

# STARS PATIENTS DAY

*Birmingham 9 October 2016*

## Plenary Talk: PoTS under the microscope

*Professor Murray Esler FRACP PhD*

*Baker IDI Heart and Diabetes Institute, Melbourne*

*Fellow of the Australian Academy of Science*

AT THE POLICE ACADEMY'S ANNUAL  
PASSING OUT PARADE



# 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**



**IT'S** Greg rests after fainting during our visit.

## MORE THAN JUST A DIZZY SPELL

**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

**A**sk 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 Types

## *Regulatory*

**Initial**

**Vasovagal**

**Low supine systolic BP**

**POTS**

## *Degenerative*

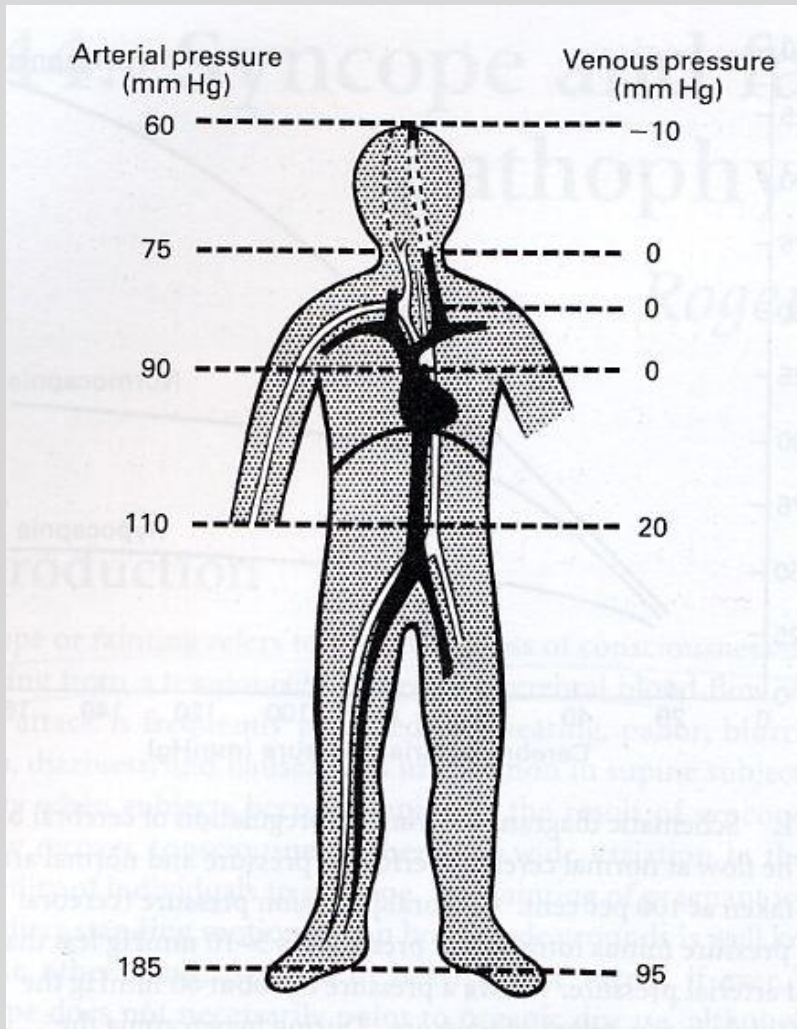
**Pure autonomic failure**

**Multiple System Atrophy**

**Parkinsonism**

**Diabetic**

# Circulatory Response to Standing



**When lying down, 25-30% of blood volume is in the chest**

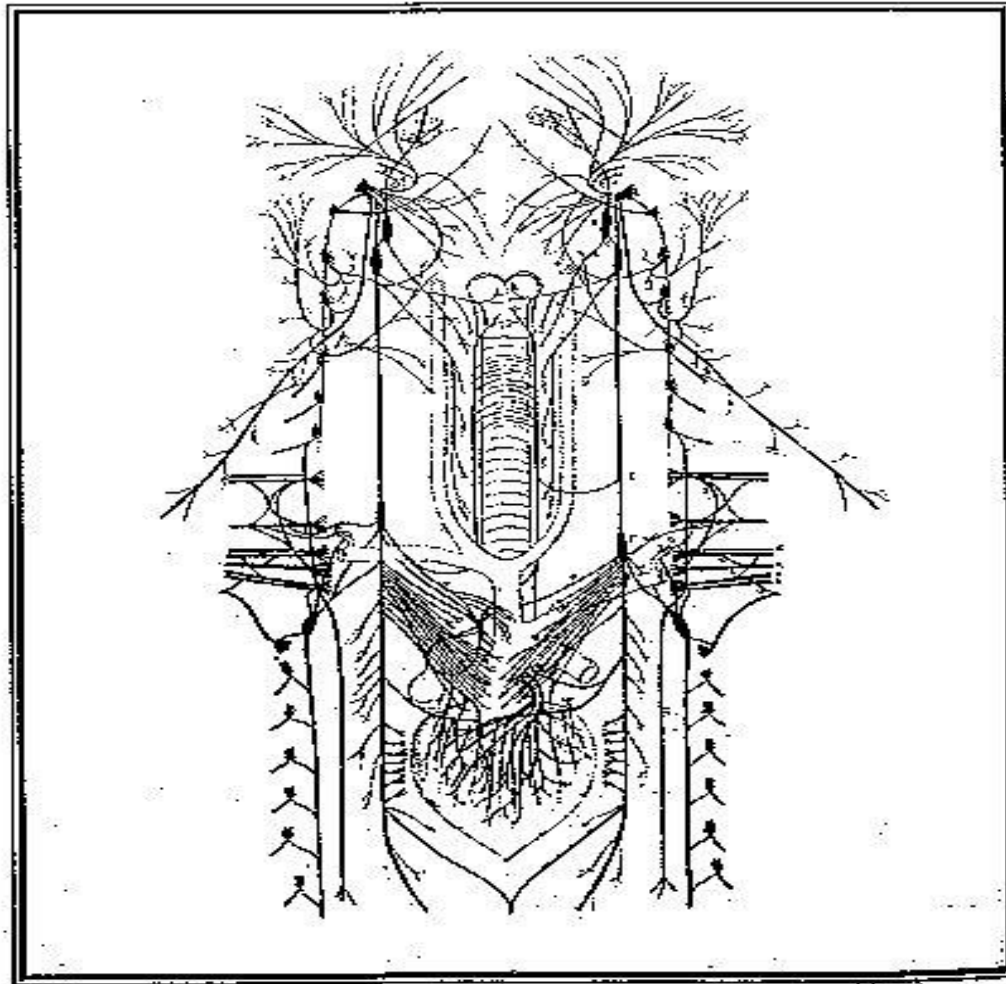
**With standing:**

- \* downward displacement of 300-800ml of blood to abdomen and legs**

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

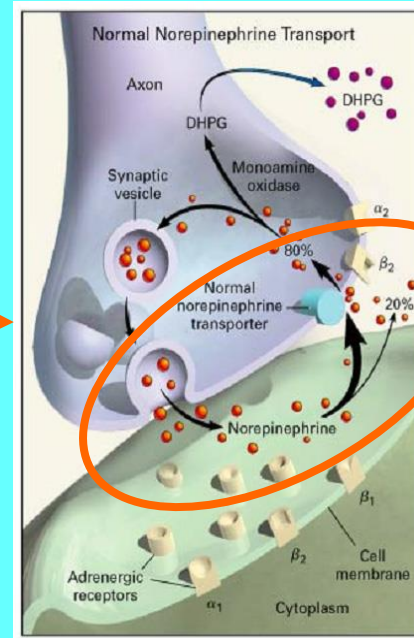
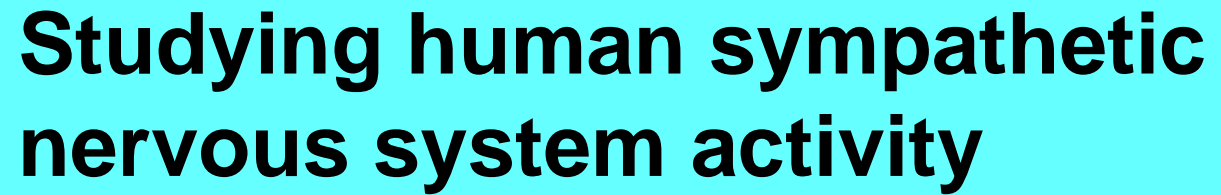
- \* *Reflex responses***

## Diagram of sympathetic nerves



**Cerebri anatome, or The Anatomy of the Brain and Nerves**

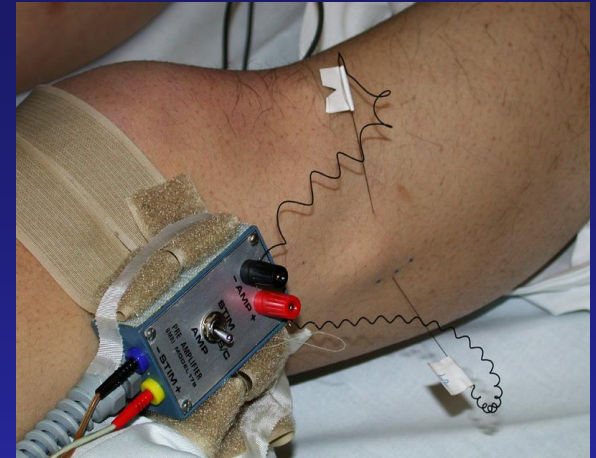
**Thomas Willis 1664**



# Noradrenaline Spillover

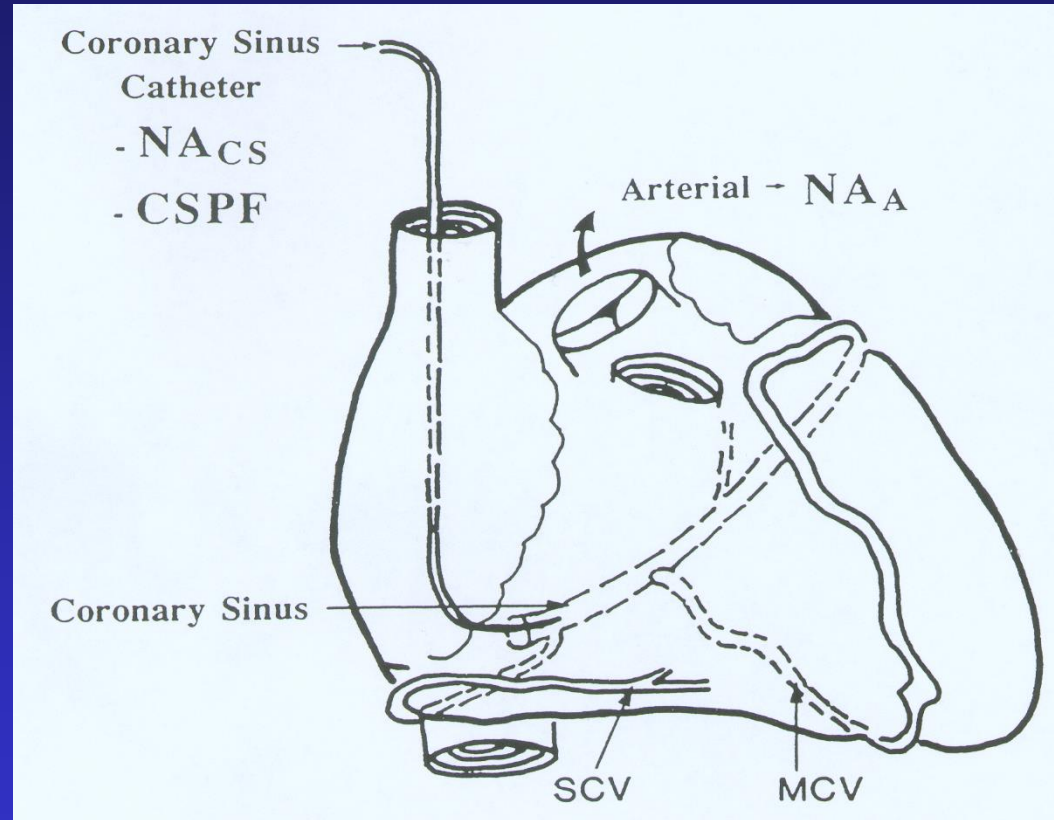
**Testing is best done by recording postganglionic nerve traffic (clinical microneurography) and measuring transmitter release from sympathetic nerves to plasma (noradrenaline “spillover”)**

# Microneurography: Sympathetic recording



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

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



$$\text{Cardiac Noradrenaline Spillover Rate} \\ = [(\text{NA}_{\text{CS}} - \text{NA}_{\text{A}}) + (\text{NA}_{\text{A}} \times \text{Ex}_{(3\text{H-NA})})] \times \text{CSPF}$$

# Postural Tachcardia Syndrome (PoTS)

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*Orthostatic intolerance accompanied by a racing heart rate*

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

# Postural Tachycardia Syndrome

- ☐ Postural tachycardia
- ☐ Orthostatic intolerance without hypotension

☐ Exercise intolerance

☐ Chronic fatigue

☐ Palpitations

☐ Sleep disturbance

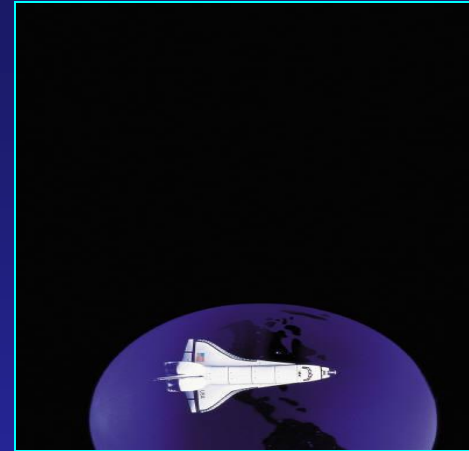
☐ Chest pain

☐ Cognitive dysfunction “brain fog”

☐ Hyper-vigilance/anxiety



*Critical to diagnosis*



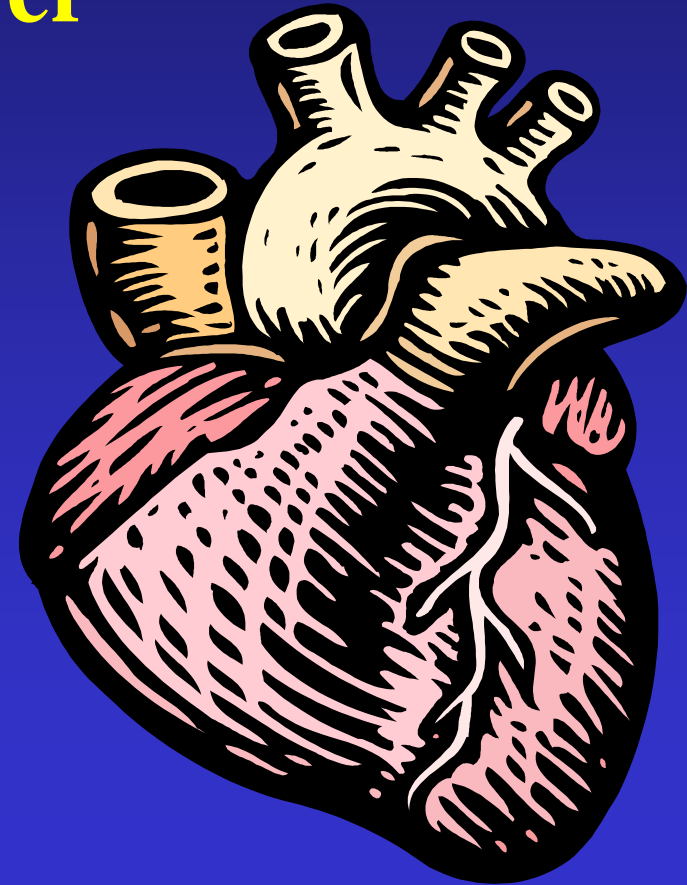
# Space Shuttle Columbia

*April 1998 ( NEUROLAB )*

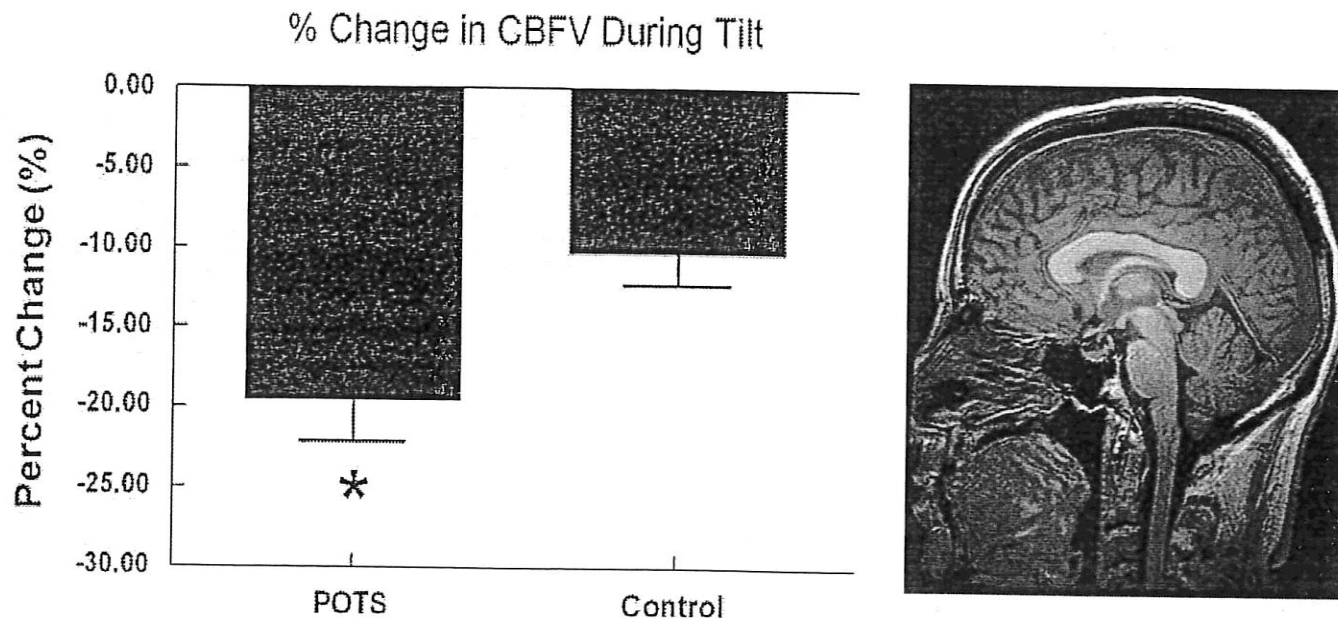
# The postural tachycardia ....

Sympathetic activity in the heart  
during standing in a PoTS sufferer

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



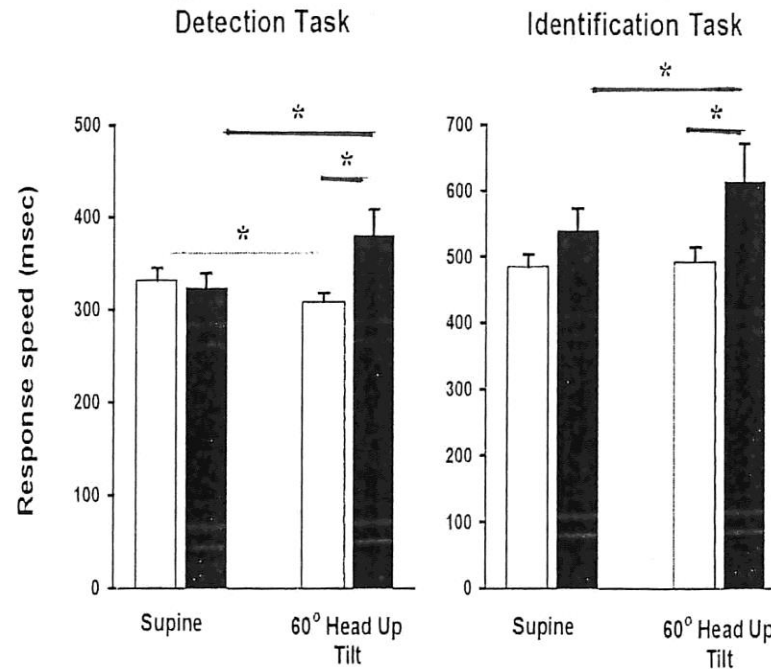
# Fainting Without Postural Hypotension



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

# PoTS: Effect of Upright Posture on Cognition

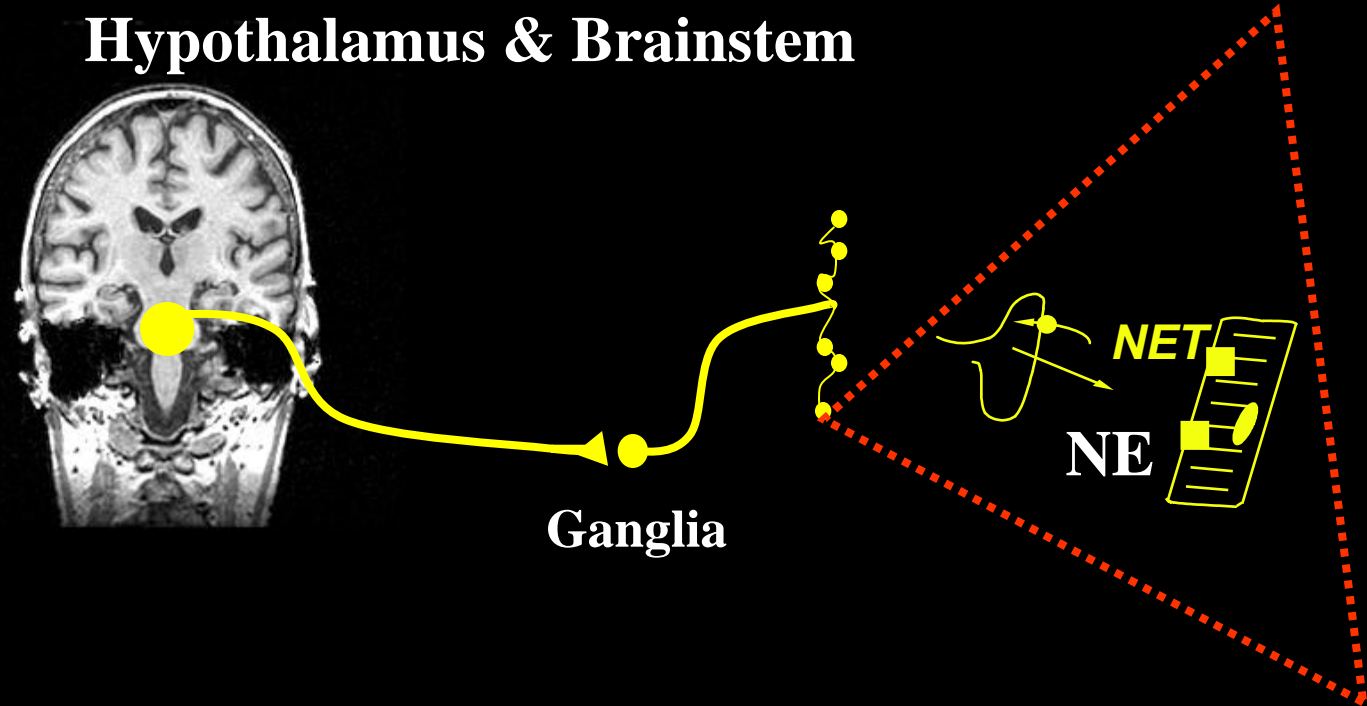


JW Anderson et al. *Frontiers in Physiology*  
2014;5:1-9 doi: 10.3389/fphys.2014.00230

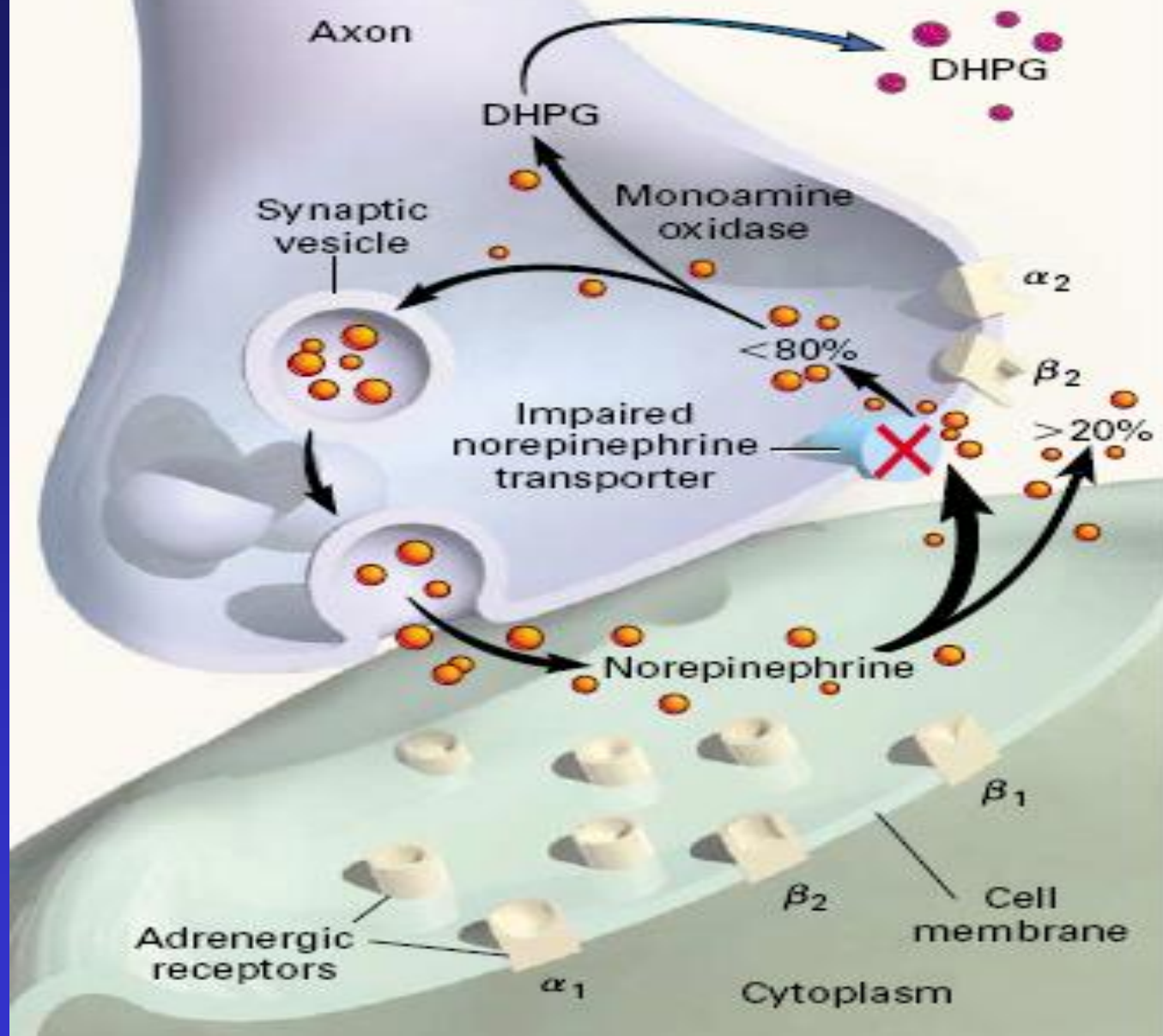
# Sympathetic Nervous System Augmentation:

## *Faulty neuronal noradrenaline reuptake in POTS ?*

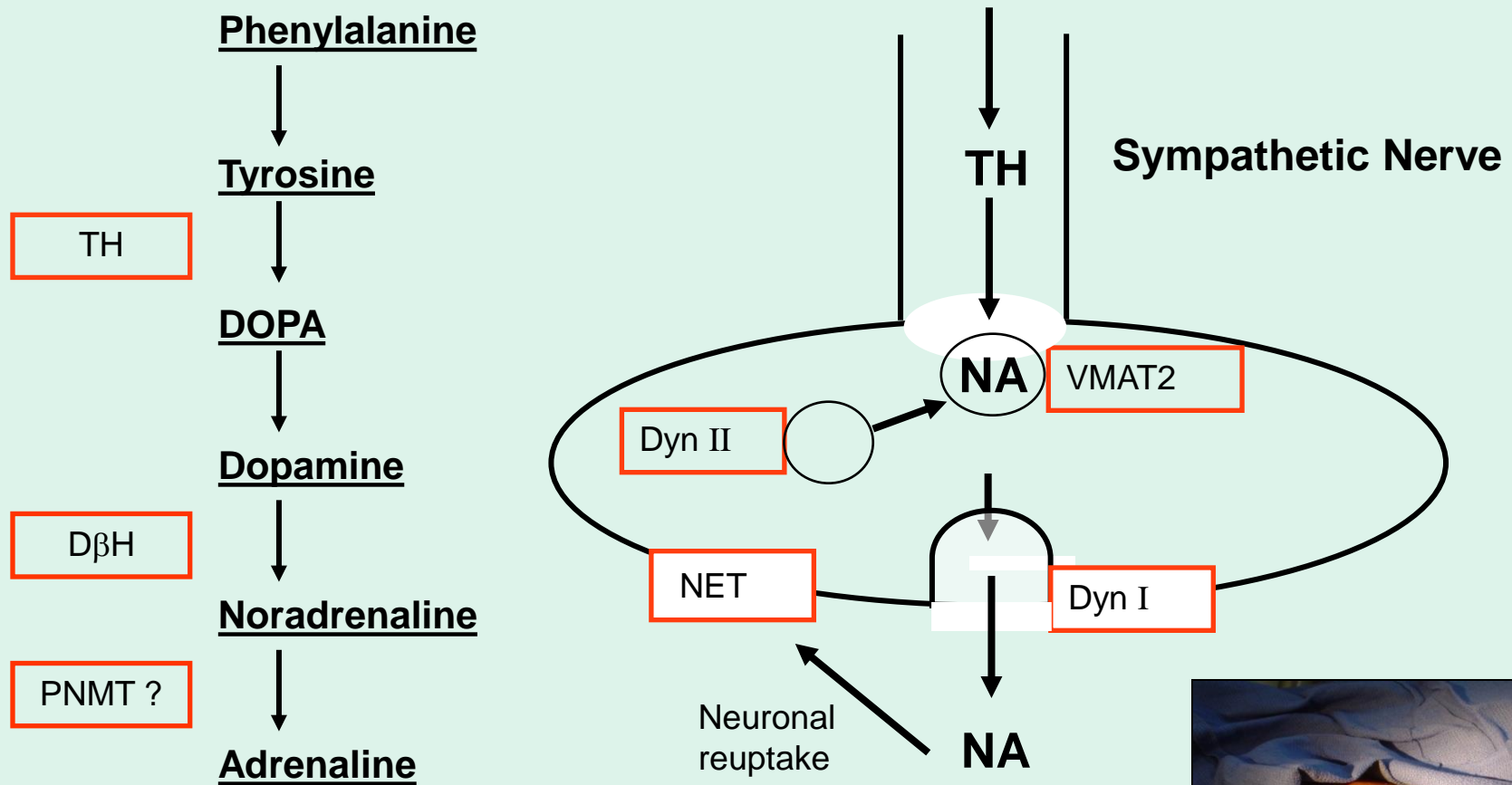
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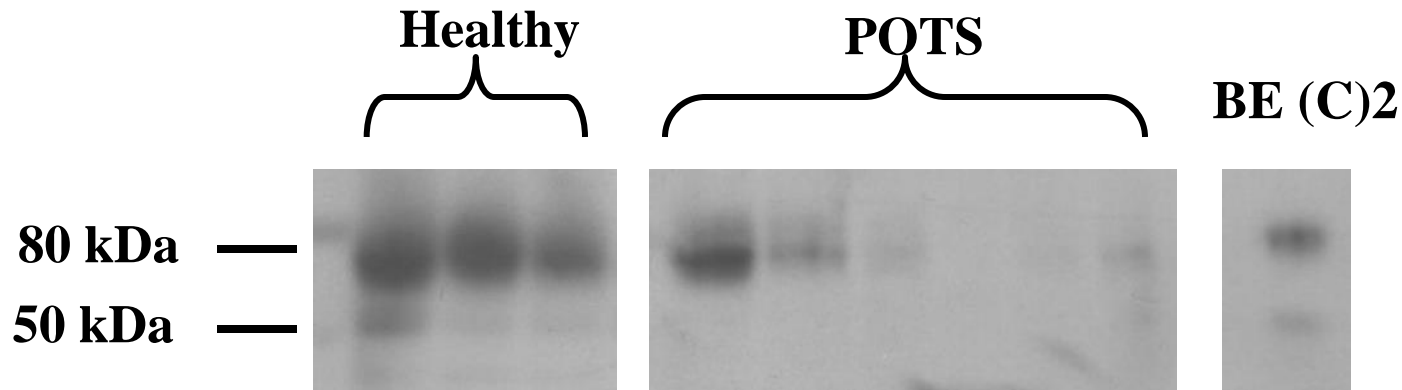
## Impaired Norepinephrine Transport



# 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: this is what goes wrong....**

**Sympathetic nerve augmentation, by faulty noradrenaline reuptake, causes:**

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

# **Sympathetic Nerves Control Brain Blood Vessels**

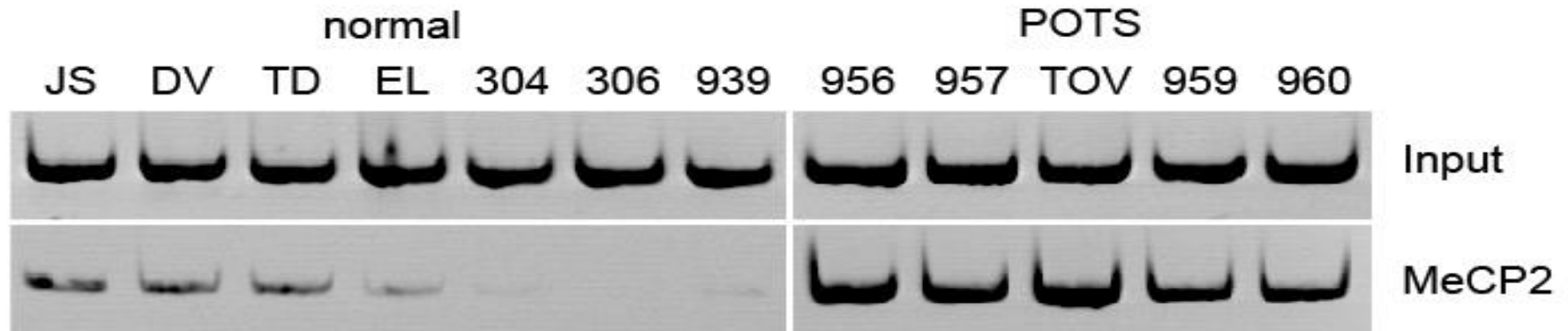
**Jugular venous overflow of noradrenaline from the brain: a neurochemical indicator of cerebrovascular sympathetic nerve activity in humans**

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

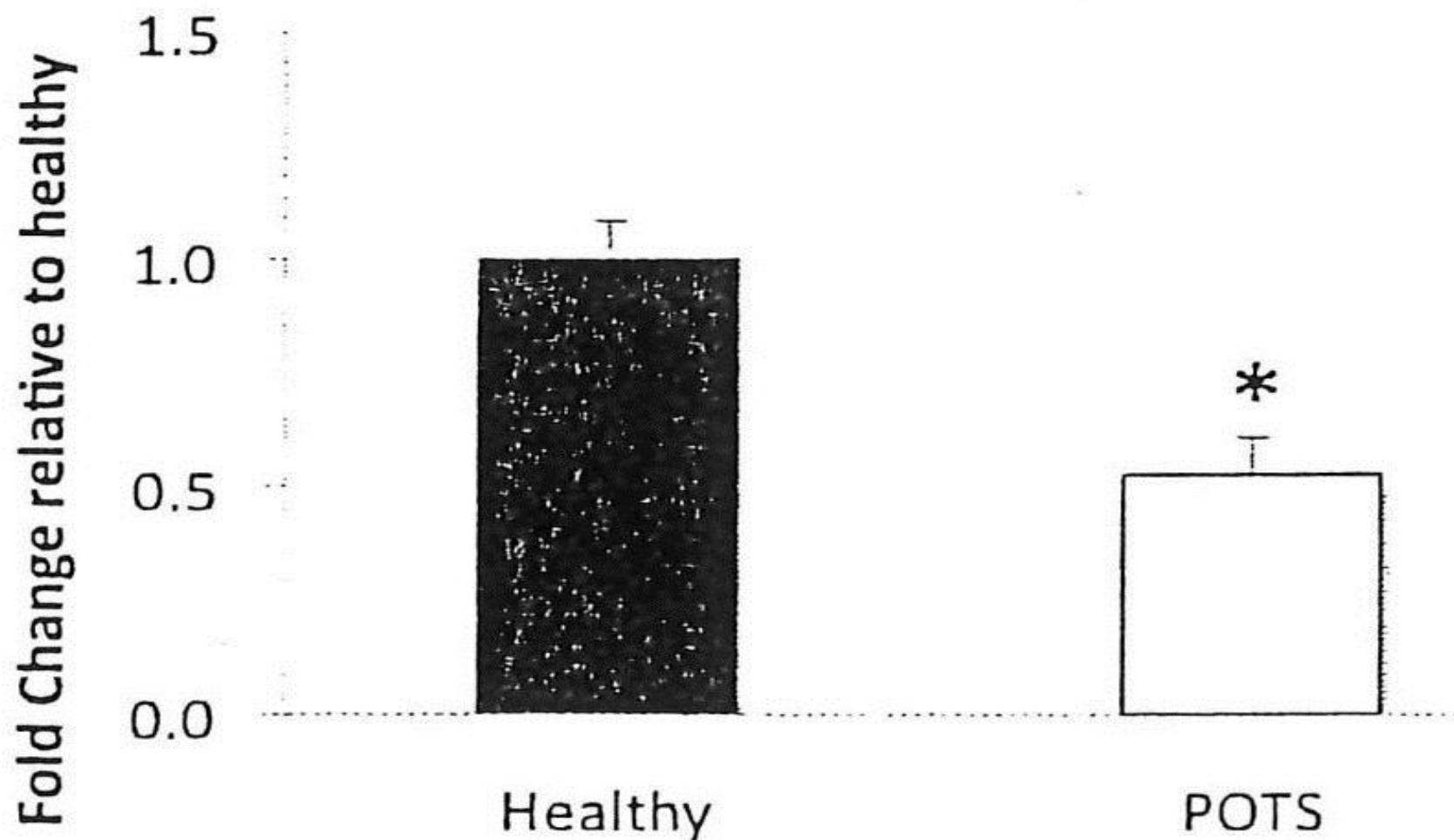
***Journal of Physiology 2009;587:2589-2597***

# POTS: An Epigenetic (Gene Control) Mechanism?

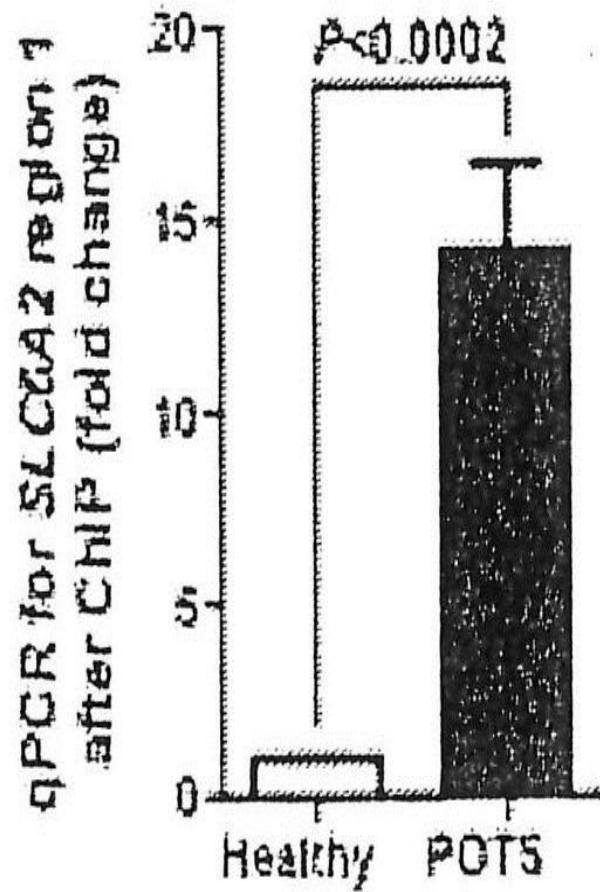
(Studied in POTS patient's white blood cells)



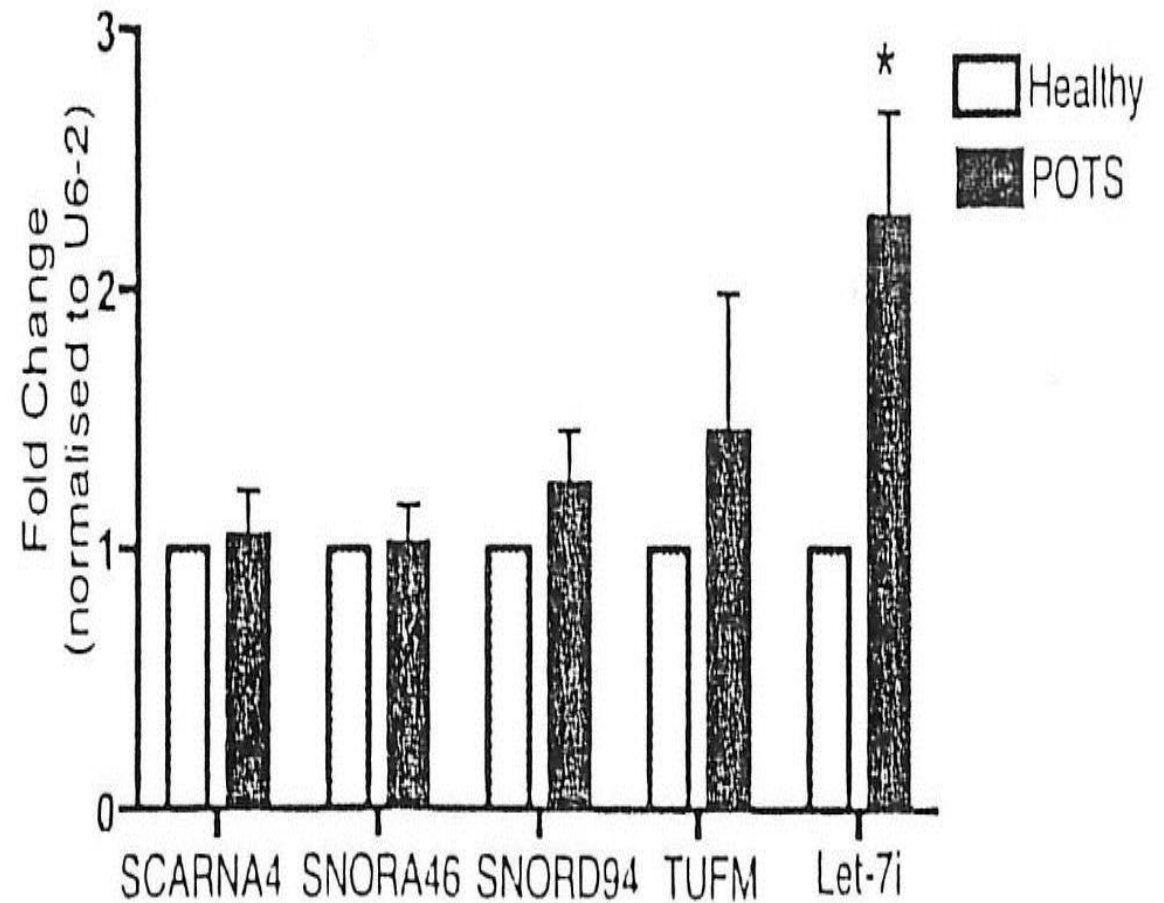
## NET Expression in POTS individuals (n=7, P0.00004)



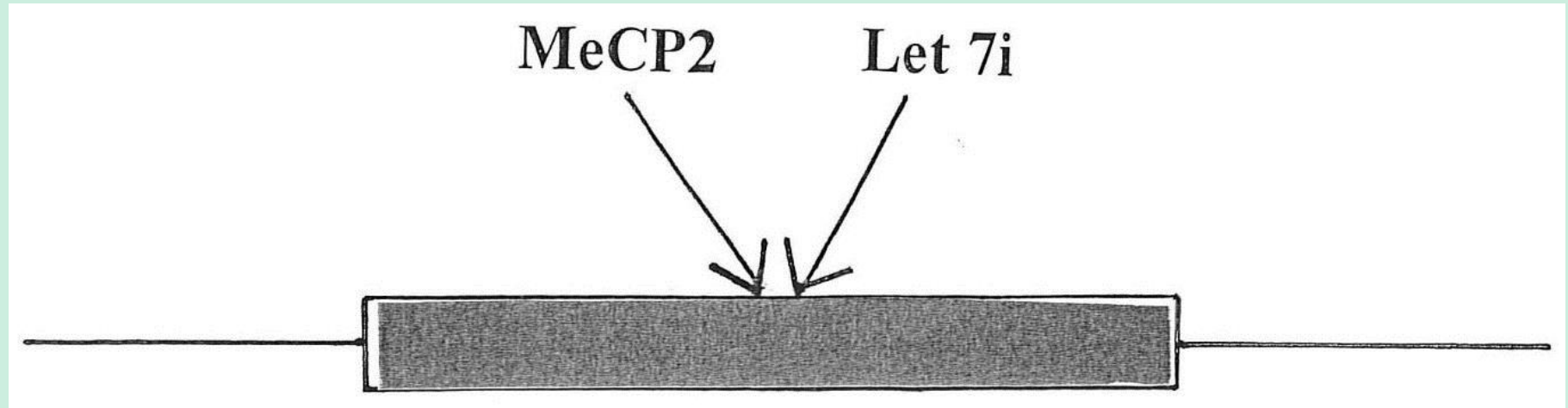
## MeCP2 ChIP



## Expression of *NET* promoter bound RNAs in hPBMCs



# Inhibition of NET Gene in PoTS



NET gene promoter region



NET gene inhibition potentially reversed by deacetylase inhibitors

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)

## NET Expression in POTS on SAHA treatment

