# Pathophysiology of trigeminal autonomic cephalalgias

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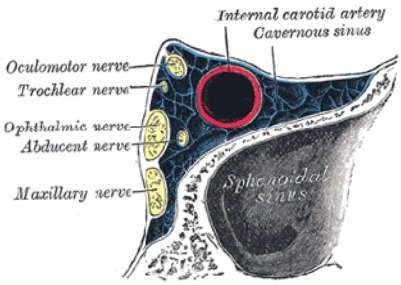
## The main features of the TACs:

1. Trigeminal distribution of the pain
2. Ipsilateral cranial autonomic features
3. An (circadian) episodic pattern of attacks

## A pathological focus on the cavernous sinus




- Cavernous sinus is the only peripheral anatomical location where a single pathology could involve trigeminal C-fibers and sympathetic fibers.

- Angiography during CH attack: localized narrowing of ACI distal to the carotid canal

*Ekbom and Greitz 1970*

- Hypothesis of intracavernous or systemic inflammation was not confirmed.

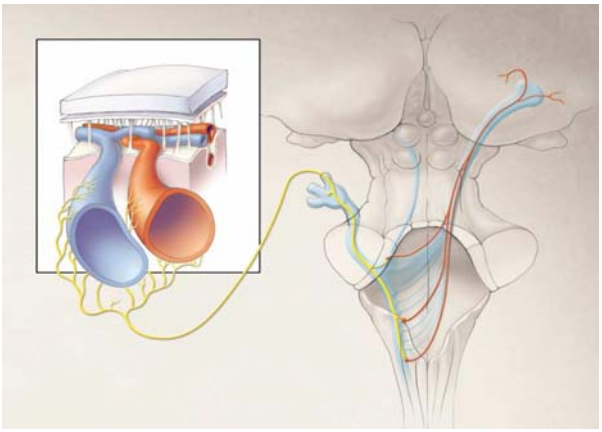
*Schuh-Hofer et al. 2006*

## Vascular changes in the cavernous sinus

- Migraine
- Experimental pain
- Cluster headache

The vascular change is driven by the trigeminal-autonomic reflex , and thus is a marker of brain activation, not a cause of the syndrome.

## Trigeminovascular system



- Afferent fibers from cranial vessels and dura mater
- Bipolar cell bodies in trigeminal ganglion
- Central projections to the caudal brainstem or high cervical cord

## Trigeminovascular system: responsible for pain

- Powerful vasodilator neuropeptides of TG:
  - calcitonin gene-related peptide - CGRP
  - substance P
  - neurokinin A

- Concentrations of CGRP are elevated during:
  - spontaneous CH attacks
  - glyceryl-trinitrate-provoked CH attacks
  - migraine attacks

*Goadsby and Edvinsson 1994, Fanciullacci et al. 1995*

- CGRP is the marker of the activation of trigeminovascular system.

## Ophthalmic division of the trigeminal nerve

- Painful stimuli administered into the skin

innervated by the V1: dilation of the ACI

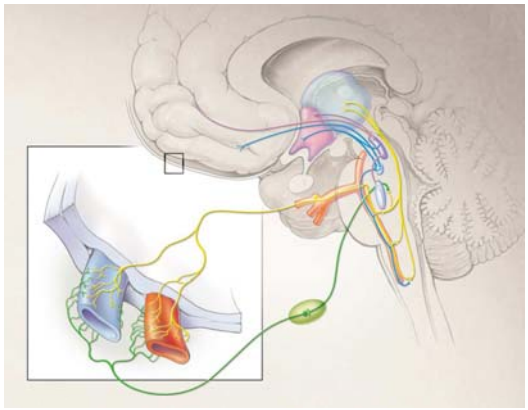
*May et al. 1998*

innervated by the V3, or into the leg: no response in the ipsilateral ACI, despite the experience of pain.

*Pareja et al. 2001*

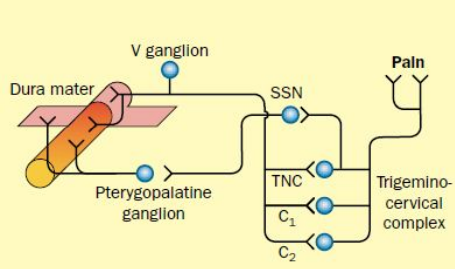
- The ophthalmic division of trigeminal nerve produces reflex activation of the cranial parasympathetic outflow.

## Trigeminal-autonomic reflex



- Afferent limb is the ophthalmic division of the trigeminal nerve
- Cranial parasympathetic cells are in the SSN in the pons
- Efferent limb is facial/greater superficial petrosal nerve through the pterygopalatine ganglion.

## Trigeminal-autonomic reflex




Concomitantly with the pain:

- The reflex activation of the parasympathetic outflow
- Vasoactive intestinal polypeptide VIP is the marker of this activation.

## Activation of the cranial parasympathetic outflow

- Leads to:
  lacrimation,
  reddening of the eye
  nasal congestion…

- The cranial sympathetic fibers from the superior cervical ganglion destined to innervate the eye, are compromised by carotid dilation or perivascular swelling as they traverse the carotid canal.

The result is a partial Horner's syndrome.

## The fundamental physiological facts relevant to primary headache syndromes.

- Ophthalmic division of trigeminal nerve will produce cranial parasympathetic autonomic activation.

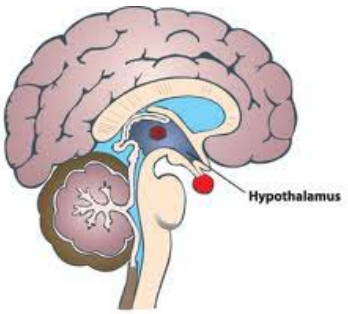
  migraine with cranial autonomic features 27-73%

  *Barbanti et al. 2002, Gupta and Bhatia 2007, Obermann et al. 2007, Lai et al. 2009*

- CH attack is a process involving trigeminal-autonomic activation.

  *Goadsby 2002*

## A role of hypothalamus in CH




- Circadian timing
- Neuroendrocrine changes
- PET studies
- Hypothalamic DBS

## Human clock system

- Two significant peaks of CH, in July and January.

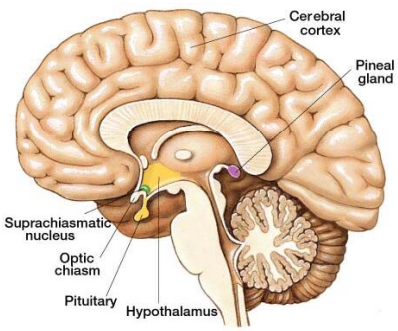
*Kudrow 1987*

- The general rise in frequency during the year was twice interrupted around the days when the clocks were put forward or back in spring and autumn.

- About 50% of attacks of CH occur at night.

*Russell 1981*

## Suprachiasmatic nucleus and melatonin




Melatonin:

- produced by the pineal gland
- the rate of secretion has a strong circadian rhythm

*Moore 1997*

- retino-hypothalamic pathway (suprachiasmatic nucleus)

*Hofman et al. 1996*

- suprachiasmatic nucleus regulates the rate of melatonin secretion

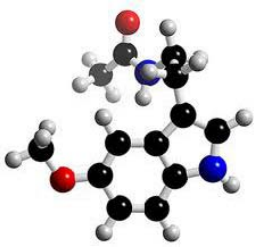
## Melatonin and CH

- The characteristic nocturnal peak of melatonin secretion is blunted during the active phase of cluster headache, and the excretion of its metabolite is abnormal.

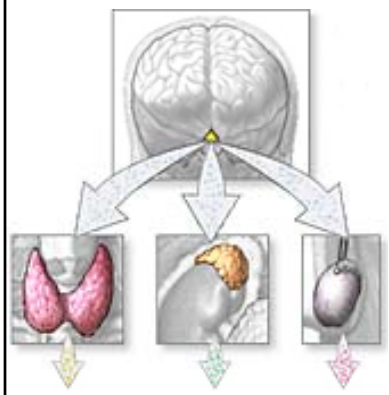
*Waldenlind et al. 1987, Leone et al. 1998*

- Melatonin in the preventive treatment of CH

*Leone et al. 1996, Peres and Rozen 2001*



## Other neuroendrocrine changes in CH



- Testosterone ↓
- Oestradiol
- Cortisol ↑, ø phase shift
- Prolactin ø circadian rhythm, ↑
- Growth hormone: bimodal peak
- response to TRH ↓

*Kudrow 1977, Nelson 1978, Romiti et al. 1983, Waldenlind and Gustafsson 1987, Chazot et al. 1984, Polleri et al. 1982, Leone et al. 1990*

## PET studies

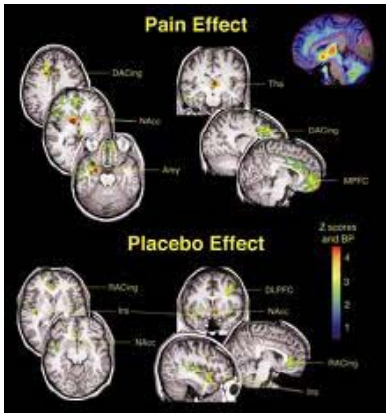
- Activated areas:

  areas generally associated with pain

  an area that seems specific to CH

  areas associated with vascular structures

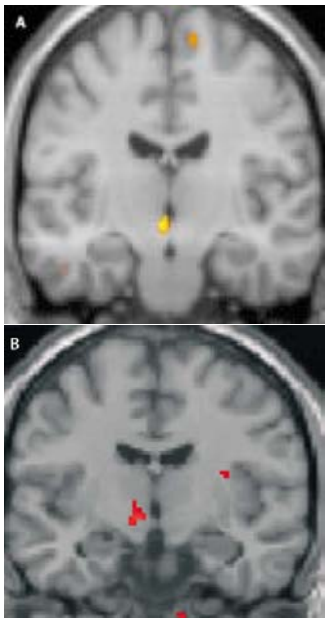
## PET studies: pain areas




- Anterior cingulate
  affective response
- Frontal cortex and insulae
- Ventroposterior thalamus
  contralateral
- Ipsilateral basal ganglia
  relate to movement
  the wish to move
  inhibition of movements

*Derbyshire et al. 1997, Chudler and Dong 1995*

## PET studies

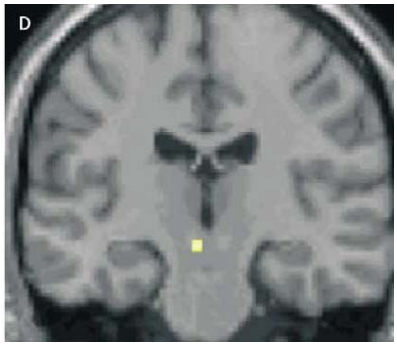



Hypothalamic gray matter

- ipsilateral to the side of pain
- noted during CH attack
  nitroglycerin-induced
  spontaneous
- not activated between attacks
- different from areas activated in migraine (midbrain, pons)

*May et al. 1998,*
*Sprenger et al. 2004*

## MRI: voxel-based morphometry




- The similar region has increased volume (increased neuronal density) of grey matter when CH patients where compared with controls.

*May et al. 1999*

## Neuroimaging in related syndromes

- The activation in the hypothalamic grey matter was found in 4 patients with spontaneous SUNCT

*May et al. 1999, Sprenger et al. 2005, Cohen et al. 2004*

- and in a patient suffering from atypical TAC.

*Sprenger et al. 2004*

- The underlying cause of TAC might be similar, and the variation in duration and frequency might be generally dependent on a different disorder of the hypothalamic neurons or a different involvement of the trigeminovascular system.

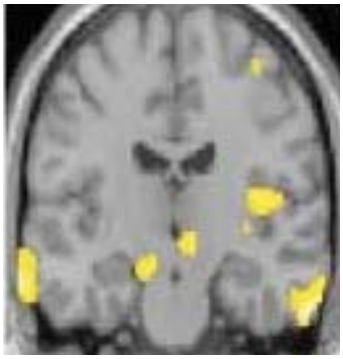
## Hemicrania continua

- A strictly unilateral, continuous headache of moderate intensity, with superimposed exacerbations of severe intensity that are then accompanied by autonomic features and migrainous symptoms.

*Matharu et al. 2003, ICHD-II*

- Clinical presentation:
overlap between TACs and migraine

## Hemicrania continua



*PET, n = 7*
*Matharu et al. 2004*

- Contralateral posterior hypothalamus
- Ipsilateral dorsal rostral pons
- Ipsilateral ventrolateral midbrain, the red nucleus, the substantia nigra bilateral pontomedullary junction.

Overlap with TACs and migraine

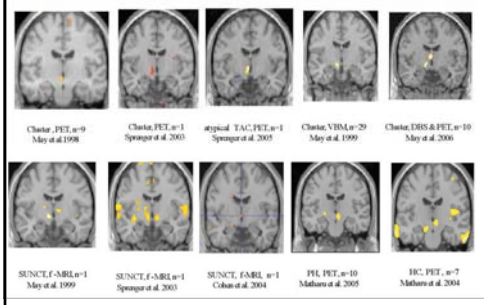
## Hypothalamic activation

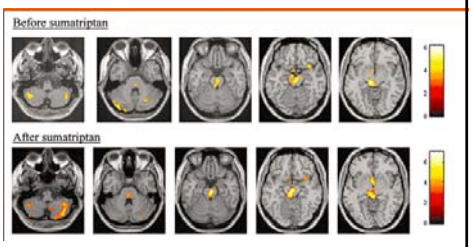
- Ipsilateral to the pain in CH
- Ipsilateral, contralateral, bilateral or absent in SUNCT
- Contralateral in PH
- Contralateral in HC
- Ipsilateral in trigeminal neuralgia
- Bilateral in migraine
- acute heat pain, response to pain

- There are different stereotactic coordinates of activated hypothalamic areas.

- NOT seen during experimentally induced pain by capsaicin

# Functional imaging data



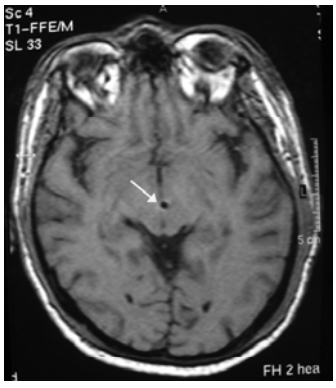



*Weiller et al.2005*

• Primary headache syndromes can be distinguished on a functional neuroanatomical basis by areas of activation specific to the clinical presentation.

*May 2005*

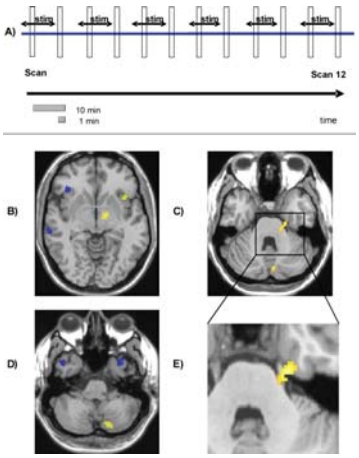
# Hypothalamic deep brain stimulation




- Intractable chronic CH
- 2000: the first DBS implant
- Ten years after (58pts):
notable clinical improvement 60%
complete control of attacks 30%

*Leone et al. 2001, Leone et al. 2010*

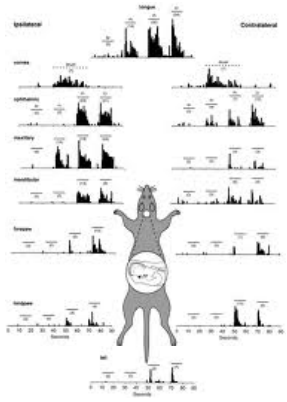
## PET study in CH patients with DBS




*May et al. 2006*

- Hypothalamic stimulation provoked activation in the ipsilateral trigeminal system.
- A functional connection in humans

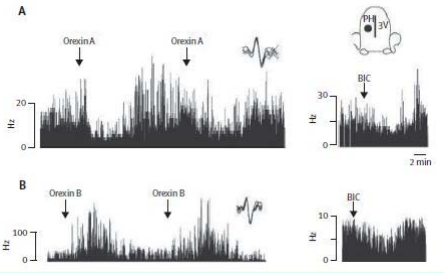
## Trigeminohypothalamic tract



- A direct connection between the trigeminal nucleus caudalis and the posterior hypothalamus
- Sensory information from cranial skin, intracranial vessels and meninges reaches the hypothalamus via this tract.

*Malick et al. 2000*

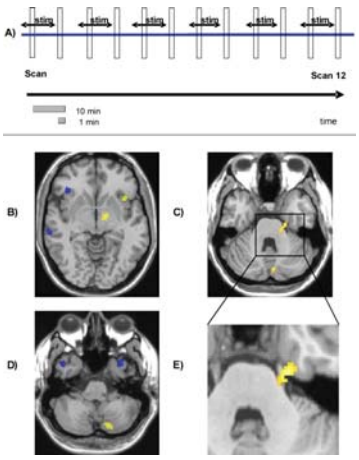
# Posterior hypothalamus and TCN




- Orexin B injection into the PH increases spontaneous TCN activity and heightens TCN responses to dural stimulation and noxious thermal stimulation of the face.
- Orexin A and the GABA-A receptor antagonist bicuculline exert the opposite effects.
- The posterior hypothalamus is a physiological modulator of TCN activity.

*Bartsch et al. 2004*

# PET study in CH patients with DBS




*May et al. 2006*

- Activation of the trigeminal system was NOT followed by CH attack.
- The trigeminal system activation is necessary for a CH attack to occur, but it is not sufficient on its own to evoke the attack.

## How DBS works?

The first hypothesis:

High frequency hypothalamic stimulation would inhibit hypothalamic hyperactivity.

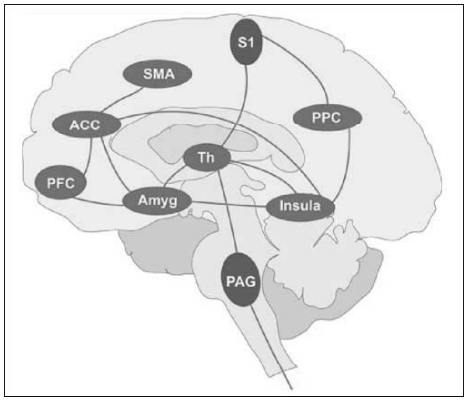
Against this hypothesis:

- the latency of chronic stimulation (days or weeks)
- inefficacy of acute stimulation

136 CH attacks in 16 pts.
23% pts, 16% of attacks

*Leone et al. 2006*

## DBS interfere with pain matrix




- Hypothalamic stimulation: ipsilateral trigeminal system and pain matrix

thalamus, somatosensory cortex, precuneus, anterior cingulate cortex
the middle temporal gyrus, posterior cingulate cortex and insula

*May et al. 2006*

## Hypothalamic DBS

- Modulation of the antinociceptive system

  modulates thermal sensitivity and increase pain thresholds

  *Jurgens et al. 2009*

- It could act by gradually restoring normal function and metabolism in hypometabolic areas in CH patients, eventually restoring deficient topdown modulation.

*Sprenger et al. 2007*

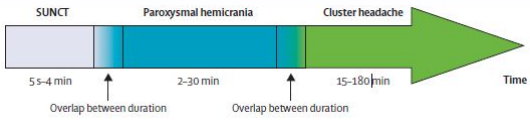
## Hypothalamus

- Plays a major role in terminating rather than triggering attacks.

*Leone and Bussone 2009*

- Regulating the duration of an attack, and the extent to which it does so would give rise to the different phenotypic expressions of the TACs which are principally distinguished by attack duration.

Leone et al. 2010



## Hypothalamic DBS for other TACs

- Severe drug-resistant SUNCT was relieved by DBS.

*Leone et al. 2005, Lyons et al. 2008*

- A patient with chronic drug-resistant PH has obtained long-term relief with hypothalamic DBS.

*Dafer, personal communication*

## Genetics related to hypothalamus

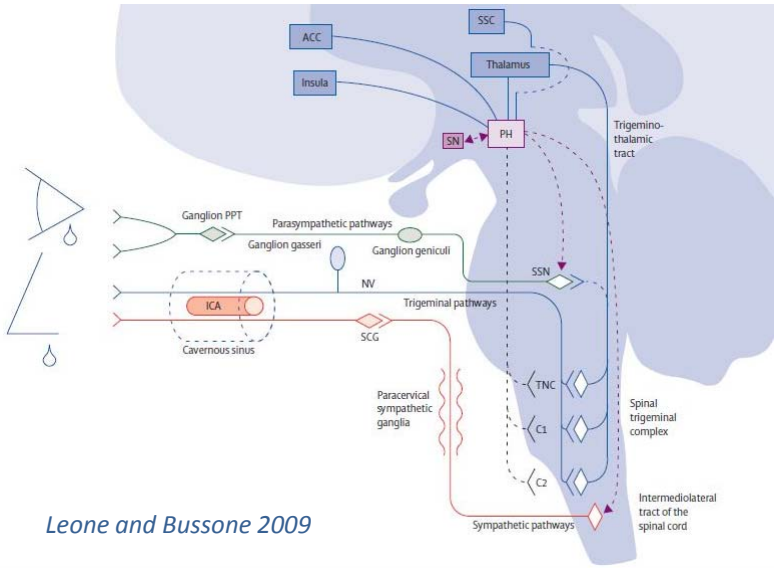
- The increased familial risk

- Hypocretin (orexin) receptor 2 (*HCRTR2)*
the ability of this gene to modulate posterior hypothalamic neurons

*Rainero et al. 2004, Schurks et al. 2006, Baumber et al. 2006*

- Despite the strong clinical indications of a genetic component in CH, no specific genes have yet been clearly associated with this disorder.

# From cavernous sinus to pain matrix




*Leone and Bussone 2009*