POTS

Autoantibodies: quirky finding or future therapy?

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Disclosures

• Fees and royalties from Cardiome, Thermofisher, Medtronic.
Gunhild Stordalen
Dx Systemic sclerosis Oct 2014

Bone marrow transplant and chemotherapy x 2
Graves’ Disease = Autoimmune Hyperthyroidism

- Autoimmune Disease
- Different autoantibodies against TSHr
- Female predominance (80%)
- Genetic predisposition
- Viral infection a possible trigger
- Causal treatment not available
- Thyroid gland is a prime target for medical interventions
- No therapy aiming at elimination of autoantibodies to date!

Robert James Graves
1796-1853
Thyrotropin receptor (G-protein coupled receptor): Autoimmune target in Graves’ Disease
Autoantibodies detected in POTS exceeding the expected prevalence in the general population

<table>
<thead>
<tr>
<th>The category of autoimmune target</th>
<th>Specific autoimmune targets</th>
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<tbody>
<tr>
<td>G-protein coupled receptors [43, 45, 47, 48]</td>
<td>1. Adrenergic receptors (<em>Alpha-1</em>Beta-1*Beta-2)</td>
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<tr>
<td></td>
<td>2. Muscarinic M1 and M2 receptors</td>
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<td>3. Angiotensin II Type 1 receptor</td>
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<tr>
<td>Ganglionic Acetylcholine-receptor (g-AChR) [26, 48]</td>
<td>1. g-AChR alpha3 subunit</td>
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<td>2. g-AChR beta4 subunit</td>
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<td>Sjögren autoantibodies [41]</td>
<td>1. Novel Sjögren Syndrome panel (carbonic anhydrase-6; parotid secretory protein; salivary protein-1)</td>
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<tr>
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<td>2. Traditional Sjögren Syndrome -A antibodies (SS-A)</td>
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<tr>
<td>Antinuclear antibodies (ANAs) [40]</td>
<td>-</td>
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<tr>
<td>Antiphospholipid antibodies [40, 41]</td>
<td>-</td>
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<tr>
<td>Anti-NMDA (N-methyl-D-aspartate)-type glutamate receptor [25]</td>
<td>-</td>
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<tr>
<td>Thyroid gland [40, 41]</td>
<td>1. Thyroid stimulating hormone receptor antibodies</td>
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<td></td>
<td>2. Thyroglobulin antibodies</td>
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<tr>
<td></td>
<td>3. Thyroid peroxidase antibodies</td>
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<td>Cardiac lipid raft-associated proteins and other cardiac proteins [42, 61]</td>
<td>-</td>
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</tbody>
</table>
Activated adrenergic β-receptor
Nobel Prize in Chemistry for 2012 to Robert J. Lefkowitz and Brian K. Kobilka
Tissue responses to activation of specific adrenergic receptor subtypes

©2010 by American Physiological Society

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

1. Cardiac receptors activating autoantibodies (Tachycardia)
   - Vascular receptors blocking autoantibodies (Vasodilation)

2. Hyperadrenergic activation
   - Sinus tachycardia

3. Hypovolemia
   - Reflex tachycardia

- Vasodilation (Splanchnic region)
- Vasodilation (Lower limbs)

Artur Fedorowski. POTS review. In preparation
Fedorowski et al. Europace (2017)
Angiotensin II Type 1 Receptor Autoantibodies in Postural Tachycardia Syndrome

Xichun Yu, MD;* Hongliang Li, MD, PhD; Taylor A. Murphy, BS; Zachary Nuss, BS; Jonathan Liles, BS; Campbell Liles, BS; Christopher E. Aston, PhD; Satish R. Raj, MD; Artur Fedorowski, MD, PhD;* David C. Kem, MD*
Tango® assays for GPCR signalling

Schematic representation of the Tango GPCR assay (Figure 1)

Ligand

Receptor

Protease site

Protease tagged arrestin

Transcription factor

TF

β-lactamase

Schematic representation of the Tango GPCR assay, courtesy of Life Technologies.
47 POTS patients vs. 24 healthy controls
(age- and gender- matched)

Axelsson J and Fedorowski A.
In preparation.
ROC curves for four different GPCRs

This is not a chance!
What to do?  
(Dr. Jonas Axelsson)

- IVIG
- Mabthera
- Plasmapheresis
- Other options – ask your immunology expert!

- "I will prescribe regimen for the good of my patients according to my ability and by judgement and never do harm to anyone…”

(The Hippocratic oath)
Inessa Schwab
& Falk Nimmerjahn
Nature Reviews Immunology 13, 176-189
(March 2013)
Plasmapheresis/Immunoadsorption

Anti-GBM/Goodpasture’s disease

n=10

n=1


Cost: 500 € per PF and 800 € per IA (Karolinska Hospital).
Other options

- Immunosuppressive or cytotoxic agents
- B cell depletion or targeting (rituximab, belimumab)

Activating B cell

- Flares
- Fluctuating autoantibodies

Bone marrow

- Niche

Memory plasma cell

Blood

- Chronicity of autoimmunity
- Persistent autoantibodies
- Refractory to immunosuppression

Inflamed kidney

Spleen or lymph node

Nature Reviews Nephrology (2016)

Hiepe & Radbruch

Nature Reviews Nephrology (2016)
Hiepe & Radbruch
Nature Reviews Nephrology (2016)
Take-home message

✓ There are multiple signals from different centers that POTS patients produce excess autoantibodies against CV receptors (GPCRs) and other autoimmune targets.

✓ These autoantibodies offer a plausible explanation of the observed symptoms.

✓ We do not have data what kind of immunomodulation could be effective in POTS – interventional studies are needed.
Thank you for your attention!