Role of Ca^{2+} in RYR-1 Myopathy … Made Ridiculously Simple

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Questions

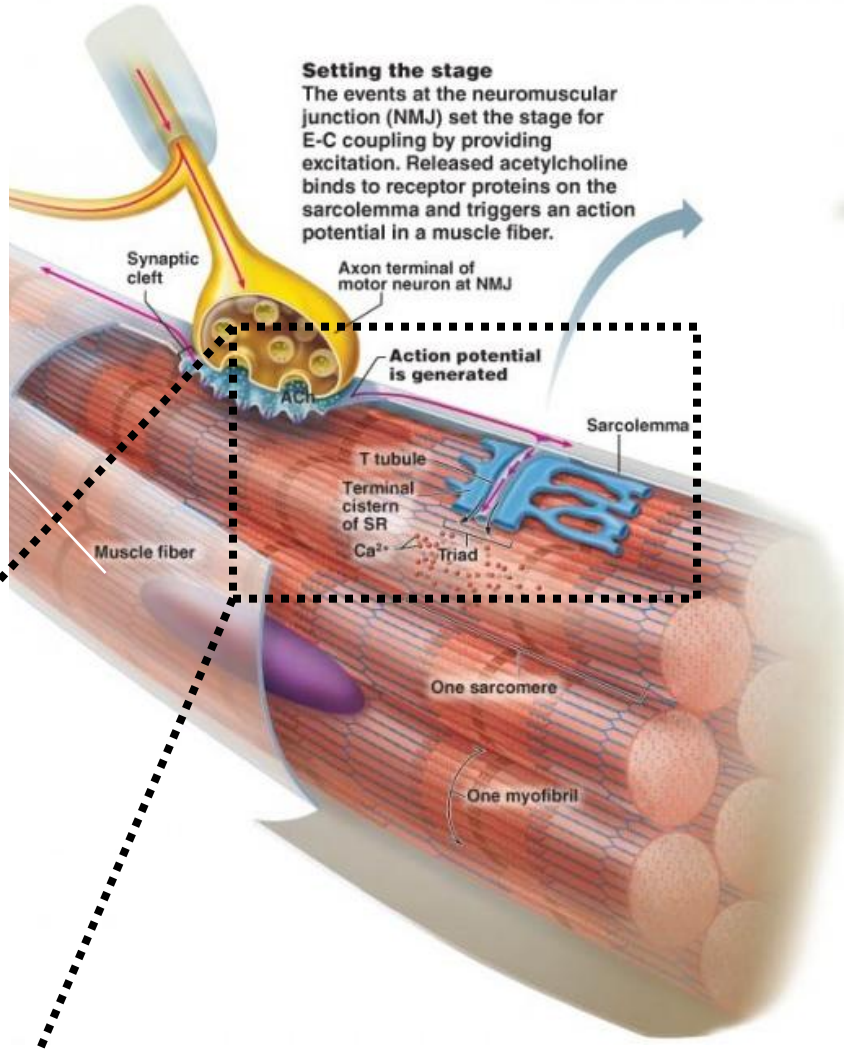
1. Why is the control of intracellular Ca^{2+} levels so important for skeletal muscle function?

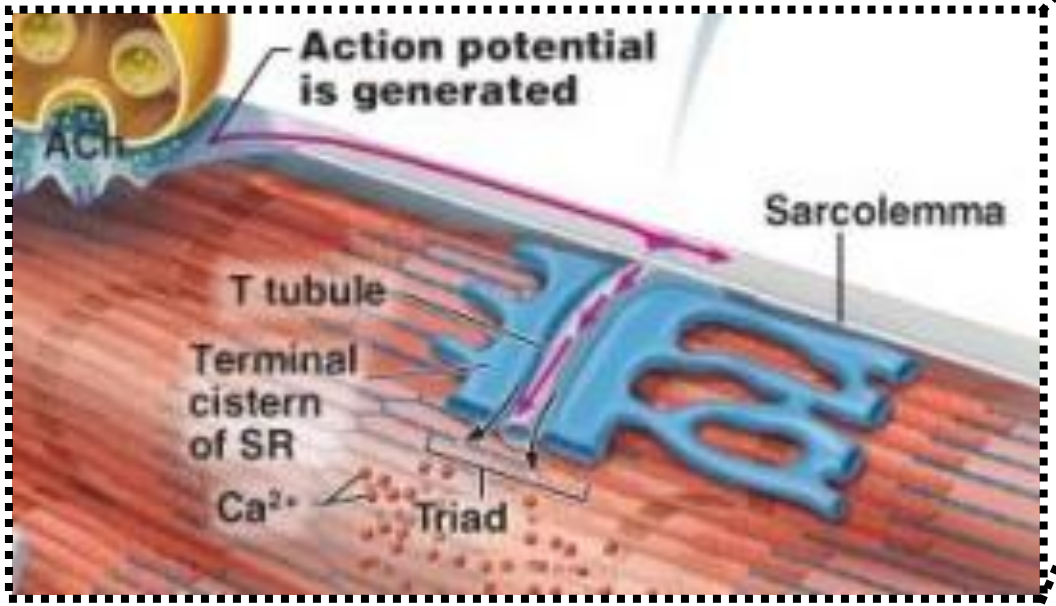
2. How does RYR-1 control Ca^{2+} levels in muscle?

3. How do mutations in RYR-1 alter the proper control of Ca^{2+} levels in skeletal muscle, and ultimately, lead to myopathy?

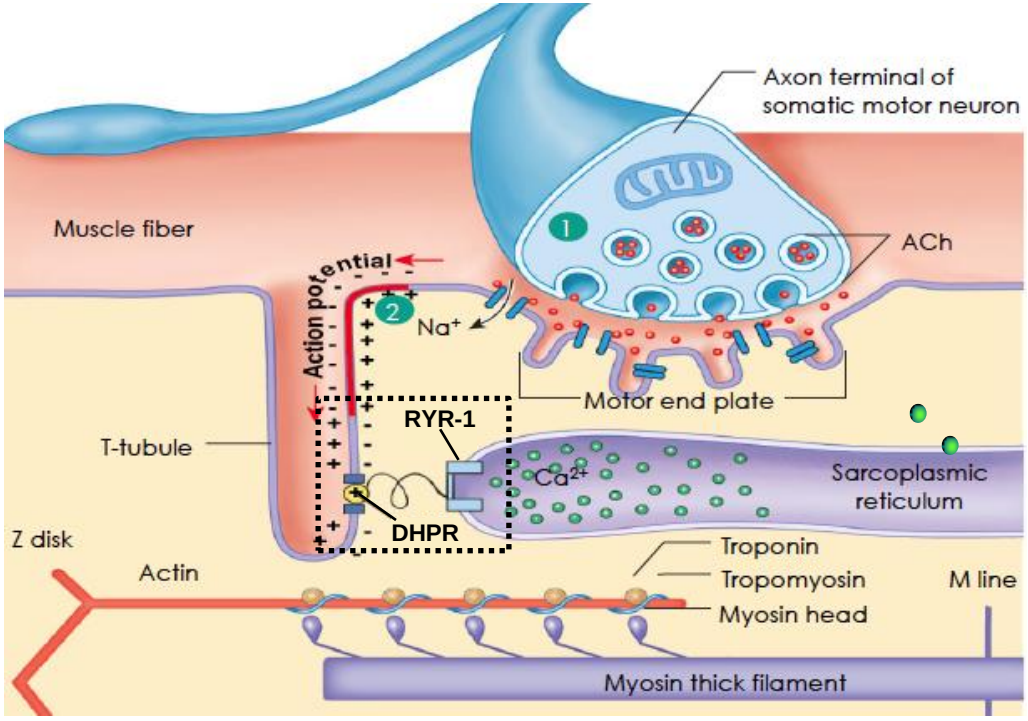
Motor Nerves Trigger Muscle Contraction

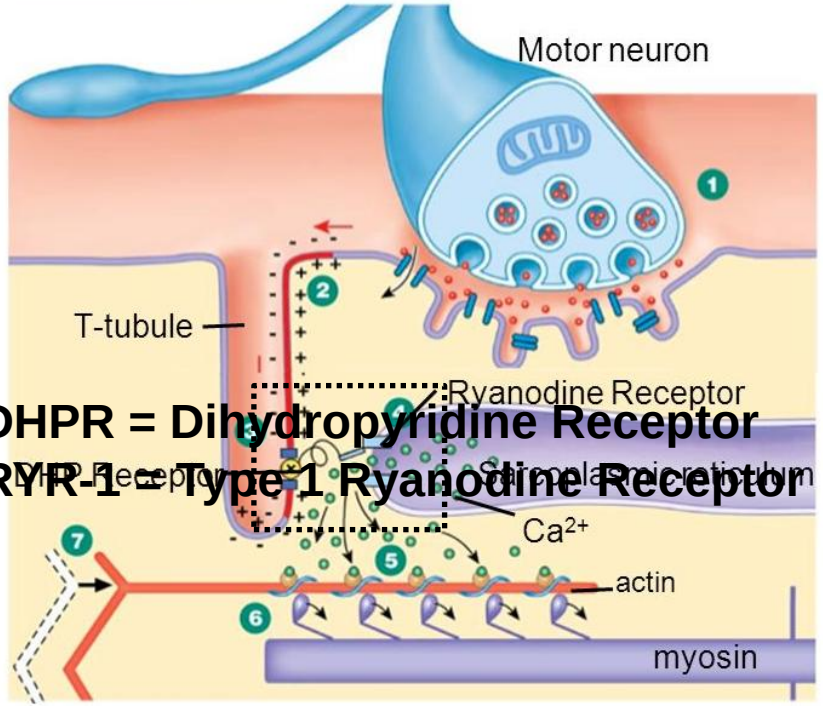
The terminal processes of a motor neuron in close proximity to the sarcolemma of a skeletal **muscle fiber**





DHPR and RYR-1 Communication In Excitation-Contraction Coupling





DHPR = Dihydropyridine Receptor
RYR-1 = Type 1 Ryanodine Receptor

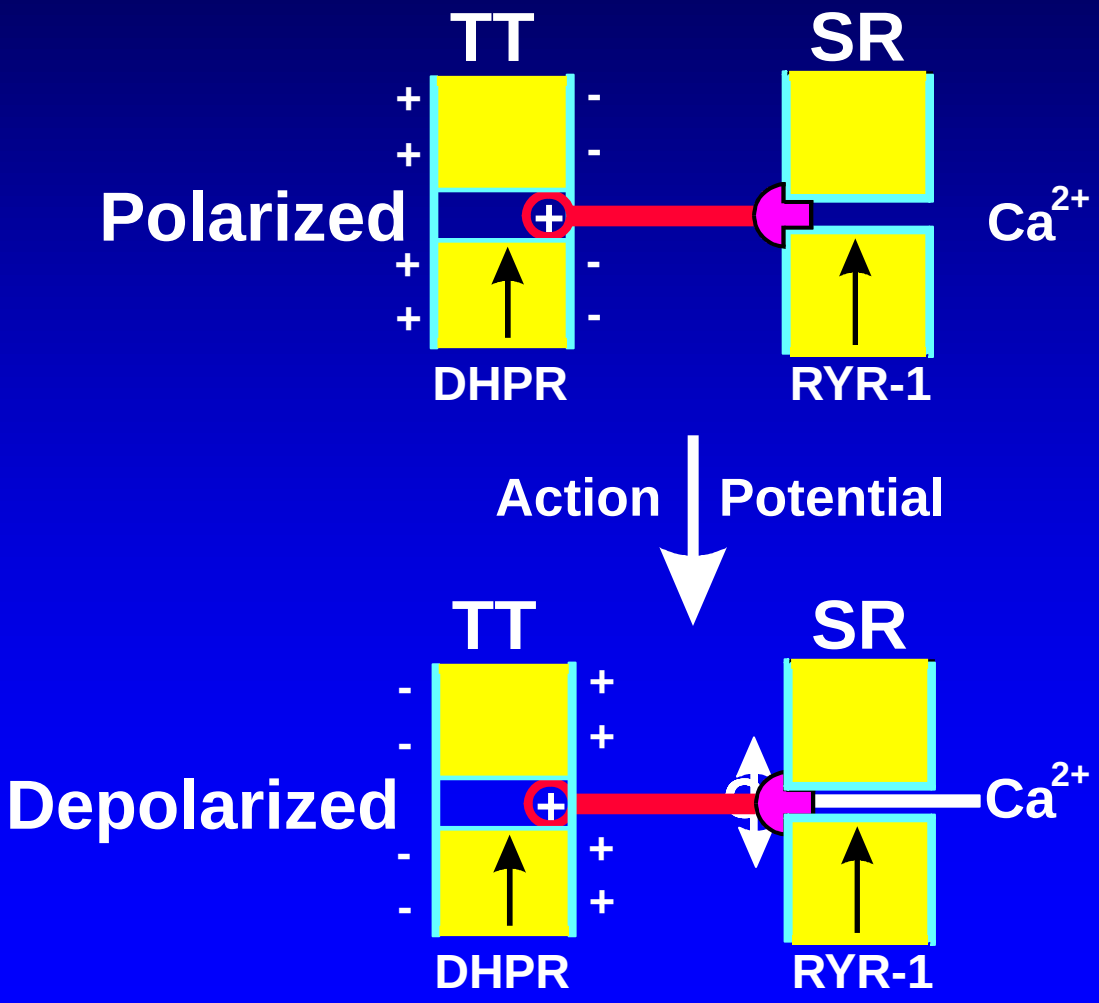
Resting State

- **RYR1 channels are closed**
- **SR Ca^{2+} stores are full**
- **Ca^{2+} levels are low**
- **Myofilaments are relaxed (not contracted)**

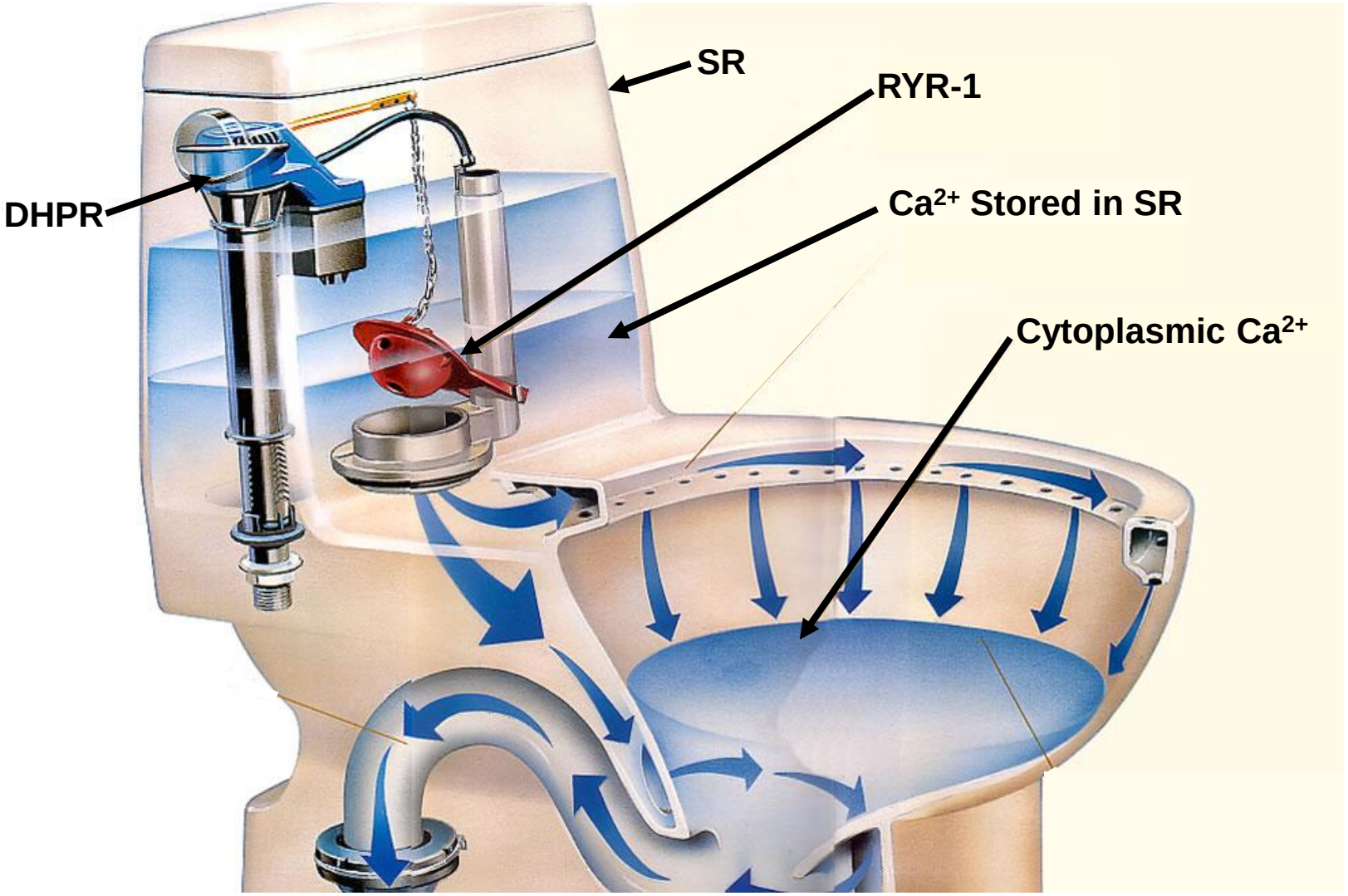
Contraction

- **RYR1 channels are open**
- **SR Ca^{2+} stores are emptying**
- **Ca^{2+} levels are increasing**
- **Myofilaments are contracting**

“Plunger” Model for DHPR-RYR1 Communication



The Function of the EC Coupling Apparatus is Analogous to a Toilet



Questions

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   Answer: An increase in Ca^{2+} drives muscle contraction needed to produce force/ambulate.

2. How does RYR-1 control Ca^{2+} levels in muscle?
   Answer: RYR-1 is the "gate-keeper" between Ca^{2+} in the SR and the contraction machinery.

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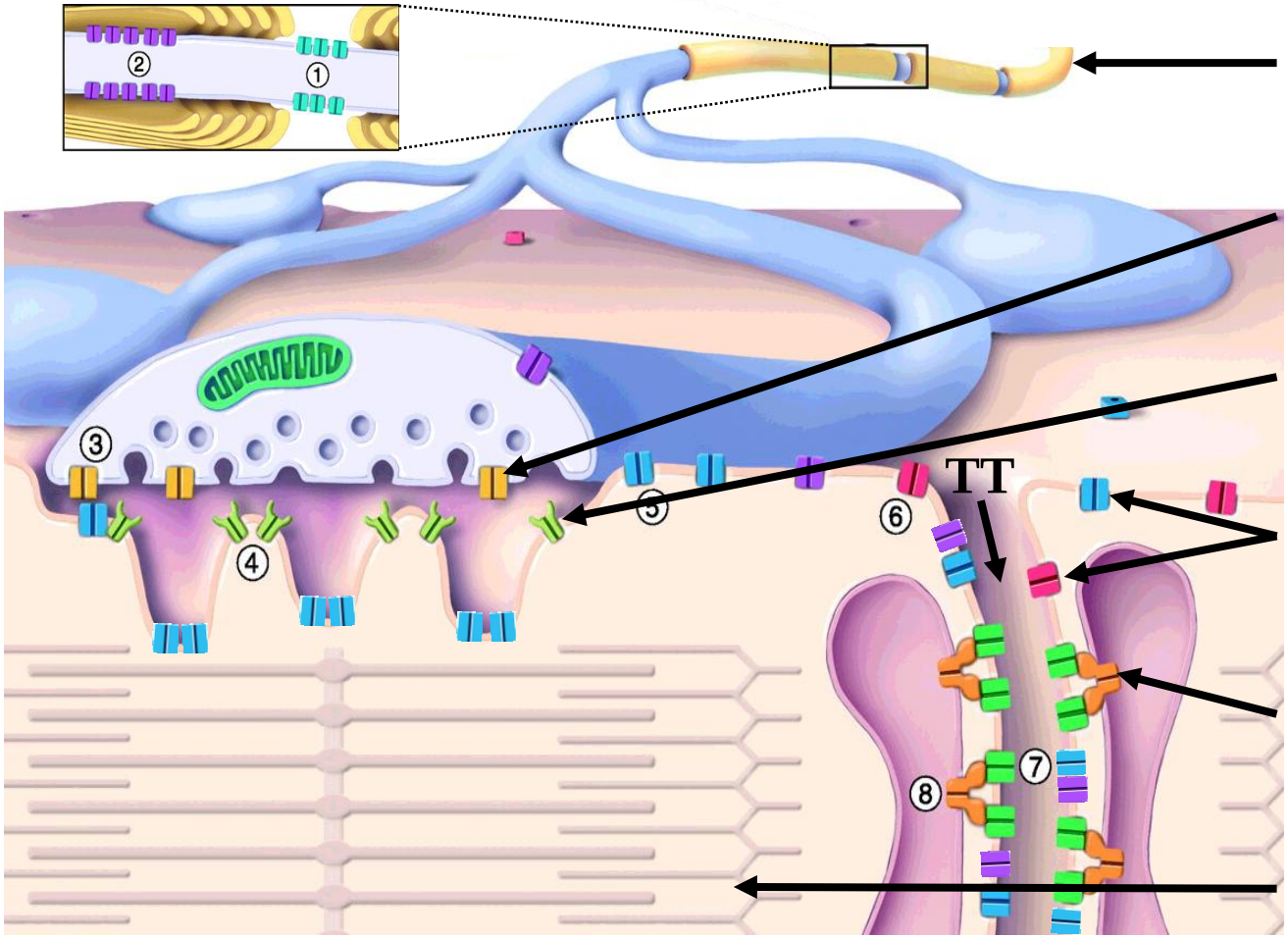
Neuromuscular Diseases



Multiple Sclerosis (MS)

Lambert-Eaton Myasthenic Syndrome

Myasthenia Gravis (MG)

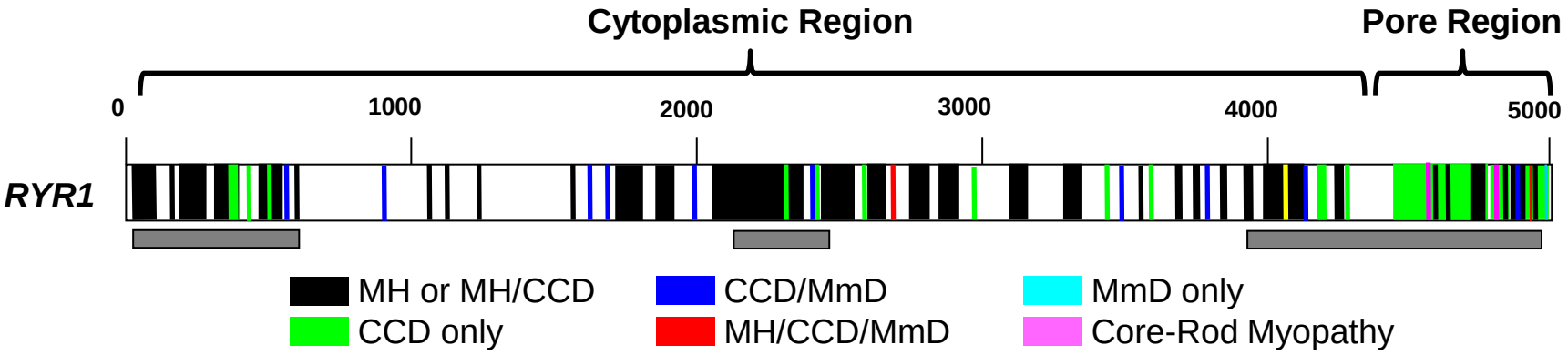
Myotonia and Periodic Paralysis

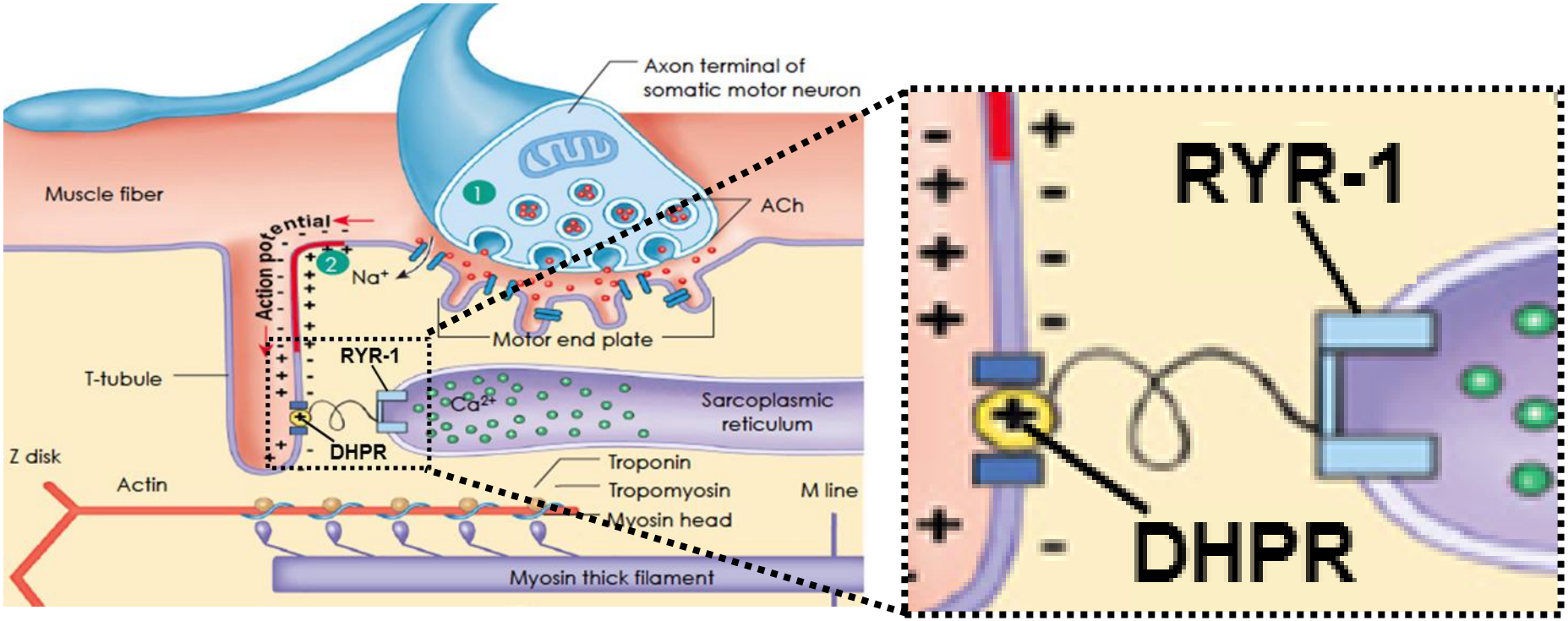
Malignant Hyperthermia and RYR-1 Myopathy

Myofibrillar Myopathy and Nemaline Myopathy

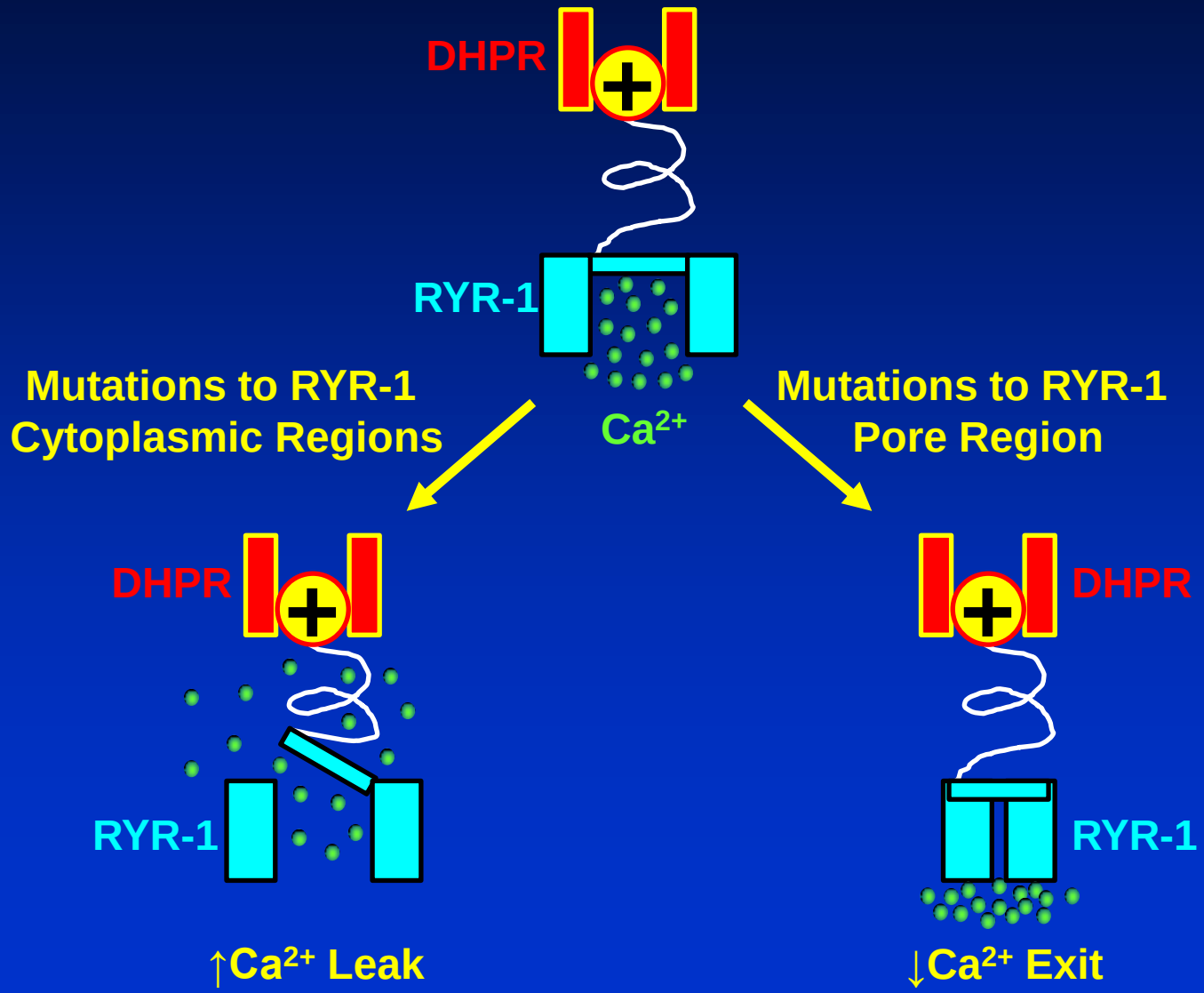
- Nerve Sodium Channel
- Muscle Sodium Channel
- Potassium Channel
- Muscle Chloride Channel
- Nerve Calcium Channel
- Dihydropyridine Receptor (DHPR)
- Acetylcholine Receptor
- Ryanodine Receptor (RYR1)

RYR-1 Myopathy Mutations Alter DHPR and RYR-1 Communication

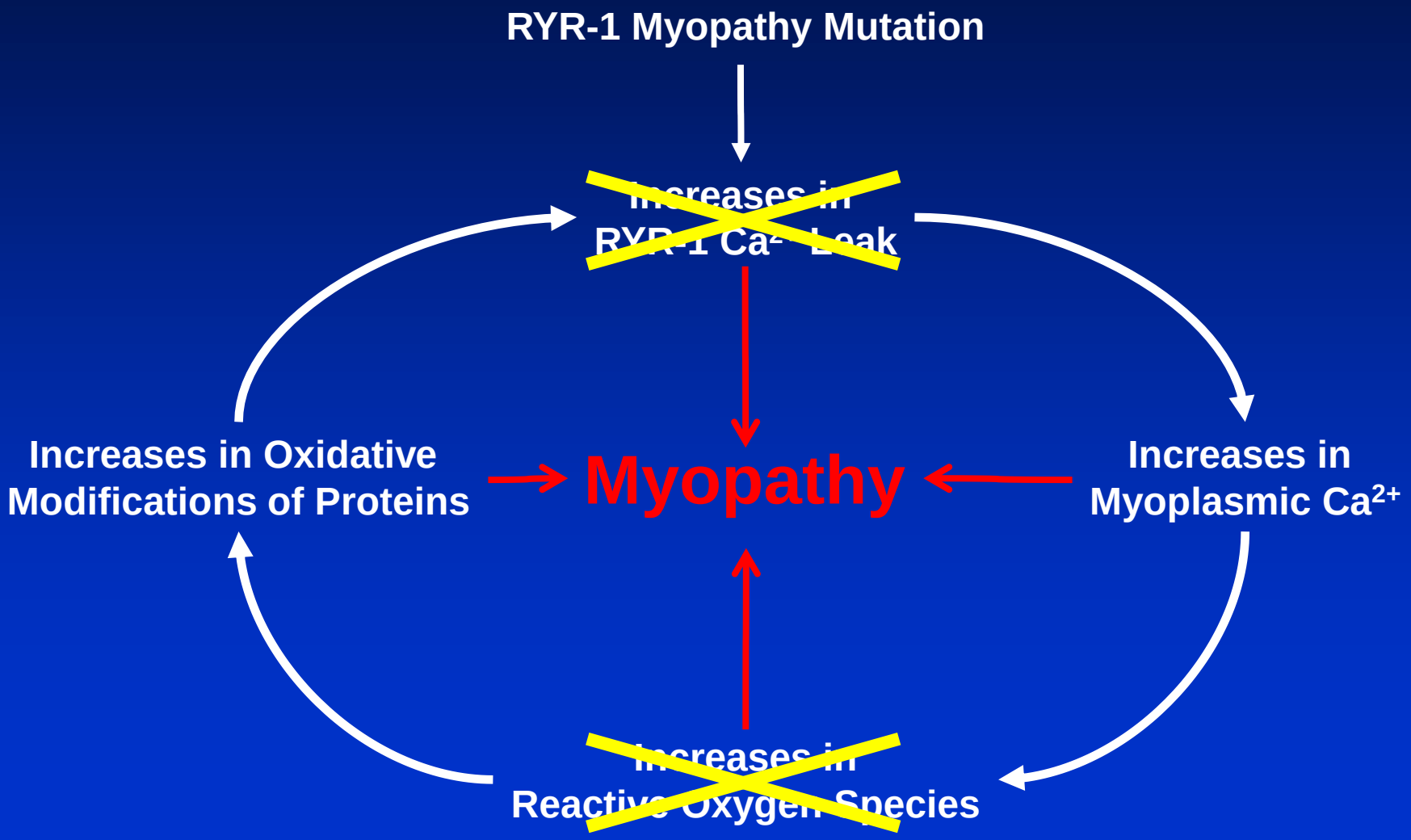




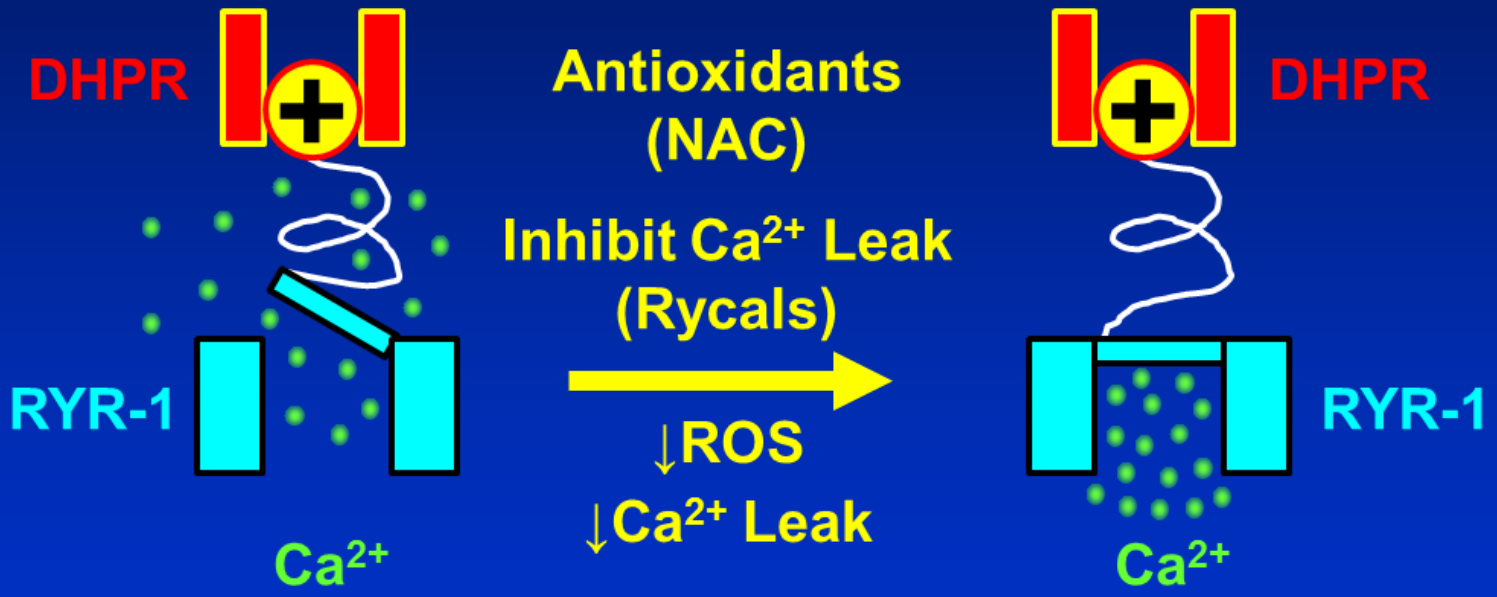
RYR-1 Myopathy Mutations Disrupt RYR-1 Control of Ca^{2+} in Two Ways



Vicious Myopathic Cycle of Increases in Ca^{2+} and Oxidative Stress



Current Investigational RYR-1 Myopathy Therapeutics are Designed to Inhibit RyR1 Ca^{2+} Leak



Future: Correction of RYR-1 Mutation via CRISPR/Cas9-medated Gene Editing?

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3. How do mutations in RYR-1 alter the proper control of Ca^{2+} levels in skeletal muscle, and ultimately, lead to myopathy?
   Answer: Mutations either promote RYR-1 Ca^{2+} leak or reduce Ca^{2+} exit through the channel.

Thank You
RYR-1 Foundation
For Bringing Us All Together!

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