

AUTOIMMUNITY IN POTS: FOCUS UPON G-PROTEIN COUPLED RECEPTORS

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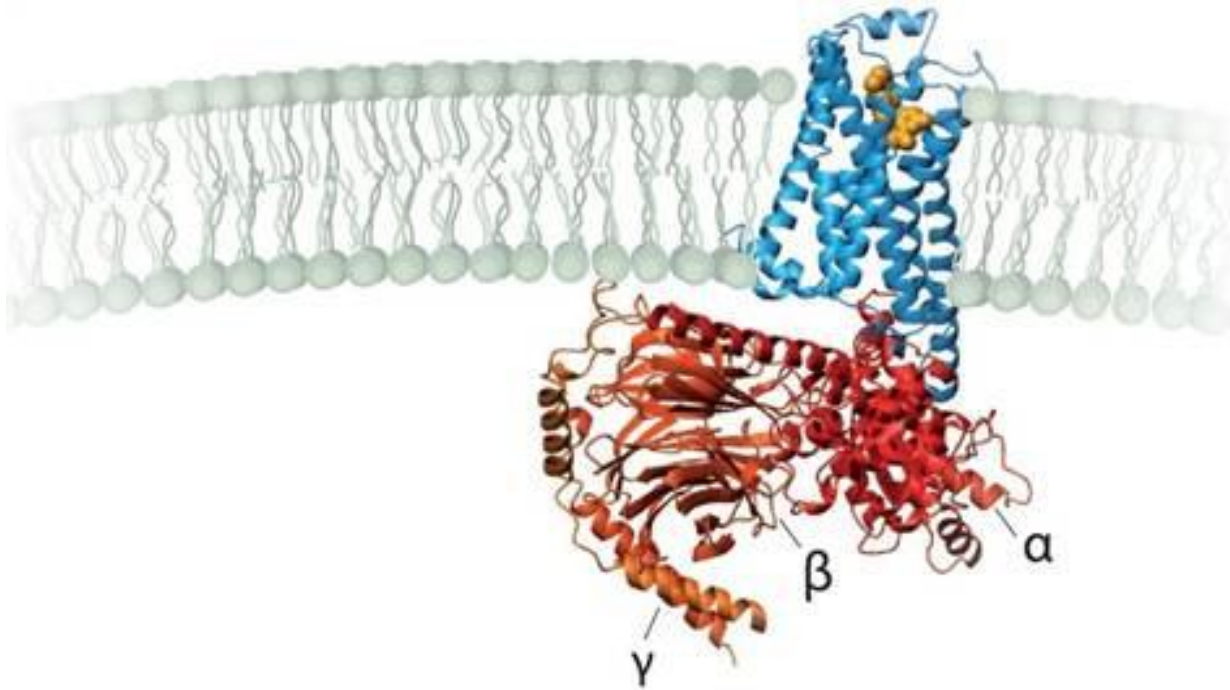
Malmö, Sweden



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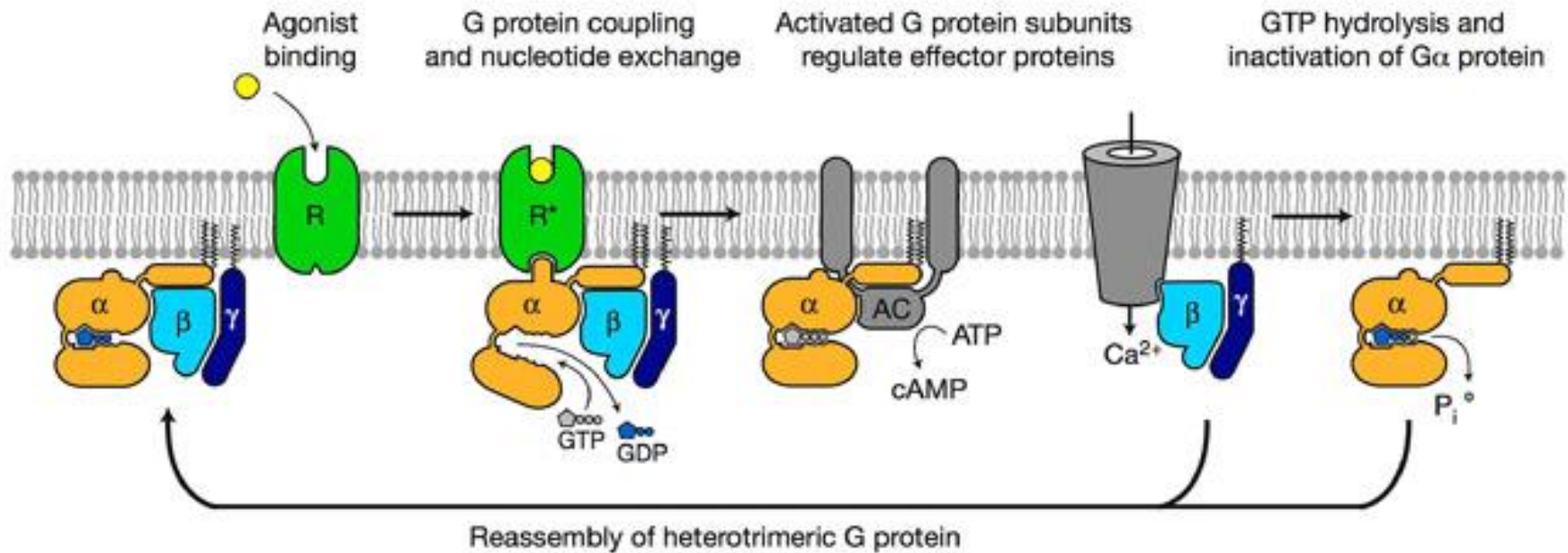
Activated adrenergic β -receptor

Nobel Prize in Chemistry for 2012 to Robert J. Lefkowitz and Brian K. Kobilka

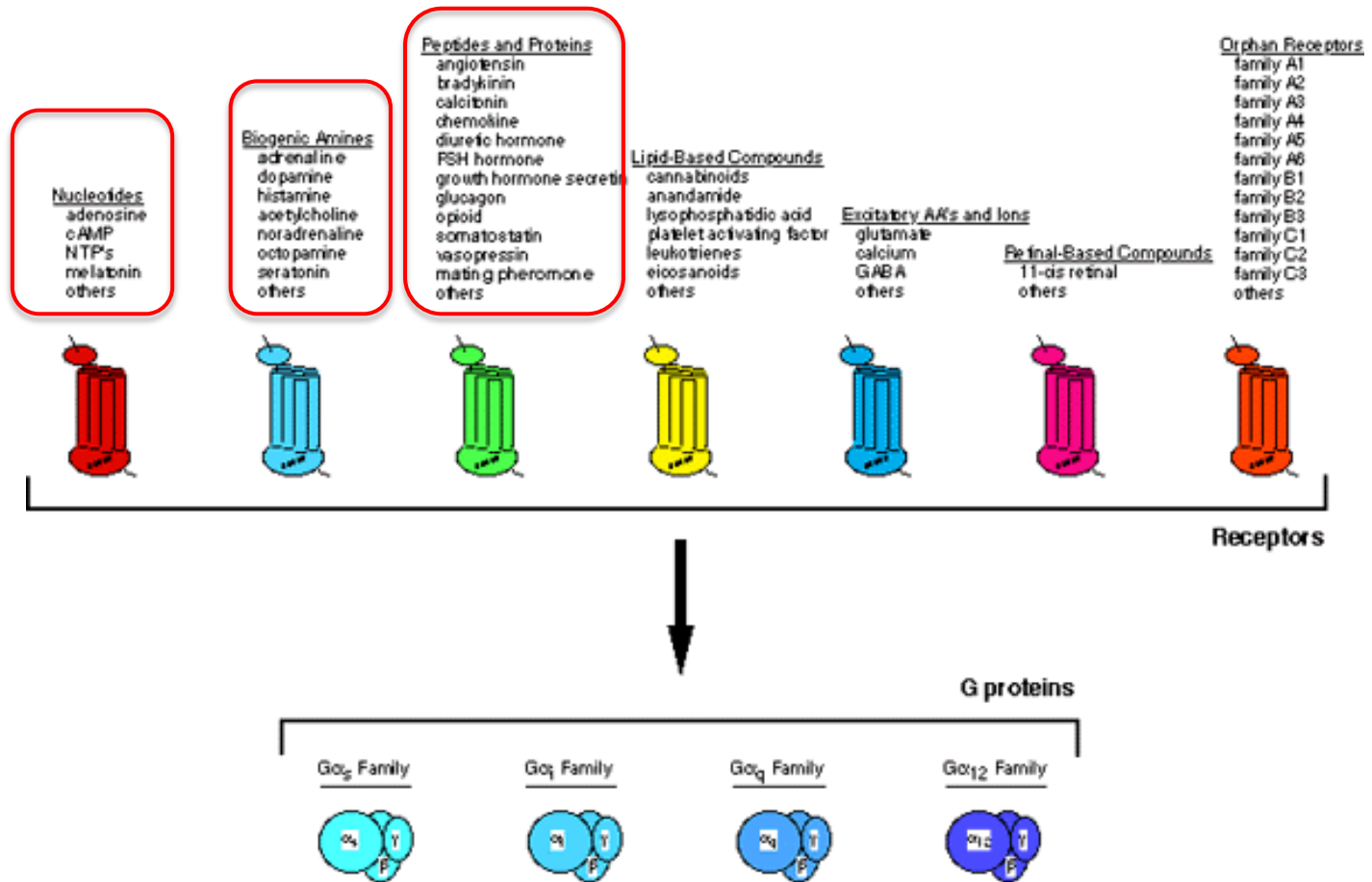


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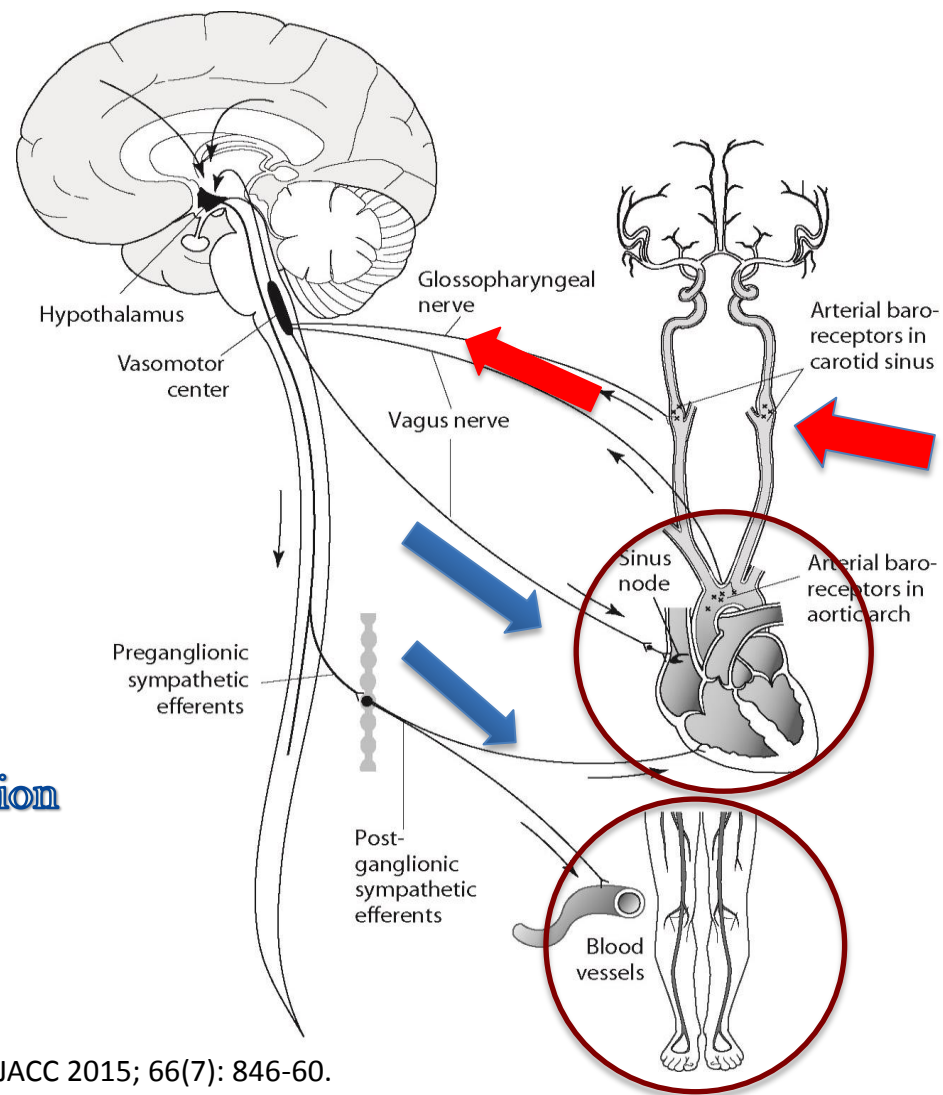
GPCR: How does it work?



Receptor and G Protein Diversity

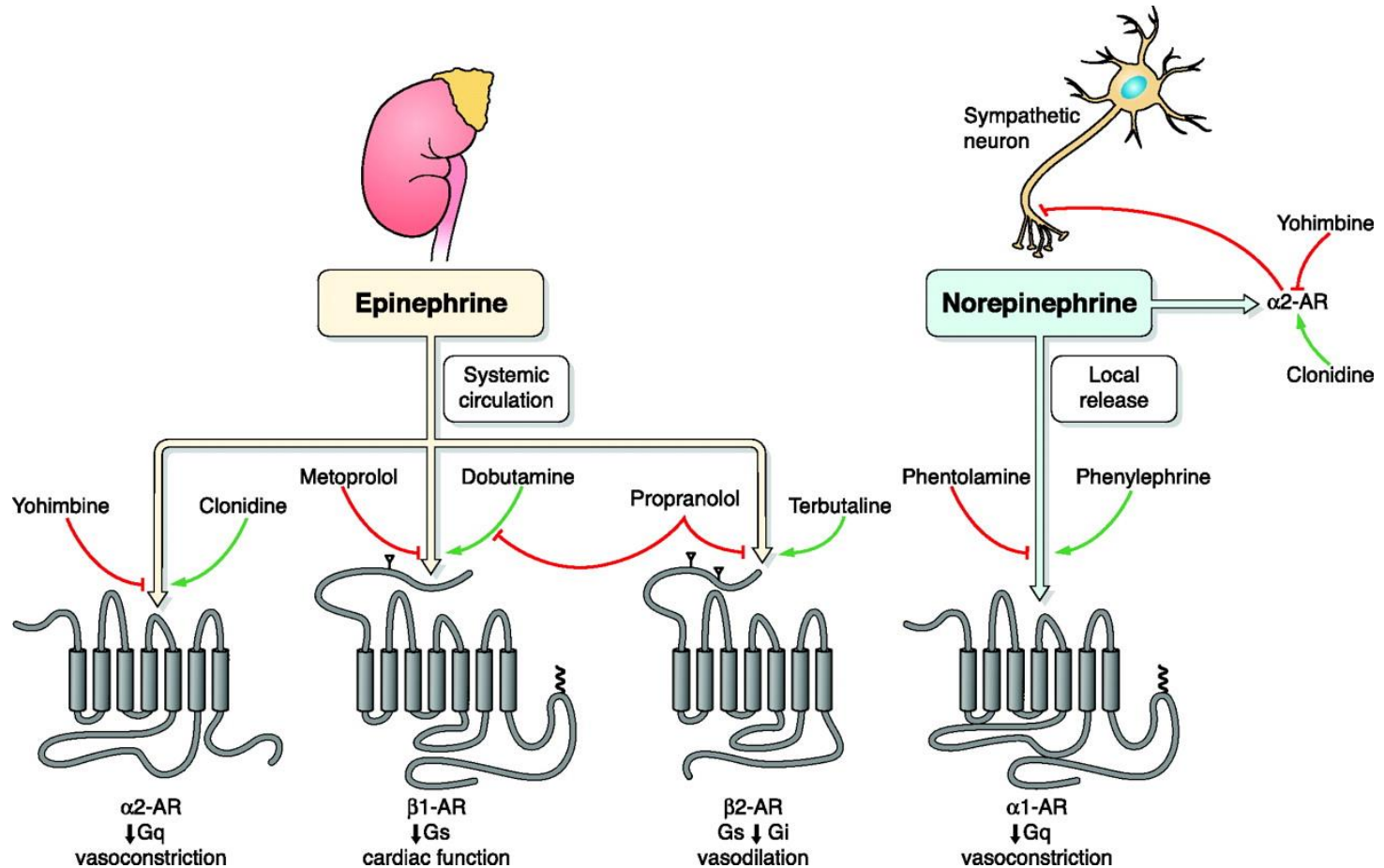


The baroreflex function

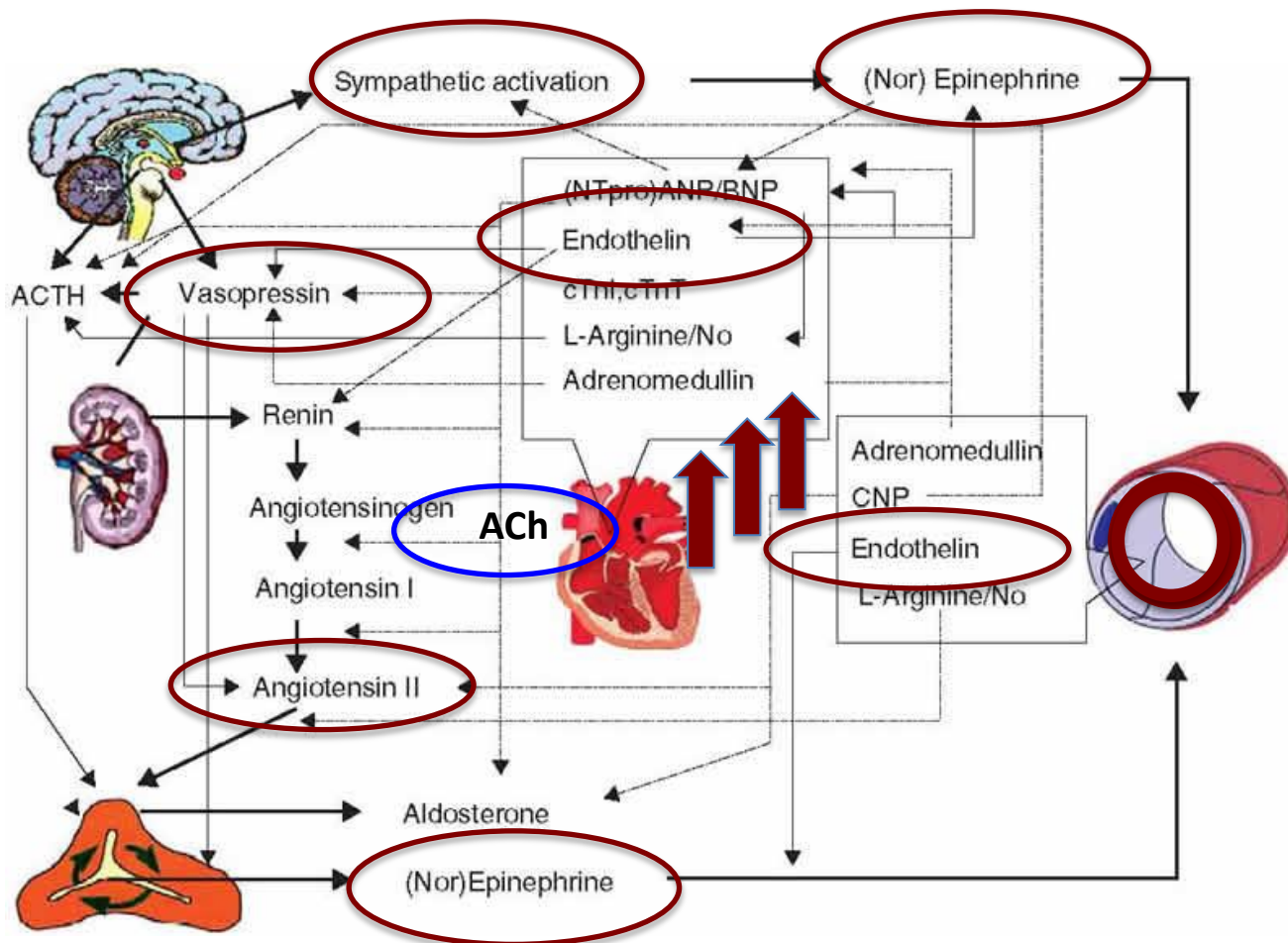


Ricci F, De Caterina R, Fedorowski A. JACC 2015; 66(7): 846-60.

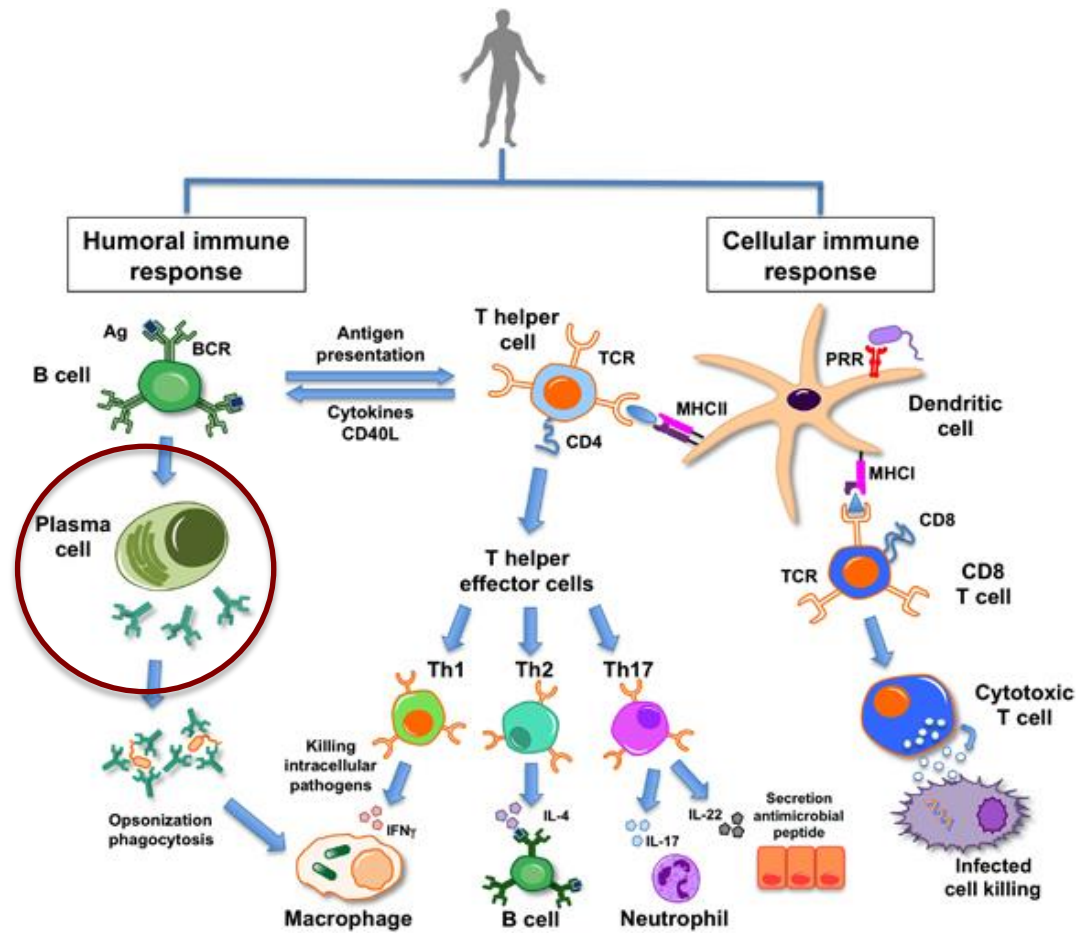
Tissue responses to activation of specific adrenergic receptor subtypes.



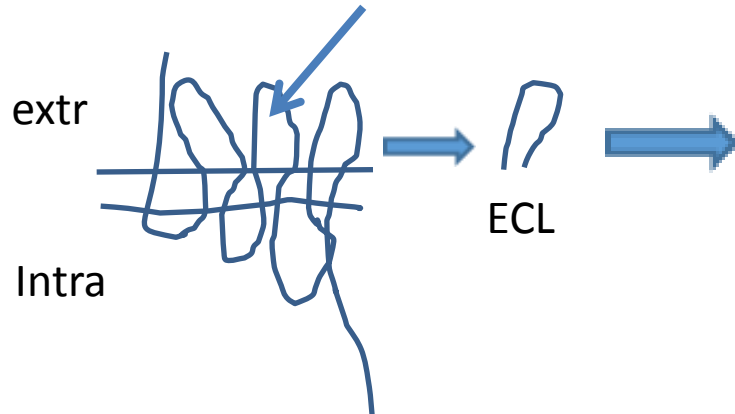
Neuroendocrine response to hypotension



THE HUMAN IMMUNE RESPONSE



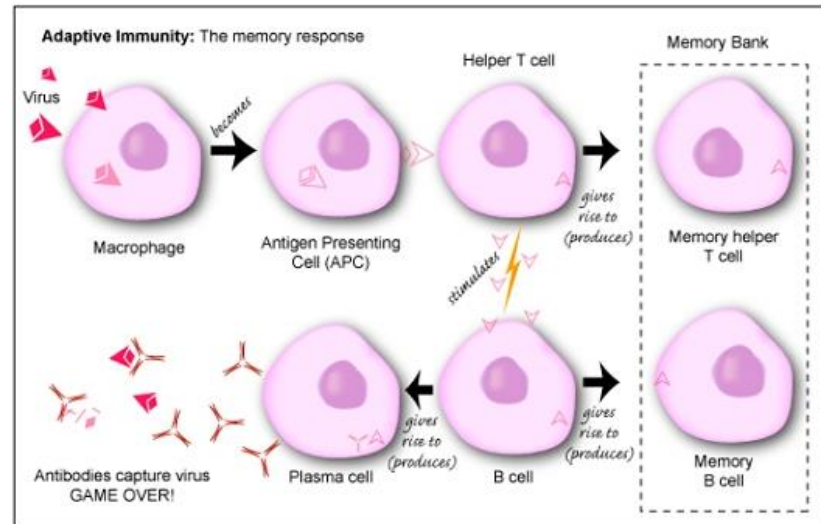
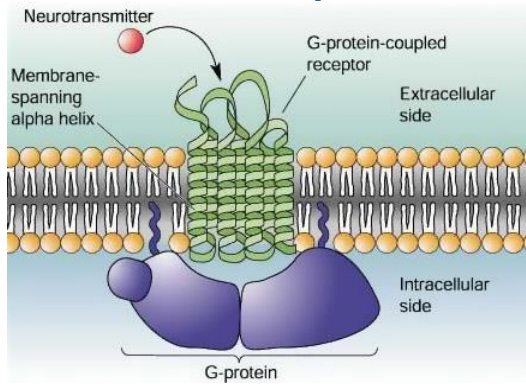
Activation of MMP-10 or equivalent endo proteinase by **virus/stress**

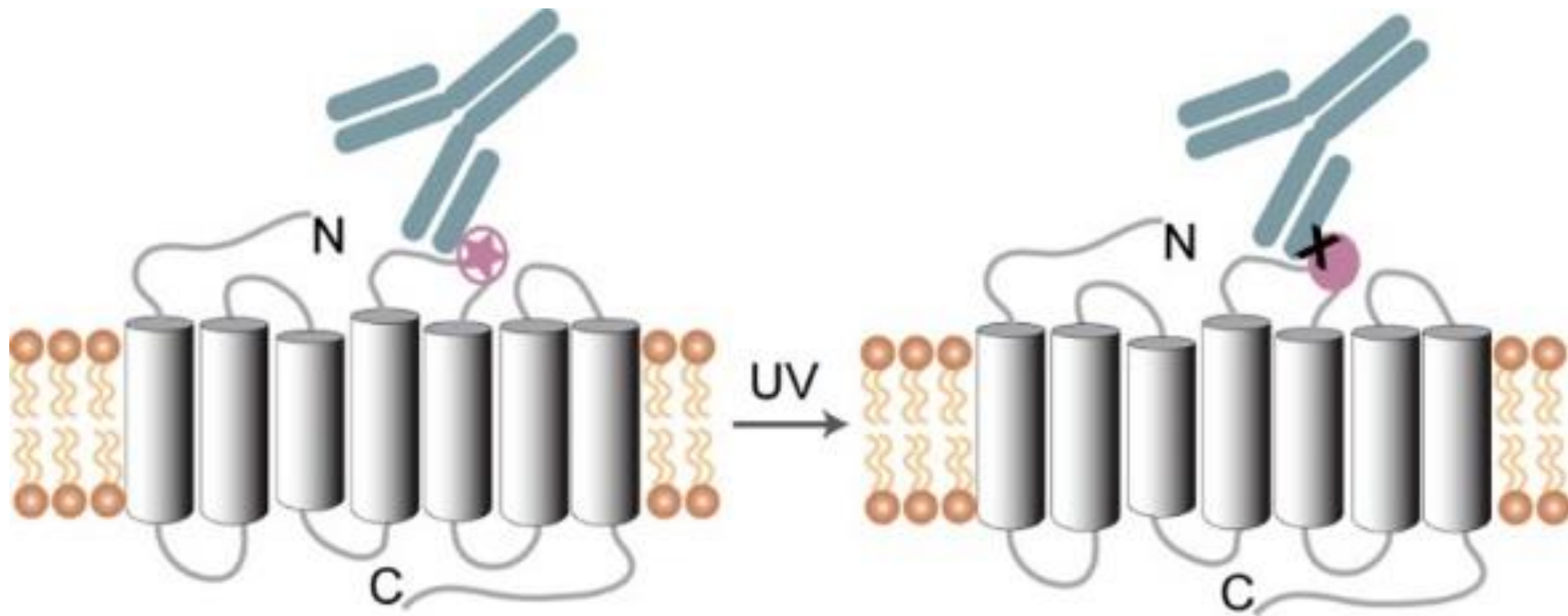


Proteasome degradation of the ECL



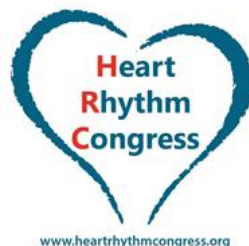
Immunoprotein complex





Presence of Activating Autoantibodies (AAb) in POTS (D.Kem)

- The CV pathophysiology of POTS may be caused by the presence of ***one or more circulating active autoantibodies (AAb)***.
- These may act as ***direct*** stimulators of GPCRs or ***allosterically alter the activity*** of their natural ligand.
- ***A unique cluster (spectrum) of AAbs in each individual*** will alter their autonomic systems and produce differing but predictable signs and symptoms.



Common POTS Symptoms

o Cardio/Vasc

- Palpitations
- Lightheadedness
- Chest discomfort/pain
- Shortness of breath
- Exercise intolerance

o NeuroMuscular

- Mental clouding (brain fog)
- Headaches (migraine)
- Sleep complaints
- Involuntary movements

Gastrointestinal

Nausea and vomiting

Constipation

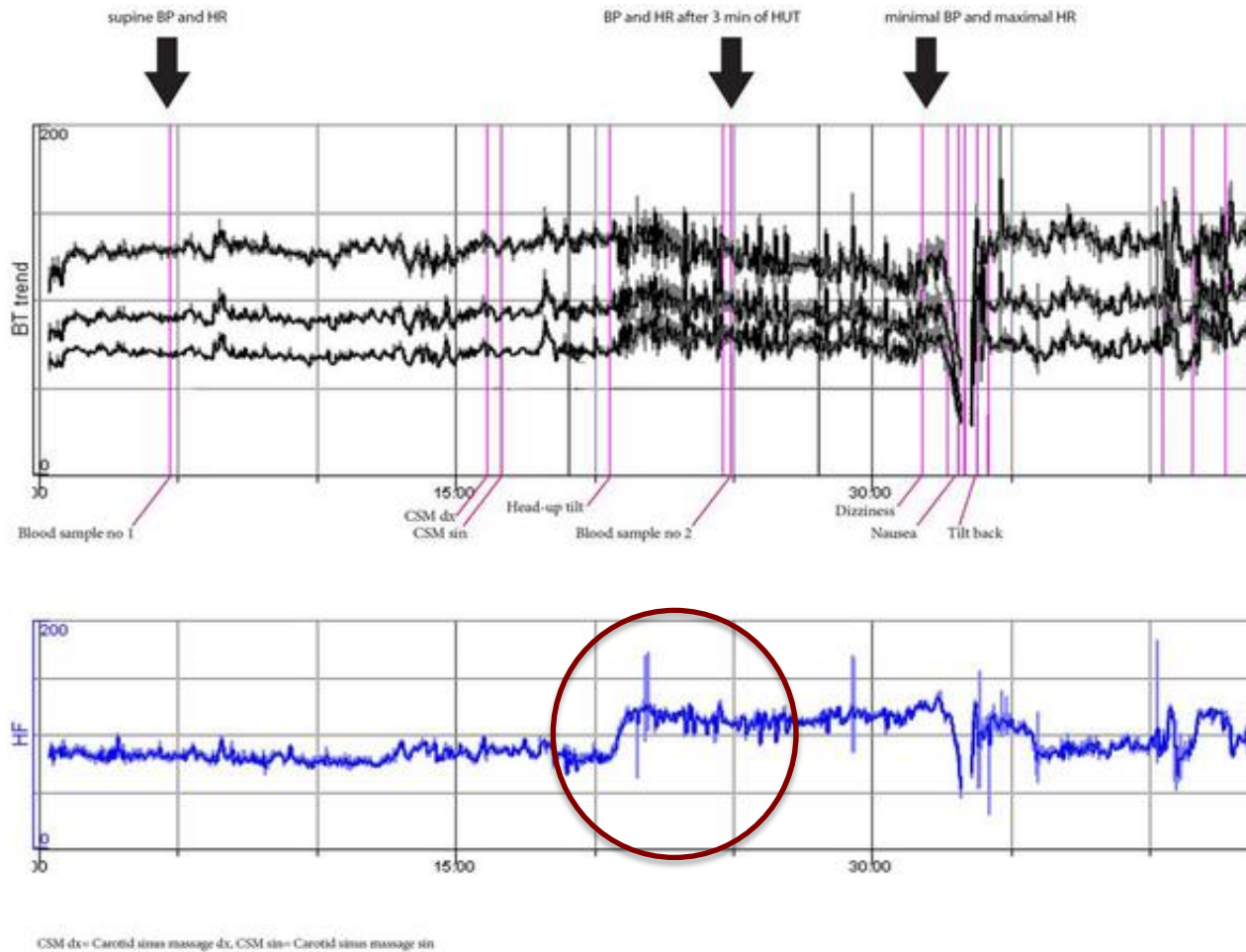
Weight loss

Chronic Fatigue

Visceral and regional pain

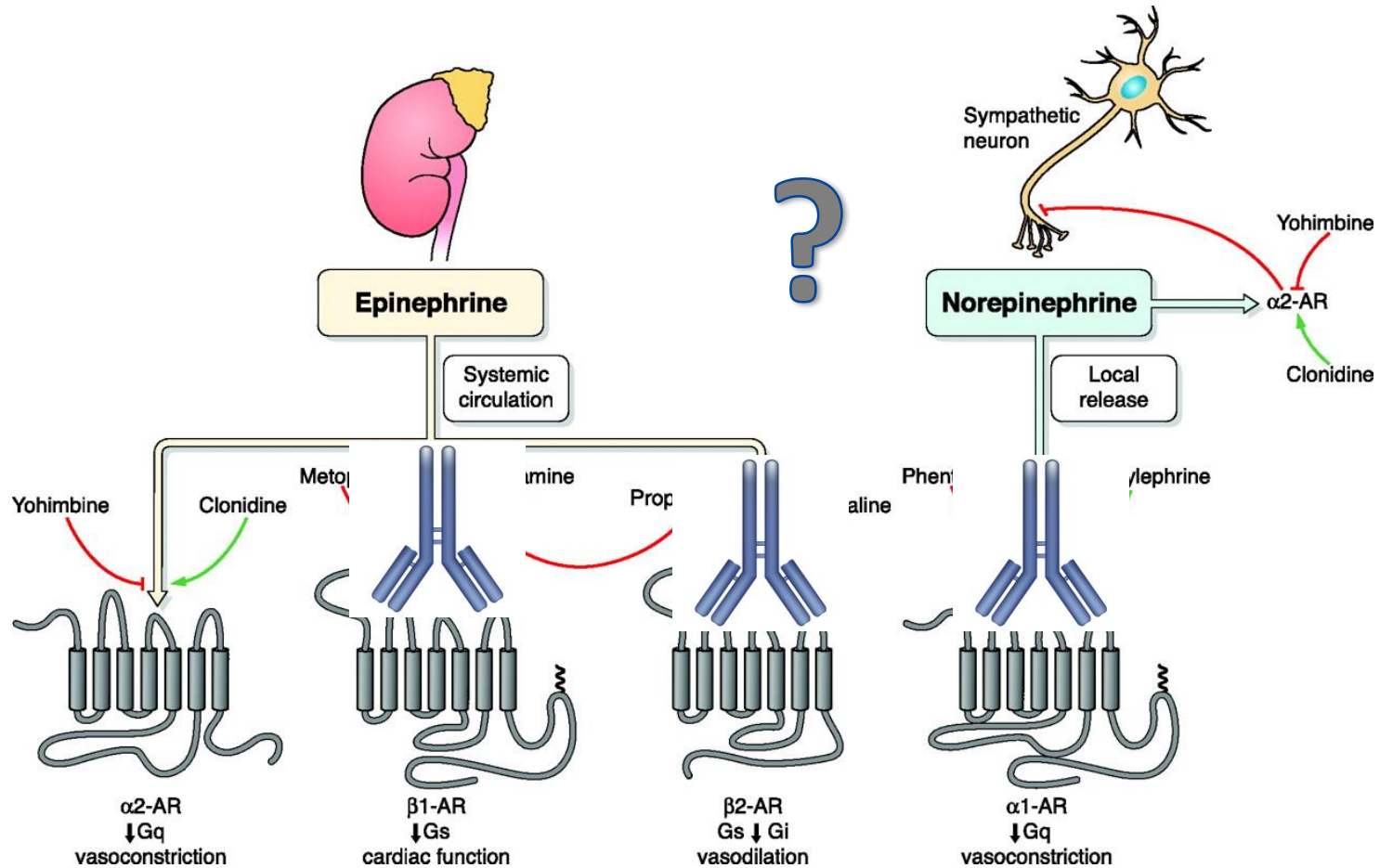


Pronounced orthostatic tachycardia (\approx POTS) and vasovagal reflex syncope (woman, 24 years).



Nilsson D, Sutton R, Tas W, Burri P, Melander O, ...Fedorowski A. (2015) PLoS ONE 10(6): e0128962

Tissue responses to activation of specific adrenergic receptor subtypes.



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Gerald W. Dorn II Physiol Rev 2010;90:1013-1062



Antiadrenergic autoimmunity in postural tachycardia syndrome

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Valerie M. Harris^{3,4}, Campbell Liles³, Taylor A. Murphy³, Syed M.S. Quadri^{3,4},
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Autoimmune Basis for Postural Tachycardia Syndrome

Hongliang Li, Xichun Yu, Campbell Liles, Muneer Khan, Megan Vanderlinde-Wood, Allison Galloway, Caitlin Zillner, Alexandria Benbrook, Sean Reim, Daniel Collier, Michael A. Hill, Satish R. Raj, Luis E. Okamoto, Madeleine W. Cunningham, Christopher E. Aston and David C. Kem

J Am Heart Assoc. 2014;3:e000755; originally published February 26, 2014;

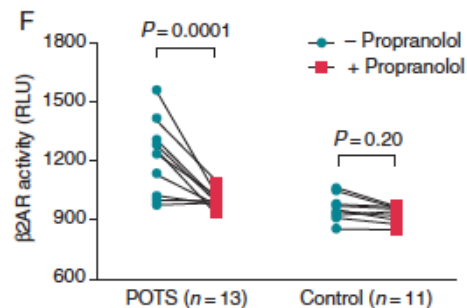
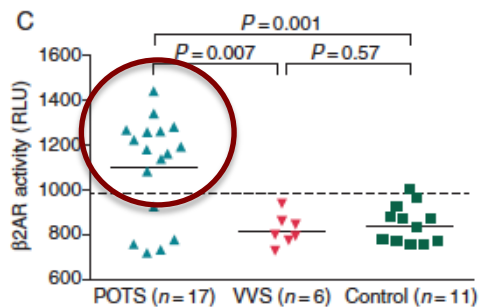
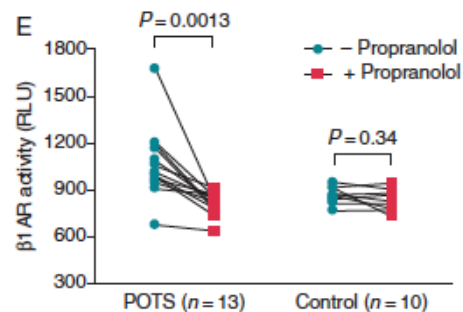
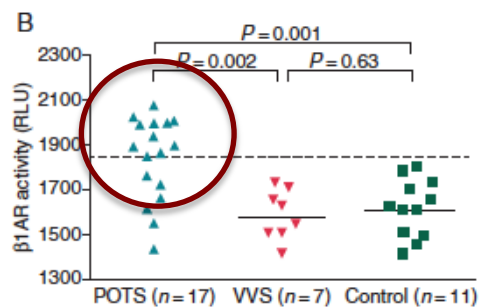
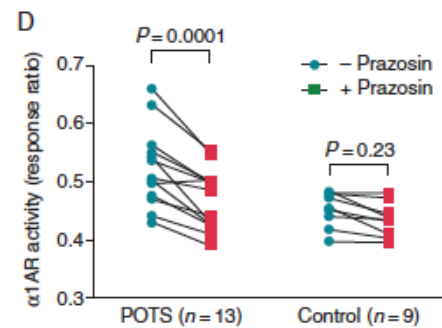
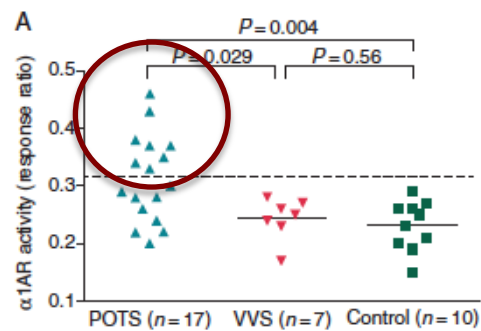
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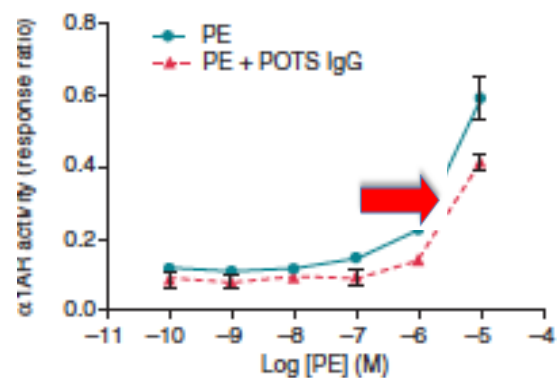


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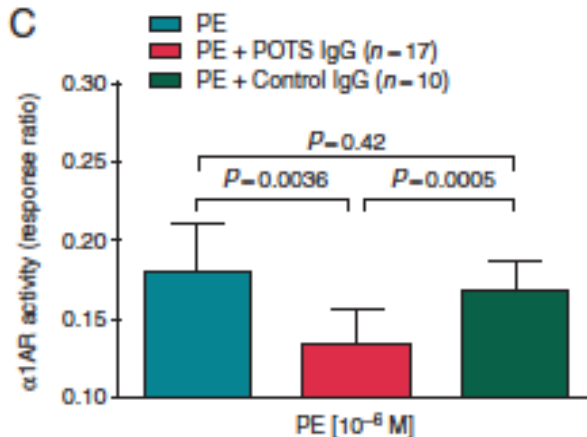


Fedorowski, Sutton, Melander, Kem. Europace (2016).

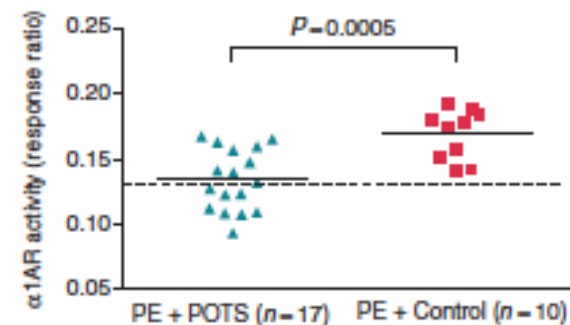
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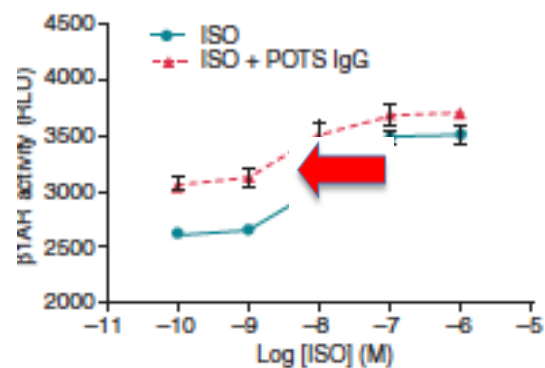
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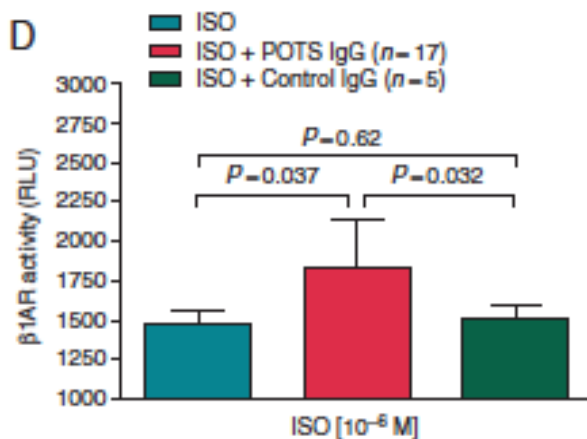
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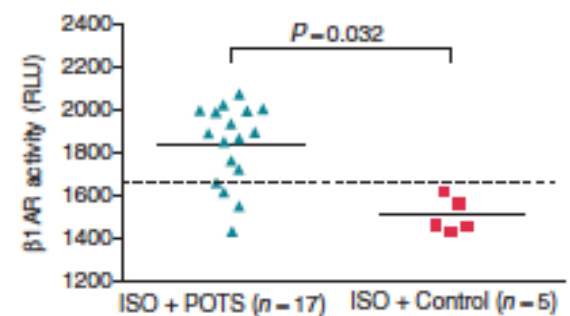
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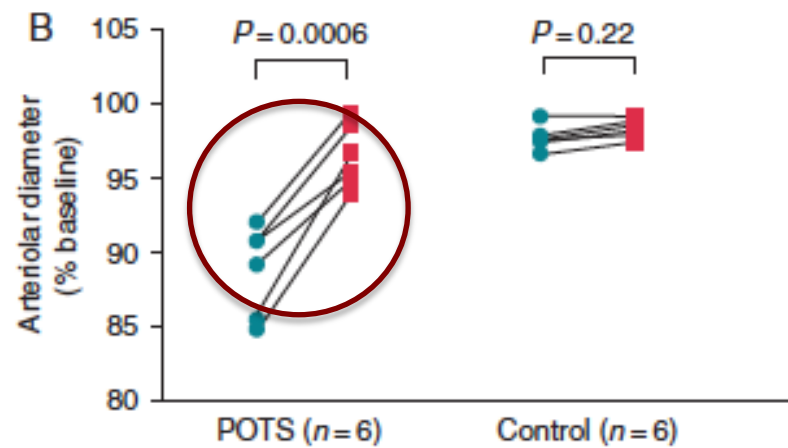
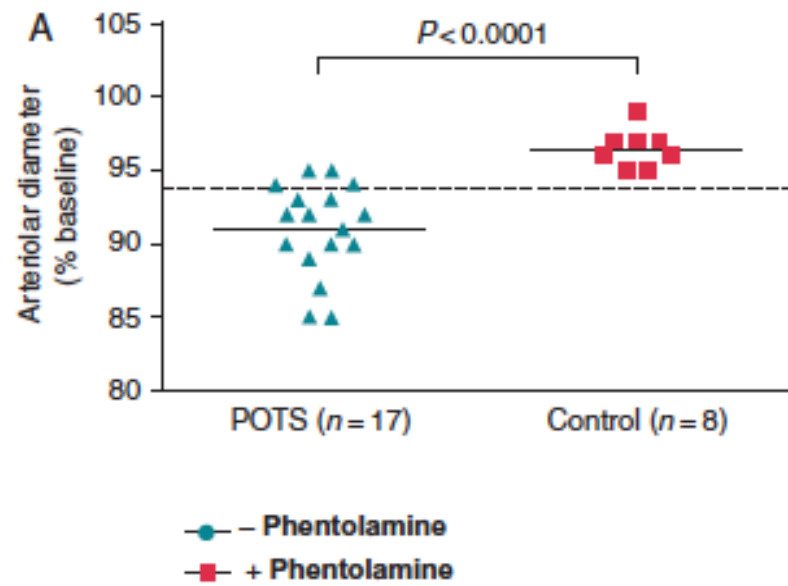


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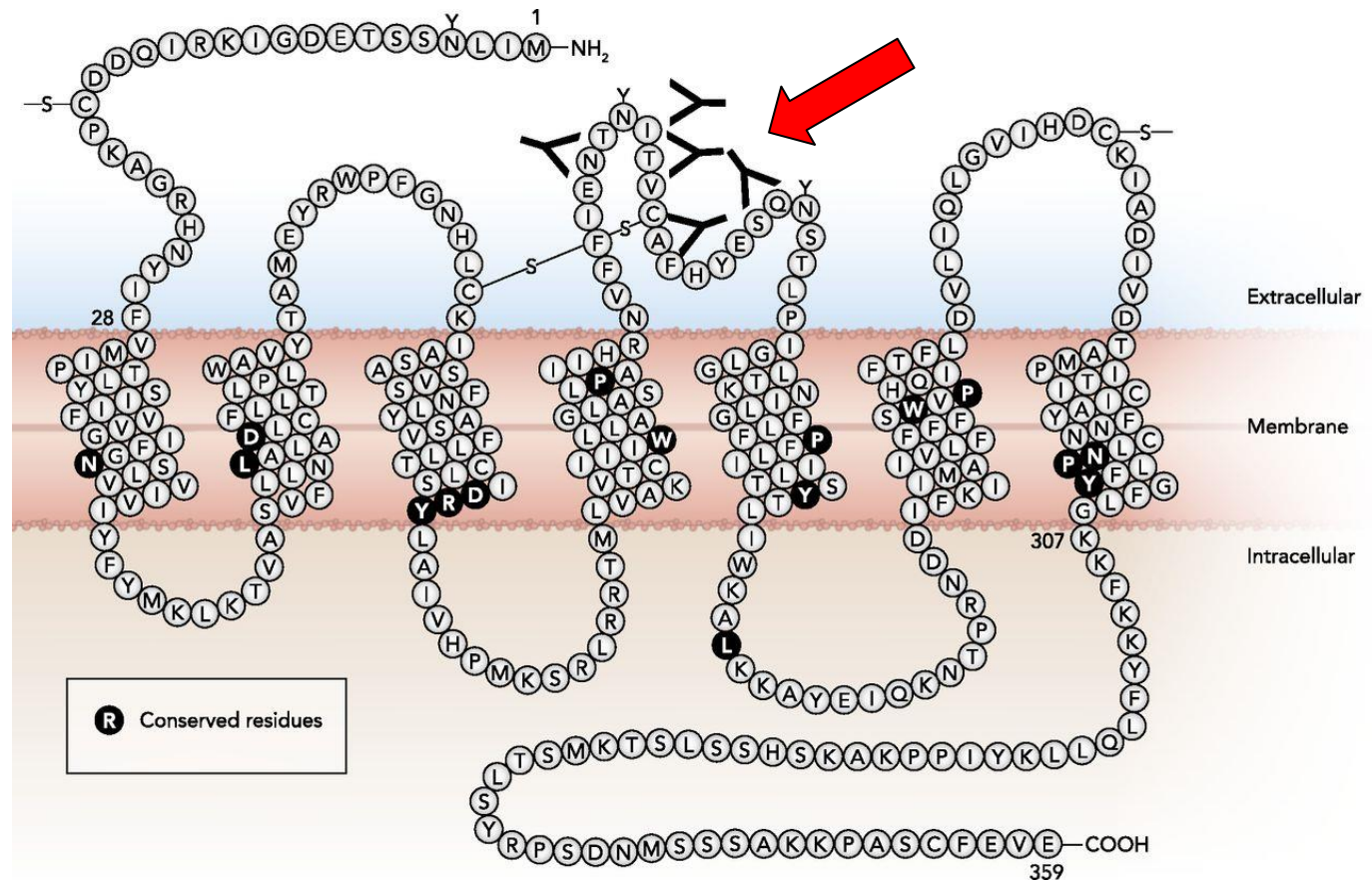
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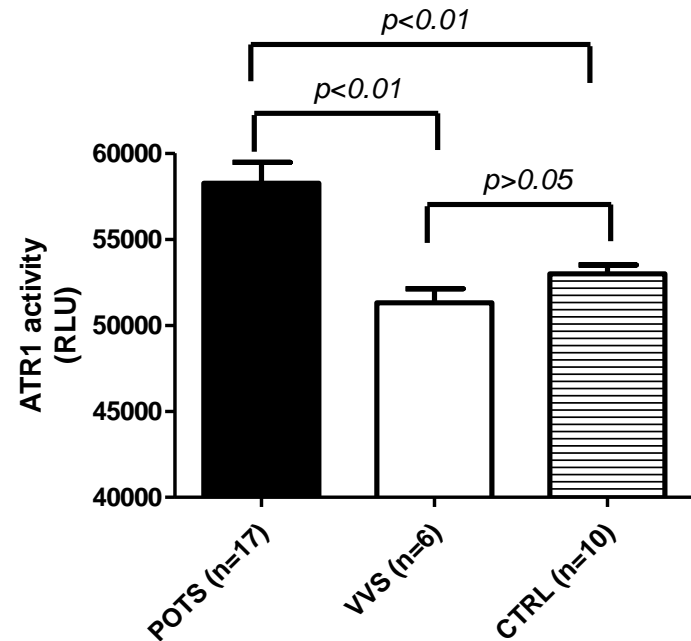
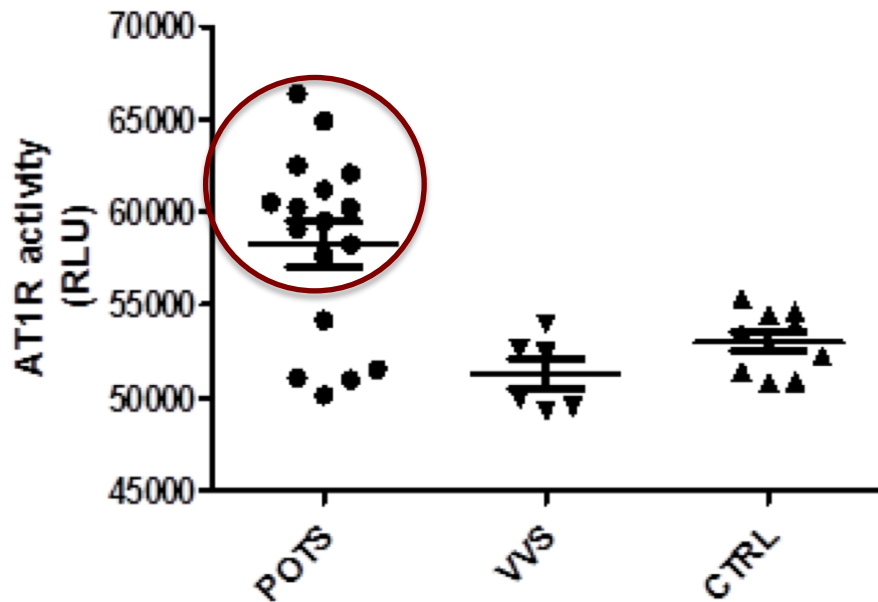
Amino-acid sequence structure of AT1RAntibody binding sites on the second extracellular loop of AT1R are identified.



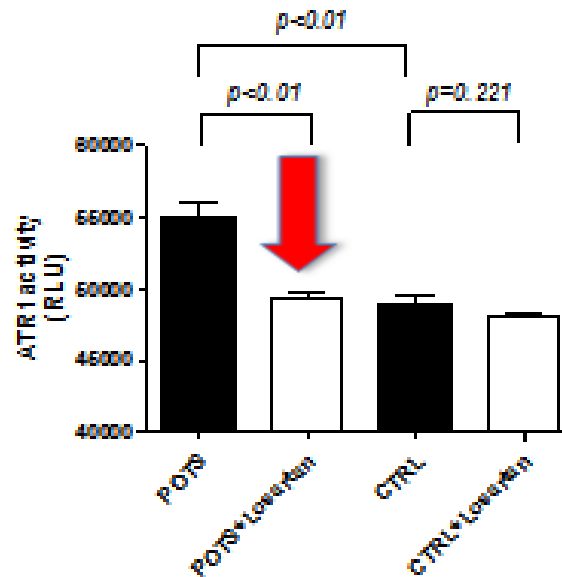
Friedrich C. Luft Physiology 2013;28:254-261

Effects of POTS IgG on AT₁ (unpublished)

Hongliang Li, Artur Fedorowski, David Kem et al.

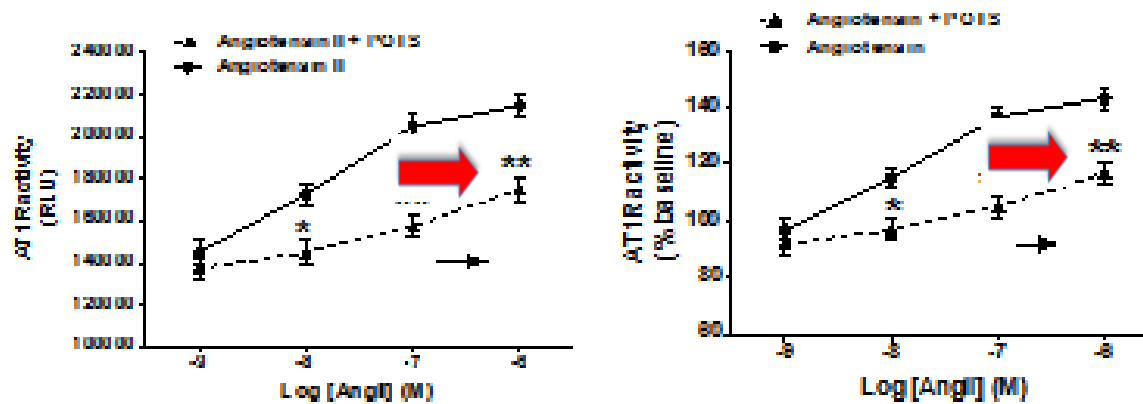


Effect of losartan on AT1R activating autoantibody induced AT1R activation in transfected CHO cells



Compared with the CTRL IgG, POTs IgG led to significant activation of AT1R, which was suppressed by AT1R blocker losartan (10 μ M).

Allosteric effects of POTS IgG on Angiotensin II dose response



Cardiovascular G-protein-coupled receptors that regulate cardiac function and blood pressure via activation by their respective ligands.

VERNINO
WALLUKAT

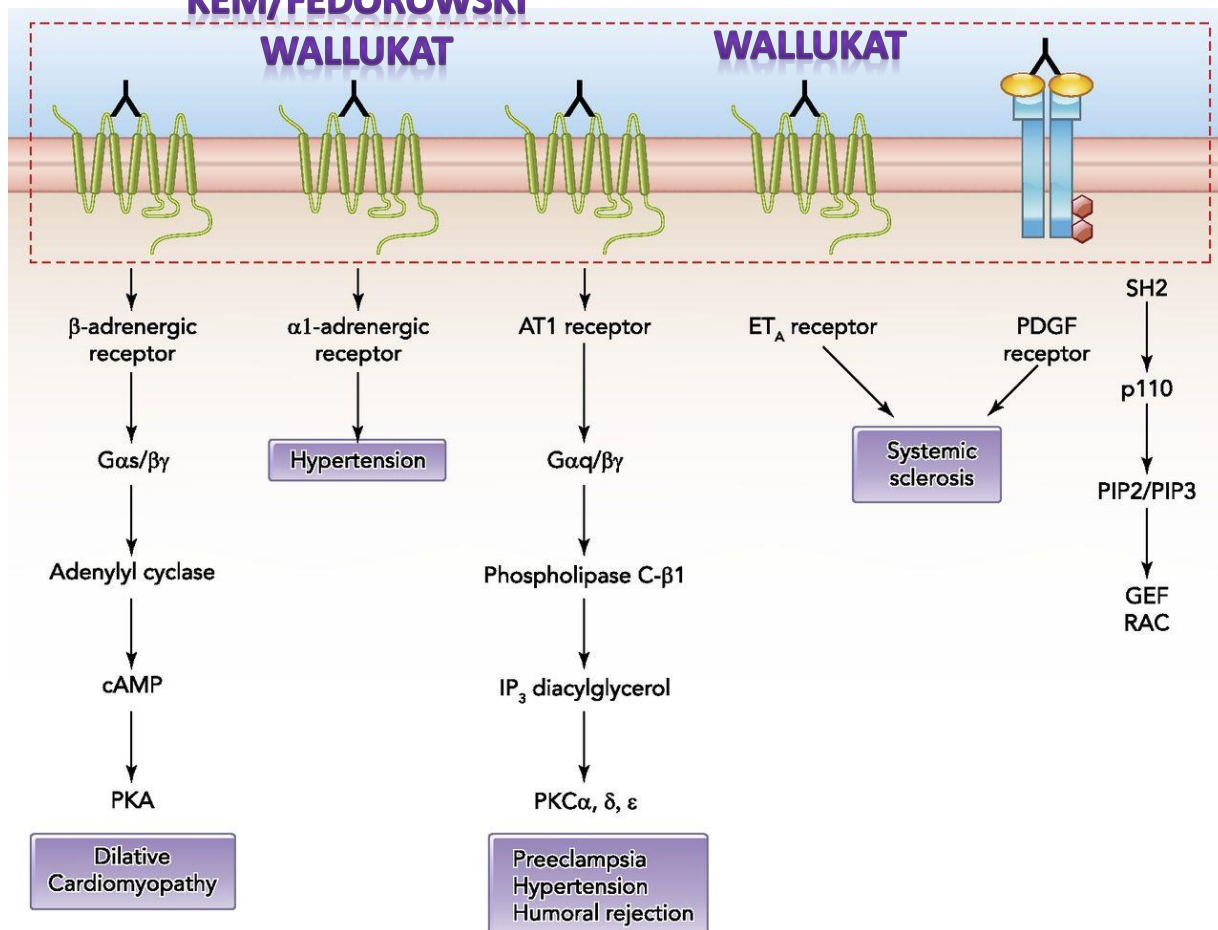
Muscarinic
receptor M2

KEM/FEDOROWSKI

WALLUKAT

WALLUKAT

POTS



Friedrich C. Luft Physiology 2013;28:254-261

Take-home messages

- Presence of AAbs against GPCRs has been demonstrated in POTS.
- POTS may have an autoimmune etiology.
- The next step is to find a way to eliminate AAbs and demonstrate improvement of symptoms.



Thank you for your attention !

Contributors:

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