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The stiff people syndromes and their pathophysiology

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NEUROLOGIE
KLINISCHE NEUROBIOLOGIE

Disclosures

None

Learning objectives

1. Know the clinical picture and be able to recognize as stiff-person syndrome

2. Understand the principles of antibody-associated disorders

3. Get a better understanding of disorders associated with reduced activity of spinal and supraspinal inhibitory circuits

Stiff person syndrome

- Acquired autoimmune disease
- Prevalence about 1:1 Million

- F/M = 2/1
- Starts in middle age

- First description Moersch and Woltman 1956
- Clinical criteria Gordon 1969, Lorisch 1989

- Prodomi with stiffness and pain
- Progress to proximal stiffness
- Painful spasms can be triggered
- Increased lumbar lordosis
- Normal sensory function, no pareses, normal cognitive functions

Moersch und Woltmann, Mayo Clin Proc 1956;31:421-427
Gordon et al. Am J Med 1967;42:582-599
Lorisch et al. Mayo Clin Proc. 1989;64:629-636

Stiff person syndrome

- Painful muscle contraction and spasms
- Good response to **benzodiazepines**

- Symptoms can be triggered by emotional stress
- Frequent agoraphobia, can be first symptom
- Falls when frightened, often with fractures
- Anxiety
- Agoraphobia

- Association with diabetes mellitus
- Rarely epileptic seizures

Stiff person syndrome

Auto antibodies to

- Glutamate-decarboxylase (**GAD-65**)
- GABA-A-receptor-associated protein (GABARAP)
- **Glycine rezeptors**
- **Amphiphysin** (synaptic protein): often paraneoplastic
- Gephyrine (anchor protein for GABA- and glycine receptors in the membrane)

- **What do they have in common?**

- **Antibodies in the inhibitory neurotransmitter system**

Treatment

- Benzodiazepines
- Baclofen

- Corticosteroids
- IVIG
- Plasmapheresis

Case 2, born 1947

- Mailwoman, walking a lot
- 2000 pain and weakness of left leg
- Increasing stiffness of legs and trunk
- Worse in stressful situations: „Psychogenic“
- Agoraphobia
- Since 2005 walker
- Since 2006 bedridden

- High titer anti-GAD-Abs
- EMG: paraspinal Th8 continuous activation

Case 2, born 1947

Before treatment

Case 2, born 1947

After 5 plasmaphereses

Case 2, born 1947

After four cycles of plasmapheresis

Pathophysiology

What can the auto-antibodies do ?

GAD-AK

- Block GABA synthesis and the transport of GABA into the synaptic vesicles

GlyR-AK

- Disturb function of the glycine receptors

Amphiphysin-Abs

- ???

Auto-Abs in SPS

Anti-GAD-Abs

GAD (Glutamatdecarboxylase):

- Intracellular enzyme
- 2 isoforms (GAD 65, GAD 67)
- GAD 67 – rate limiting enzyme for GABA-synthesis
- GAD 65 – vesicular GABA-transport in presynaptic terminals

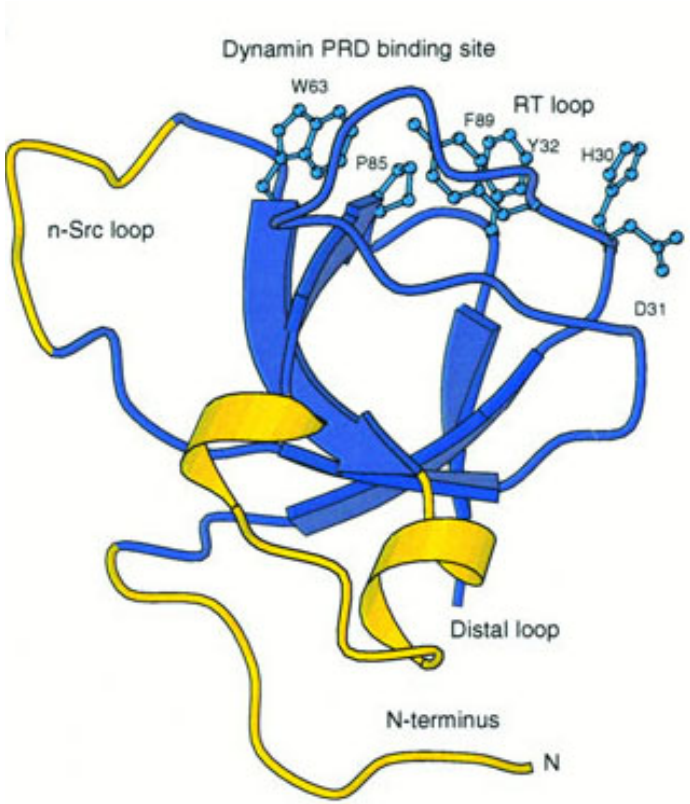
Anti-Amphiphysin-Abs

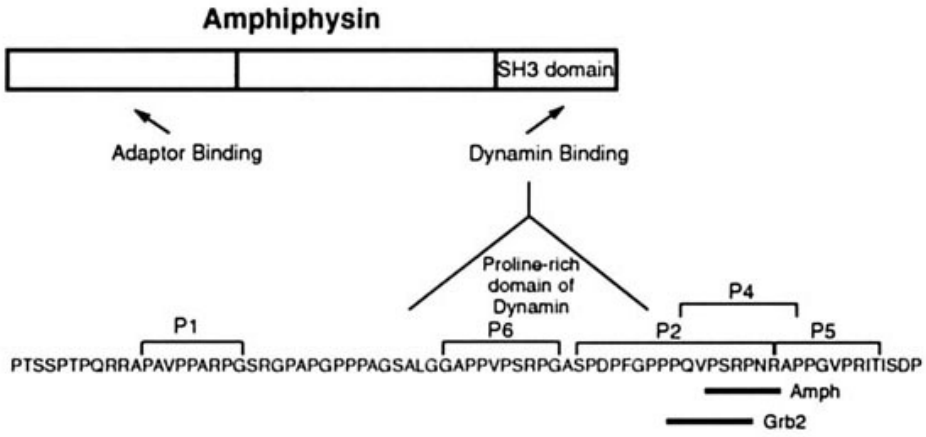
Amphiphysin:

- Intracellular, synaptic protein (128 kDa)
- Binds to dynamin via SH3-domaine
- Key molecule in clathrin mediated vesicle endocytosis
- In vitro: anti-amphiphysin Abs block vesicle endocytosis (Shupliakov et. al., Science, 1997)

Amphyphysin

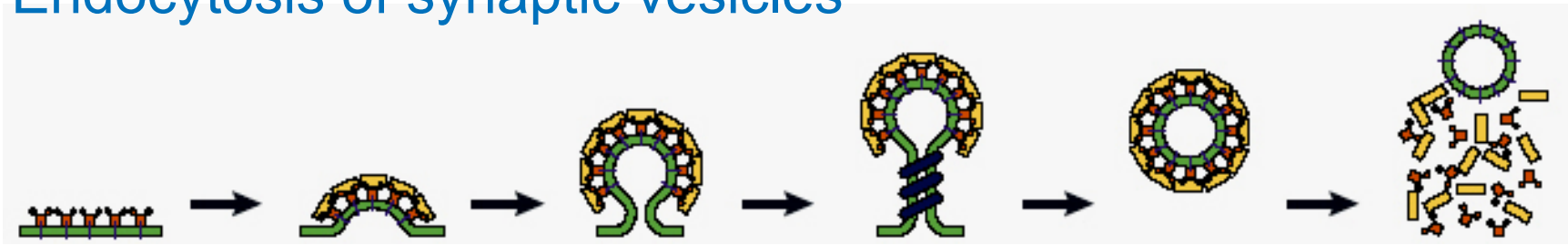
- Intracellular, synaptic protein (128 kDa)
- Binds dynamin via its SH3-domaine
- Key player in the clathrin-mediated vesicular endocytosis
- Anti-amphiphysin AB can block vesicular endocytosis (Shupliakov et. al., Science, 1997)

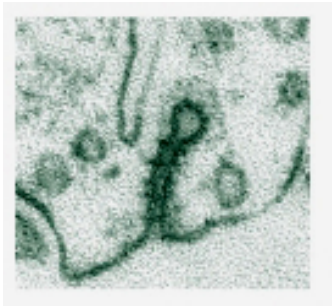


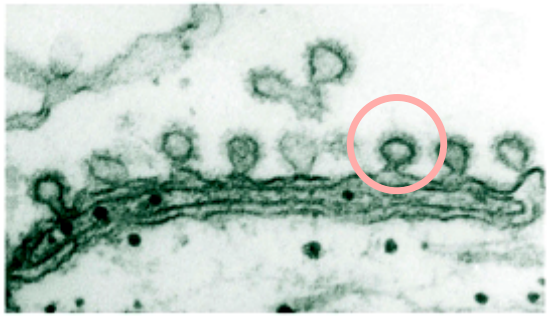


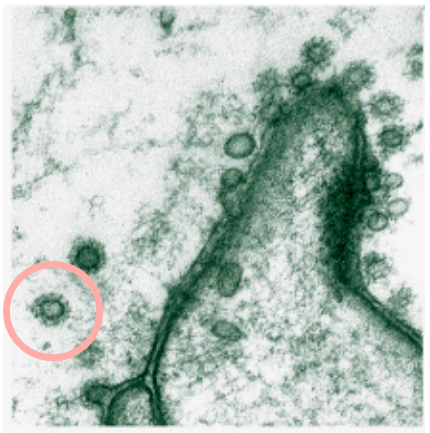
Role of amphiphysin

Endocytosis of synaptic vesicles



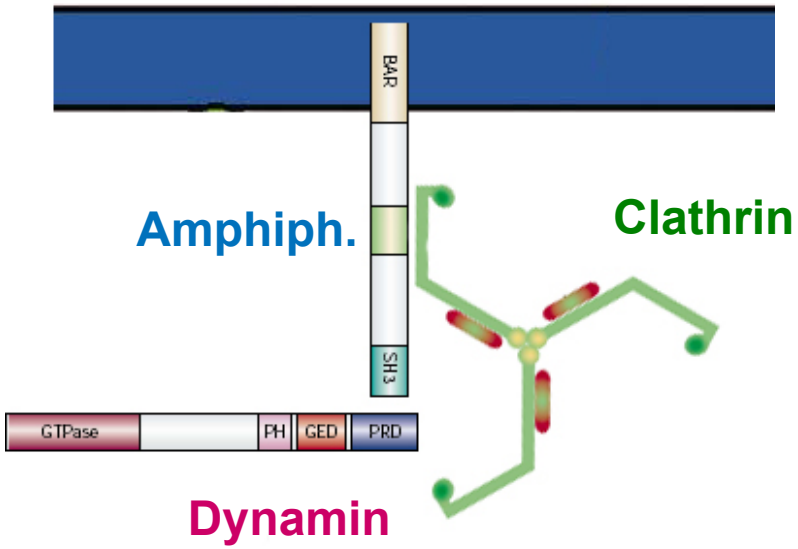


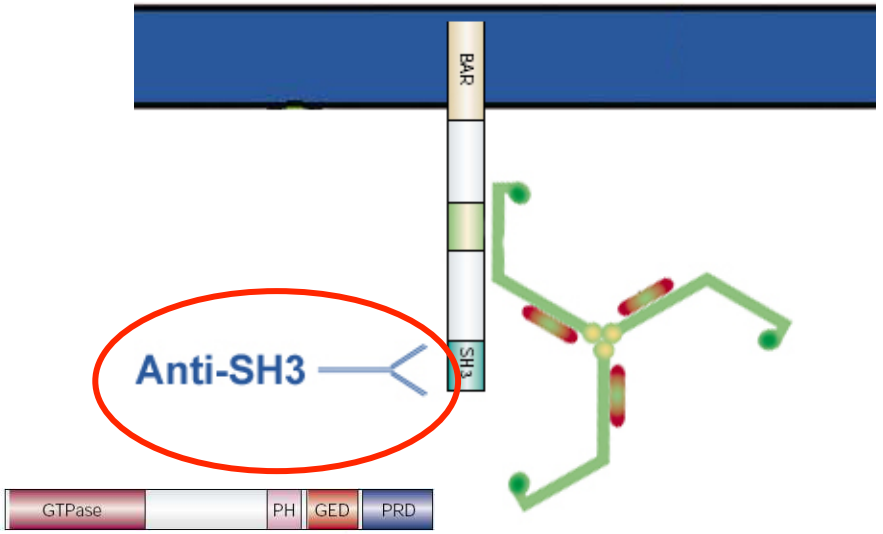


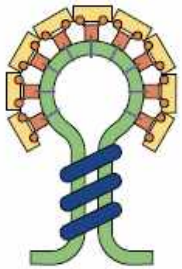


from Slepnev and de Camilli, Nat Rev Neurosci 2000:1:161-72

Amphiphysin antibodies







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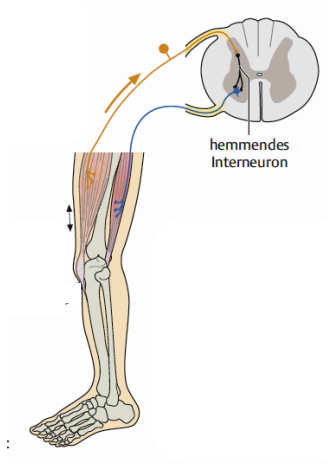
Stiff-person syndrome, Summary

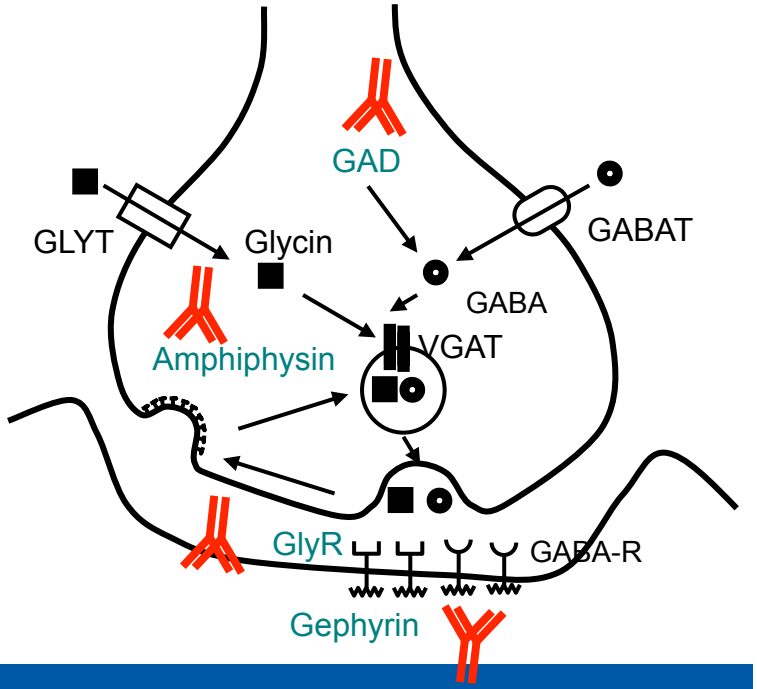
Treatment
- Increase GABAergic neurotransmission
- Reduce Auto-Abs by
  - Plasmaphereses
  - Corticosteroids
  - IVIG
  - B-cell-therapy

Symptoms
- Stiffness
- Pain
- Falls
- Anxiety

Reduces inhibition



Immunopathophysiology



Further reading

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