

Heart Rhythm Congress

Birmingham 11 October 2016

**Molecular Phenotypes of POTS
and Vasovagal Syndrome**

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Orthostatic Intolerance: “Yellow Wiggle Disease”

Good health



WHEN YELLOW WIGGLE GREG PAGE ANNOUNCED THAT HE WAS LEAVING THE GROUP, A PUZZLING MEDICAL CONDITION WAS TO BLAME. HERE'S WHAT IT IS - AND HOW TO MANAGE IT

MORE THAN JUST A DIZZY SPELL



IT'S Greg rests after fainting during our visit.

Case study
Orthostatic intolerance

Cause
Often unknown
Most commonly affects ...
Women between 15 and 40 years old. It does seem to run in families. Can come on at any age, but most patients show symptoms before the age of 35

Ask most Australians if they've ever heard of orthostatic intolerance (OI) - the disorder suffered by former Yellow Wiggle Greg Page - and the answer is no. But incredibly, around 30,000 Australians - 1.4 per cent of the population - have this debilitating disorder.

"When someone with OI stands up they often feel dizzy, nauseated, extreme fatigue, palpitations, or they may faint," explains Greg's cardiologist, Dr Sue Corcoran.

The disorder is not fatal, but symptoms can be devastating. "At its worst, patients can't drive, work, socialise or go out by themselves, because they feel so bad and worry they could faint," Thankfully, "with treatment,

most patients can return to a normal life," says Dr Corcoran. She is about to research OI, along with a small team at Melbourne's Baker Heart Research Institute, under the supervision of Professor Murray Esler.

"Little is known about the disorder, so I'm thrilled vital research is underway here and I'm delighted to lend my name to the fund supporting the research," says Greg, who recently toured the Institute.

"On average it takes a patient many visits to physicians - and sometimes years, as in Greg's case - before the disorder is diagnosed," says Professor Esler.

"Unfortunately, many doctors aren't familiar enough with it, which means patients have to endure the worry and expense [of medical tests] for too long."

Reasons vary as to why people get OI, which is more common in women than in men. And it can take a long time to manage symptoms.

"I tell patients it may be five years before they are fully recovered," Professor Esler explains.

Although there is no cure for OI, Dr Corcoran says the earlier a patient is diagnosed, the faster they will respond to treatment. She first became aware that Greg had OI when she attended

'AT ITS WORST, PATIENTS CAN'T DRIVE, SOCIALISE OR GO OUT'

Orthostatic Intolerance Phenotypes

Regulatory

Initial

POTS

Vasovagal OI

Low supine systolic BP

Degenerative

Pure autonomic failure

Multiple System Atrophy

Parkinsonism

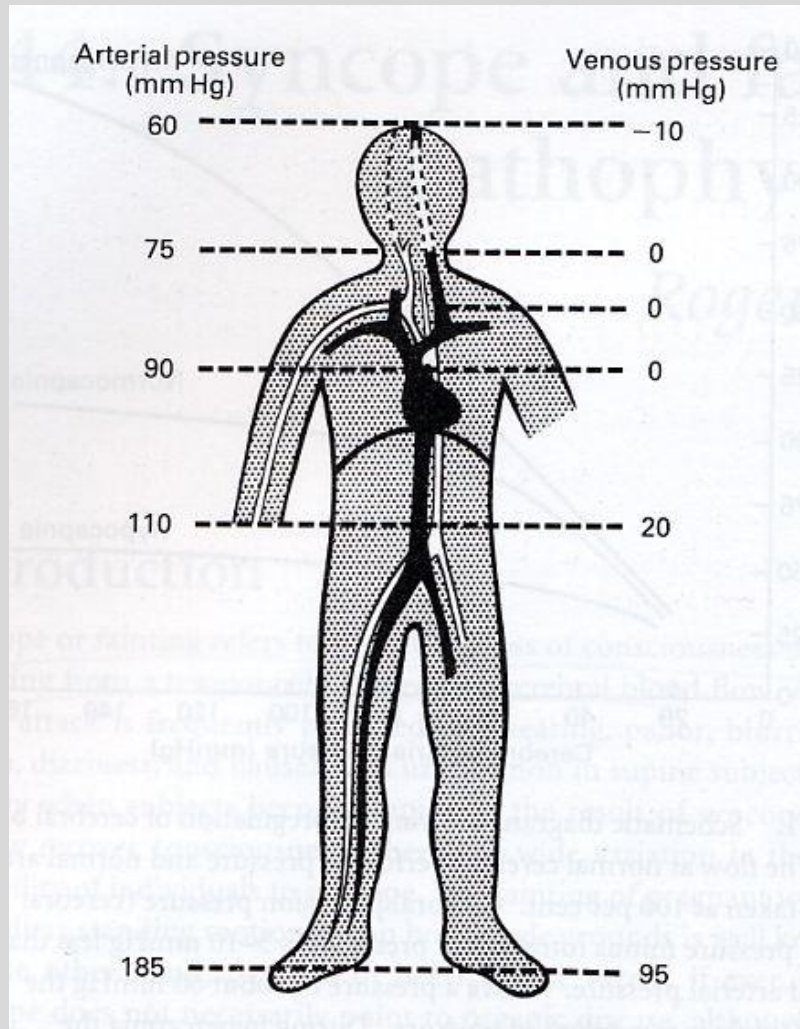
Diabetic

Orthostatic Intolerance Medication

.... *“one size fits all”*

(but regrettably not well)

Circulatory Response to Standing

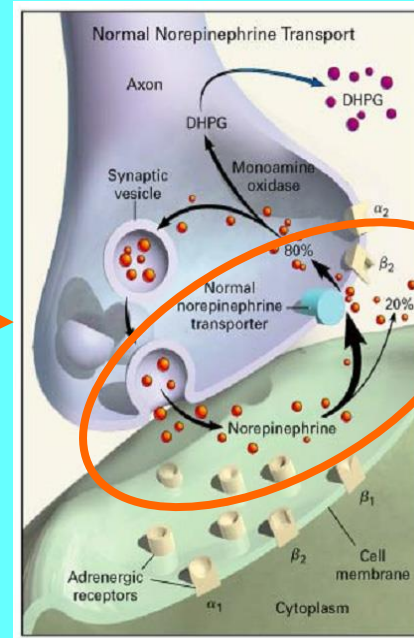
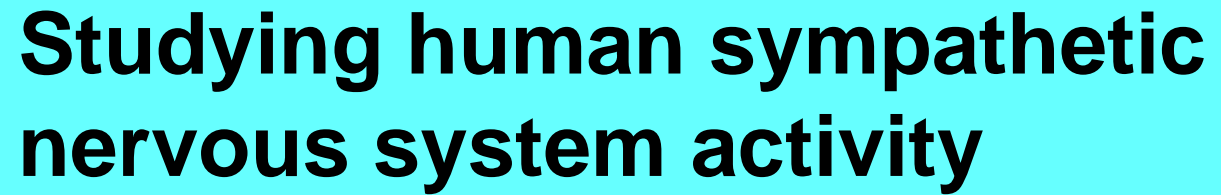


With standing:

- * downward displacement of 300-800ml of blood from the chest to the abdomen and legs**

- * plasma leaks out of circulation: 10% reduction in plasma volume by 30 minutes**

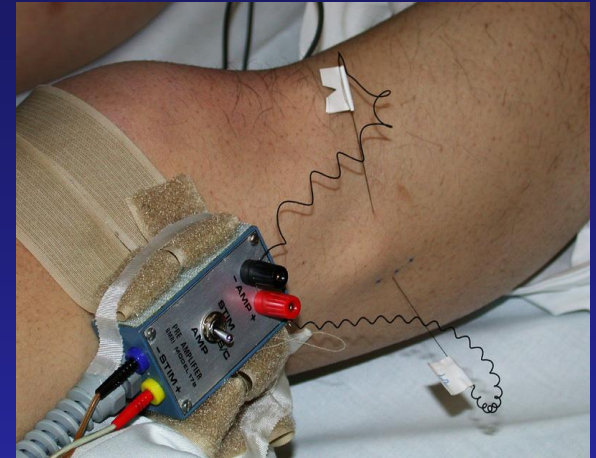
- * *Reflex responses***



Noradrenaline Spillover

Testing is best done by recording postganglionic nerve traffic (clinical microneurography) and measuring transmitter release from sympathetic nerves to plasma (noradrenaline “spillover”)

Microneurography: Sympathetic recording



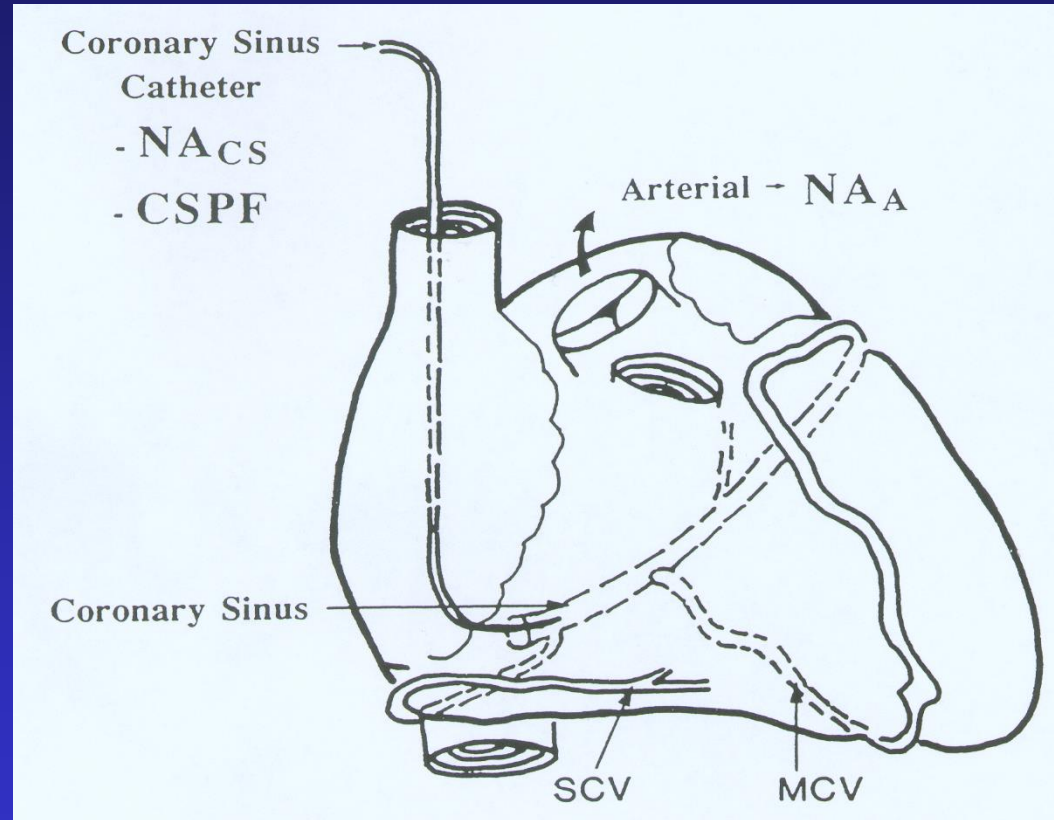
The recording electrode is inserted in sympathetic nerve bundles in the motor portion of the peroneal nerve

Postural Tachcardia Syndrome (POTS)

Orthostatic intolerance plus tachycardia

The postural tachycardia defines the disorder; also important in diagnosis is this clinical characteristic ... recurrent postural presyncope and syncope without postural hypotension

Measurement of Sympathetic Nervous Activity in the Heart: *Cardiac Noradrenaline Spillover*

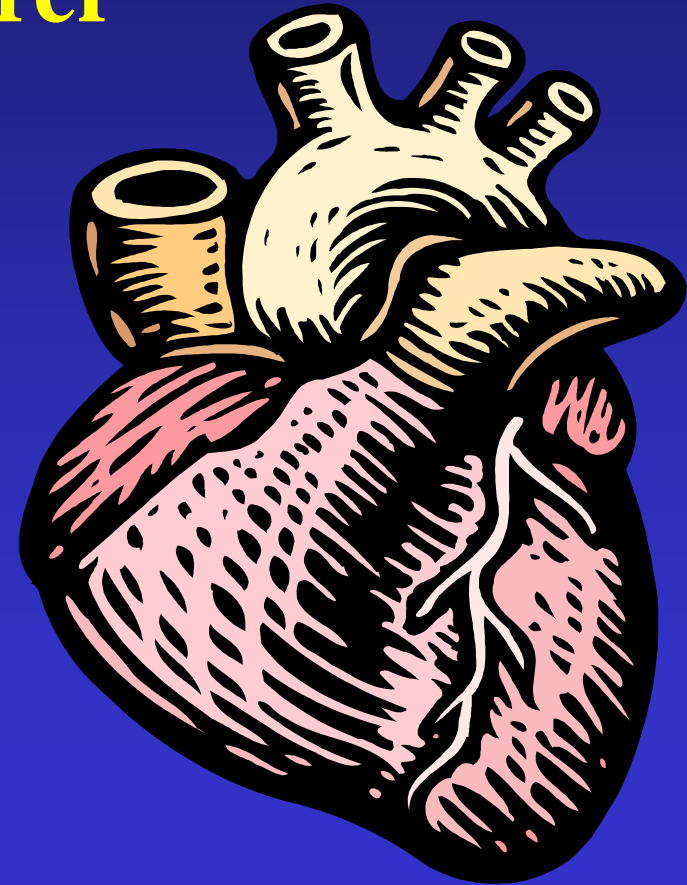


$$\text{Cardiac Noradrenaline Spillover Rate} \\ = [(NA_{CS} - NA_A) + (NA_A \times Ex_{(3H-NA)})] \times CSPF$$

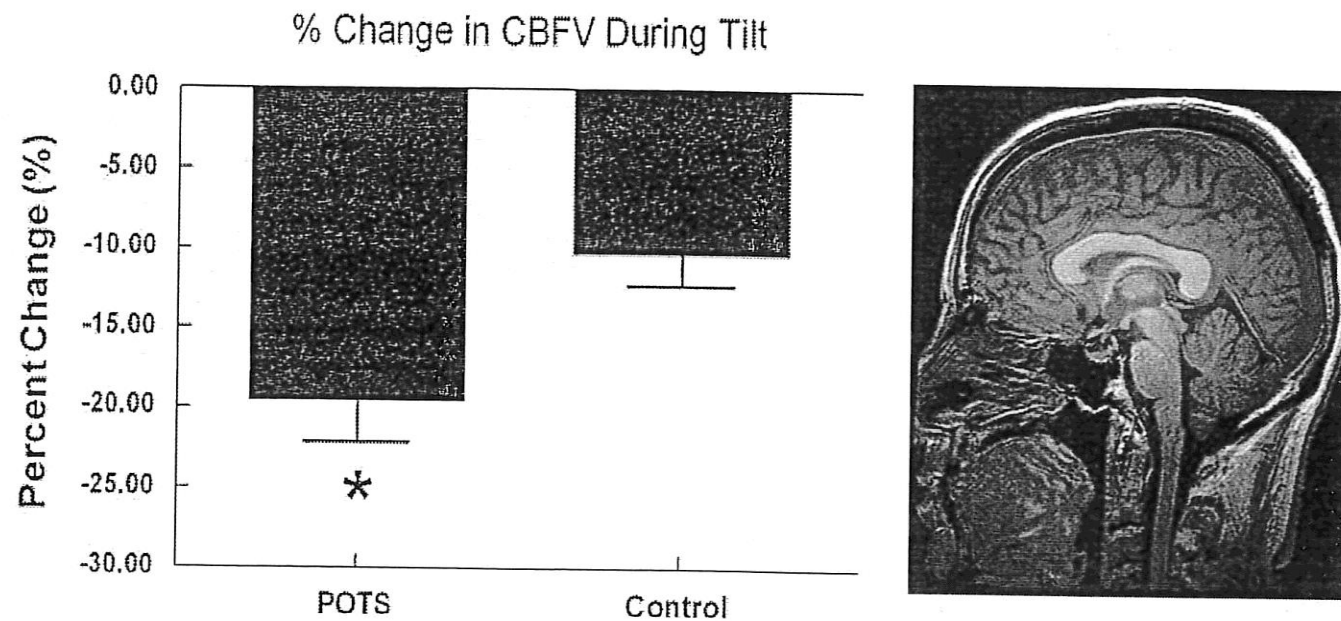
The Postural Tachcardia

Sympathetic activity in the heart
during standing in a POTS sufferer

| | <i>Heart Rate</i> | <i>Cardiac Noradr. Spillover</i> |
|-----------------|-------------------|--------------------------------------|
| Resting | 86/min | 17 ng/min |
| Standing | 163/min | 120 ng/min |



Fainting Without Postural Hypotension

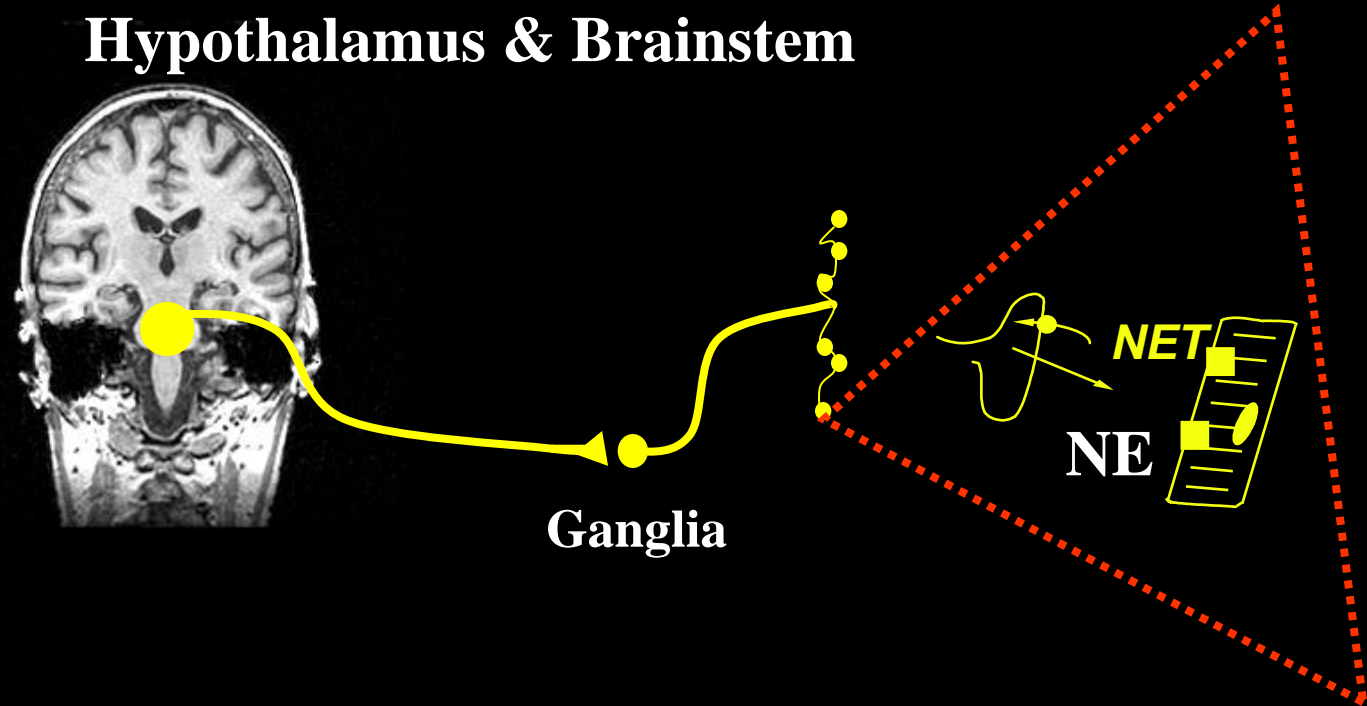


Decreased upright cerebral blood flow and cerebral autoregulation in normocapnic postural tachycardia syndrome

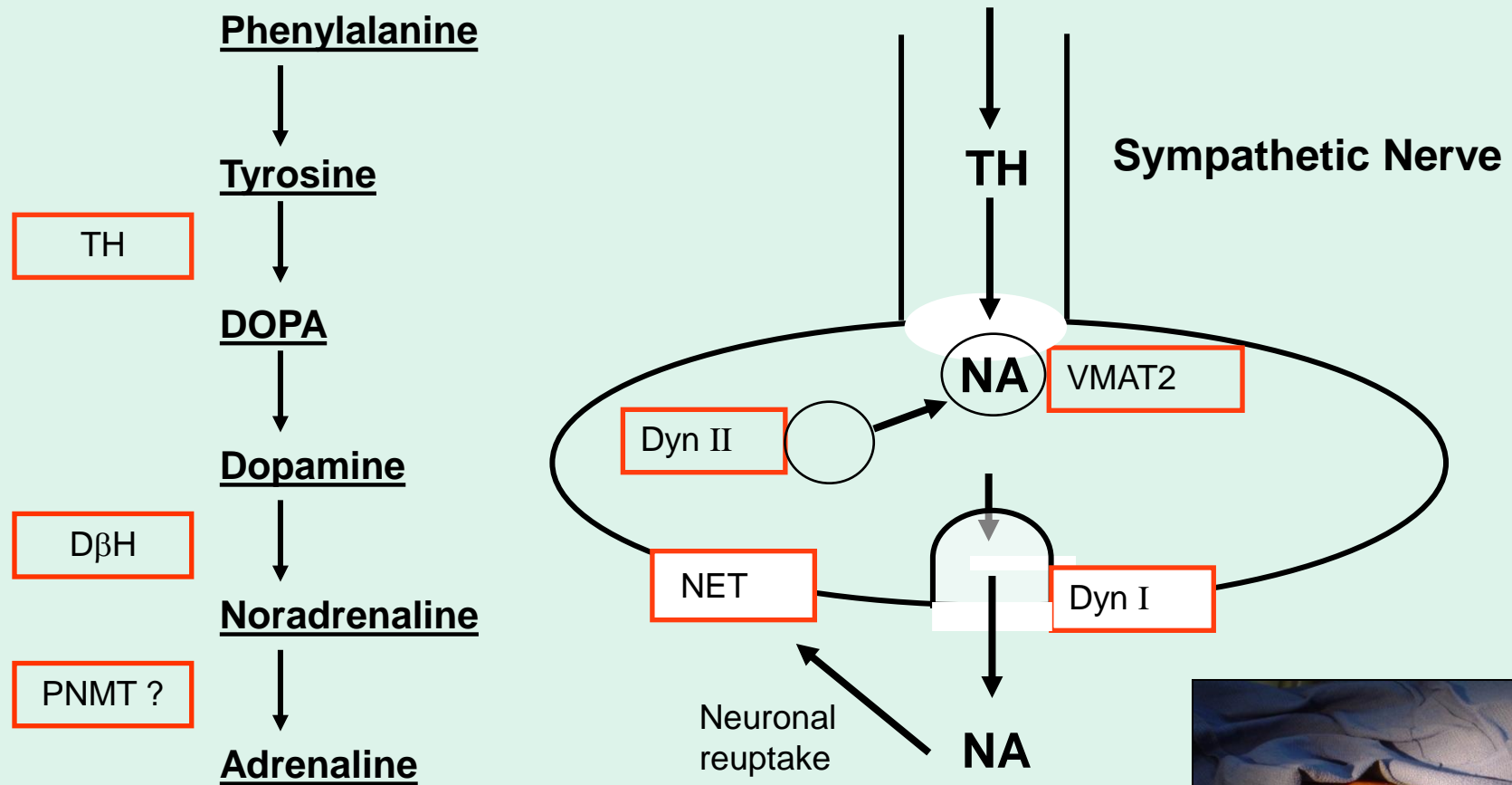
Ocon AJ, Medow MS, Taneja I, Clarke D, Stewart JM.
American Journal of Physiology 2009;297:H664-H673

Sympathetic Nervous System Augmentation:

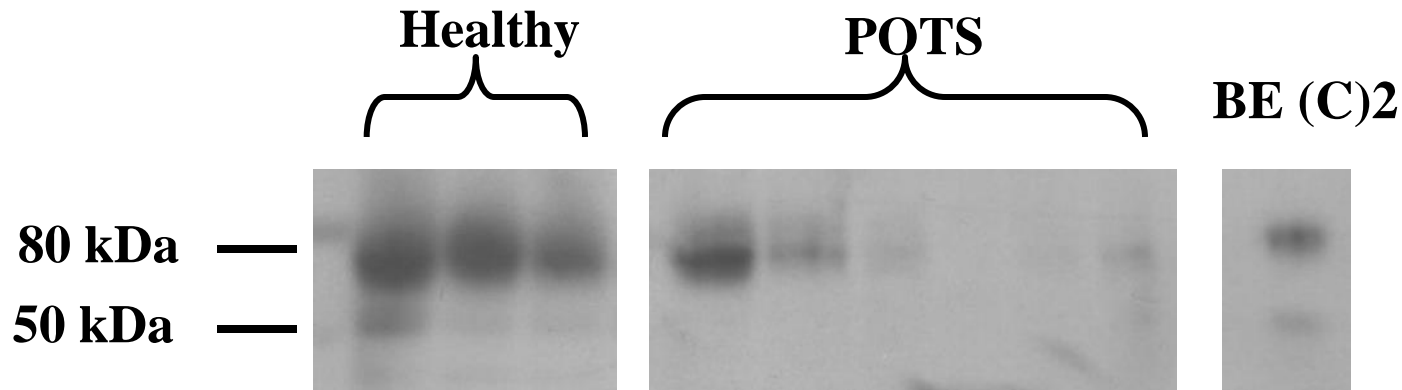
Faulty neuronal noradrenaline reuptake in POTS ?



Analysis Of Human Sympathetic Nerve Proteins Accessed Via A Subcutaneous Vein Biopsy



NET Protein: Sympathetic Nerves of Forearm Veins



Proteins were extracted from vein biopsy samples. Aliquots containing 25 µg of total protein were taken from all samples. An aliquot of total cell lysate from neuroblastoma cells (BE (C)2), containing 0.5 ug of total protein was used as a positive control. The blot was probed with a monoclonal antibody for hNET, followed by a goat anti-mouse HRP-conjugated secondary antibody.

E Lambert, N Eikelis, M Esler, T Dawood, M Schlaich, R Bayles, F Socratous, A Agrotis, G Jennings, G Lambert, G Vaddadi. Circulation Arrhythmia Electrophysiology 2008;1:103-109

POTS

The Pathophysiological Formulation

Sympathetic nerve augmentation, by faulty noradrenaline reuptake, causes:

- 1. In the heart - postural tachycardia**
- 2. In the brain - postural cerebral neural vasoconstriction and reduced blood flow (“fainting without BP fall”)**

.... not “just deconditioning”

Sympathetic Nerves Control Brain Blood Vessels

Jugular venous overflow of noradrenaline from the brain: a neurochemical indicator of cerebrovascular sympathetic nerve activity in humans


David A. Mitchell, Gavin Lambert, Niels H. Secher,
Peter B. Raven, Johannes van Lieshout and Murray D. Esler

Journal of Physiology 2009;587:2589-2597

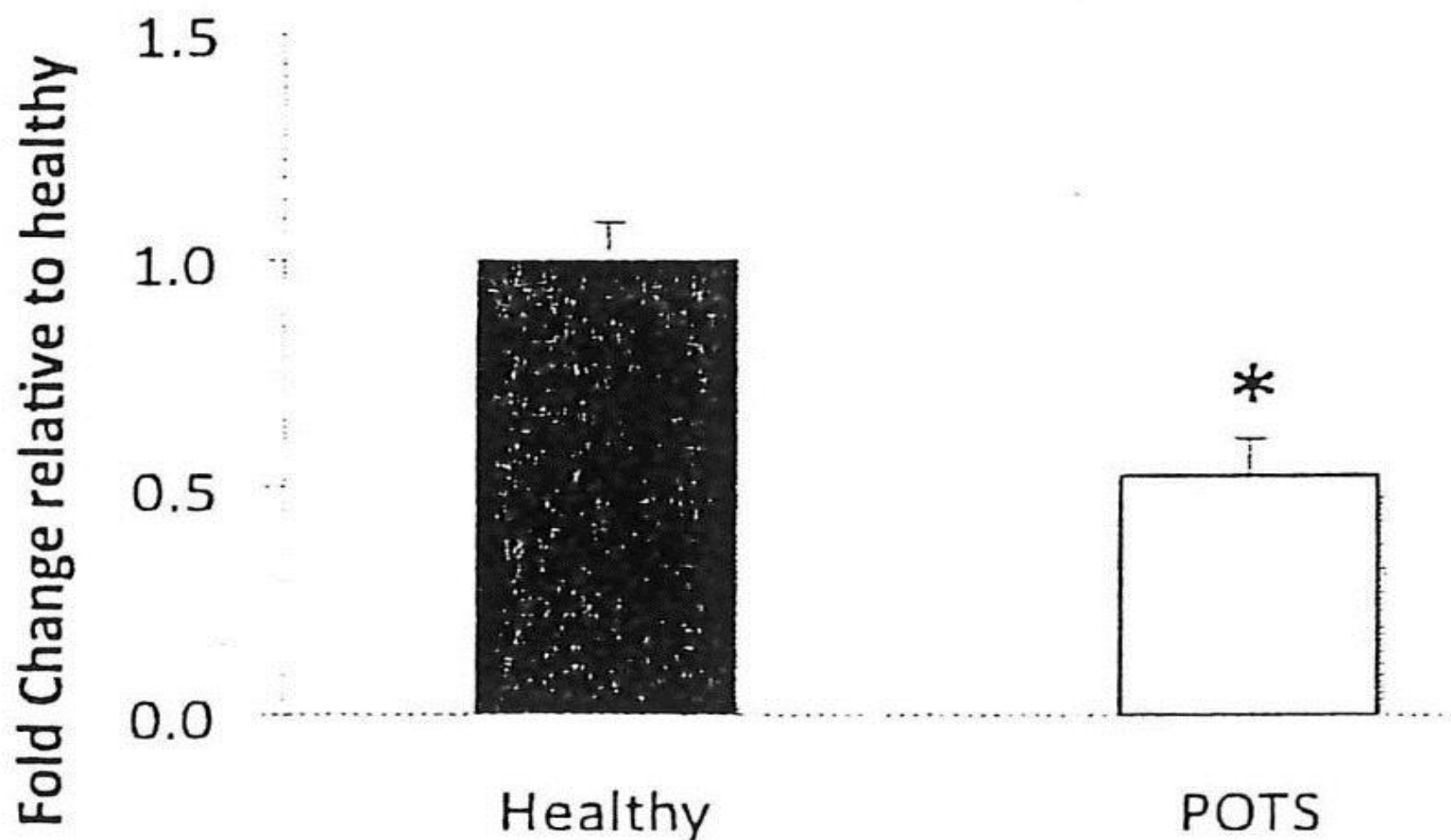
POTS

*An Epigenetic Mechanism
of NET Gene Suppression ?*

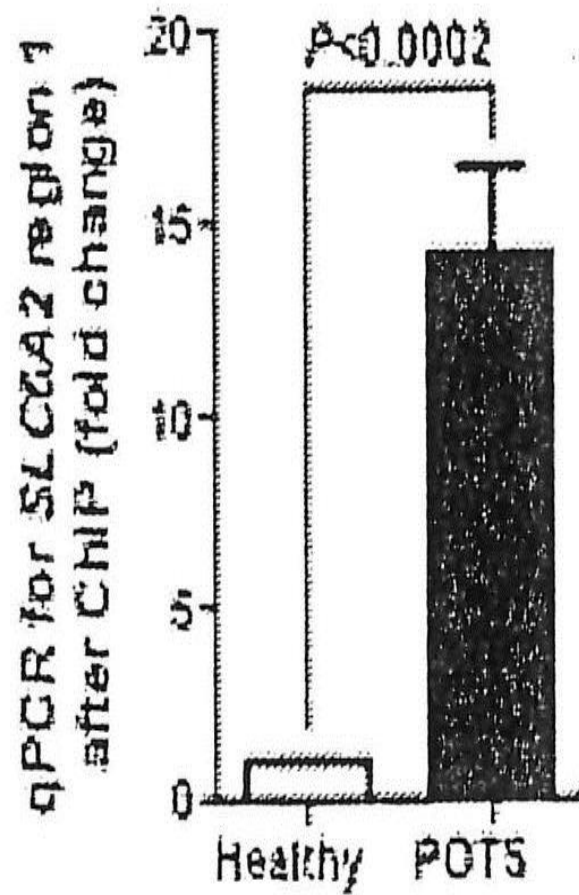
Ex vivo studies on harvested
human leucocytes



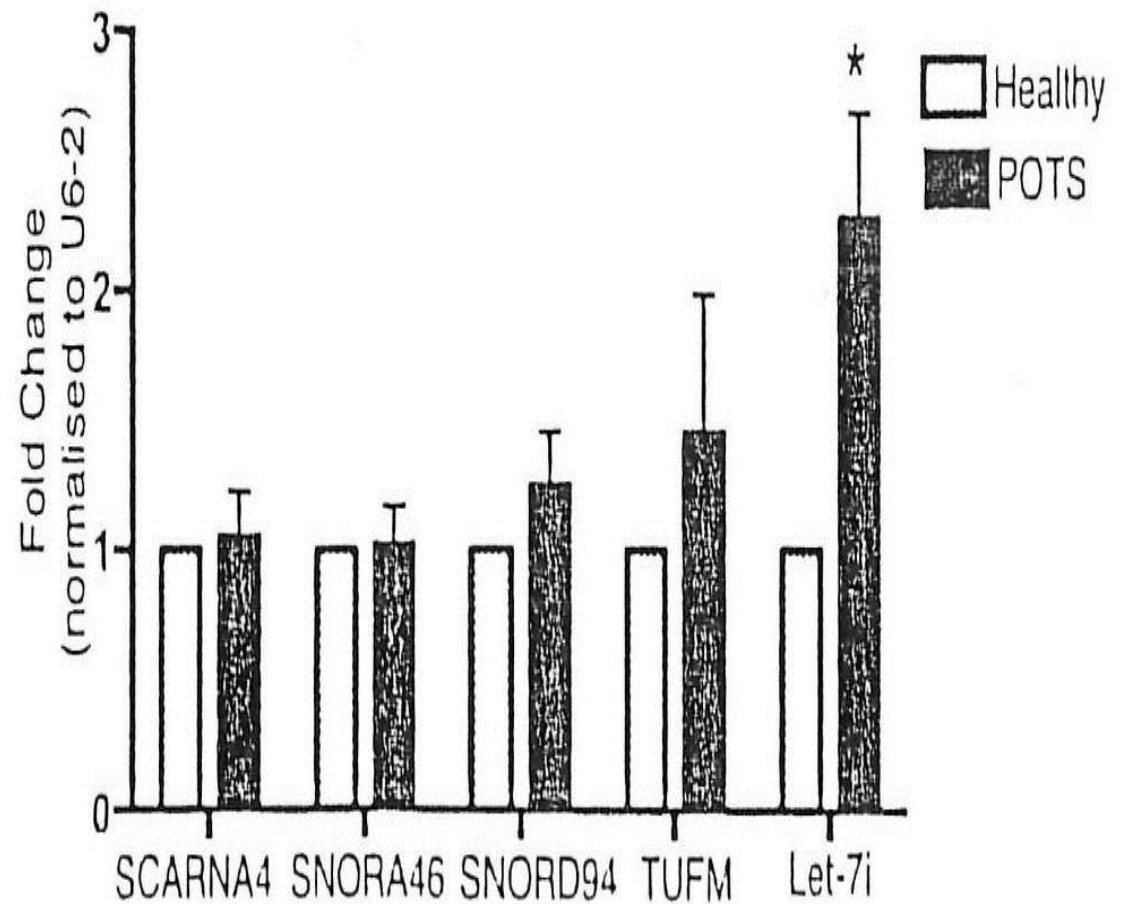
NET Expression in POTS individuals (n=7, P0.00004)



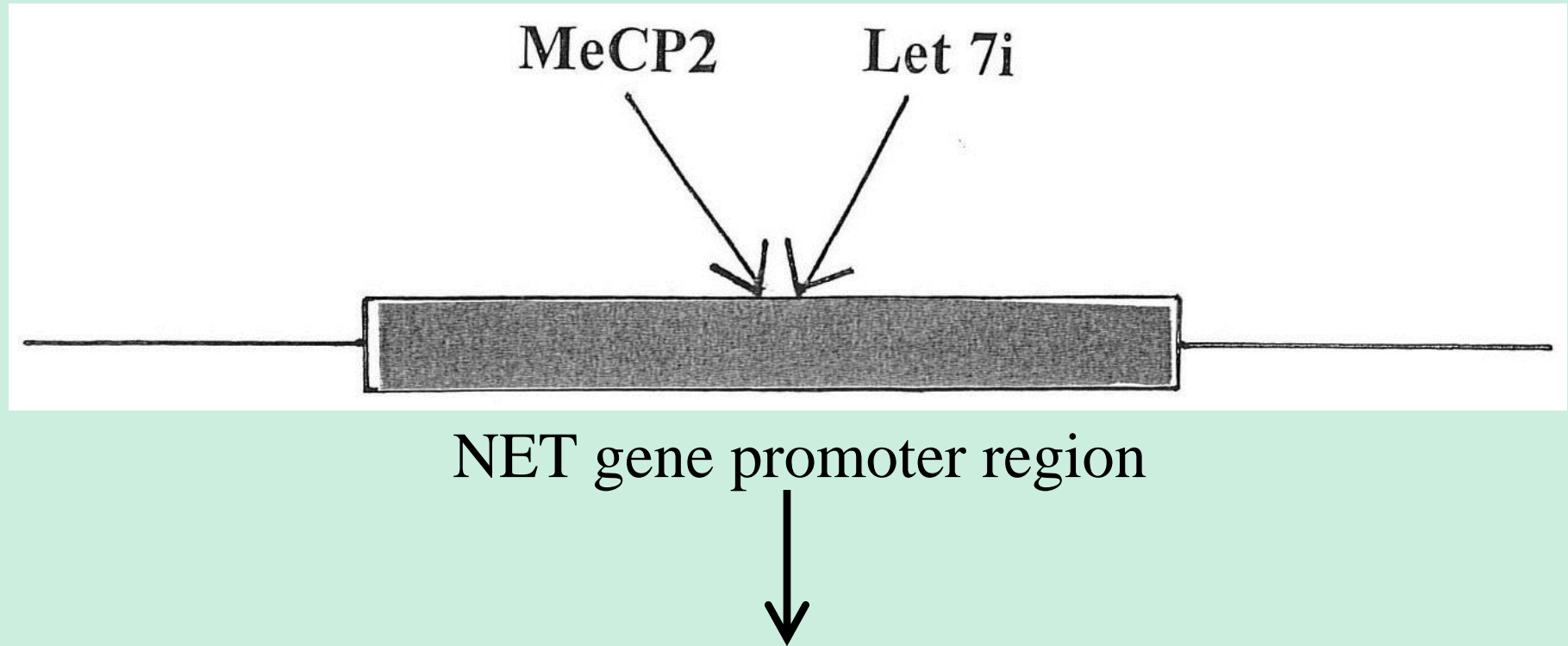
MeCP2 ChIP



Expression of *NET* promoter bound RNAs in hPBMCs



Inhibition of NET Gene in POTS



NET gene inhibition potentially reversed by a deacetylase inhibitor (SAHA)

Khan AW, Ziemann M, Corcoran S, Harikrishnan KN, Okabe J, Rafehi H, Esler M, El-Osta A

NET Silencing by Let-7i in Postural Tachycardia Syndrome (submitted)

Phenotypes of Regulatory Orthostatic Intolerance (non-POTS)

- **Normal Supine BP Vasovagal Syncope (n=15)**
- **Low Supine BP Fainters (n=18)**
 - supine systolic BP 75-95 mm Hg
- **Controls (n=18)**

Vaddadi et al. Circulation Arrhythmia 2011;4:711-718

Assessment of Sympathetic Function

- Electrical

Sympathetic nerve recording

- Neurochemical

Transmitter release (noradrenaline spillover)

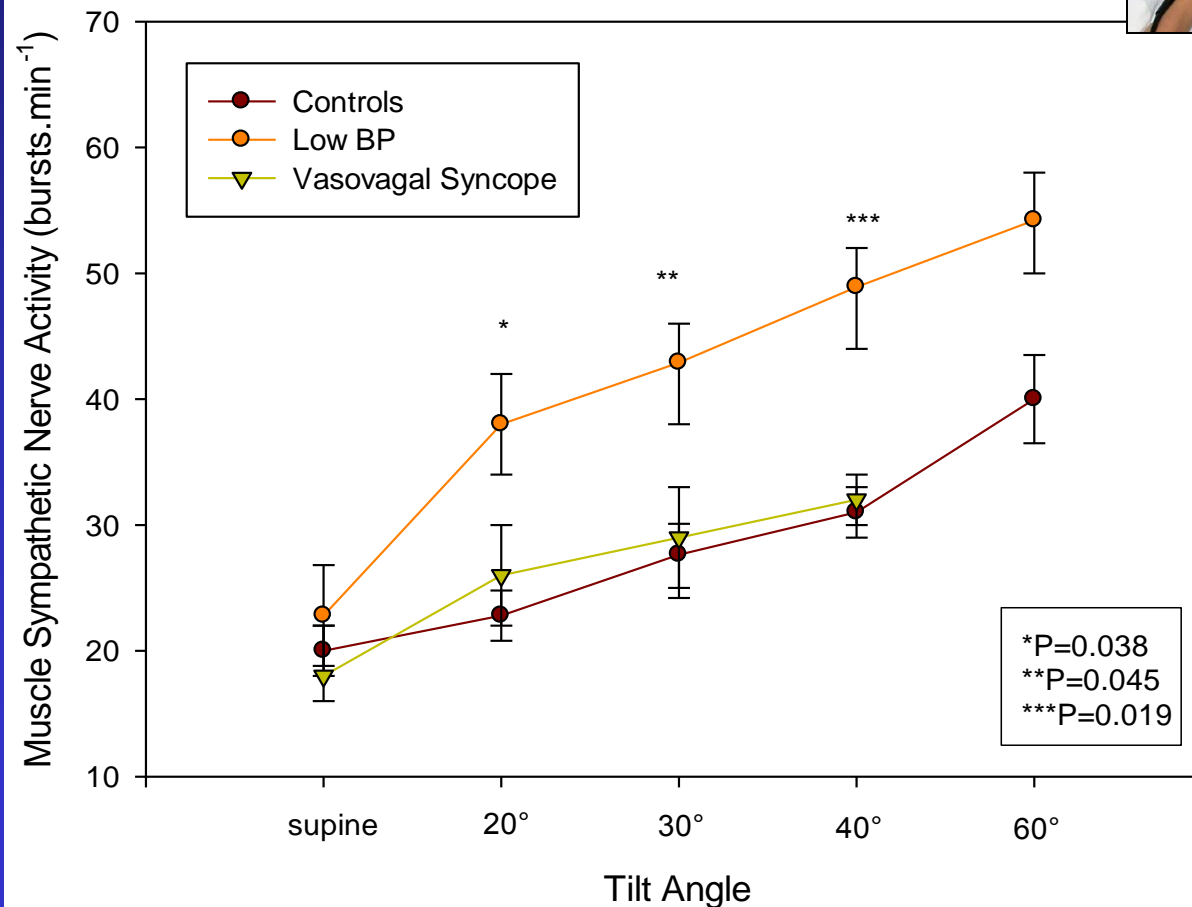
- Molecular

Sympathetic nerve protein analysis



**Head-Up
Tilt**

High symp. nerve firing with tilting in Low Supine BP postural hypotension variant



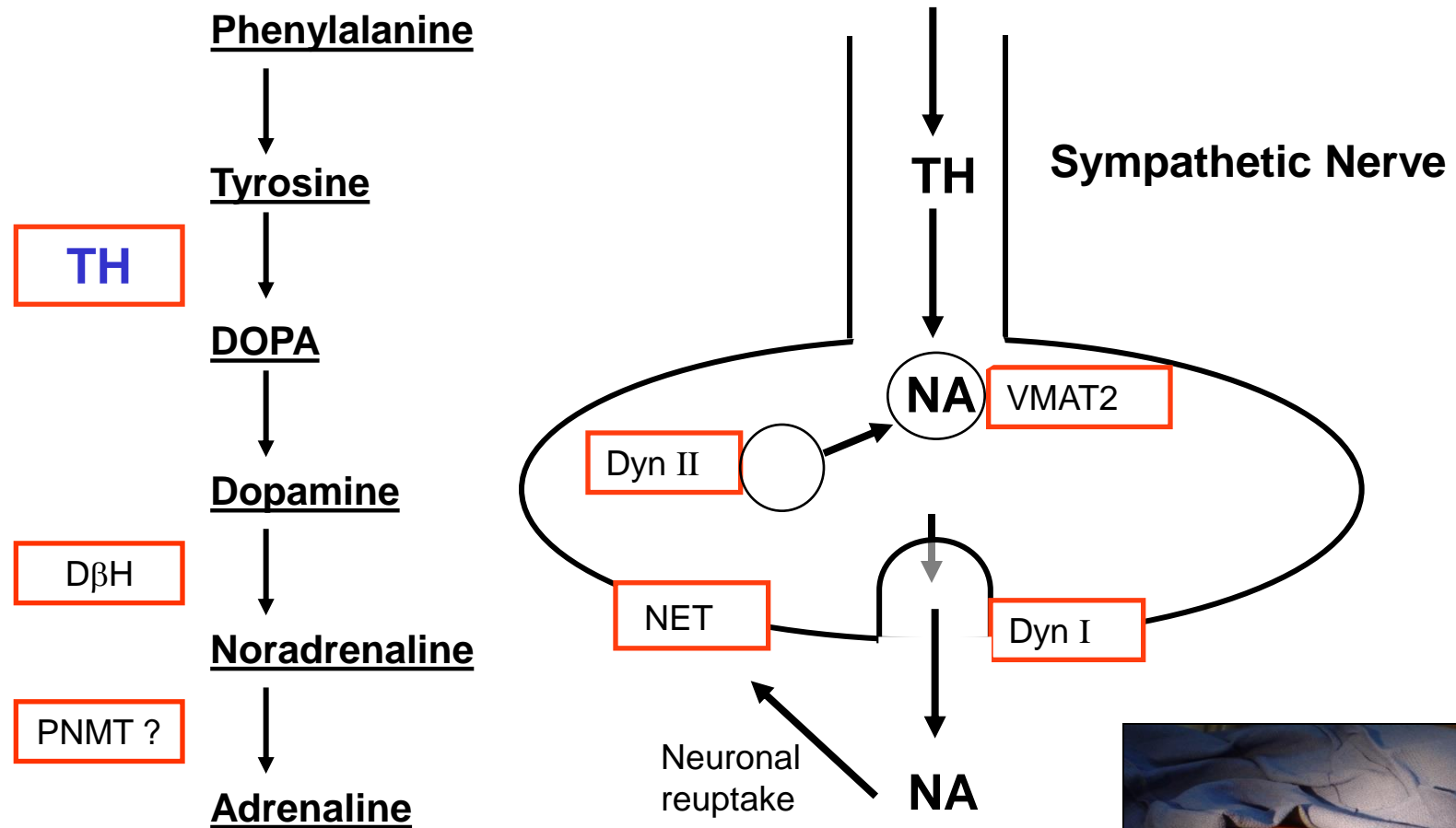
Noradrenaline Spillover During Head-up Tilt

| | NA spillover supine (ng/min) | NA spillover tilt 40°/60° (ng/min) |
|---|---|--|
| Healthy (n=18) | 392± 26 | 678± 65 |
| Normal Supine BP Vasovagal Syndrome (n=15) | 271± 26 (<i>p</i> =0.13) | 287± 32 (<i>p</i> =0.002) |
| Low Supine Blood Orthostatic Intolerance (n=18) | 238± 43 (<i>p</i> =0.13) | 394± 51 (<i>p</i> =0.025) |
| | <i>p</i> values compared to healthy controls NA= noradrenaline | |
| | | |

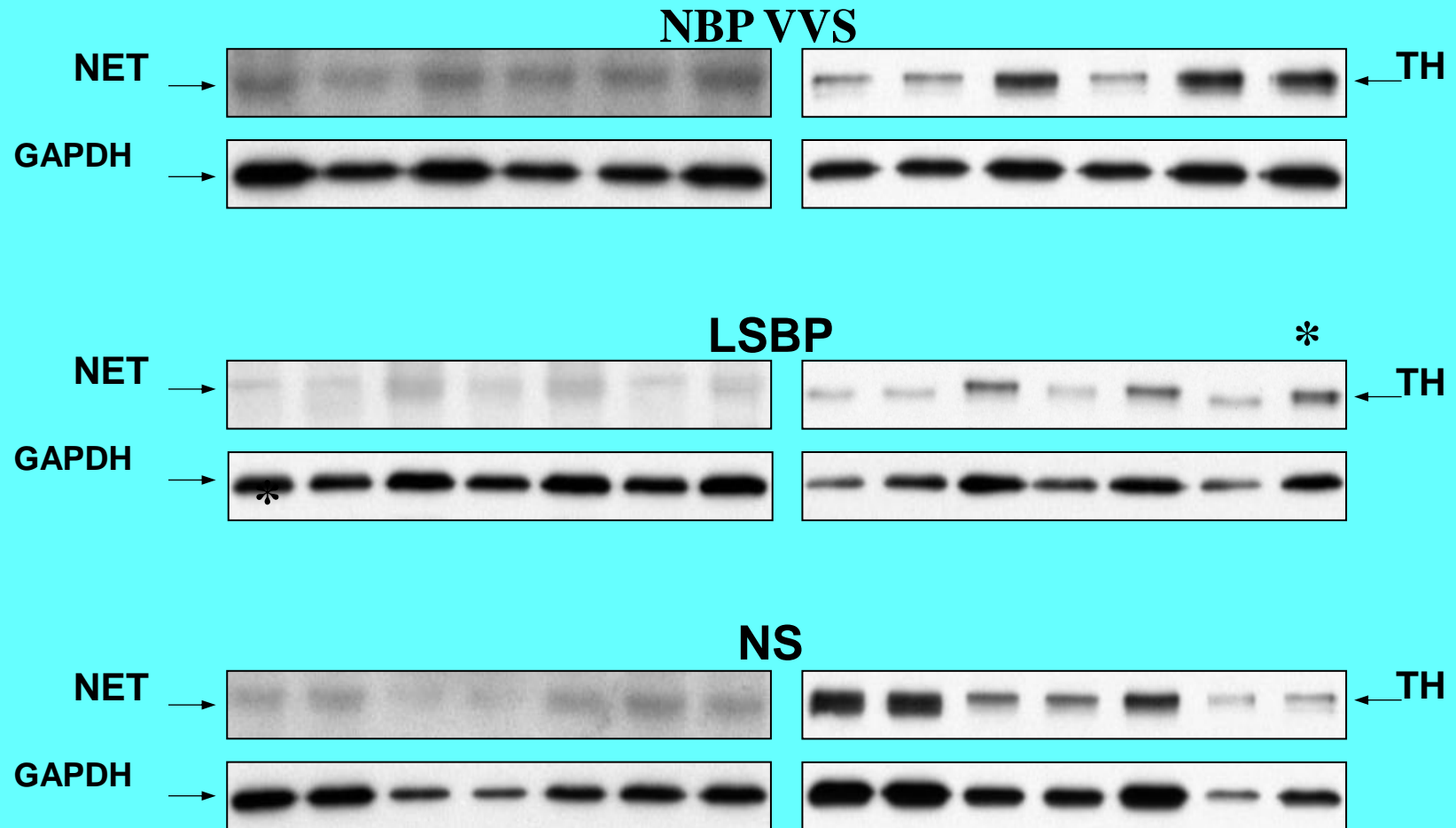
Electrochemical Disjunction in patients with Recurrent Orthostatic Intolerance

- *Low Supine Blood Pressure OI Phenotype*
High nerve firing rates with low norepinephrine spillover to plasma
- Normal Supine BP Phenotype (VVS)
No increase in norepinephrine spillover during tilting, with normal nerve firing increase

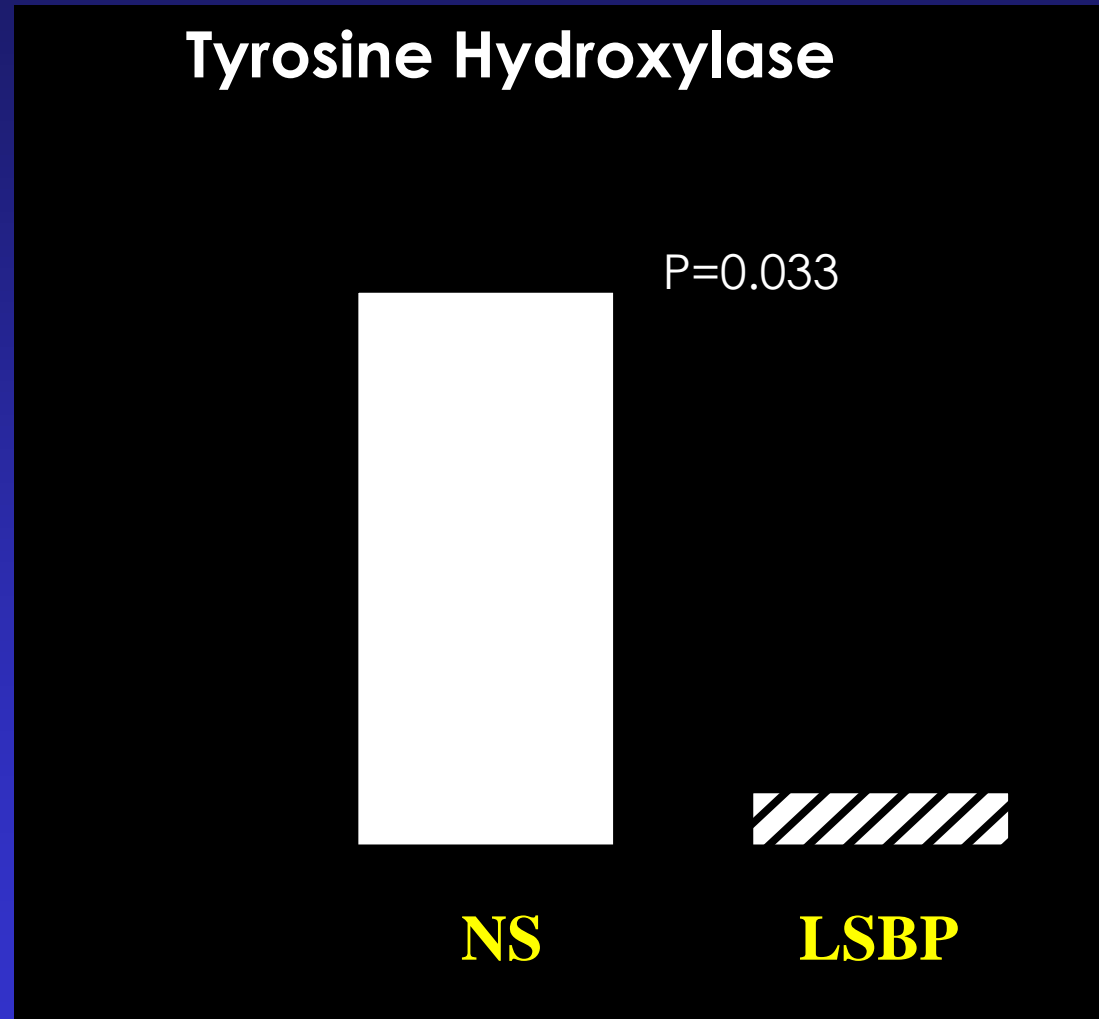
Analysis Of Human Sympathetic Nerve Proteins Accessed Via A Subcutaneous Vein Biopsy



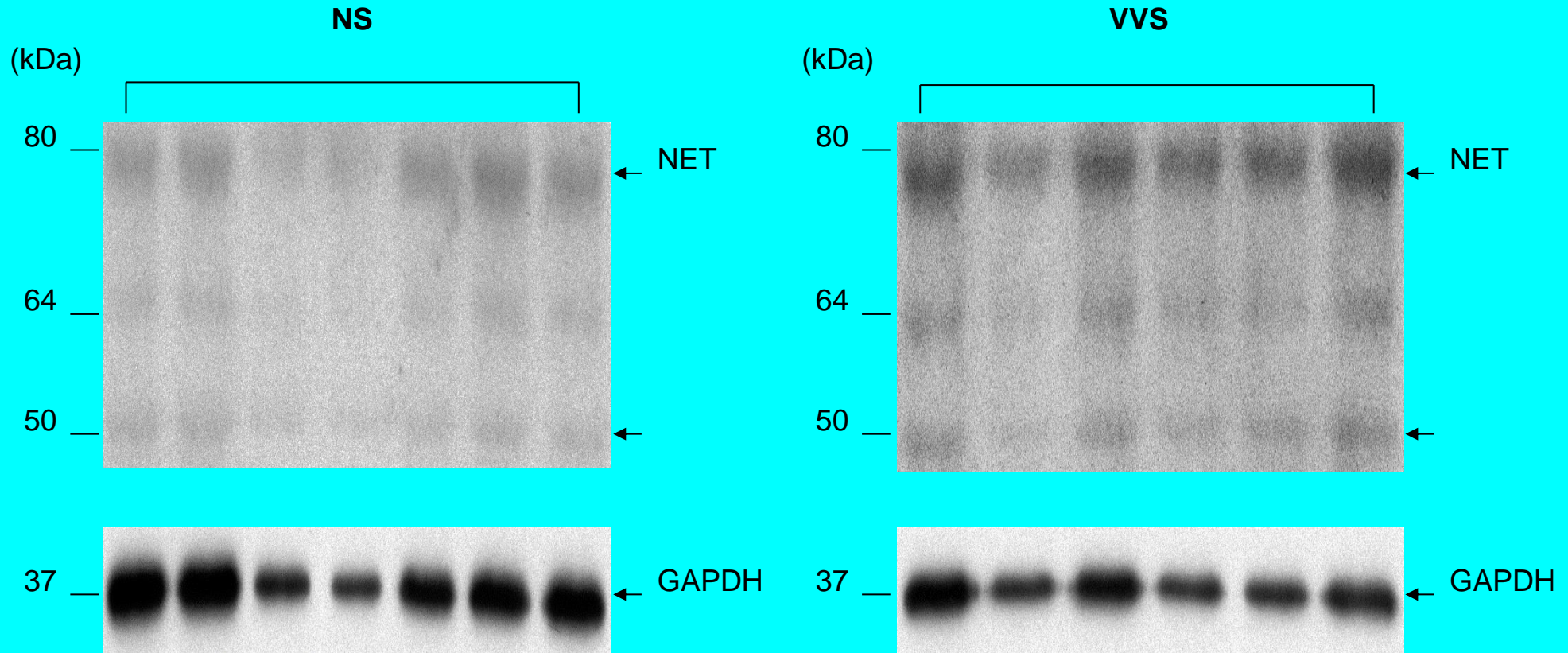
Sympathetic nerve proteins in Orthostatic Intolerance



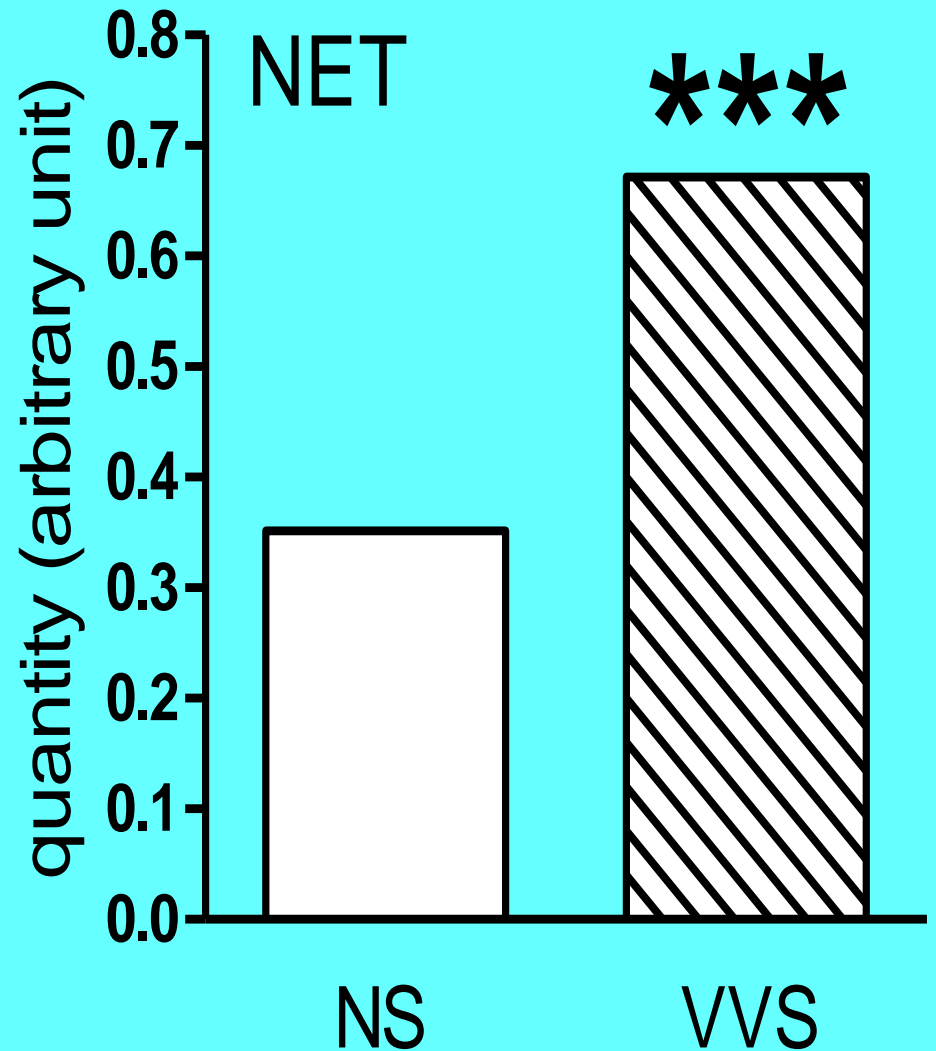
Sympathetic nerve tyrosine hydroxylase in Low Supine BP Orthostatic Intolerance Patients



NET Protein Expression in Vasovagal Syndrome Vs. Healthy Volunteers



NET Protein Expression in Vasovagal Syndrome Vs Healthy Volunteers



**Disorders of orthostatic circulatory
intolerance: a unique sympathetic nerve
protein “signature” ?**

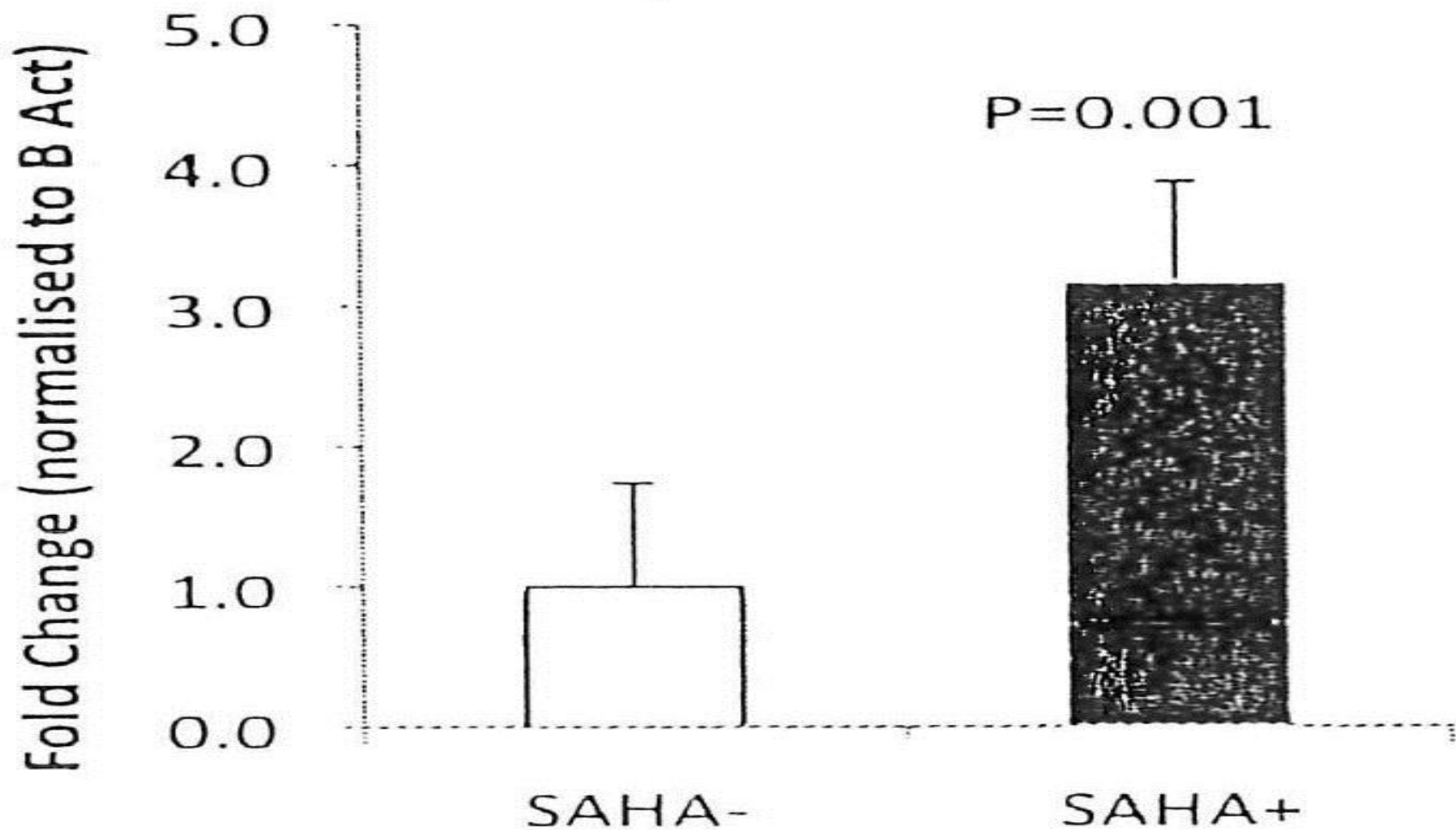
Vasovagal syndrome – increased NET protein

Low Supine BP - low tyrosine hydroxylase

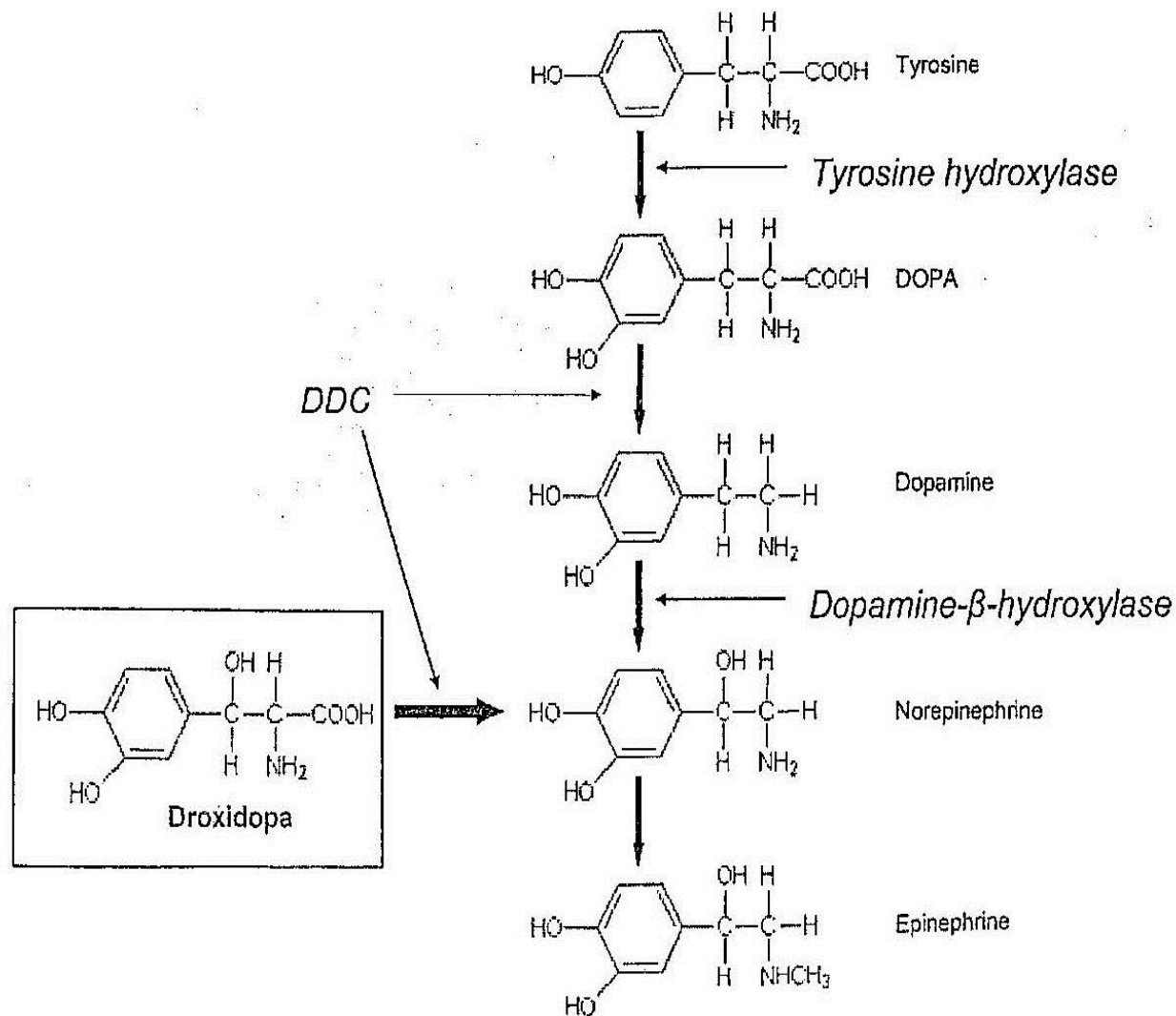
POTS - low NET protein

An aid to diagnosis ? A basis for therapy ?

NET Expression in POTS on SAHA treatment



L-DOPS Administration



**In the Low BP
OI Phenotype,
on LDOPS ...**

- * BP elevated**
- * Symptom relief**