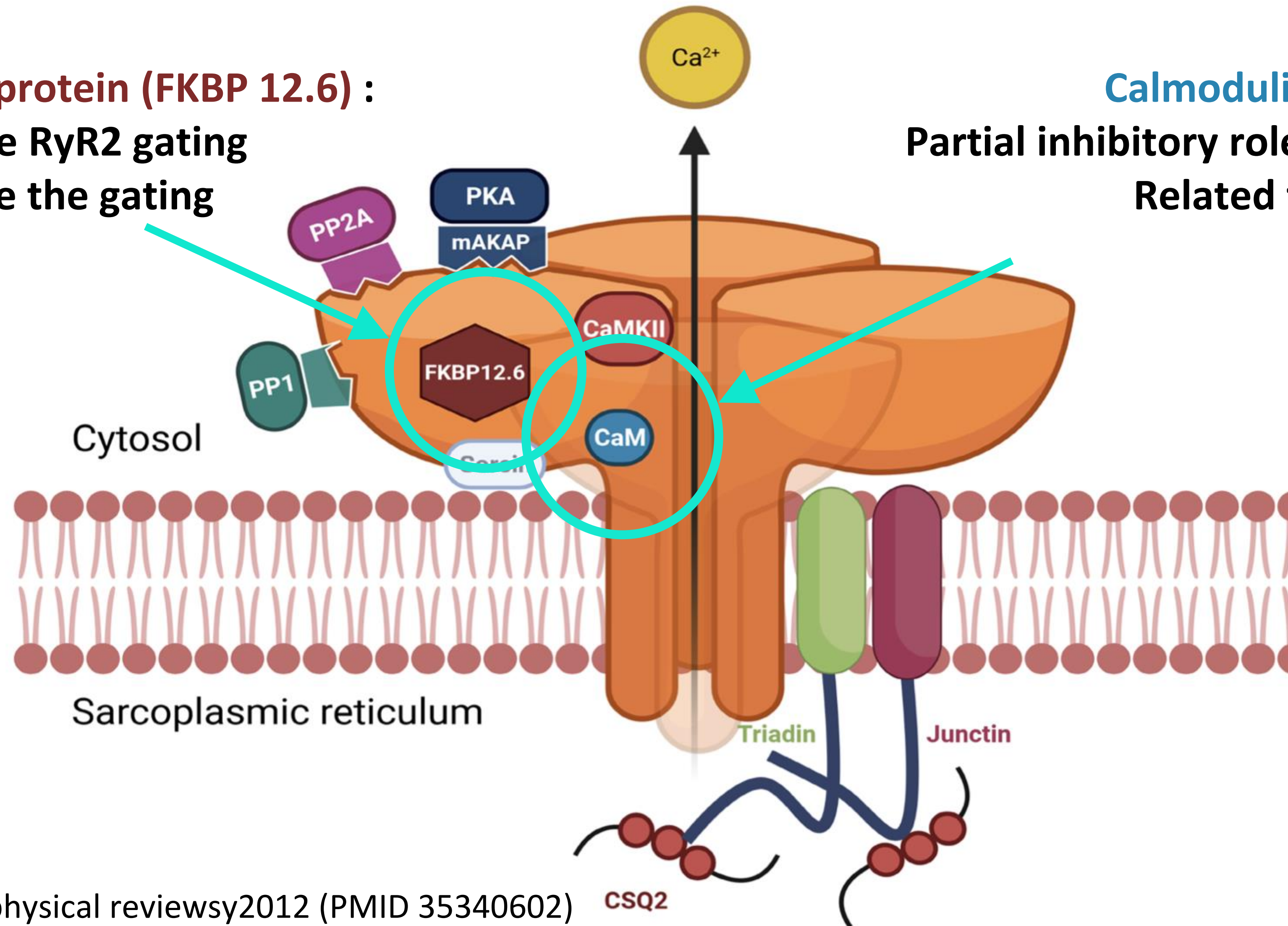
Typical CPVT



Molecular factors that affect RyR2 open probability

FK506-binding protein (FKBP 12.6) :
stabilize RyR2 gating
Couple the gating

Calmodulin (CaM):
Partial inhibitory role on RyR2 activation
Related to CPVT

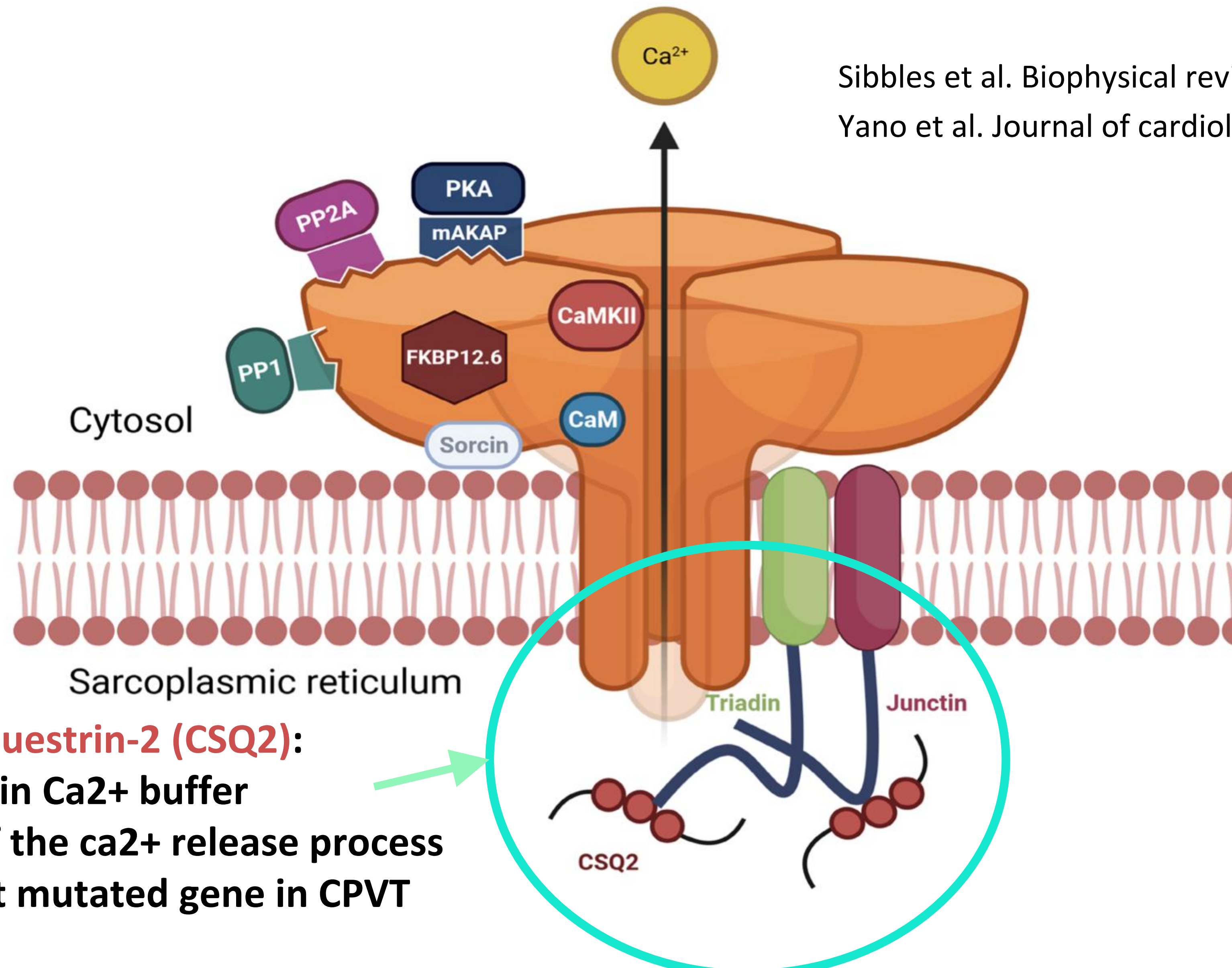


Sibbles et al. Biophysical reviews 2012 (PMID 35340602)

Yano et al. Journal of cardiology 2009 (PMID 19167631)



Molecular factors that affect RyR2 open probability



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Calsequestrin-2 (CSQ2):

Main Ca^{2+} buffer

Modulation of the Ca^{2+} release process

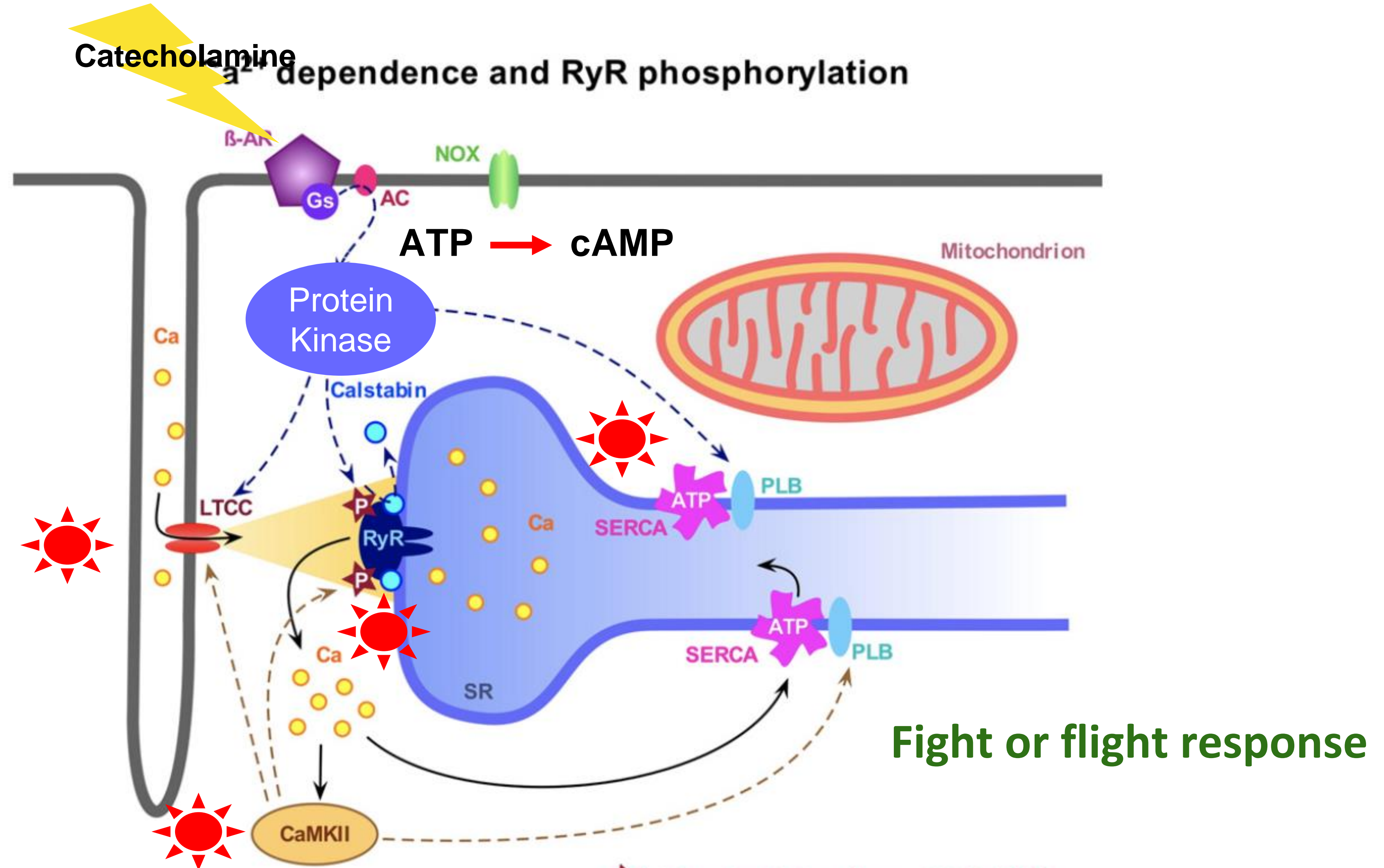
Second most mutated gene in CPVT



Mutation in CPVT

Type	MIM*	Gene	Protein	Genetic Locus	Frequency	Inheritance
CPVT 1	604772	<i>RYR2</i>	Ryanodine receptor 2	1q42.1-q43	50%–60%	AD
CPVT 2	611938	<i>CASQ2</i>	Calsequestrin 2	1p13.1	Rare	AR
CPVT 3	614021	<i>TECRL</i>	Trans-2,3-enoyl-CoA reductase-like	7p22-p14	Rare	AR
CPVT 4	614916	<i>CALM1</i>	Calmodulin 1	14q31-q32	Rare	AD
CPVT 5	603283	<i>TRDN</i>	Triadin	6q22.31	Rare	AR

Post-translational modification

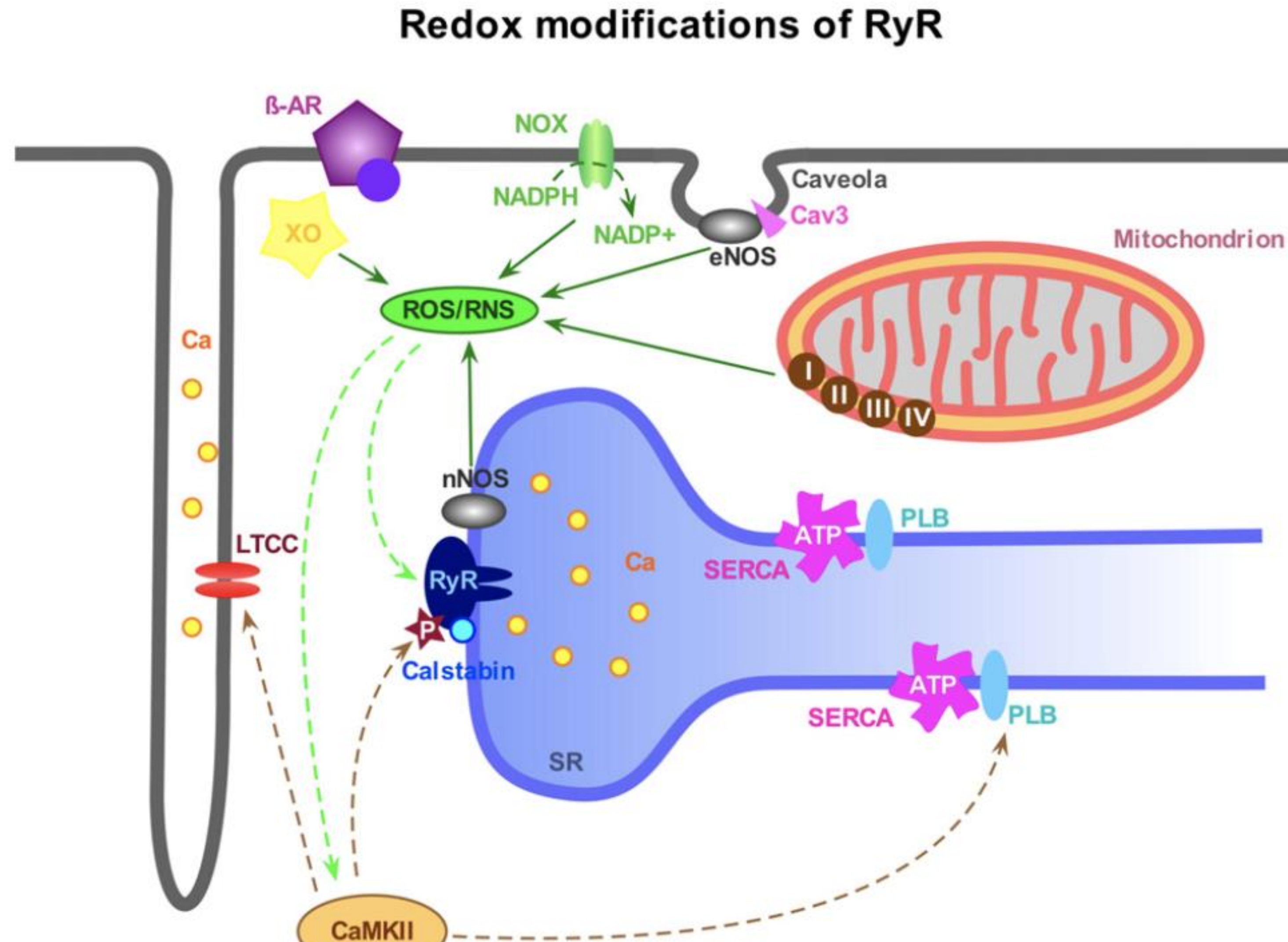


Niggli et al. MOLECULAR CELL RESEARCH 2013 (PMID 22960642)

Dashwood et al. ACS PHARMACOLOGY & TRANSLATIONAL SCIENCE 2020(PMID 32382863)

Phosphorylation sites:
S2808 (PKA)
S2814 (CaMKII)
S2030 (PKA)

Post-translational modification

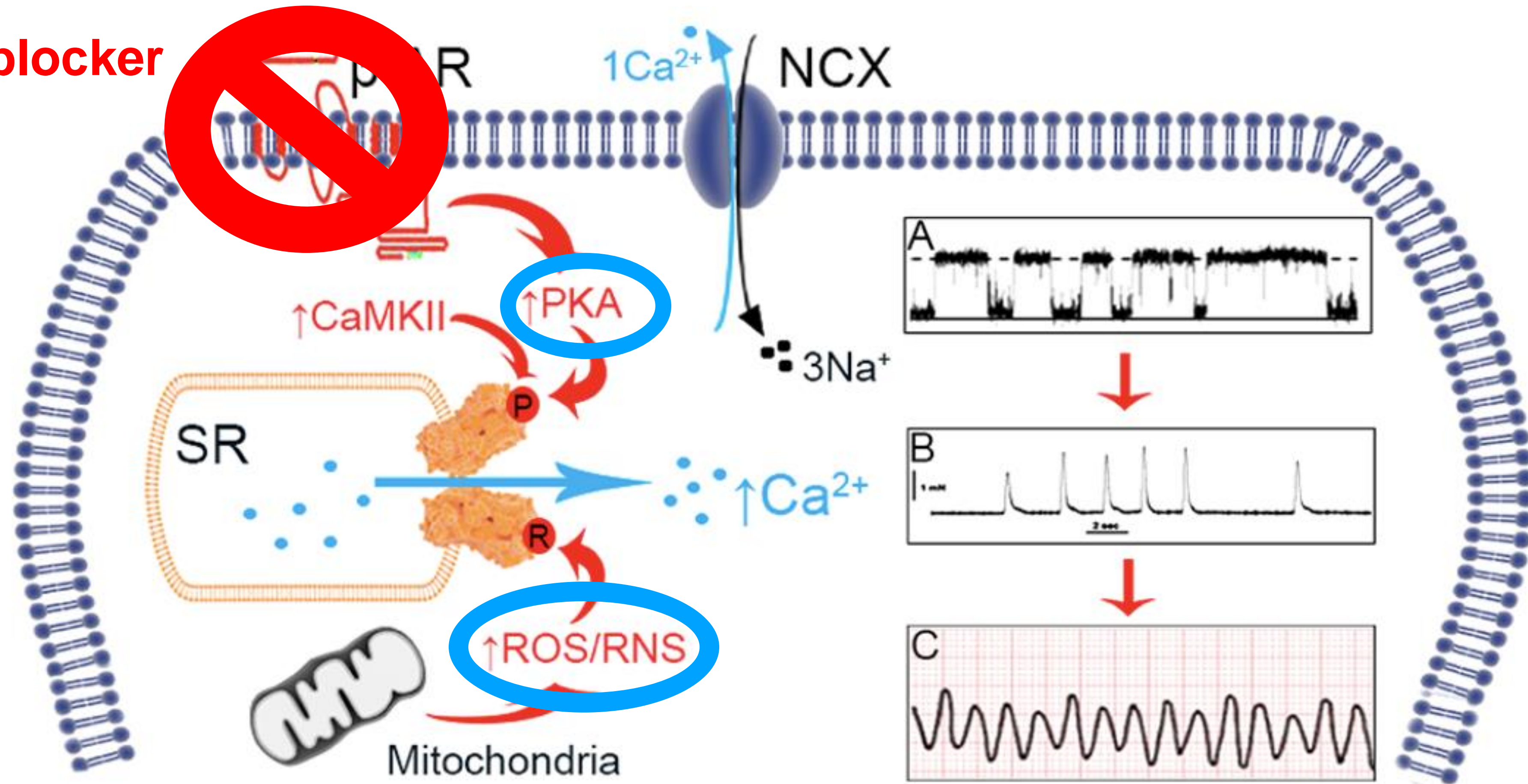


Niggli et al. MOLECULAR CELL RESEARCH 2013 (PMID 22960642)

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Stress-induced mechanisms of arrhythmia

Beta-blocker



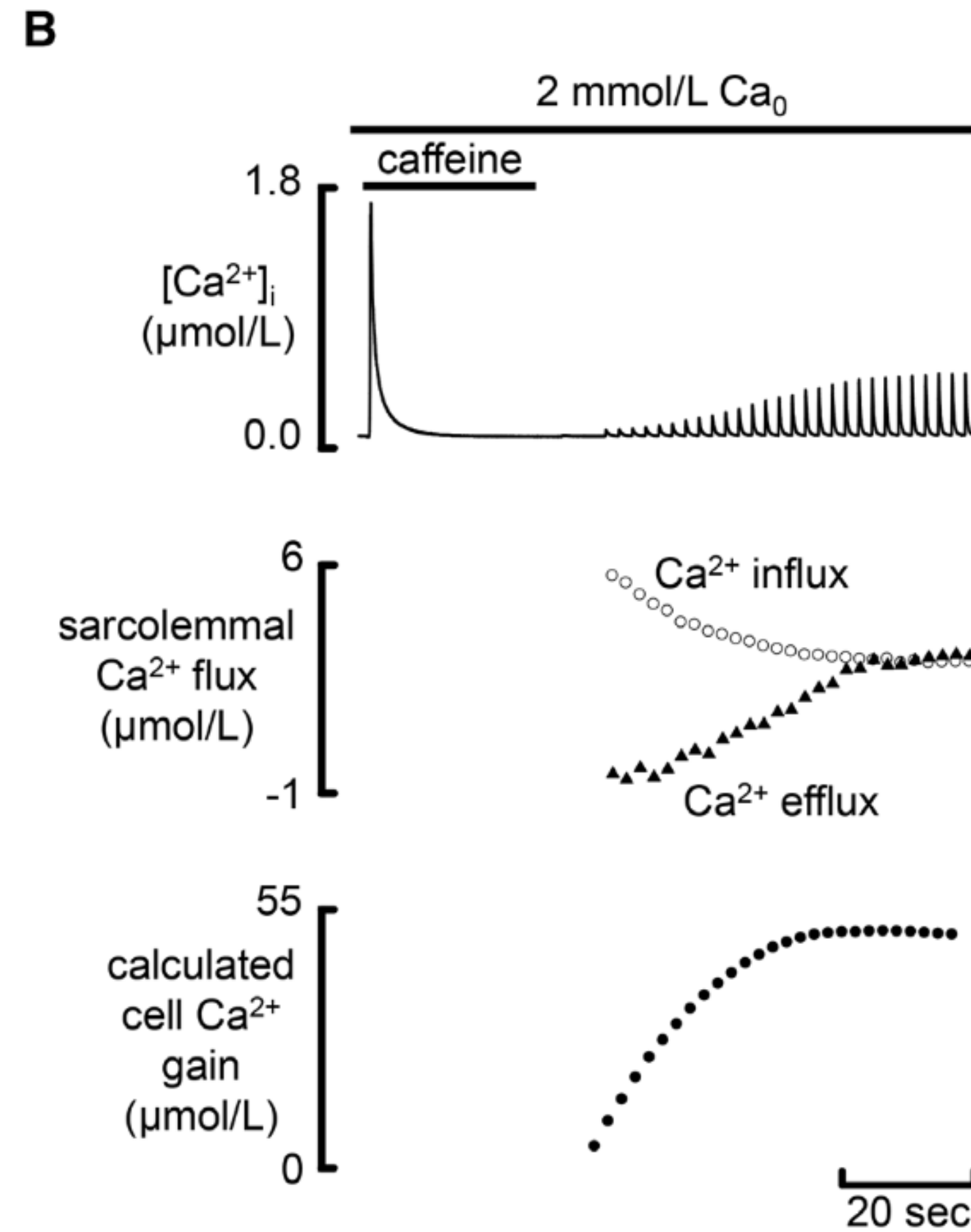
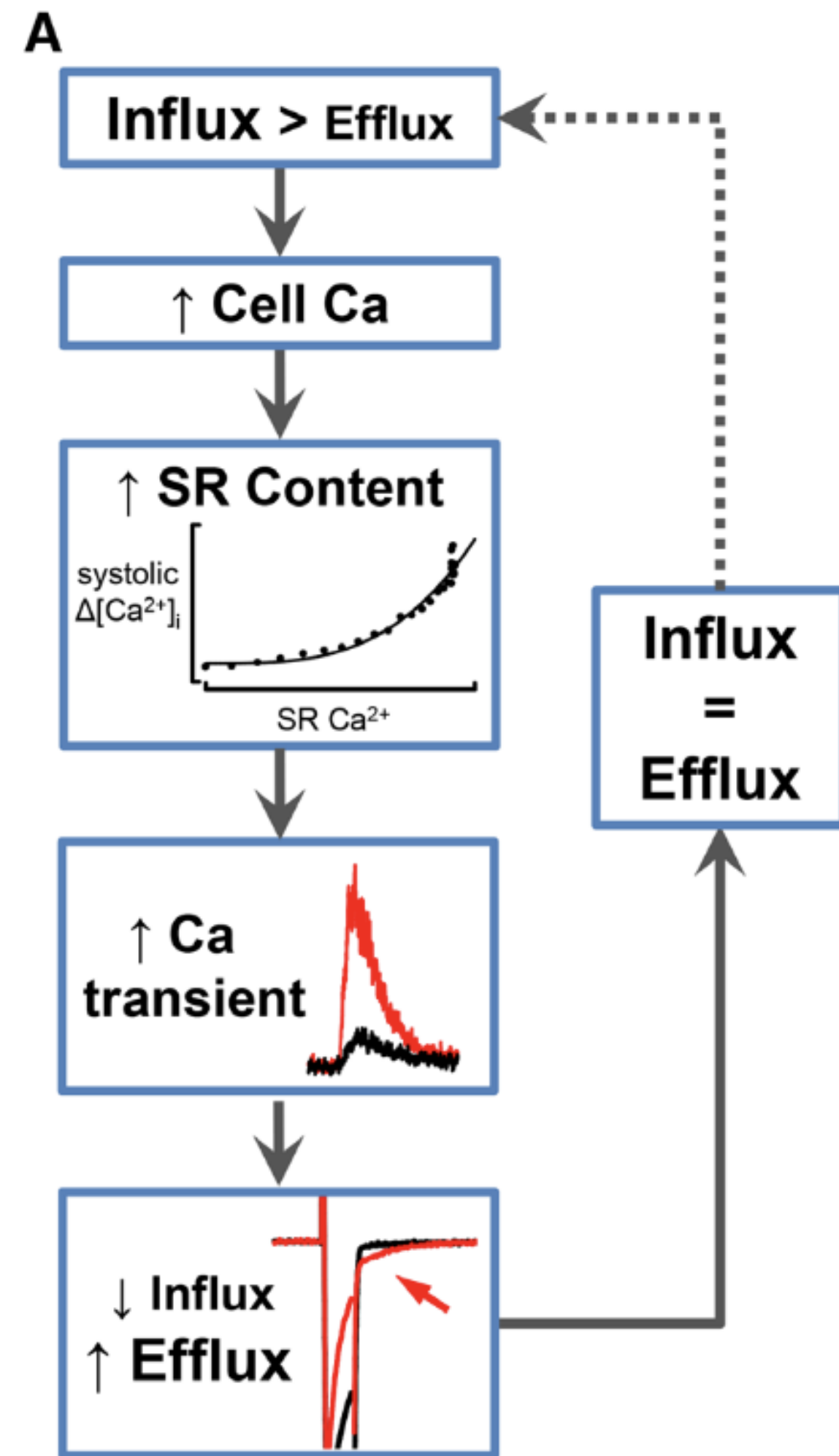
Summary

- The RyR2 obviously plays a major part in the pathogenesis of different diseases.
 - related to **cardiac**, neurodegenerative, and metabolic disorders
- **Calcium homeostasis** regulated by the RyR2 is crucial for cell metabolism.
- **Ryanopathies and RyR2 post-translational modifications** lead to a **SR Ca²⁺ leak** that is responsible for various pathogenic patterns such as ventricular arrhythmia.
- Understanding basic behavior about Ryanodine receptor is important to treat CPVT and Heart failure patients.

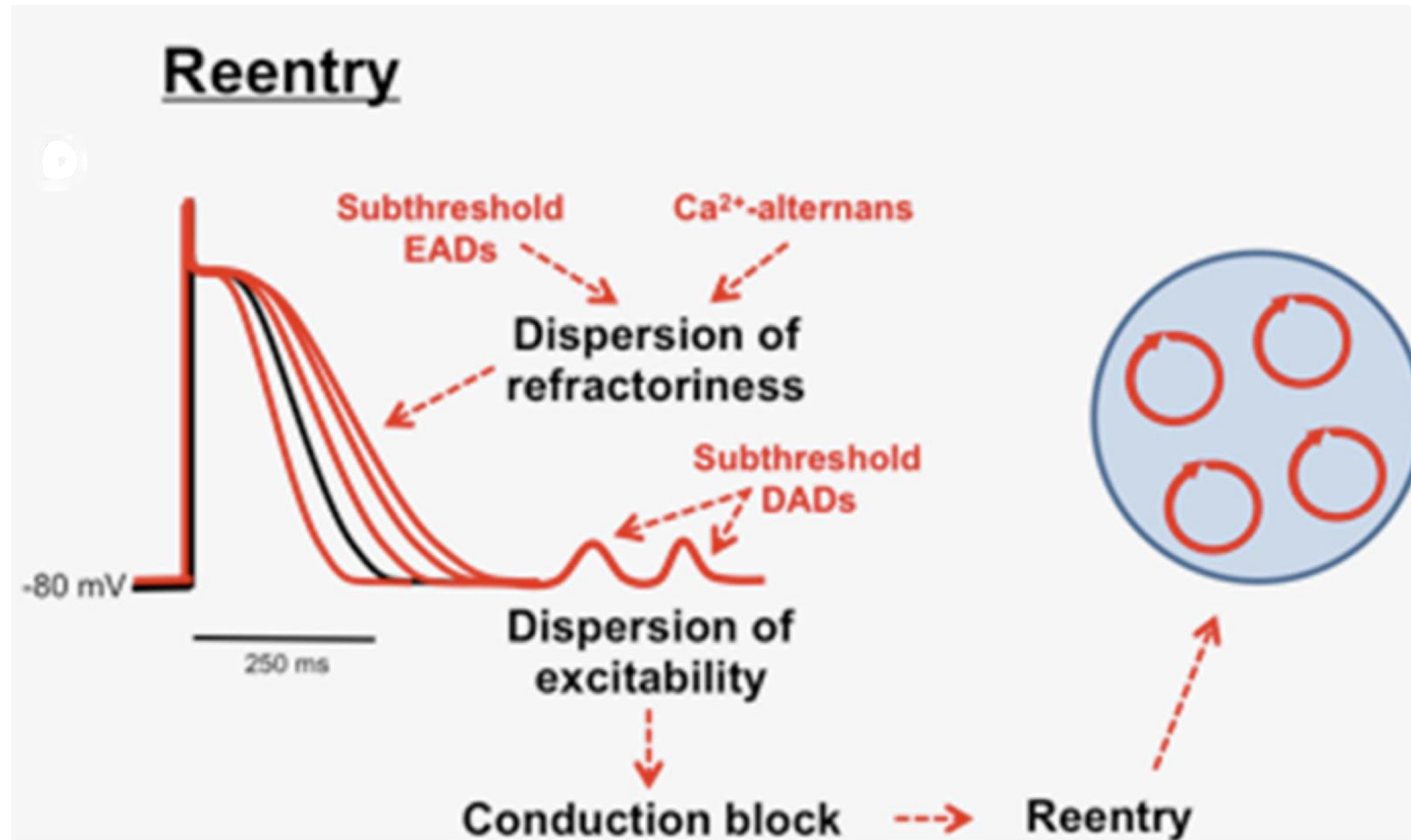
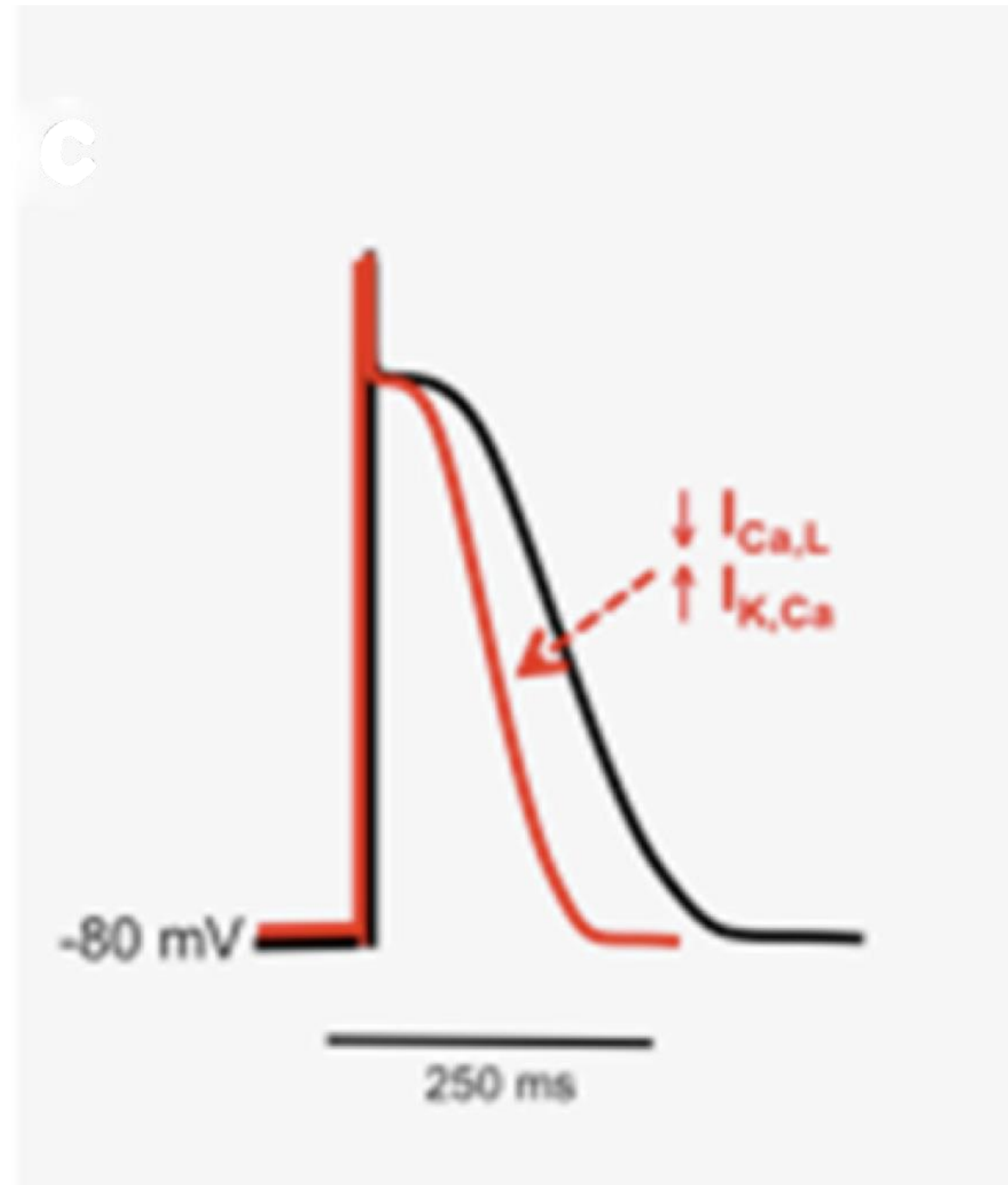
Thank you for your attention



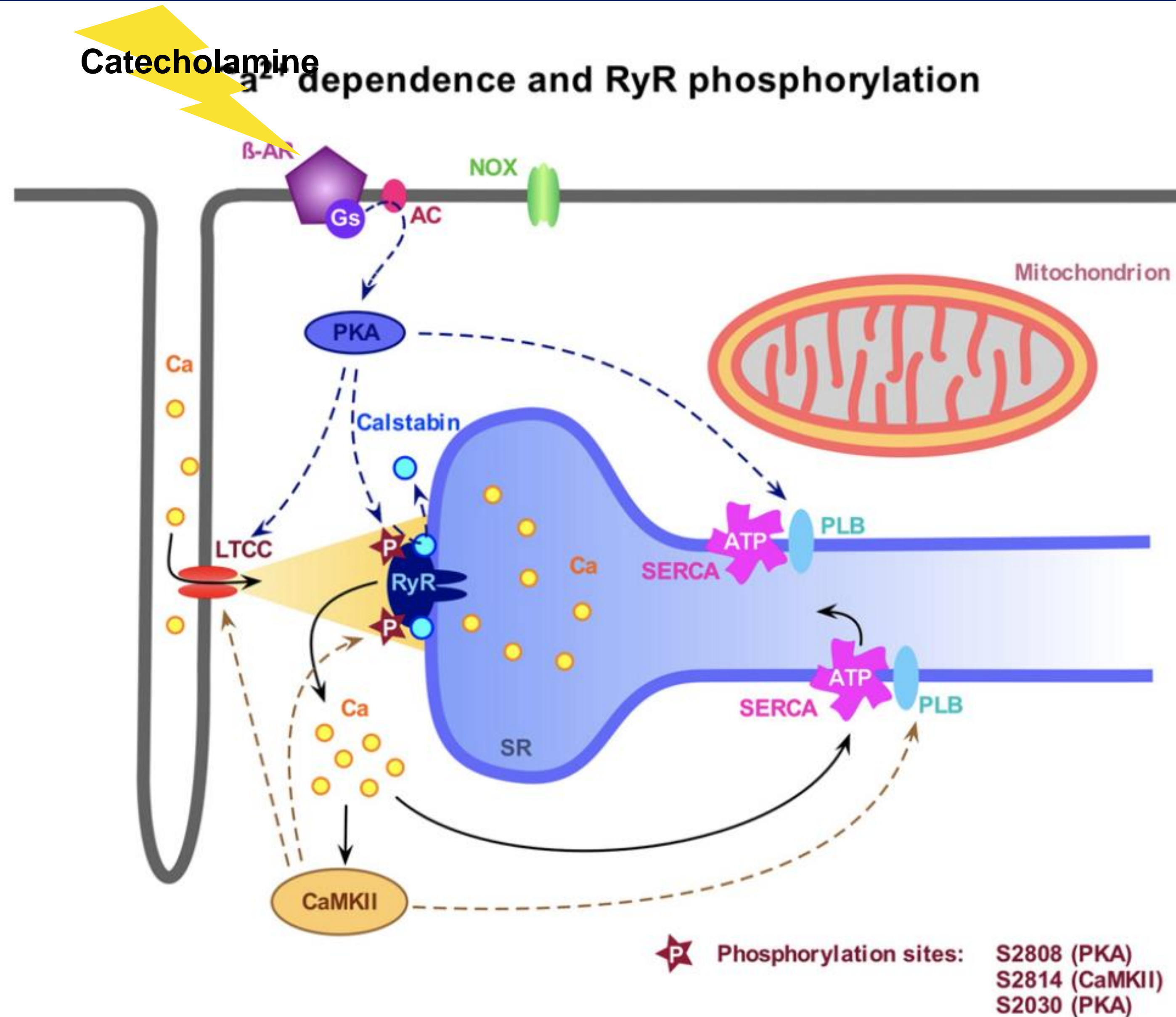
Calcium flux balance



Fundamental arrhythmia mechanism

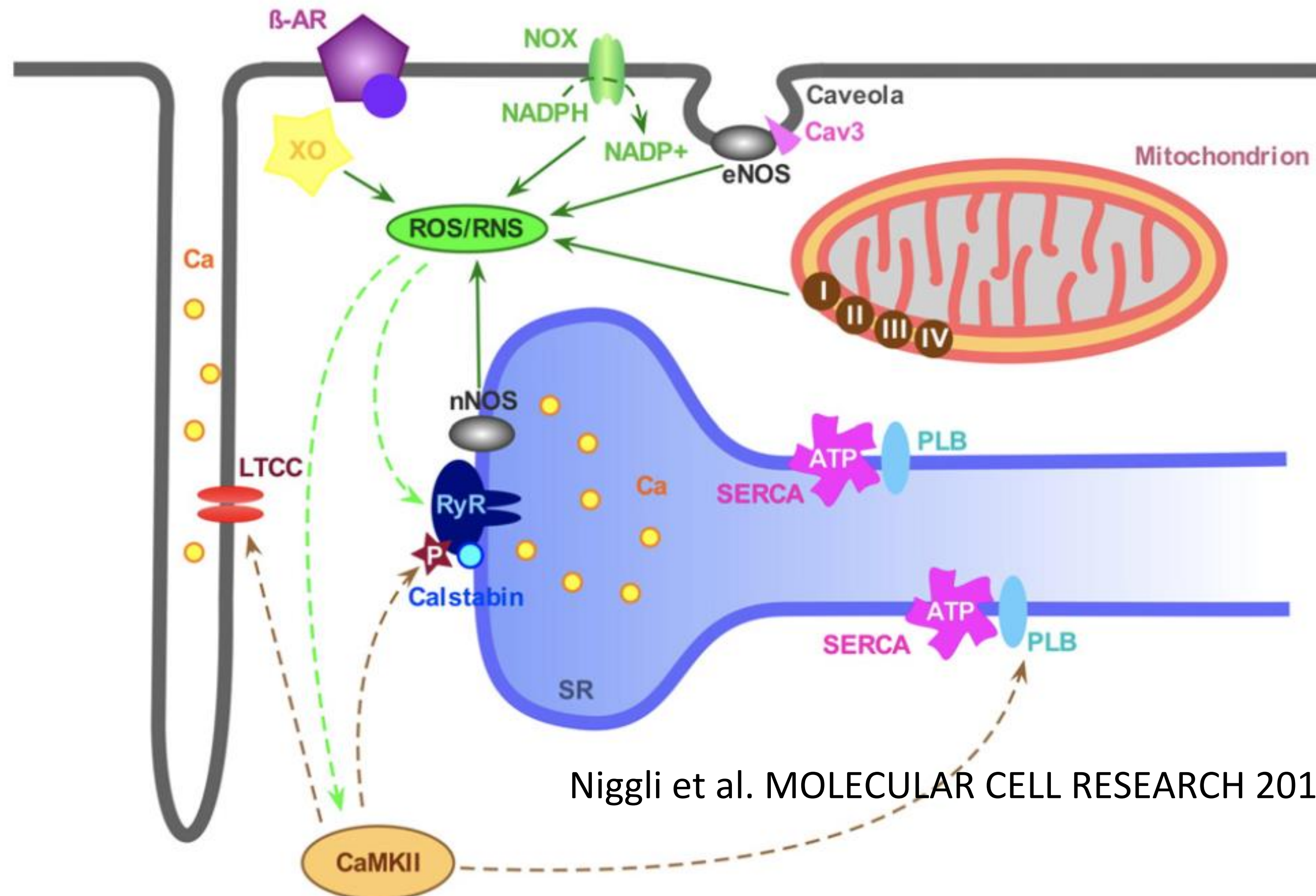


Post-translational modification



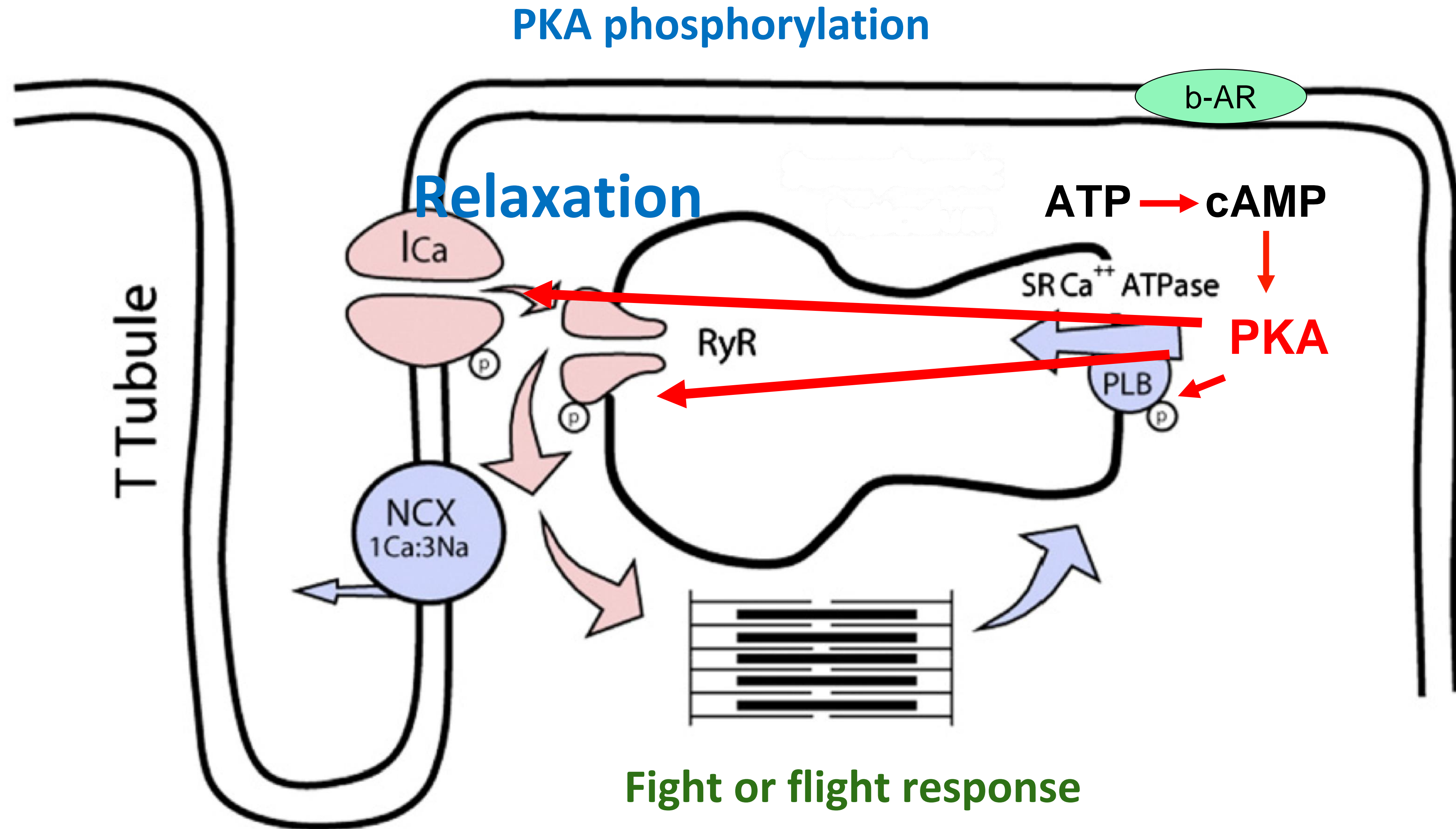
Post-translational modification

Redox modifications of RyR



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Post-translational modification



Action potential

