



Electron Donor/Acceptor Properties of Drugs Affect Ryanodine Receptors

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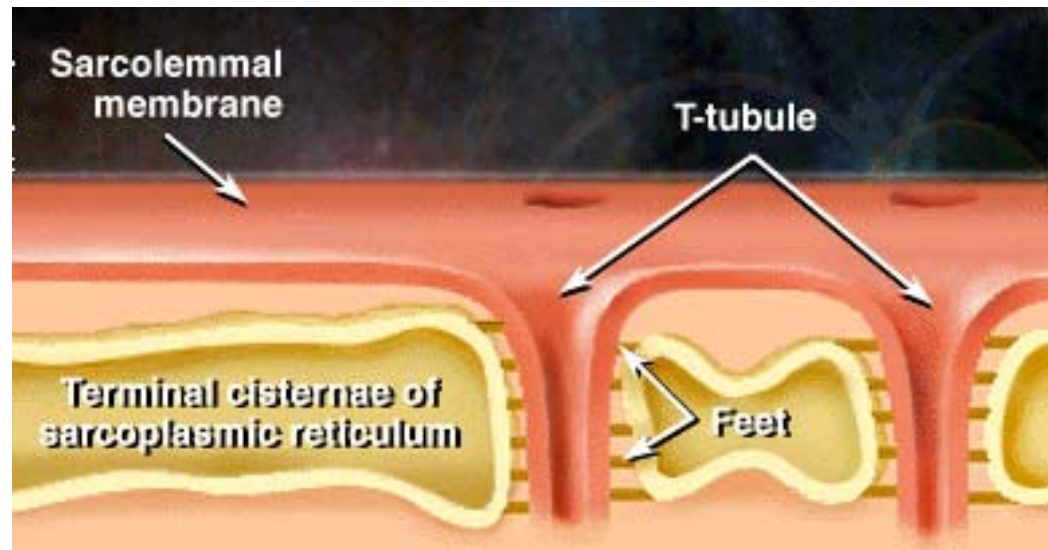
Dr. Jon Abramson's biophysics lab

Summer 2006

Background

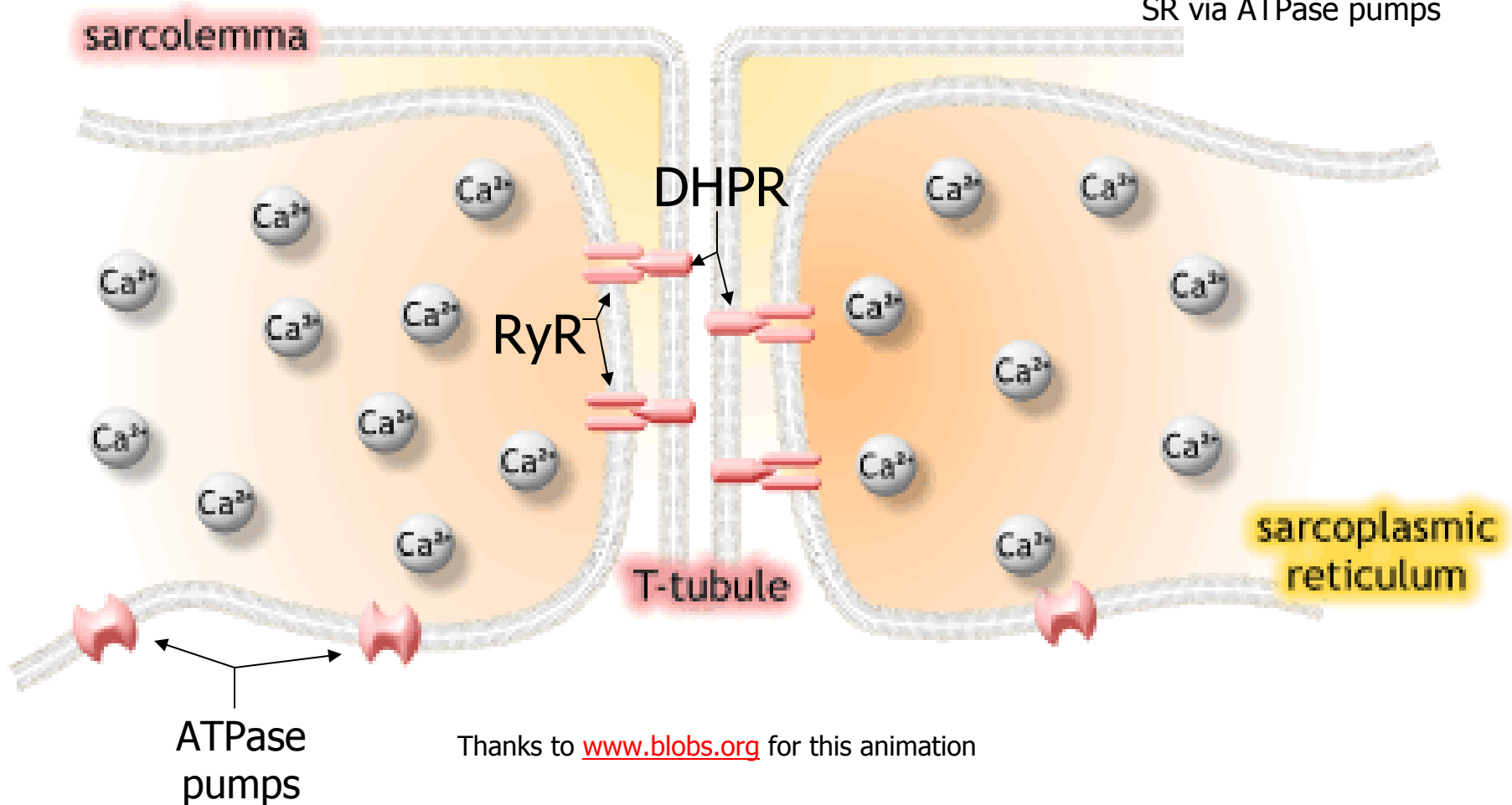
■ SR

- Modified ER
- Calcium release channel/RyR
- Ryanodine binds when RyR is open
- Contraction/relaxation mechanism



Background contd.

- (a) Relaxed state
- (b) Action potential (purple) propagates down T-tubule
- (c) DHPR undergoes conformational change to activate RyR
- (d) Ca^{2+} exits SR via RyR
- (e) Contraction [interaction with troponin]
- (f) Ca^{2+} is transported back into SR via ATPase pumps



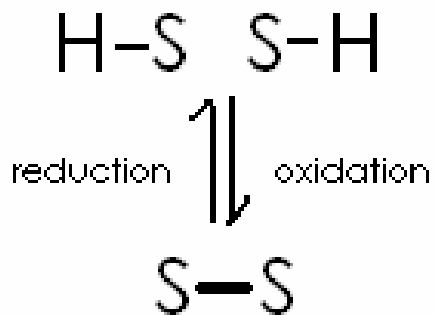
Thanks to www.blobs.org for this animation



Background contd.

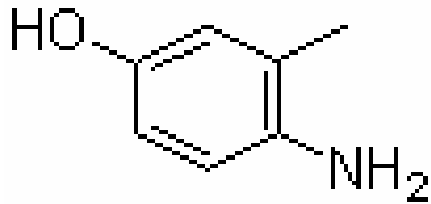
- Calcium Release Channel

- Redox potential indicates thiols state
- Oxidized vs. reduced environment
 - Free thiols = reduced, disulfides = oxidized
- Modification of drugs for desired effect
 - Donor = inhibitor, acceptor = activator

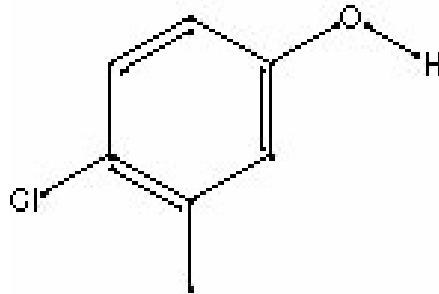


Methods

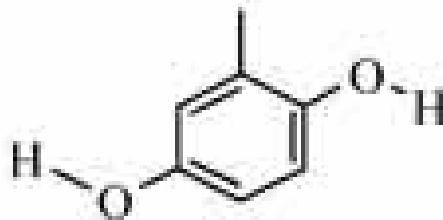
4-amino-m-cresol



4-chloro-m-cresol



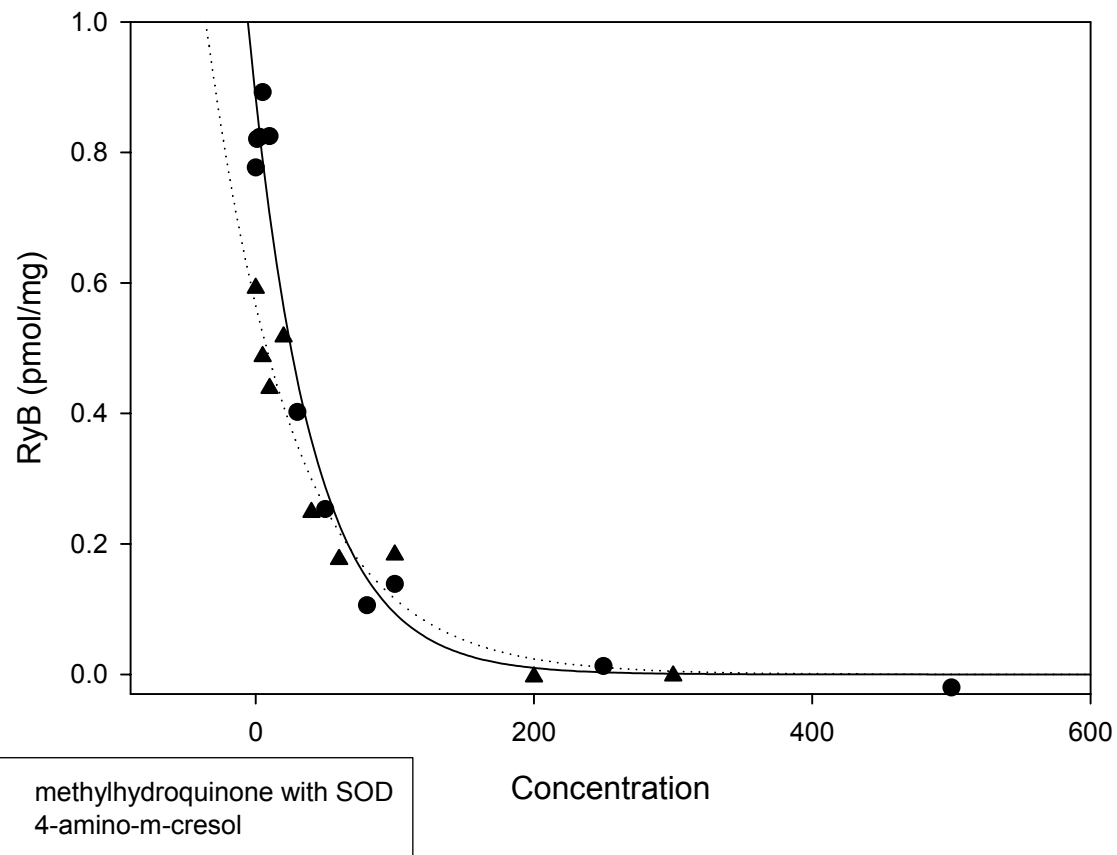
Methylhydroquinone



- Equilibrium binding
- [³H]Ryanodine
 - Low energy betas are relatively harmless
- Ryanodine binds when RyR is open; assay summarizes activity
- Hydroquinone → superoxide problem

Results

Equilibrium Binding of 4-chloro-m-cresol derivatives





Discussion

- Recent paper declares no derivatives of 4cmc are activators
 - 3 are donors, 2 actually inhibit markedly
- Pharmaceuticals/medical research benefit from these studies
- Results from Benjamin/Diana plus binding assays correlate donor activity to inhibition
- Future improvements



Acknowledgements

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