Autonomic Dysfunction and POTS: A Practical Guide

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Disclosures

- Consultant / Share holder – Dolor Technologies

Dude.....

It's about time to know about POTS

by naughtylittlemastcells.com

in the USA...

1.5 MILLION have Lupus

1.5 MILLION have Rheumatoid Arthritis

1.3 MILLION have Crohn's Disease or Ulcerative Colitis (IBD)

1.25 MILLION have Type I Diabetes

1 MILLION have Multiple Sclerosis (MS)

1 MILLION have Chronic Fatigue Syndrome (ME/CFS)

1 MILLION have Parkinson's Disease

100,000 have Sickle Cell Anemia

30,000 have Cystic Fibrosis

15,000 have ALS (Lou Gehrig's Disease)

1 TO 3 MILLION have POTS

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

POTS is a life altering illness commonly misdiagnosed as anxiety.

= 100,000 people

LEARN MORE

dysautonomiainternational.org

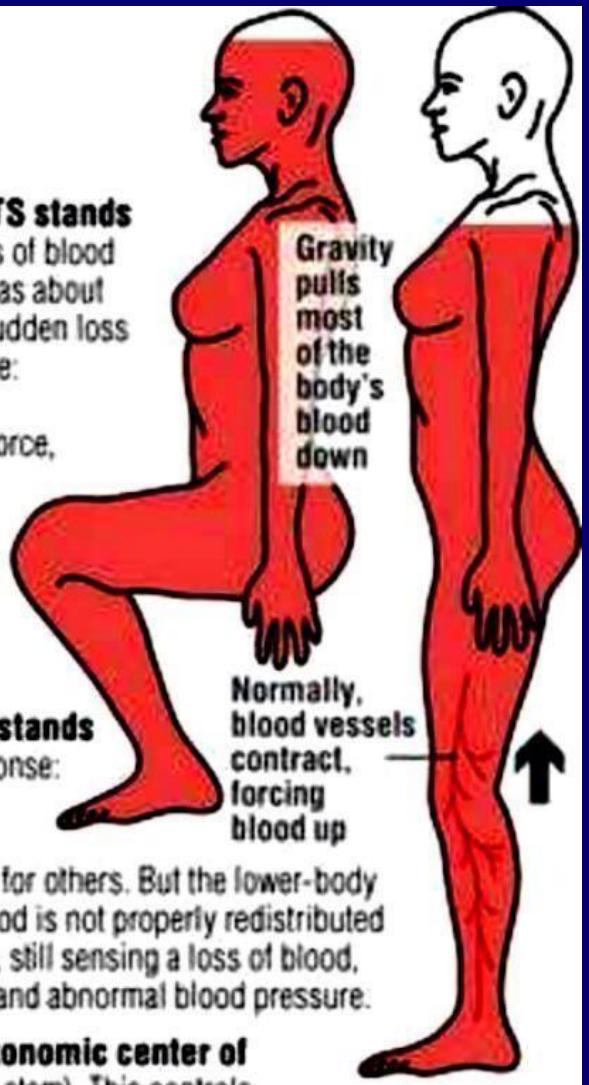
PLEASE SHARE TO PROMOTE POTS AWARENESS!

How POTS affects the body:

When an adult without POTS stands up, gravity pulls 1.5 to 2 quarts of blood into the lower body. (An adult has about 6 quarts.) The brain senses a sudden loss of blood and triggers a response:

- The heart beats faster.
- The heart beats with greater force, increasing blood pressure.
- Vessels in the lower half of the body constrict.

All of this forces more blood into the upper body, usually within two heartbeats.



When a person with POTS stands up, the brain triggers this response:

- The heart beats faster.
- Blood pressure increases for some POTS patients and drops for others. But the lower-body vessels do not constrict, so blood is not properly redistributed throughout the body. The brain, still sensing a loss of blood, maintains the rapid heartbeats and abnormal blood pressure.

The problem lies in the autonomic center of the brain (located in the brain stem). This controls heart rate, blood pressure, body temperature, sweating and urinary, digestive and sexual function. Any of those functions can be affected. Reduced blood flow to the brain may also cause symptoms, including light-headedness, dizziness, fainting, fatigue and poor concentration.

POTS Diagnostic Criteria

- Heart rate increase ≥30bpm from supine to standing within 10 minutes (≥40bpm for adolescents)
- In the absence of orthostatic hypotension (OH defined as 20/10mmHg drop within 3 min. of standing)
- Symptoms of orthostatic intolerance lasting ≥6 months
- Symptoms exacerbated by standing and improved with recumbence
- Absence of other overt causes of orthostatic symptoms or tachycardia

Which of the following POTS symptoms have you experienced?

MyHeart.net

http://bit.ly/POTS-SYNDROME

Profile of Patients with POTS

(Postural Orthostatic Tachycardia Syndrome)

Statistics are from a recent survey of 779 UK POTS Patients as found in

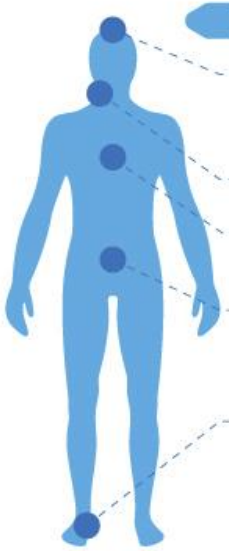
A profile of patients with Postural Orthotastic Tachycardia Syndrome
and their experience of healthcare in the UK

92% were female

81% were aged
between 18 -49

Most Common Symptoms

- 91% Fatigue
- 90% Dizziness
- 86% Palpitations
- 58% Fainting / Blackouts



More than 40% reported...

- Brain fog
  Daily headache
  Visual disturbances
- 'Coat hanger' pain
- Breathlessness
  Chest pain
- Nausea
  Bloating
  Abdominal pain
- Tingling hands/feet
  and/or acrocyanosis
- Poor sleep, shakiness, physical weakness, heat/exercise intolerance, sweating...

Positional Orthostatic Tachycardia Syndrome (POTS)

- Partial Dysautonomic POTS
  - Orthostatic Intolerance
  - 120 bpm or ↑>30bpm within 10 min of upright posture
  - 90% of all POTS
- Hyperadrenergic POTS
  - ↑SBP>10mm Hg during upright posture and tachycardia
  - Serum norepinephrine >600pg/ml
  - Associated with Mast Cell dysfunction?

(Kanjwal et al., 2011)

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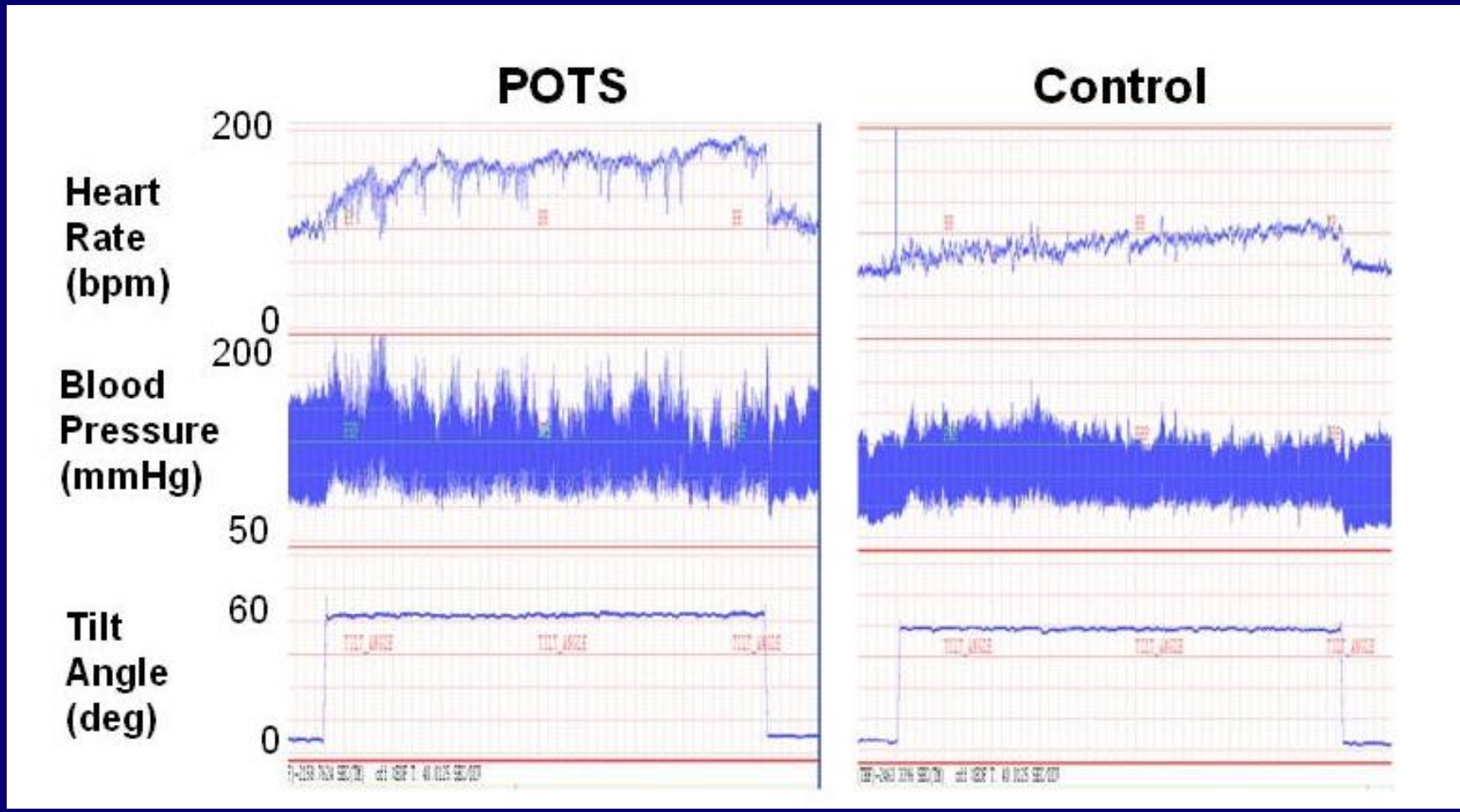
Tilt Table Testing



Hyperadrenergic POTS

- Clinical Symptoms:
  - Migraine > 50%
  - Flushing > 60%
  - Hypermobility 20%
  - Anxiety 60%
  - Sweat 60%
  - Fatigue 40%

- Possible related Mast cell mediators:
  - Histamine
  - Renin
  - ACE
  - CGRP
- May contribute to vasogenic edema and syncope
- Associated “viral prodrome”

(Shibao et al., 2005)

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Chronic sympathetic nervous system activation contributes to POTS

- Depletes:
  - Norepinephrine
- Increases:
  - Dopamine
  - Adenosine triphosphate
  - Adenosine
  - Prostagladins

POTS and Anxiety

- Anxiety associated with hyperadrenergic state
- Possibly more prognostic for progression and intractability
- Autonomic hypersensitivity?
- Associated migraine?

(Smitherman et al., 2008)
(Aurora et al., 2009)

Migraine Comorbidity

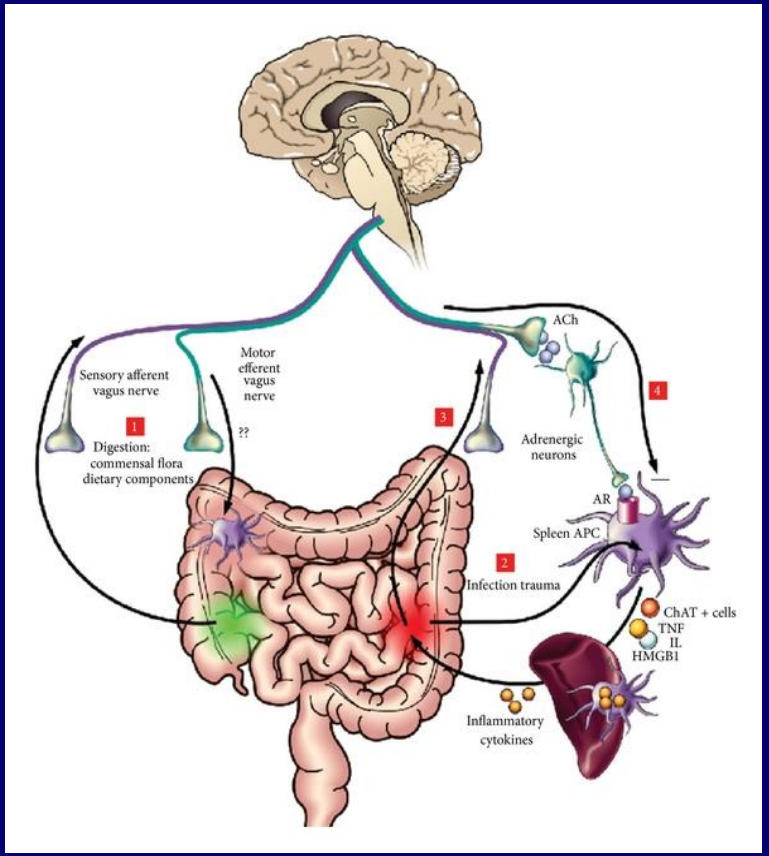
Disorders highly associated with migraine that occur at a rate significantly greater than chance

Gut Cluster

- Irritable bowel syndrome
- Gastritis
- Peptic ulcer disease
- H. pylori
- GERD
- Colitis

Enteric Nervous System

- Derived from neural crest cells
- Secretes familiar neurotransmitters
  - Acetylcholine
  - Dopamine
  - Serotonin
  - CGRP
- Precursor cells migrate along vagus nerve
  - Differentiate in the gut
- Up to 600 million neurons!
  Rivaling spinal cord

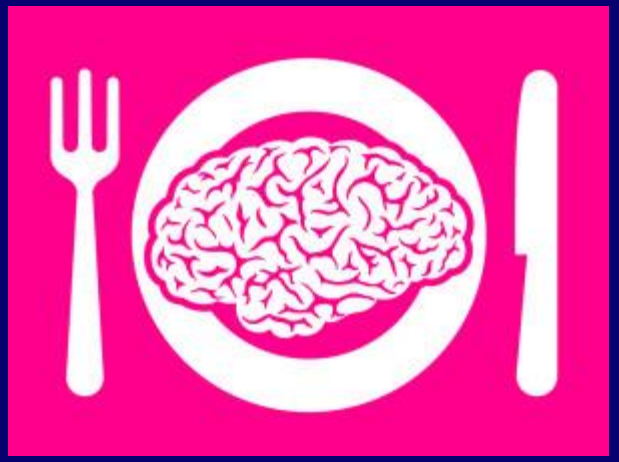


Gershon MD, Chalazonitis A, Rothman TP. From neural crest to bowel: development of the enteric nervous system. J Neurobiol. 1993;24:199–214.

IBS and Migraine

- National Health Insurance Research Database (NHIRD) – Taiwan
  - 14,117 newly diagnosed migraine
  - 56,468 controls
  - IBS incidence 1.95 fold higher in migraine
  - 3.36 fold increase in <30 years old

  (95% confidence interval 2.44-4.63)



Lau CI, Lin CC, Chen WH, et al. Association between migraine and irritable bowel syndrome: A population-based retrospective cohort study. *Eur J Neurol*. 2014;21:1198-1204.

Chronic Pain and Hypermobility

Childhood Joint hypermobility identified as predisposing factor for Chronic Pain

(Murray & Woo, 2001)

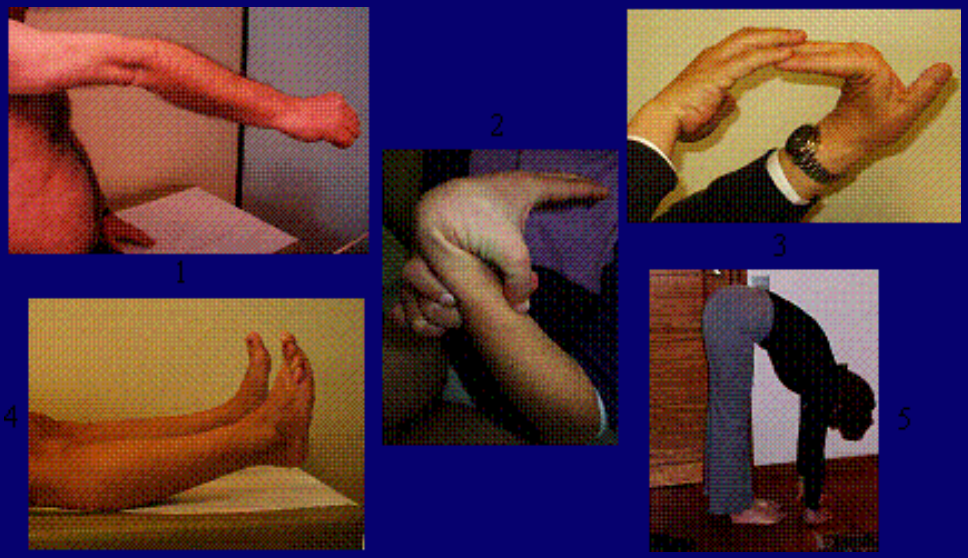


Table 2 Beighton score (9). One point given for each positive manoeuvre. Each limb tested separately

1. More than 10° hyperextension of the elbows
2. Passively touching the forearm with the thumb, while flexing the wrist
3. Passive extension of the fingers or a 90° or more extension of the fifth finger
4. Knee hyperextension greater than or equal to 10°
5. Touching the floor with the palms of the hands when reaching down without bending the knees

Hypermobility associated with fibromyalgia and New Daily Persistent Headache Syndrome

(Rozen, 2007)

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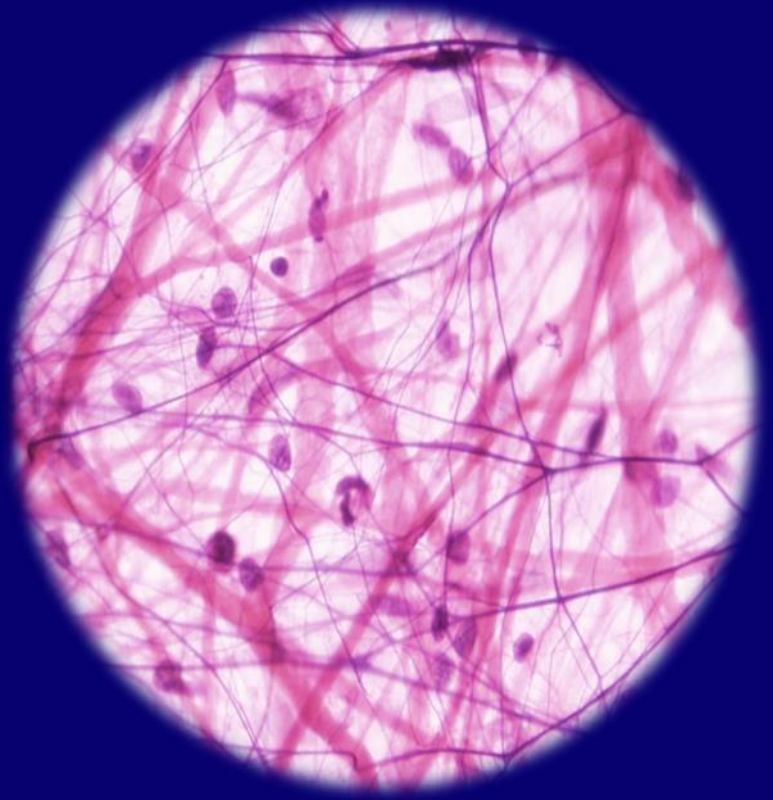
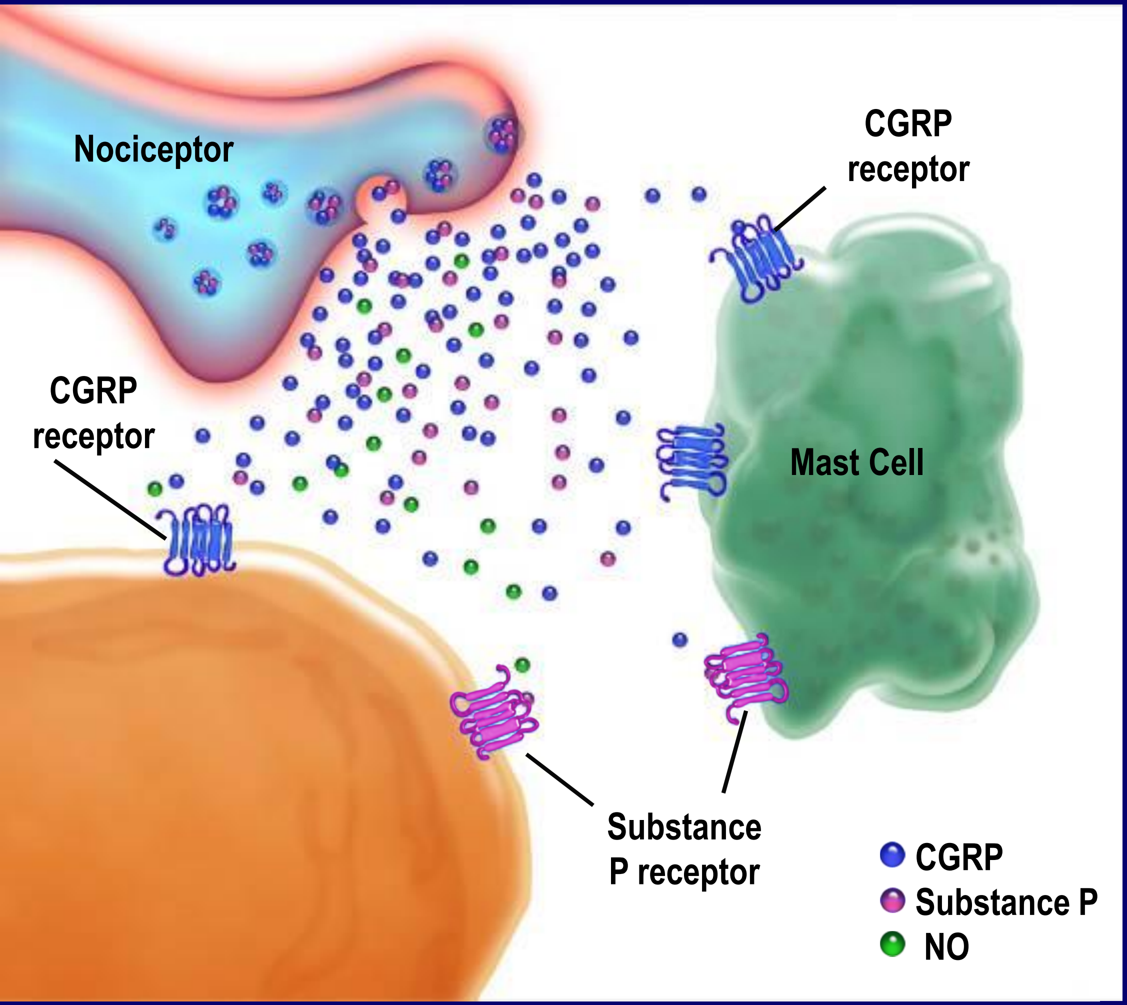
Increased Mast Cell Count and Activity Undifferentiated Connective Tissue Dysplasia

- ↑ Mast Cell Density
  - 1.7 fold increase in UCTD compared to controls
- ↑ Intracellular Chymase Activity
- Increased mast cell count in benign joint hypermobility
- Increased in skin samples of patients with fibromyalgia



(Luzgina et al., 2010)
(Enestrom S. et al., 1997)

Neuroinflammation



- Activated nociceptors release CGRP and substance P
- CGRP and substance P attract mast cells
- Cause inflammatory response
- NO also released
- Leads to
  - Vasodilation
    CGRP, NO, substance P
  - Mast cell degranulation
    CGRP, substance P
  - Plasma extravasation
    substance P
- Mast cell degranulation
  - Histamine
  - NGF
  - Serotonin
  - Proinflammatory cytokines
    - TNF-α, IL-1, IL-6

Mast Cells and the Nervous System

- Reside in the dural layer of the meninges
- Close proximity to blood vessels and nociceptors
- Plasma Histamine is elevated in migraine subpopulations
- Histamine infusion may trigger migraine

- Known triggers of migraine also trigger mast cell activity
  - Stress
  - Estrogen
  - Foods
  - Environmental stimuli
  - Alcohol

(Levy D, 2011)

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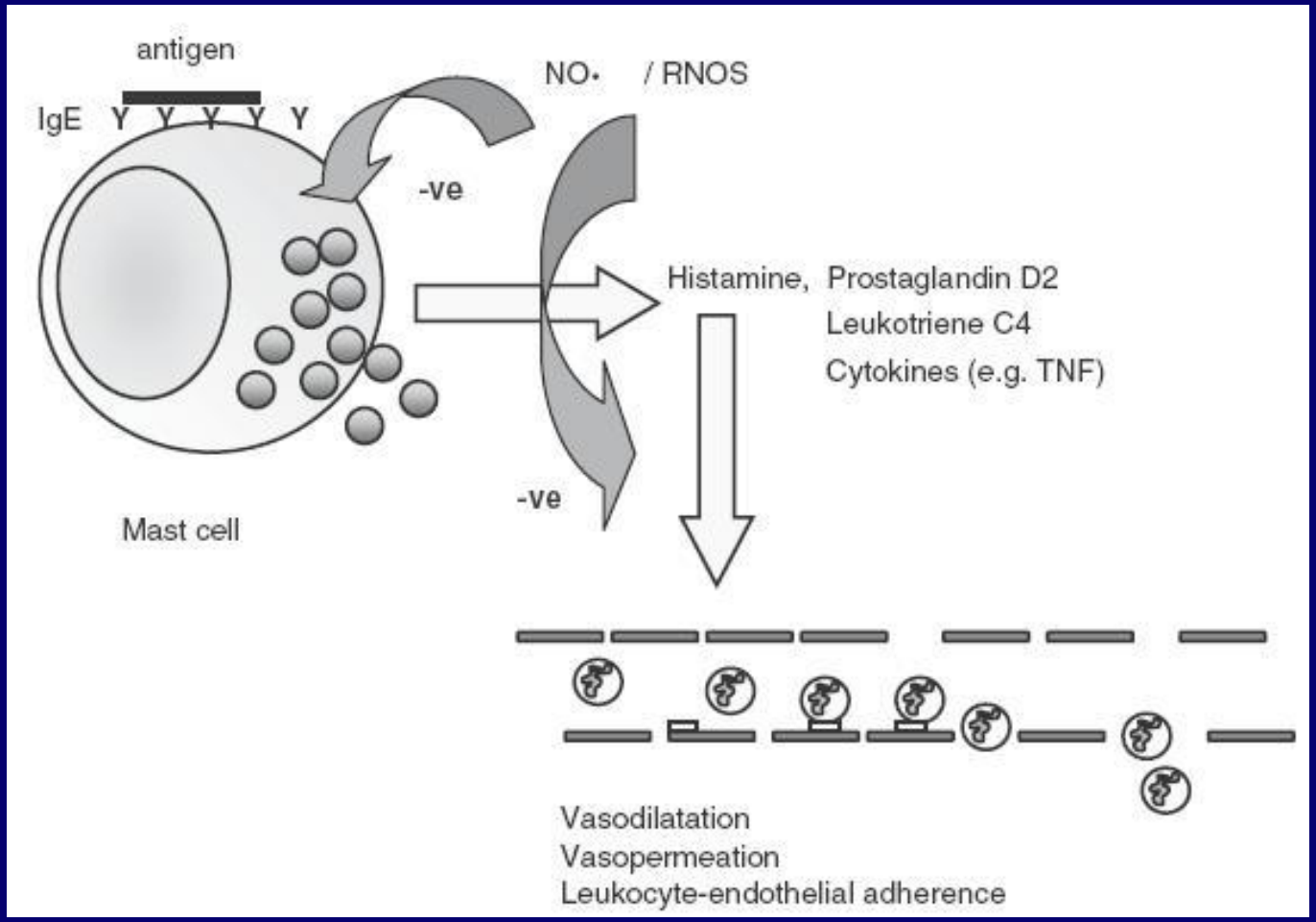
Activated Mast Cells

- Release proinflammatory substances
  - Histamine
  - Serotonin
  - Cytokines
  - Leukotrienes
    - IL6
    - LTC_4
  - Prostaglandins
    - PGD_2
    - PGI_2

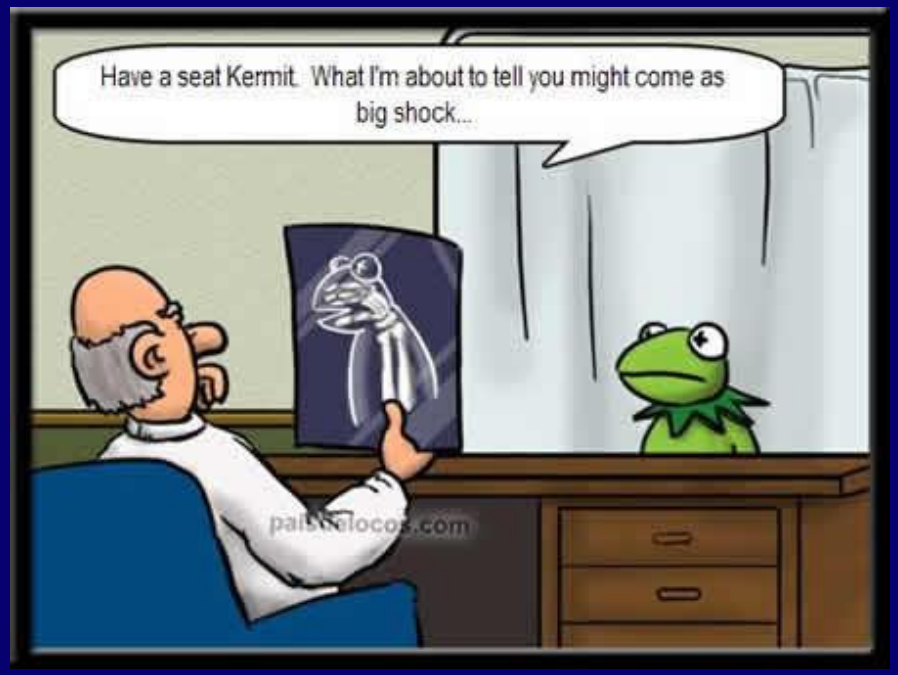
> 200 substances are associated with mast cell activation

Mast Cell Role in POTS



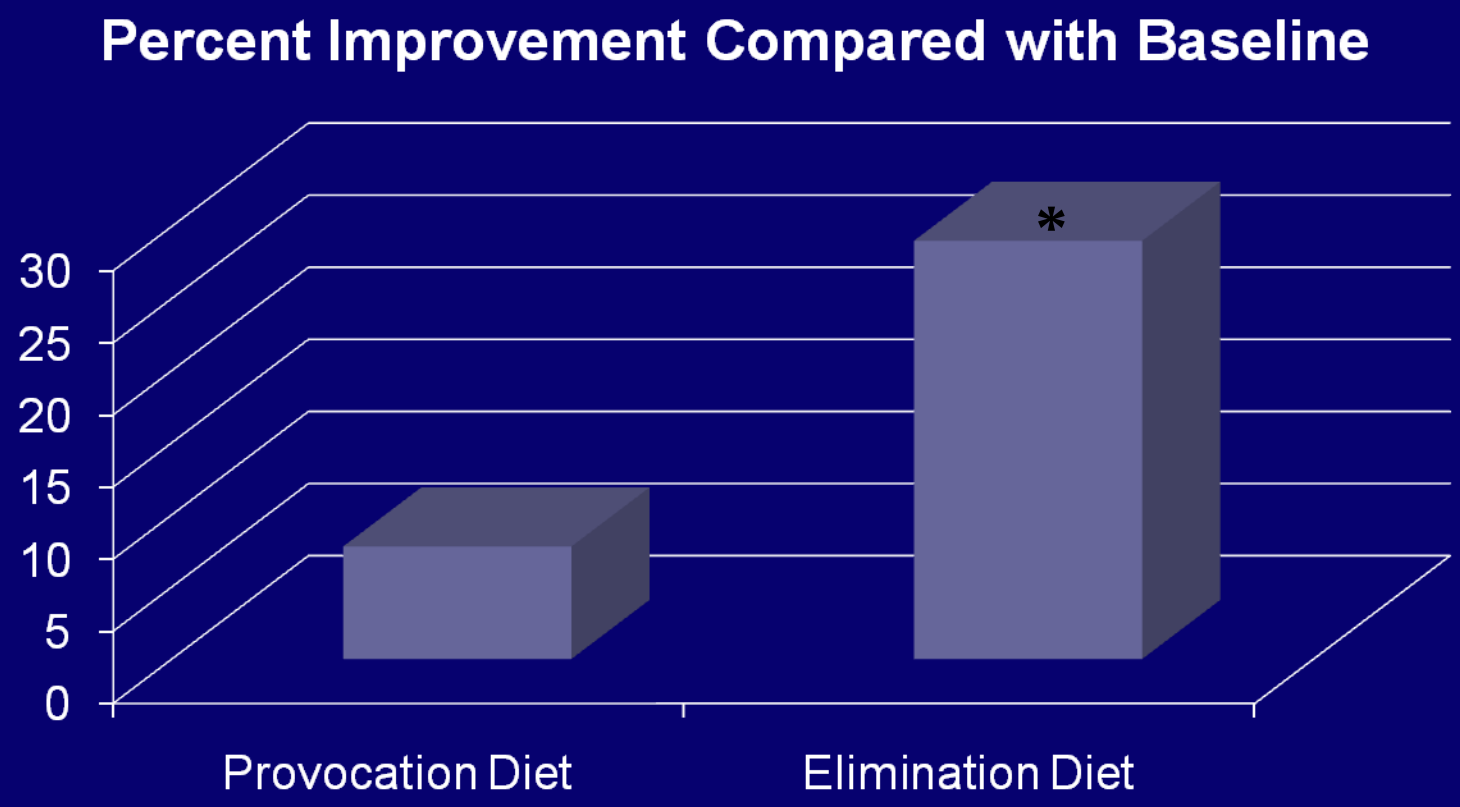
IGG Food Sensitivity Testing

- Foods may trigger migraine
- Challenge to identify which food may trigger migraine
- Accepted diagnostic tool
  - Celiac Disease
  - Asthma
  - Eosinophilic Esophagitis



Pasquel J & Orterino A. Cephalalgia 2010;30:777-81

IgG Antibody Based Elimination Diet



*P<0.05 vs baseline

Alpay K. Cephalalgia 2010; 30: 829-835,

Celiac Disease and autonomic dysfunction

- 25 subjects with CED
  - Neurologically asymptomatic
- 30 Controls

- HR variability
  - Rest
  - sympathetic stimulation
  - parasympathetic stimulation

- CED more likely to have

- 36% had HRV with sympathetic dominance
- 20% had HRV with parasympathetic dominance

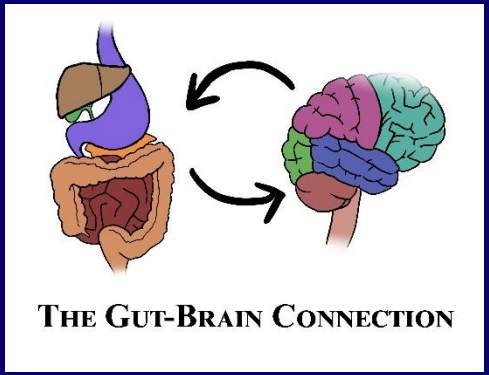
Przybylska-Felus M, Furgala A, Zwolinska-Wcislo M, Mazur M, et al. Disturbances of autonomic nervous system activity and diminished response to stress in patients with celiac disease. J Physiol Pharmacol. 2014 Dec;65(6):833-41.

Migraine comorbid with Celiac Disease and Gluten Sensitivity

- Chronic headache reported by
  - 30 % of Celiac disease
  - 56 % of Gluten sensitivity
  - 23 % of Irritable bowel syndrome
  - 14 % of controls

- Migraine reported by
  - 21% Celiac Disease
  - 40% of Gluten sensitivity

*all significantly higher than controls



Dimitrova AK, Ungaro RC, Lebwohl B, et al. Prevalence of migraine in patients with celiac disease and inflammatory bowel disease. Headache. 2013;53:344–55.

Migraine and Orthostatic Intolerance

- Lifetime prevalence
  - Syncope
    - 46% migraine
    - 31% controls
  - Orthostatic Intolerance
    - 32% Migraine
    - 12% Controls

(Thijs et al., 2006)

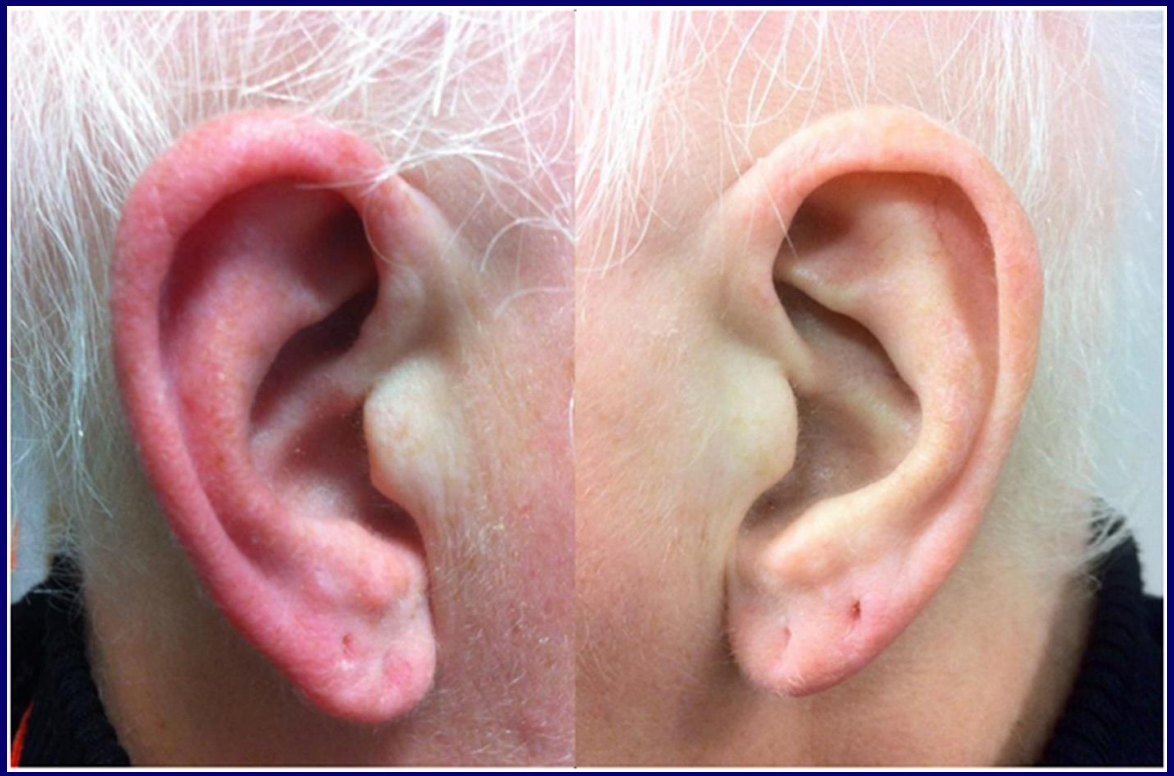
Raynauds Phenomenon

Well established comorbidity with migraine / anxiety

- Typically not treated
- Marker of neural hypersensitivity?

- Environmental intolerance
  - Meal skipping
  - Heat
  - Sleep pattern

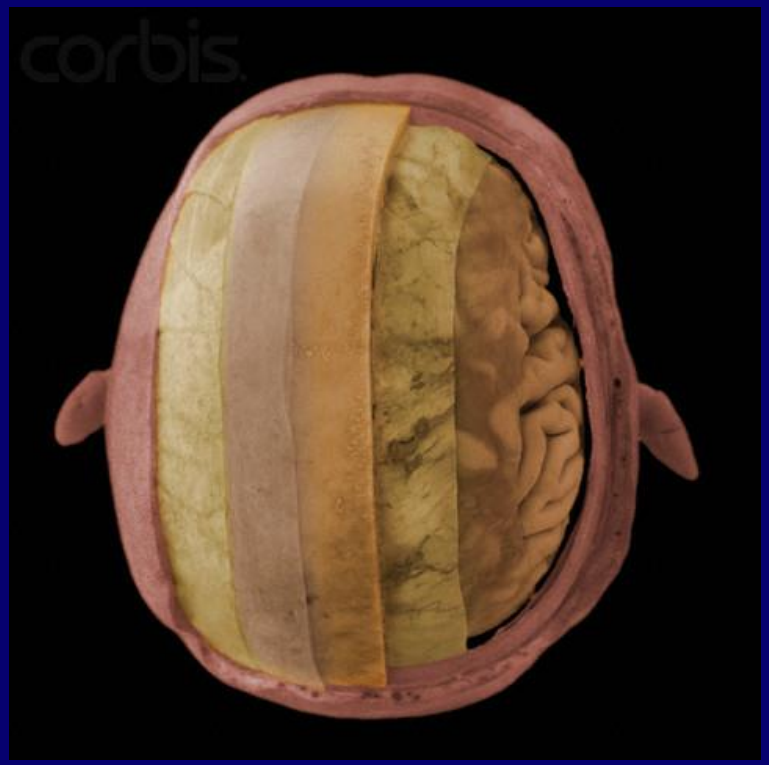
Red Ear Syndrome



Lambru et al. The red ear syndrome. The Journal of Headache and Pain 2013, 14:83

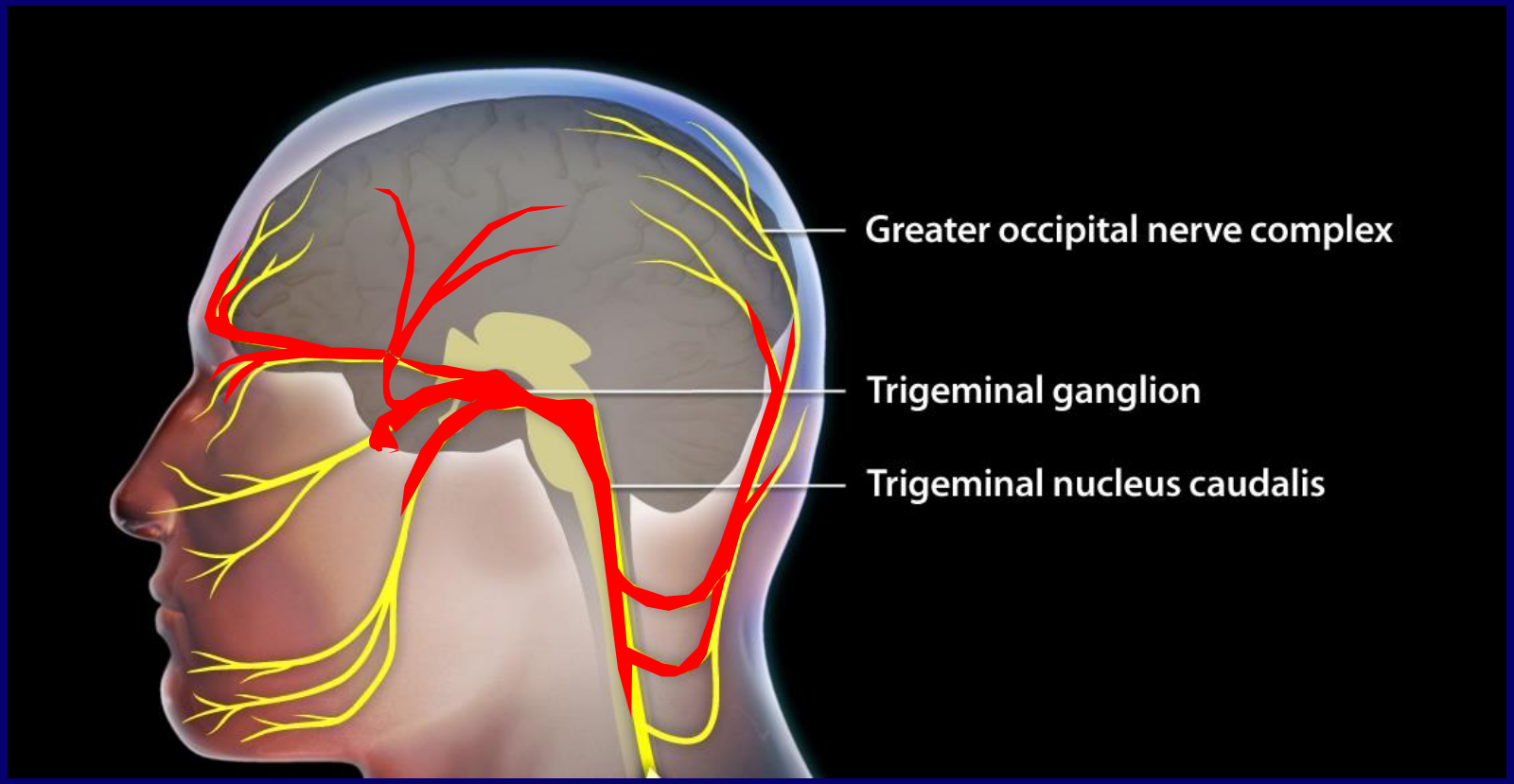
Autonomic influence on the Dura mater

- Dense network of autonomic and sensory fibers within the Dura Mater
- Parasympathetic stimulation (Carbachol) did not change levels of CGRP or PGE_2
- Sympathetic stimulation (Norepinephrine) show increased PGE_2 and reduced serotonin

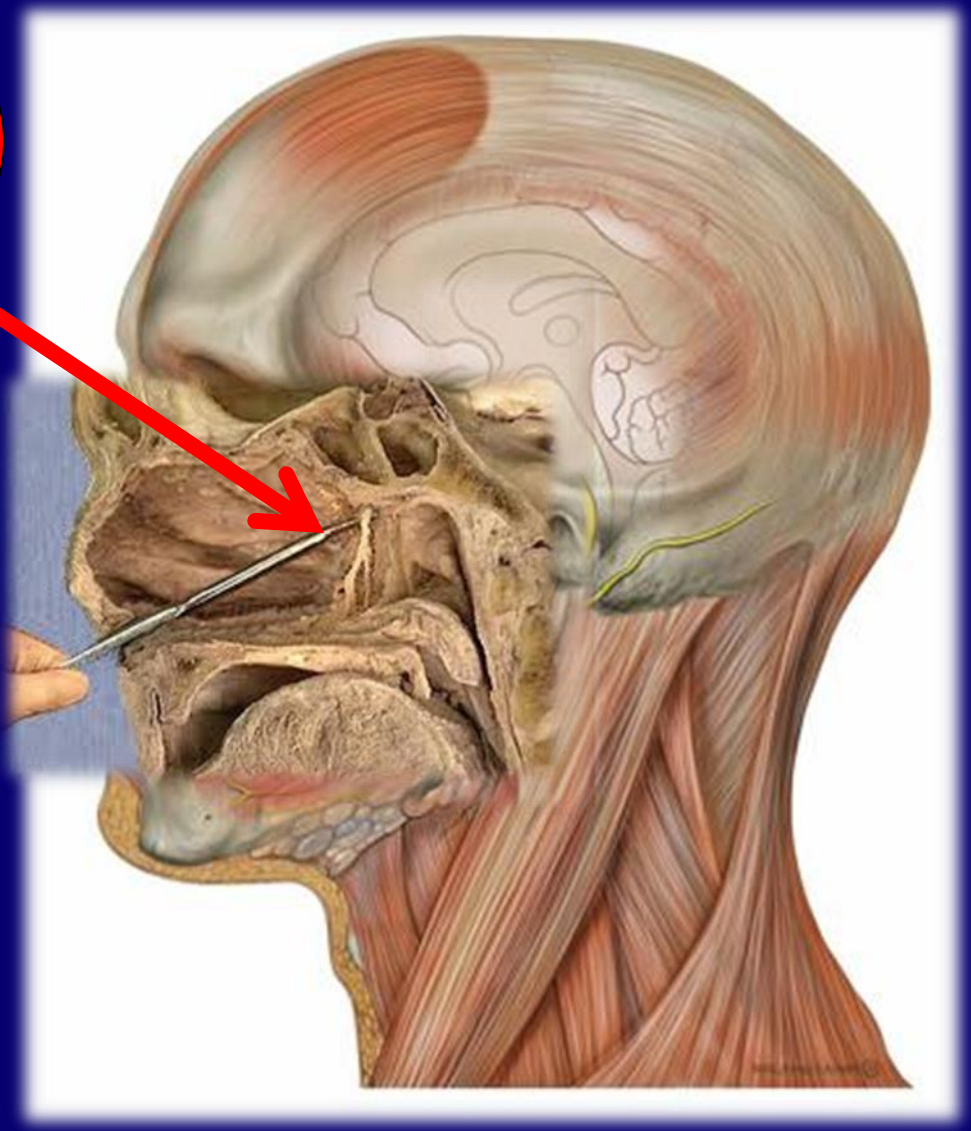


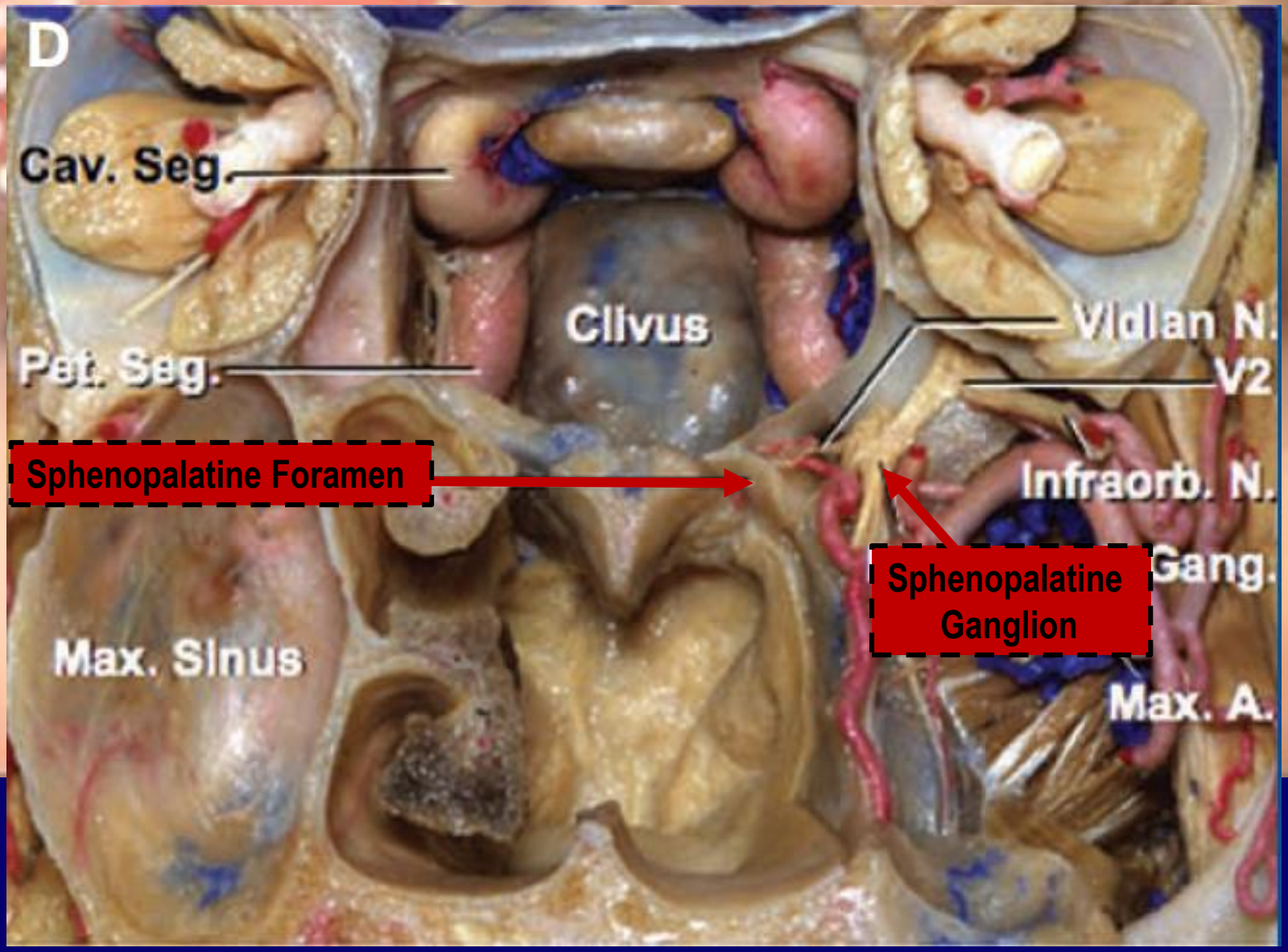
Ebersberger A et al. Effect of sympathetic and parasympathetic mediators on the release of calcitonin gene-related peptide and prostaglandin E2 for rat dura mater in vitro. Cephalalgia. 2006: 26:282-289.

Trigeminal Nucleas Caudalis



Sphenopalatine Ganglion




D
Cav. Seg.
Clivus
Vidian N.
Pet. Seg.
V2
Sphenopalatine Foramen
Infraorb. N.
Sphenopalatine Ganglion
Gang.
Max. Sinus
Max. A.

What role does the Sphenopalatine Ganglion have in migraine?

- Sympathetic activity
  - Sympathetic fibers course through the SPG on way to cranial structures
- Parasympathetic synapse
  - Fibers from the brainstem (superior salvitory nucleaus) synapse in the SPG, then travel to cranial structures
- Trigeminal nociception
- All the above

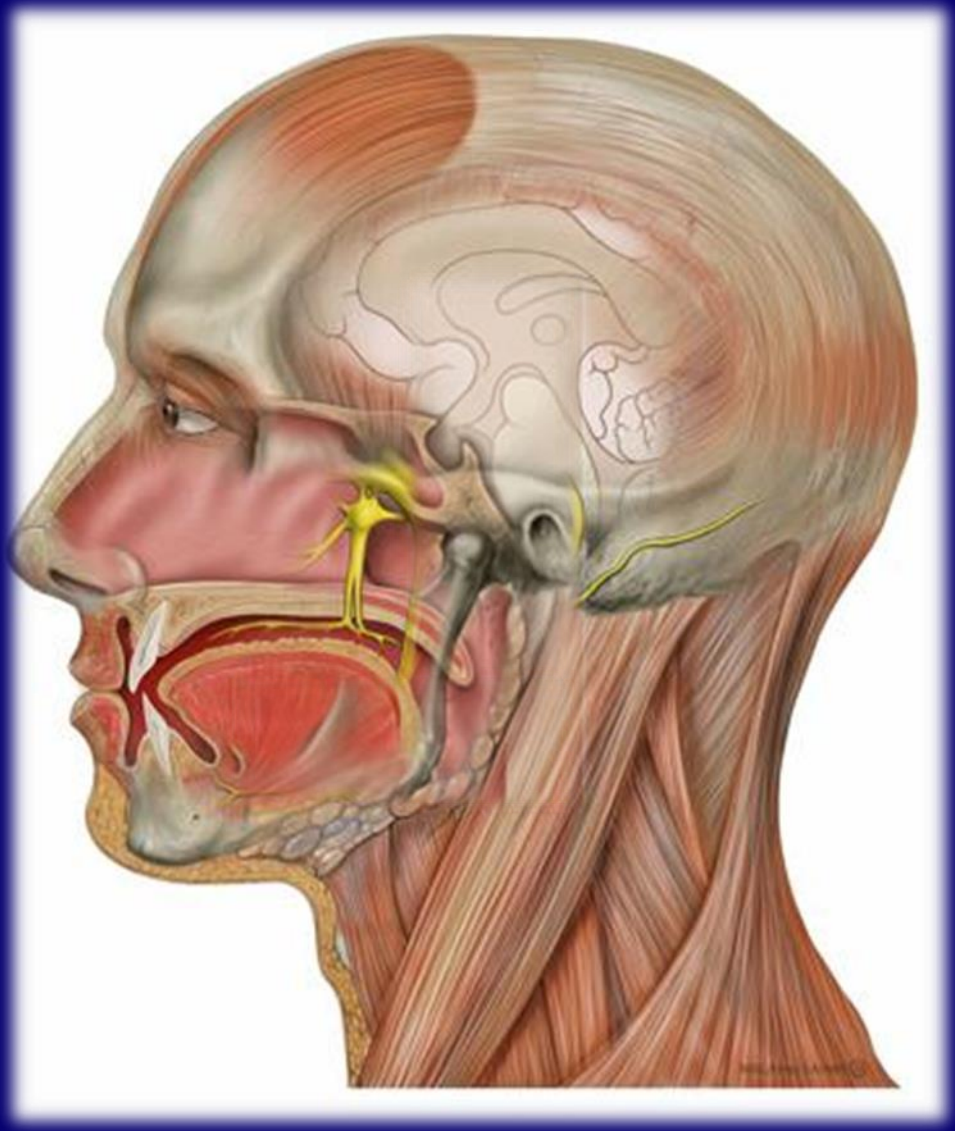
Sphenopalatine Ganglia Role in Head Pain

- Trigeminal nociception
  - Part of Maxillary nerve (V2)
  - Branches to the Ophthalmic nerve (V1)
  - Middle Meningeal nerve
    - Innervates periorbital and parietal dura

SPG has nociceptive activity

5ht1D receptors

CGRP receptors

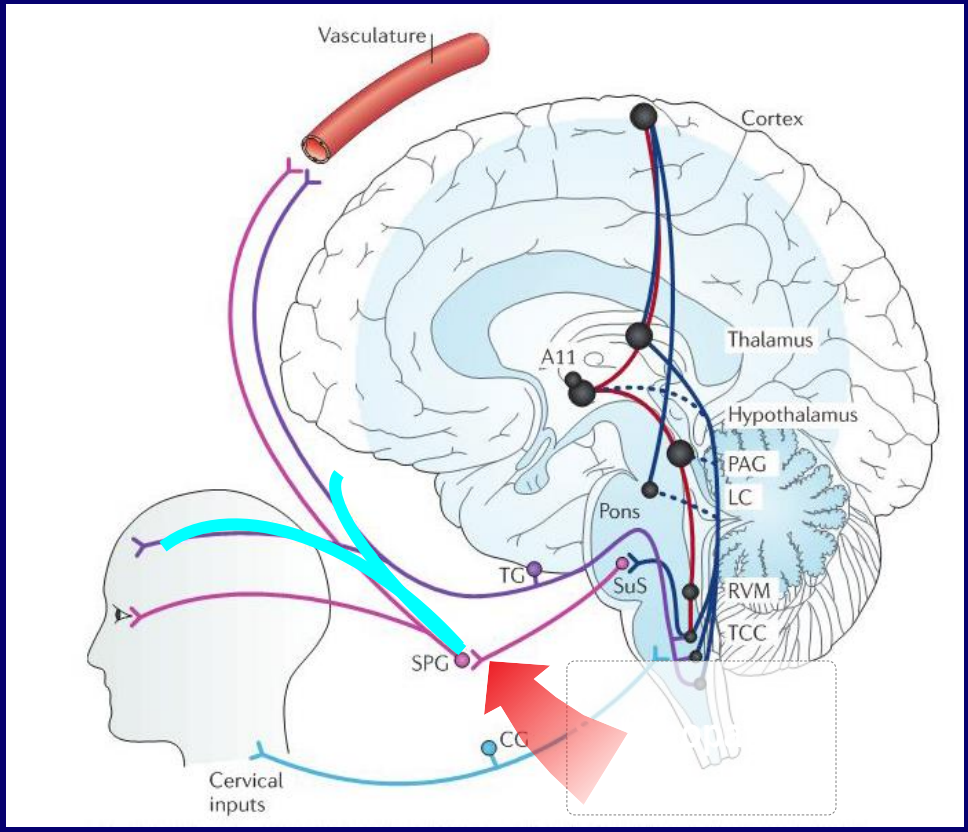


(Csati et al., 2012)
(Ooman et al., 2011)
(Ivanusic et al., 2011)

SPG Circuit - Role in Migraine

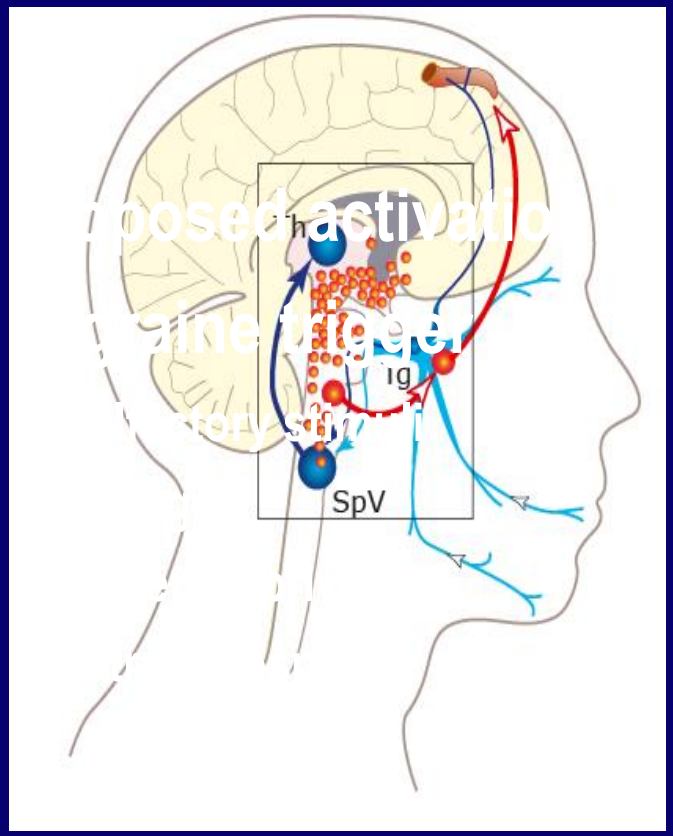
Autonomic Nervous System

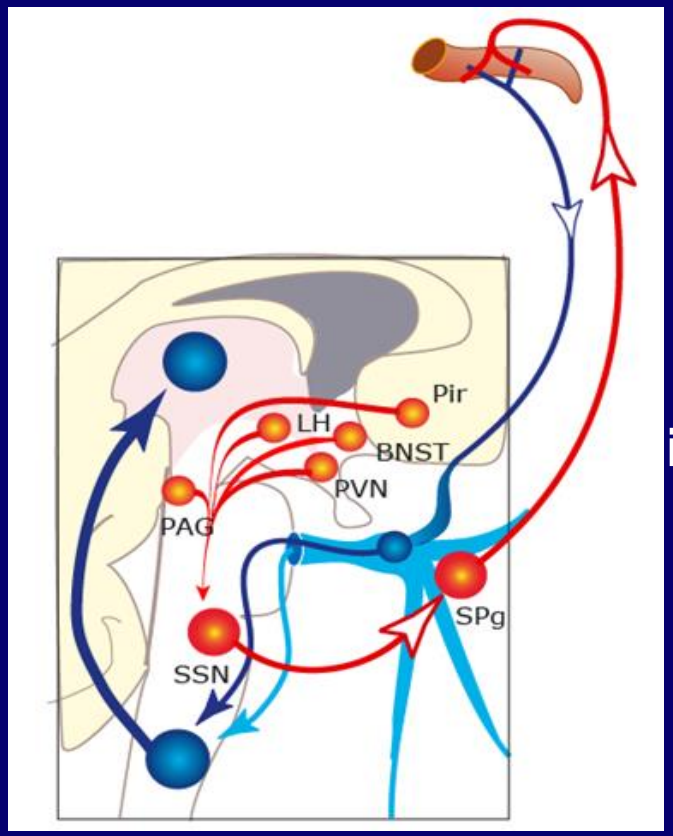
- Parasympathetic Component
  - Meningeal Vasodilation
  - Neurogenic Inflammation
  - Clinical signs
    - Facial fullness
    - Lacrimation
    - Nasal edema
- Sympathetic Component
  - Cerebral vasoconstriction



Akerman S, Holland PR, Goadsby PJ. Diencephalic and Brainstem Mechanisms in Migraine. Nat Rev Neurosci. 2011; 12:570-84..

Parasympathetic Pathway of Meningeal Nociceptors

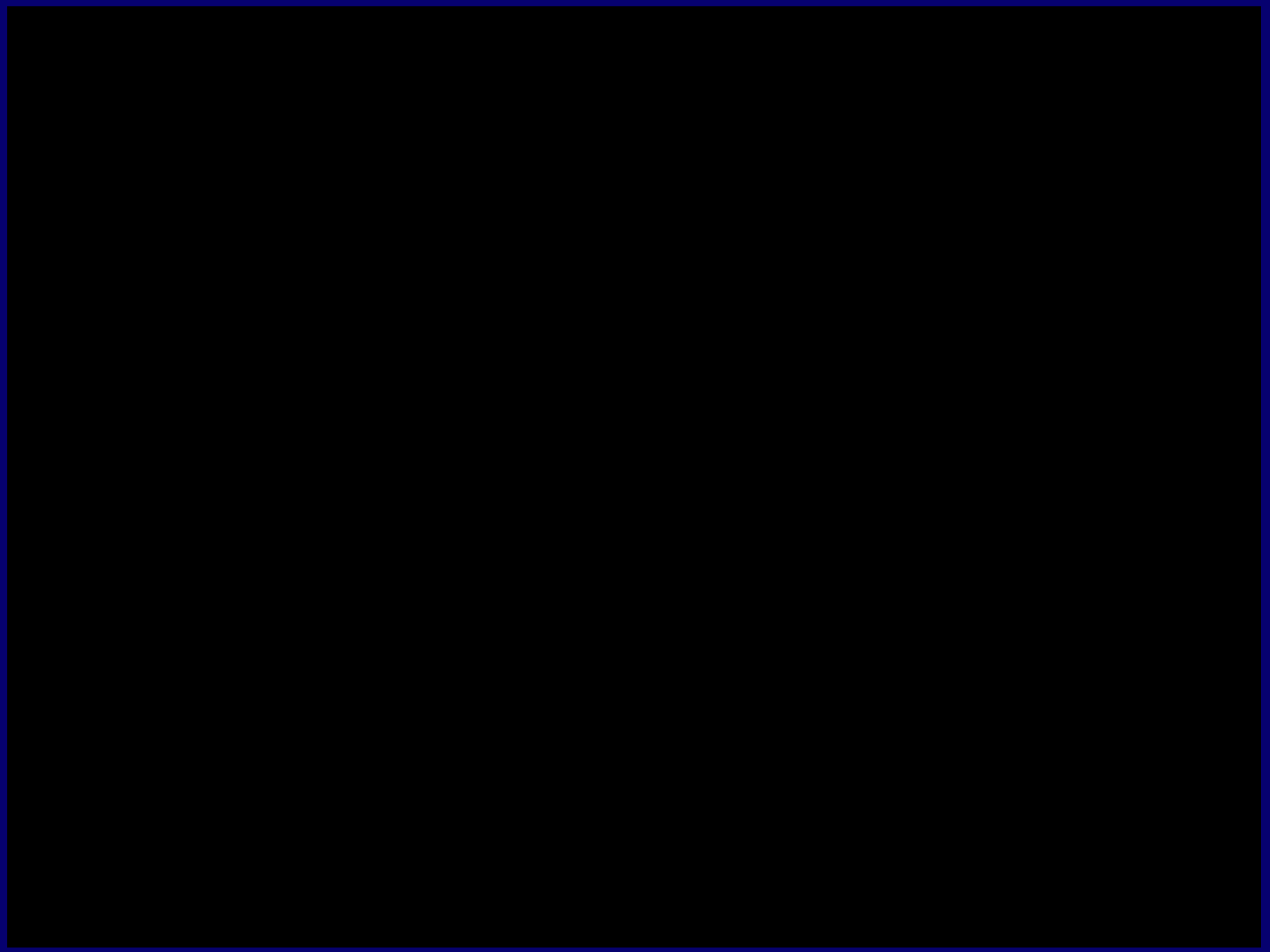




Burstein R, Jakubowski M. *J Comp Neurol*. 2005;493(1):9-14

How you help makes a lasting impression

Exercise is a key treatment



Medication – Heart Rate Control

- Beta Blockers
  - Propranolol
  - Nebivolol
  - Labetolol
  - Carvedilol
- Pyridostigmine (Mestinon)
  - Increases acetylcholine in peripheral autonomic nervous system
- Ivabradine
  - Slows HR through ↓ SA node activity

Medication – Blood Pressure Support

- Fludrocortisone
  - Systemic corticosteroid
  - Volume expander
  - Potassium monitoring with each dose increase and q 3-6 month intervals
- Midodrine
  - Inotrope / pressor
  - Stimulates vasoconstriction
  - Avoid lying flat for 4 hours after each dose (supine hypertension)

Other Medication

- Stimulants
  - Modafinil, methylphenidate, amphetamine/dextroamphetamine
  - Considered for fatigue / “brain fog”
- SSRI
  - Sertraline, fluoxetine
  - Assists with autonomic regulation

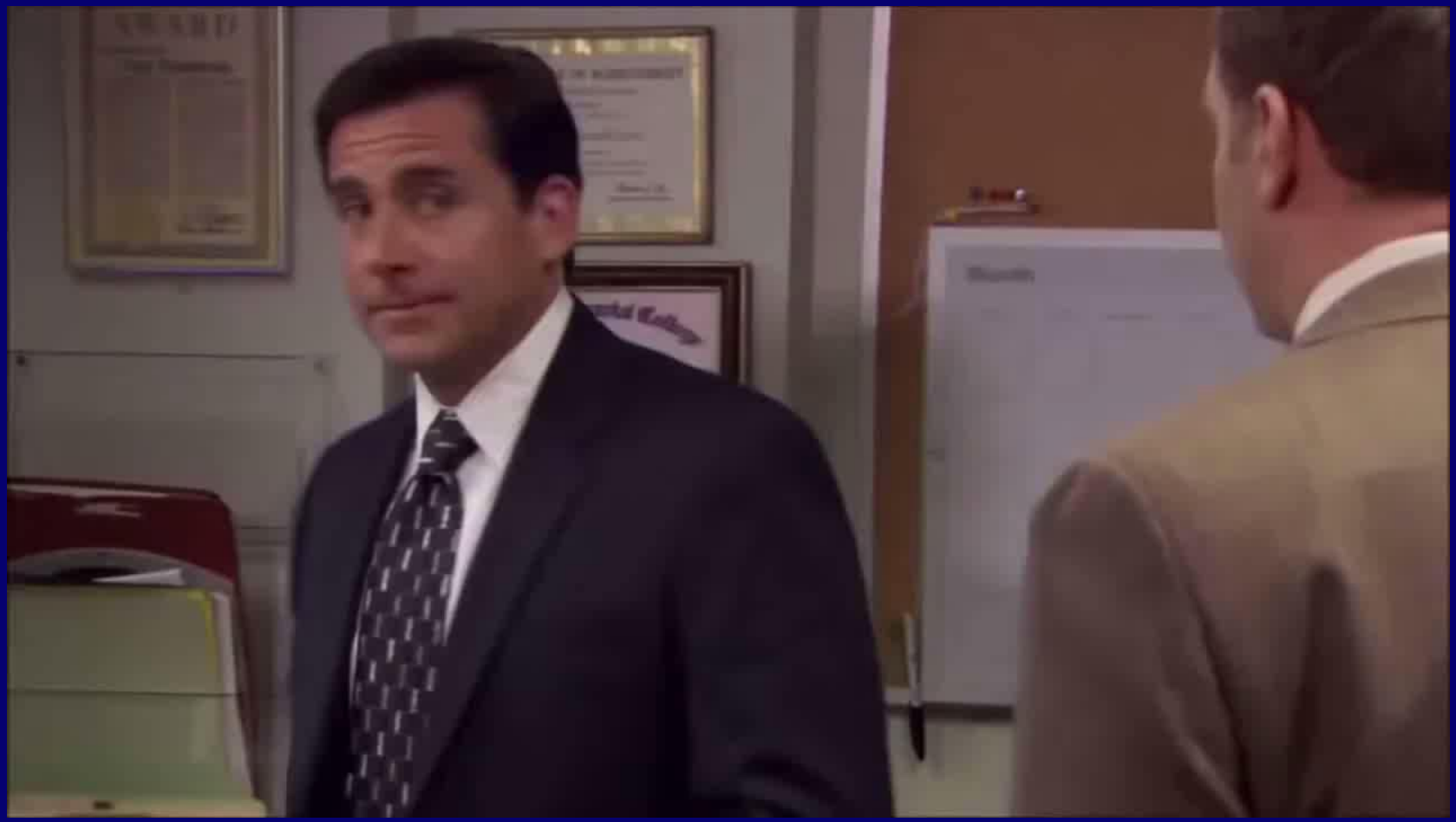
Intermittent IV Saline as maintenance for POTS

- 57 subjects
- Average medications prior to study – 3.6
- 1.5 L every 11 days (on average)

"Intermittent IV infusions of saline dramatically reduce symptoms and improve quality of life in patients with POTS"

Ruzieh M, Baugh A, Dasa O, Parker RL, Perrault JT, Renno A, Karabin BL, Grubb B. Effects of intermittent intravenous saline infusions in patients with medication-refractory postural tachycardia syndrome. J Interv Card Electrophysiol. 2017 Apr;48(3):255-260.

I will just leave the treatment of POTS to the experts



Cranial Autonomic Parasympathetic Symptoms in Chronic Migraine

82% reported at least one CAPS

- Lacrimation 49%
- Conjunctival inj. 44%
- Eyelid edema 39%
- Ear fullness 30%
- Nasal congestion 20%

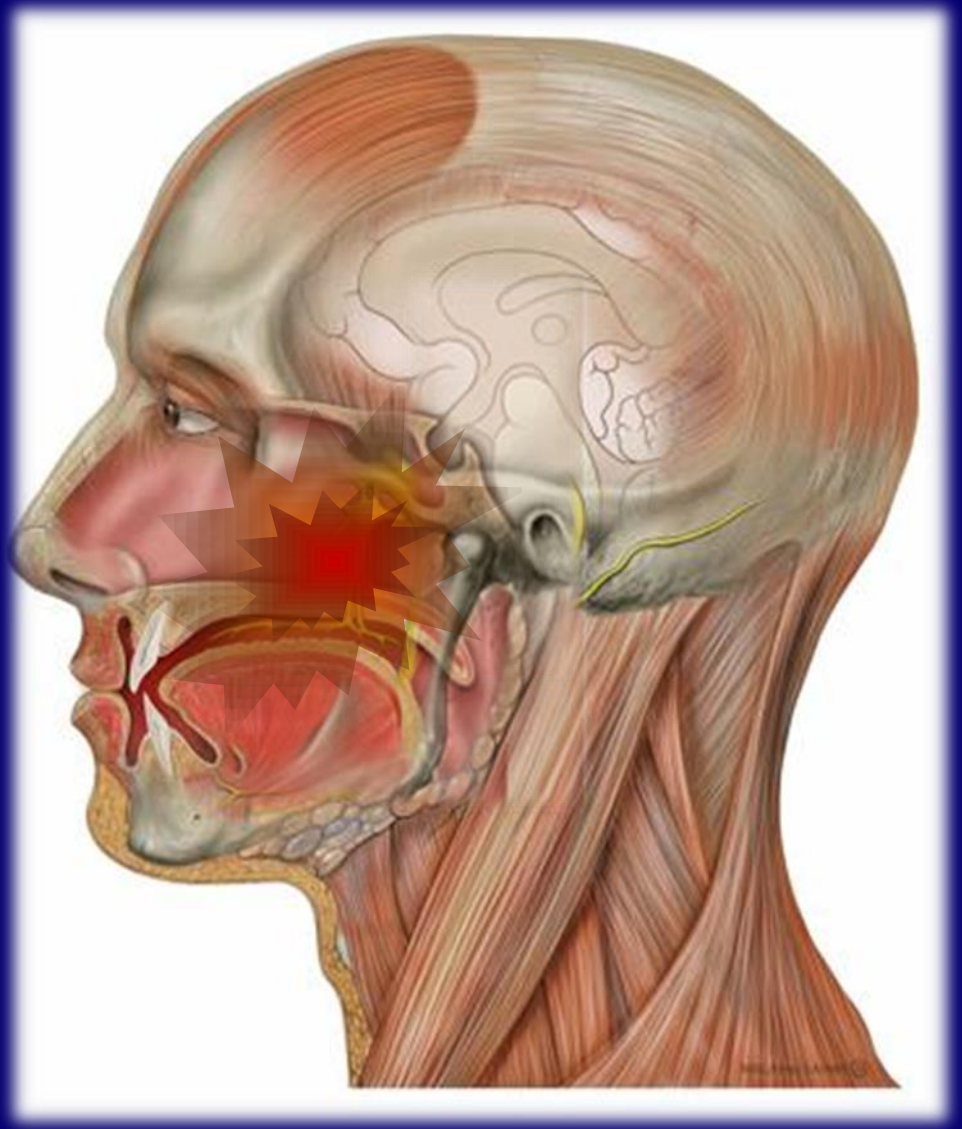
- Eyelid ptosis 42%

(Cranial Sympathetic Autonomic Symptom)

Riesco N, Perez-Alvarez AI, Verano L, Garcia-Cabo C, Martinez-Ramos J, Sanchez-Lozano P, Cernuda-Morollon E, Pascual J. Prevalence of cranial autonomic parasympathetic symptoms in chronic migraine: Usefulness of a new scale. Cephalalgia. 2015.

SPG Circuit - Treatment

- Local anesthetic blockade may terminate Migraine or Cluster
- Reduced pain signals from dura
  - middle meningeal nerve
- Autonomic nervous system effects
  - ↓ Neurogenic inflammation
  - ↓ Meningeal vasodilation



Research Submissions

2003 Wolff Award: Possible Parasympathetic Contributions to Peripheral and Central Sensitization During Migraine

David Yarnitsky, MD; Itay Goor-Aryeh, MD; Zahid H. Bajwa, MD; Bernard I. Ransil, PhD, MD; F. Michael Cutrer, MD; Anna Sottile, MD; Rami Burstein, PhD

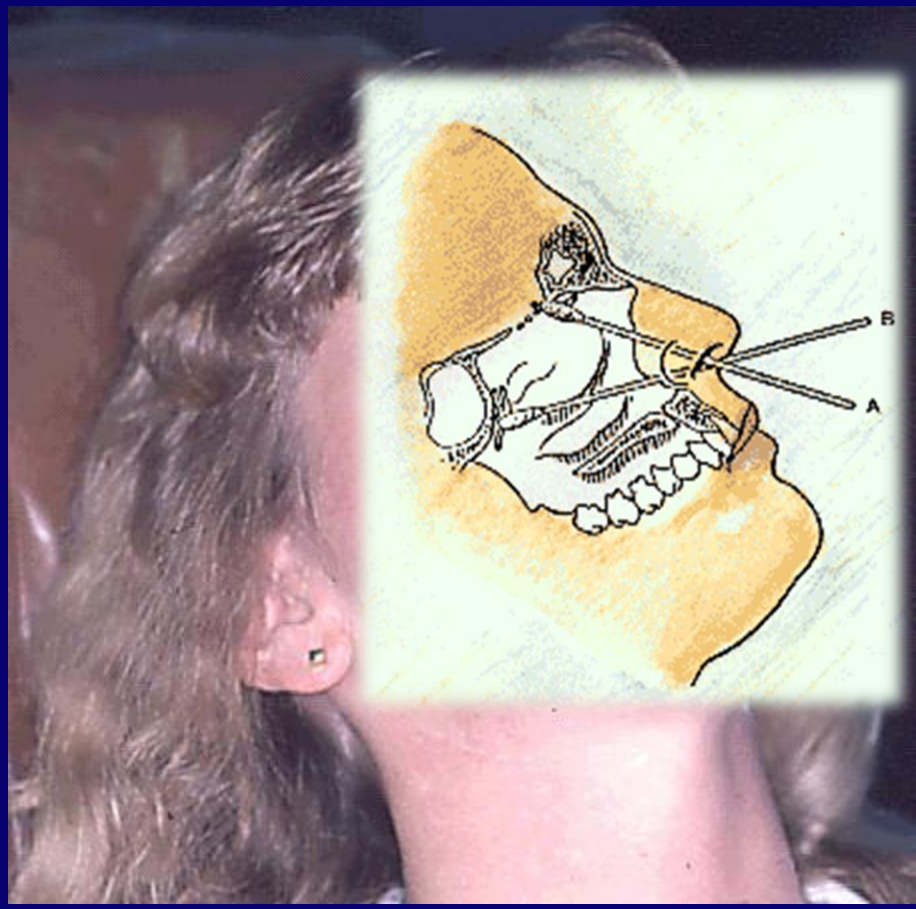
Their mean pain score was 7.5 of 10 (standard deviation, 1.4) during untreated migraine and 3.5 of 10 (standard deviation, 2.4) after the nasal lidocaine-induced sphenopalatine ganglion block ($P < .0001$).

Conclusion.—These findings suggest that cranial parasympathetic outflow contributes to migraine pain by activating or sensitizing (or both) intracranial nociceptors, and that these events induce parasympathetically independent allodynia by sensitizing the central nociceptive neurons in the spinal trigeminal nucleus.

Yarnitsky D, Goor-Aryeh I, Bajwa ZH, Ransil BI, Cutrer FM, Sottile A, Burstein R. 2003 Wolff Award: Possible parasympathetic contributions to peripheral and central sensitization during migraine. *Headache* 2003;43:704-714

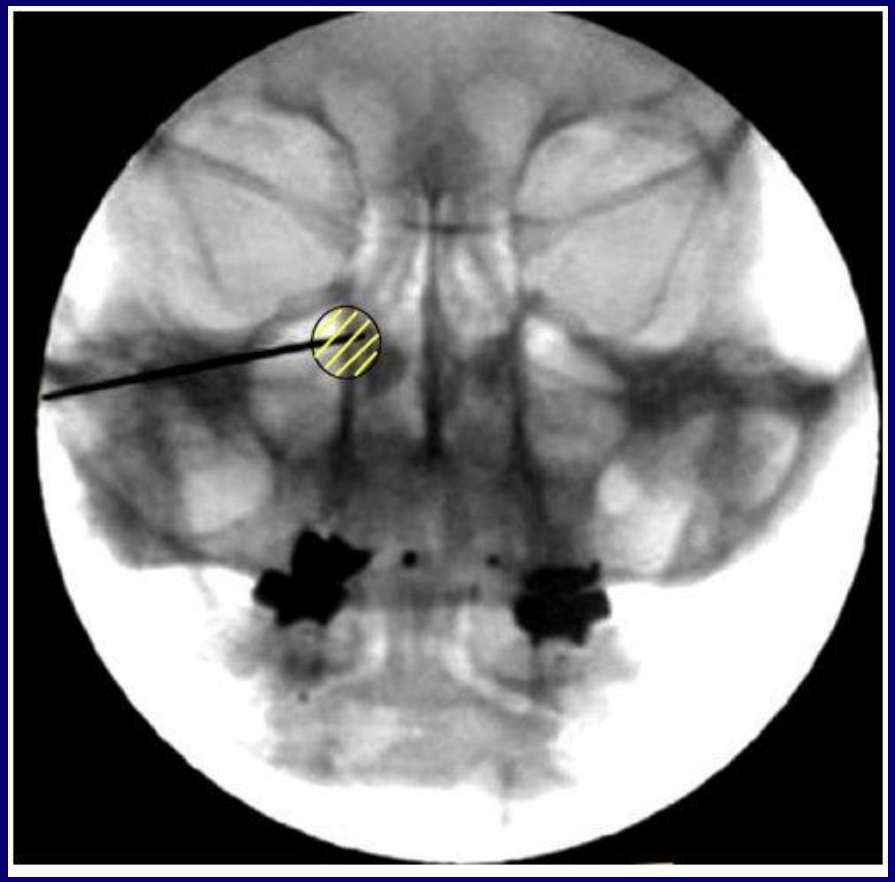
Sphenopalatine Ganglion Block
Intranasal Rigid Applicator (Q-tip)

- Topical anesthetic near SPG
- Minimally invasive
- Duration - 1 day to 6 weeks
- Nasal anatomy does not permit easy placement
  - Turbinates block access
  - Lateral location of sphenopalatine foramen



Sphenopalatine Ganglion Block Infra-Zygomatic Approach

- Long needle advanced to pterygoid plate
- Injection of medication to the pterygopalatine fossa
- Relative poor tolerability
  - Risk of hemorrhage
  - Needle trauma
  - Pain



SPG Block - Clinical Autonomic Effects

Physiologic manifestations of “blocking” components of cranial autonomic circuit:

- Cutaneous temperature changes
  - Typically ipsilateral cheek ↑ 3-5° F
- Tearing
  - Lateral canthus of ipsilateral eye
    Occurs within seconds
- Facial erythema

Summary

- POTS is very common
- Increased heart rate triggered by positional changes are the cardinal feature
- Treatment options for POTS may be very effective
  - Exercise
  - Beta Blocker
  - Stimulant