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Headache and pain

Josef Bednařík

Department of Neurology, University Hospital Brno and Faculty of Medicine, Masaryk University Brno

FAKULTNÍ NEMOCNICE BRNO

NEUROLOGICKÁ KLINIKA LF MU a FN BRNO

MUNI FACULTY OF MEDICINE

PHYSIOLOGICAL MEANING OF PAIN

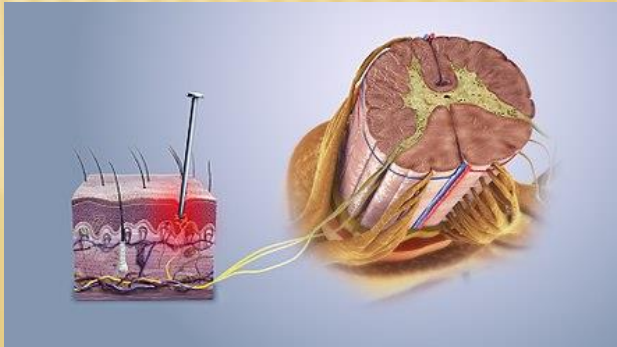
- Pain is said to be one of nature´s **earliest** symptoms of morbidity.
- Pain is one of **the most frequent** symptom; only a few maladies do not have painful phases and in most of them pain is a characteristic without which diagnosis must always be in doubt.
- At the very beginning, pain serves as a **signal** while in the chronic stage it becomes **disease itself**.

ACUTE AND CHRONIC PAIN

- **Acute pain**: it lasts several days or weeks and is usually well localised. It is a sign of tissue involvement caused by a trauma or disease. In higher intensity it serves as a great psychic burden to the patient. Therapy directed against the original cause together with analgesic therapy leads usually to the diminution or replacement of acute pain.
- **Chronic pain**: the relation between the cause and the pain is not usually seen; it lasts longer (more than 3 or 6 months), is unproportional to the evoked stimulus, badly localised. Social and psychological factors play important roles. It has no signal meaning but becomes the disease itself and the therapy is directed exclusively against the pain.

NOCICEPTIVE AND NEUROPATHIC PAIN

- **Nociceptive pain**: pain arises from actual or thereatened damage to non-neural tissue. Nervous system function is normal. The pain tends to be episodic and poorly localized. It is usually time limited, meaning when the tissue damage heals, the pain typically resolves. It tends to respond well to treatment with opioids. Example is inflammation or trauma.



NOCICEPTIVE AND NEUROPATHIC PAIN

- **Neuropathic pain**: it is the result of lesion or disease of the peripheral or central nervous system. The pain may persist for months or years beyond the apparent healing of any damaged tissues. In this setting, pain signals no longer represent an alarm about ongoing or impending injury, instead the alarm system itself is malfunctioning.
- Neuropathic pain is frequently chronic, and tends to have a less robust response to treatment with opioids, but may respond well to other drugs such as anti-seizure and antidepressant medications. Usually, neuropathic problems are not fully reversible, but partial improvement is often possible with proper treatment.

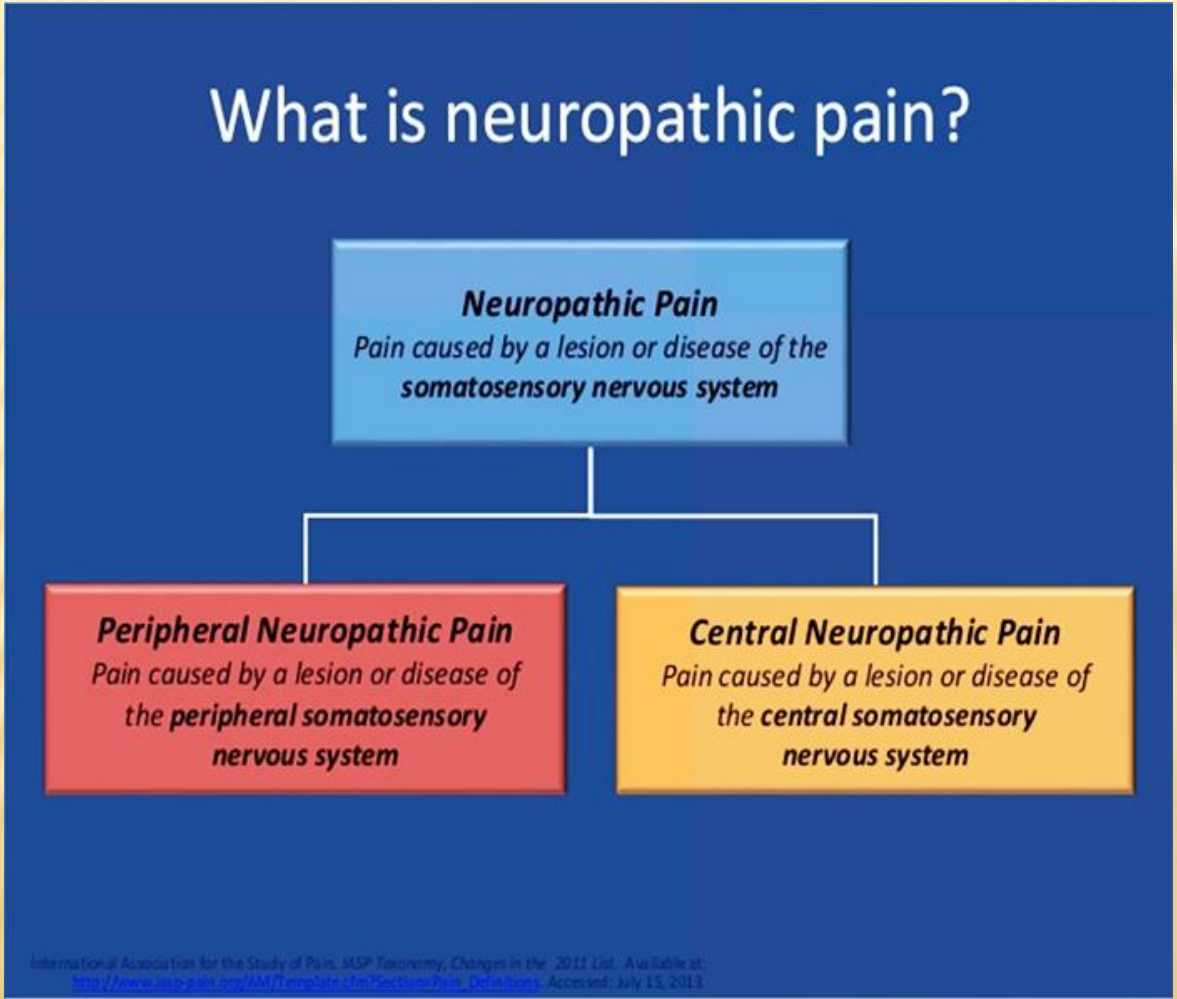
DEFINITION AND DIAGNOSIS OF NEUROPATHIC PAIN

Definition (IASP 2012):

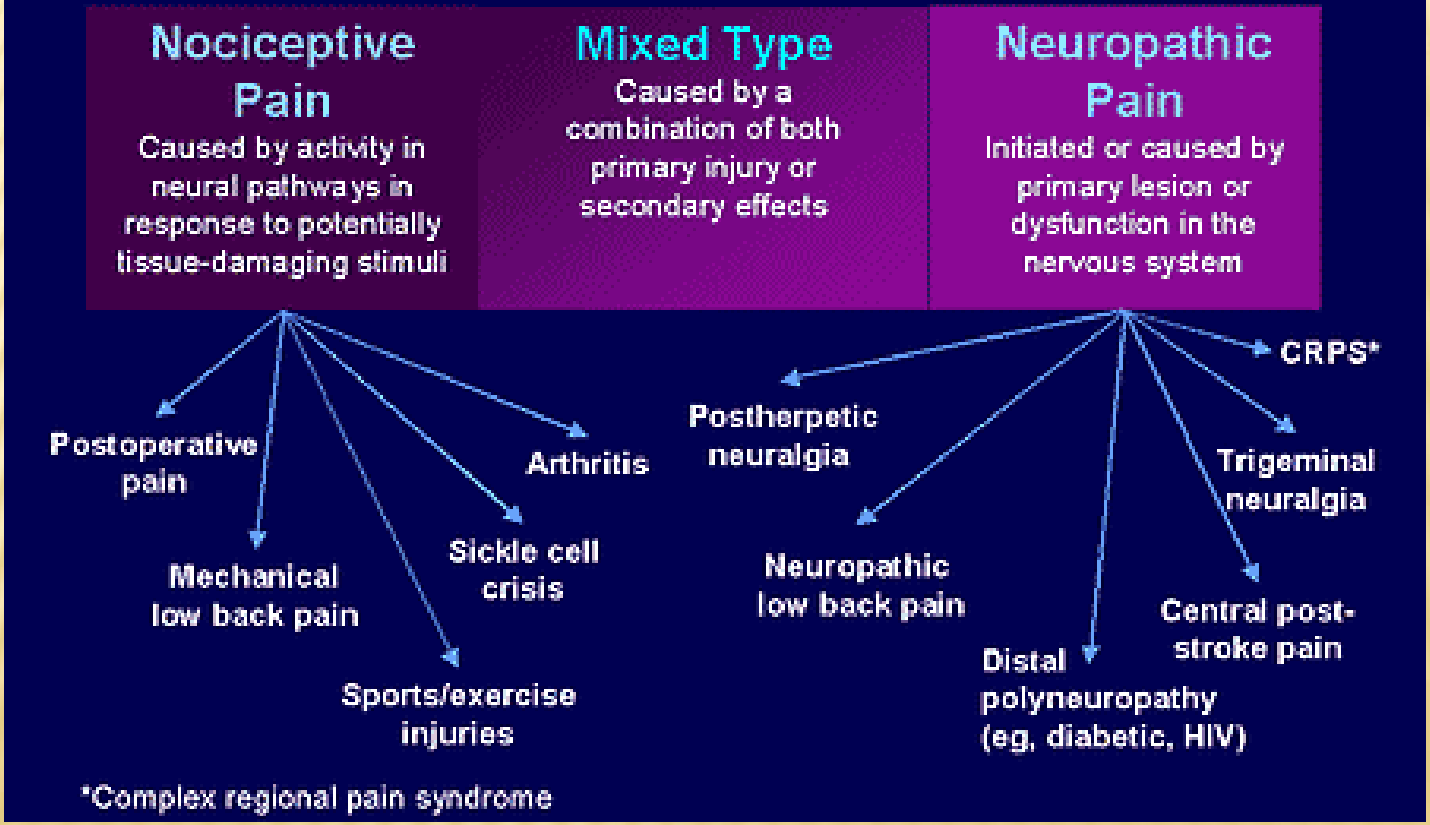
"….pain caused by a lesion or disease affecting the somatosensory system."

Diagnosis:

1. the pain has a neuroanatomically plausible distribution (corresponding to a peripheral or central territory of innervation or representation),
2. the history suggests a lesion or underlying disease that can damage the somatosensory system, and
3. both (1) and (2) have been securely demonstrated either clinically or by ancillary testing.


What is neuropathic pain?
Neuropathic Pain
Pain caused by a lesion or disease of the somatosensory nervous system
Peripheral Neuropathic Pain
Pain caused by a lesion or disease of the peripheral somatosensory nervous system
Central Neuropathic Pain
Pain caused by a lesion or disease of the central somatosensory nervous system
International Association for the Study of Pain. IASP Taxonomy. Changes in the 2011 List. Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions. Accessed: July 15, 2013.

Nociceptive vs Neuropathic Pain



PHARMACOTHERAPY OF NEUROPATHIC PAIN

Binder and Baron, 2016

The pharmacotherapy of neuropathic pain: number of trials, number of patients, number needed to treat, evidence levels (GRADE [27]), and common side effects (modified from [6])

	Number of trials	Number of patients	Number needed to treat [95% CI]	Evidence level (GRADE)	Examples of common side effects (may vary depending on drug and manufacturer)
Tricyclic antidepressants	15	948	3.6 [3.0; 4.4]	High	Drowsiness, fatigue, dizziness, hypotension, weight gain
Serotonin-norepinephrine reuptake inhibitors	10	2541	6.4 [5.2; 8.4]	High	Nausea, dry mouth, somnolence, headache
Pregabalin	25	5940	7.7 [6.5; 9.4]	High	Drowsiness, somnolence, peripheral edema, weight gain
Gabapentin	14	3503	7.2 [5.9; 9.1]	High	Somnolence, dizziness
Tramadol	6	741	4.7 [3.6; 6.7]	Intermediate	Dizziness, nausea
High-potency opioids	7	838	4.3 [3.4; 5.8]	Intermediate	Sedation, dizziness, headache, constipation, nausea, itch
Capsaicin 8% patch*	6	2073	10.6 [7.4; 18.8]	High	Pain or erythema at the site of application

*Only peripheral neuropathic pain. CI, confidence interval. Only evidence of high or intermediate quality was considered in the construction of this table

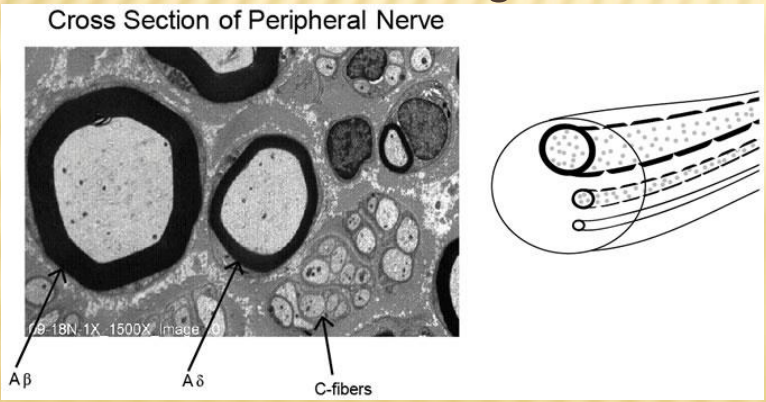
CZECH NATIONAL GUIDELINE FOR PHARMACOTHERAPY OF NEUROPATHIC PAIN 2011

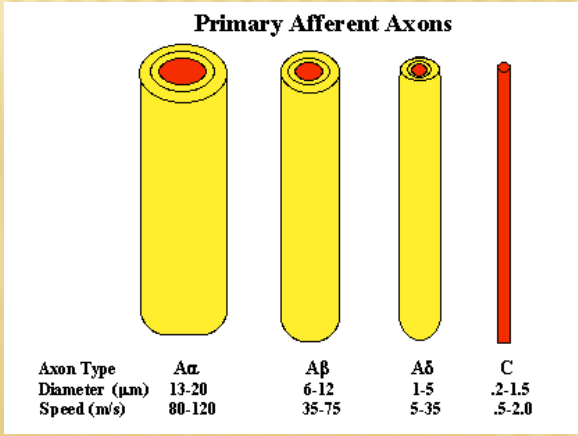
Painful clinical syndrome	**1. Choice drugs**		**2.Choice drugs**		**3.Choice drugs**	
Painful polyneuropathy incl. Painful diabetic polyneuropathy	Calcium blocker modulators (A)	pregabalin	tramadol/opioids: Independently or in combination with paracetamol/ Drugs of 1. choice (A)	tramadol	antiepilep-tics	phenytoin (C)
		gabapentin		morphin		Carbamaze-pine (C)
	TCA (A)	amitriptylin		oxycodon	NMDA receptor inhibitors	dextromethor-fane (B)
		nortriptylin		fentanyl		
		imipramin				
		klomipramin				
	SNRI (A)	duloxetin venlafaxin			Thioctic acid (B)	

SPECIFIC PAIN NERVE FIBERS

In terms of peripheral pain mechanisms there is indeed a high degree of specificity, though not an absolute specificity in the von Frey sense. There are two types of afferent fibers, i.e. the distal axons of primary sensory neurons, that respond maximally to noxious stimuli.

One type is the very fine, **unmyelinated**, so called **C fibre** and the other is the **thinly myelinated A-delta fiber**. The peripheral terminations of these fibers, or receptors, are the **free** profusely branched **nerve endings** in the skin and other organs.



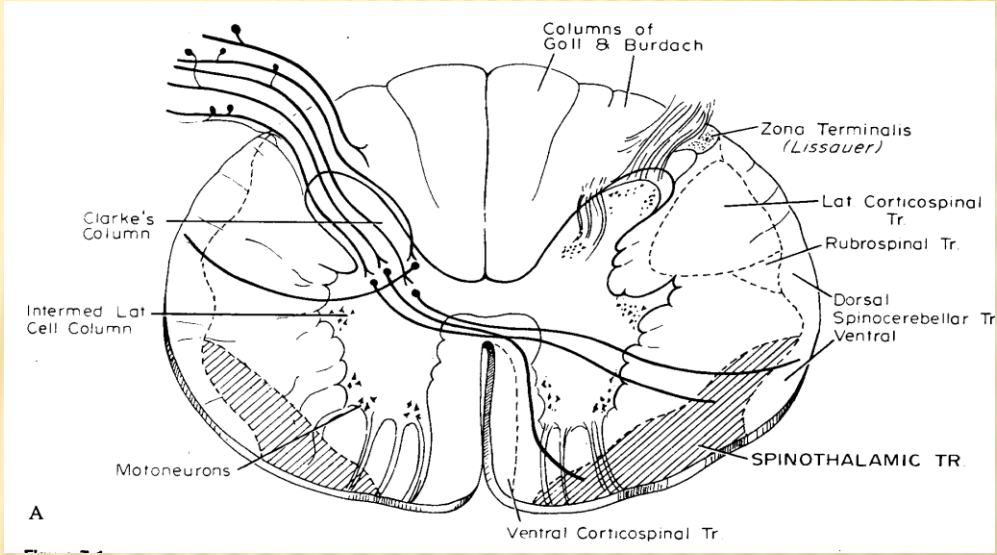


PAIN RECEPTORS

Receptor characteristics				
Histology	**Type**	**Adequate stimulus**	**Nerve fiber type**	**Sensory quality**
Naked endings	Mechano-sensitive	Noxious mechanical stimuli	Small myelinated	Sharp fast pain
Naked endings	Polymodal	Noxious stimuli: 1.mechanical 2.thermal-above 43° C and below 14° C 3. various chemicals	Unmyelinated	Dull or burning sloww pain, itch
Naked endings	Termosensi-tive	Thermal 34-50° C	Unmyelinated	Warmth
Naked endings		Thermal	Small myelinated	Cold

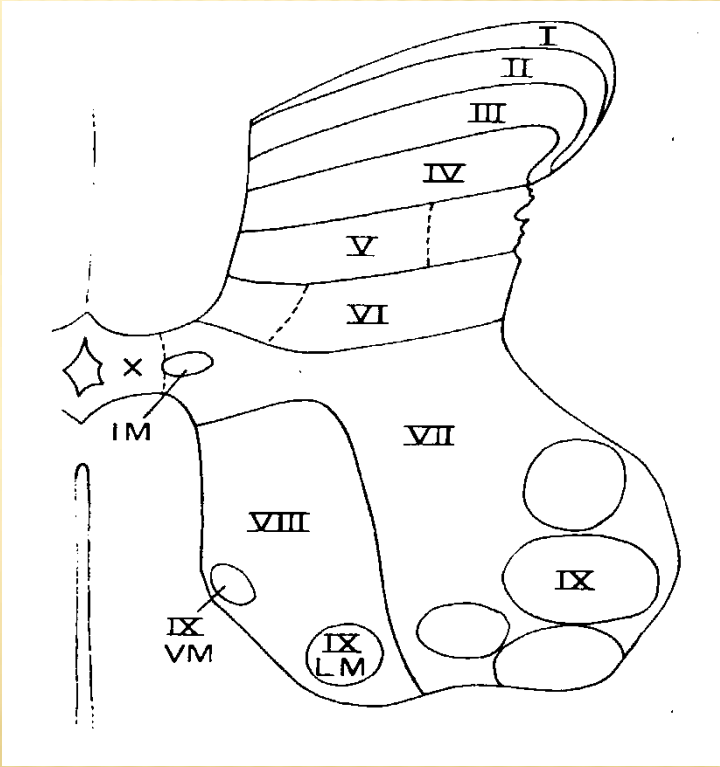
PERIPHERAL SENSORY NEURON

The peripheral afferent fibers have their cell bodies in the dorsal root ganglia; central extensions of these nerve cells project, via the dorsal root, to the dorsal horn of the spinal cord (or , in the case of cranial nerve afferents, to the nucleus of the trigeminal nerve, i.e. the medullary dorsal horn). The fine myelinated and unmyeli-nated fibers occupy mainly the lateral part of the root entry zone and form the tract of Lissauer. The lateral division of the posterior root contains mainly the small pain fibers.



THE DORSAL HORN

The afferent pain fibers, after traversing Lissauer´s tract, terminate in the posterior gray matter or dorsal horn. From the cells of termination (mostly in **laminae I,II and V** of Rexed), secondary neurons connect either with ventral and lateral horn cells in the same and adjacent spinal segments and subserve both somatic and autonomic reflexes, or project contralaterally and to a lesser extend ipsilaterally to higher levels and subserve pain sensation. A-delta pain afferents, when stimulated, release several peptide neuro-transmitters; among them is substance P. Opiate receptors have been found on both presynaptic terminal axons and postsynaptic dendrites. Opiates heave been found to decrease substance P. Small neurons in lamina II, capable of releasing enkefalin (i.e. endogenous morphine-like substance), are presumably inhibitory in nature and modulate nociceptive input in the spinal segments.

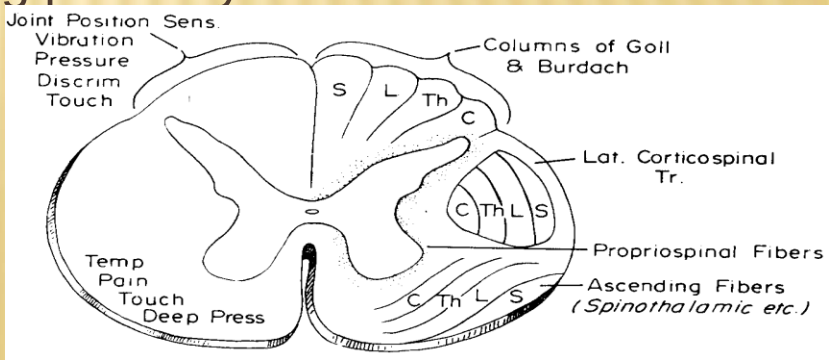


AFFERENT TRACTS FOR PAIN

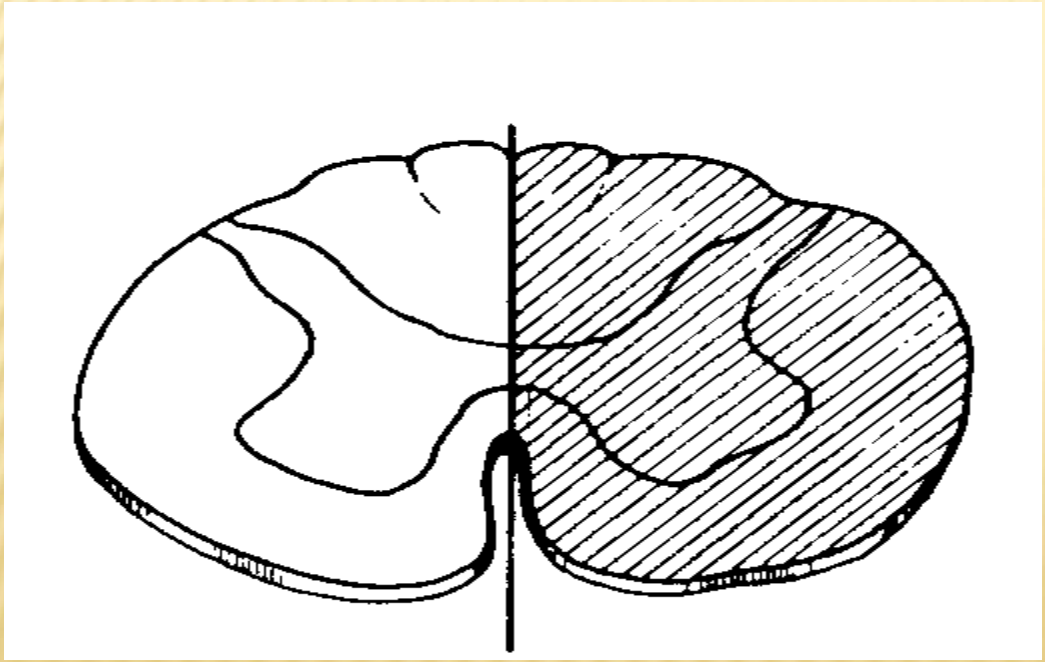
- **lateral spinothalamic tract** - a fast conducting pathway that projects directly to the thalamus; it subserves the ***sensory-discriminative*** aspect of pain, i.e., processes that underlie the localization and identification, and possibly the intensity, of the noxious stimuli.
- ***spinoreticulothalamic or paleospinothalamic*** pathway contains a more **slowly conducting, medially placed system** of fibers, which projects via short interneuronal chains to the reticular core of the medulla and the midbrain, and then to the medial and the intralaminar nuclei of the thalamus; it subserves the **affective-motivational aspects** of pain.

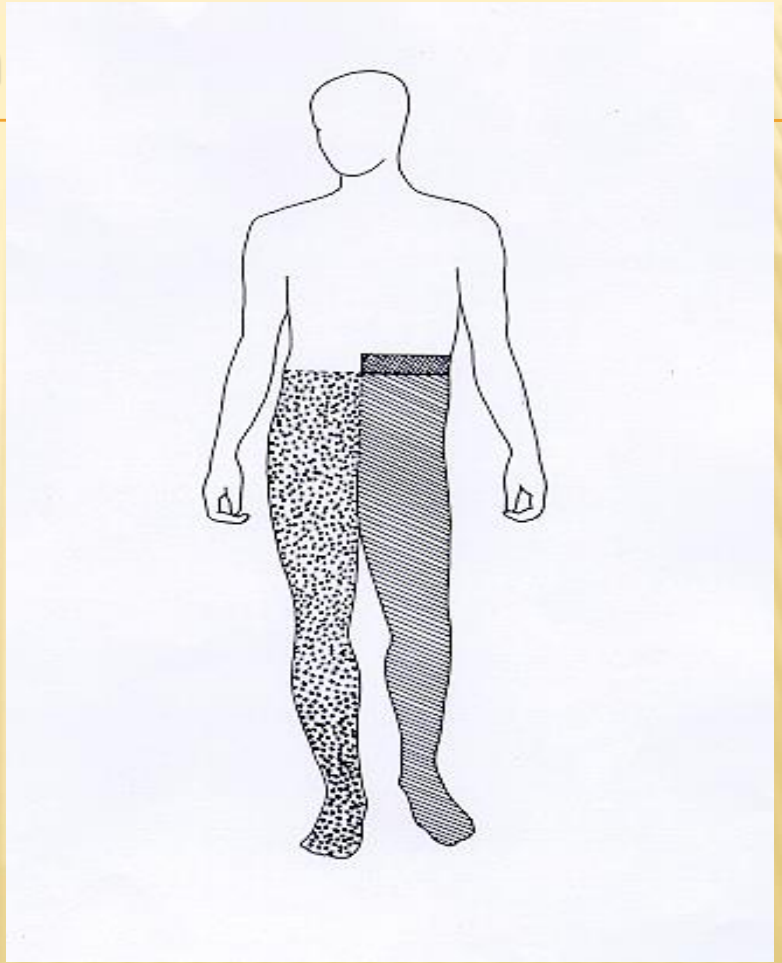
ANTEROLATERAL MEDULLAR FUNICULUS

Unilateral section of the anterolateral funiculus produces a relatively complete loss of pain and thermal sense on the opposite side of the body, extending to a level three or four segments below the lesion. After a variable period of time, pain sensation usually returns, perhaps because of the presence of pathways, that lie outside the anterolateral quadrants of the spinal cord and that gradually assume the capacity to conduct pain impulses. It has been suspected that a longitudinal polysynaptic bundle of small myelinated fibers in the center of the dorsal horn (the dorsal intracornual tract) constitutes an ancillary pain conducting pathway.



Unilateral medullar hemisection syndrome Brown-Sequard





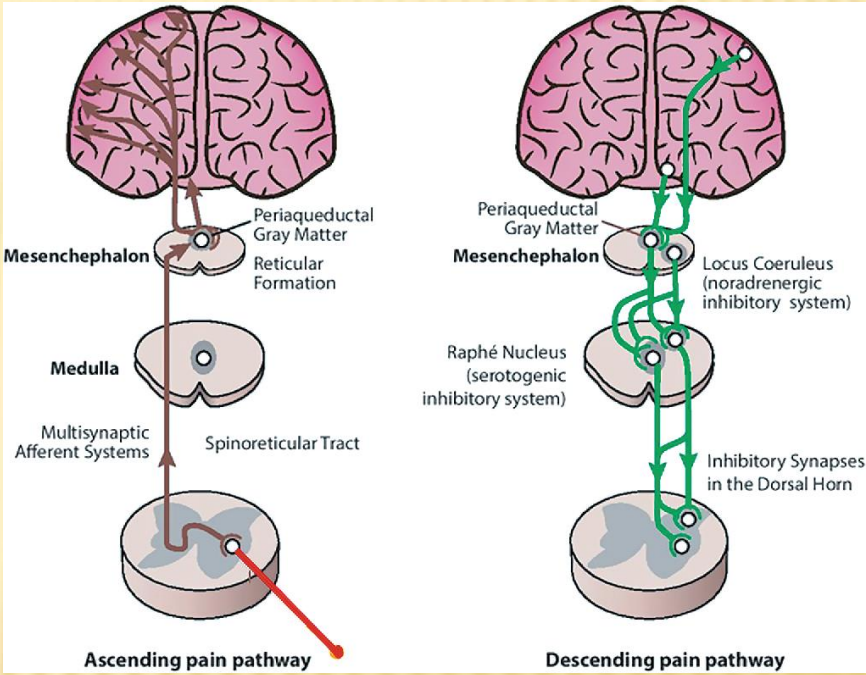
THALAMIC TERMINUS

- The direct spinothalamic fibers segregate into two bundles.
  - The lateral division terminates in the ventrobasal and posterior groups of nuclei;
  - The medial contingent terminates mainly in the intralaminar complex of nuclei and in the nucleus submedius;
- Spinoreticulothalamic fibers (paleospinothalamic tract) project onto the medial intralaminar thalamic nuclei (the same as the medially projecting direct spinothalamic pathway);
- Projections from the dorsal column nuclei, which have a modulating influence on the pain transmission, are mainly ventrobasal and posterior group of nuclei.

INHIBITORY DESCENDING PAIN PATHWAYS

There are also **descending fibers** from the brainstem structures that have an **inhibitory effect on pain**.

- One such pathway emanates from nuclei in the **periaqueductal region of the midbrain** and descends in the anterolateral columns of the spinal cord to the posterior horns;
- Other goes from the **mesencephalic reticular formation**, dorsal raphe nucleus, locus coeruleus, and nucleus reticularis gigantocellularis.



THALAMOCORTICAL PROJECTIONS

The ventrobasal complex and posterior group of nuclei send their axons to two main cortical areas**: the postcentral cortex (S1)** and the **upper bank of the sylvian fissure (S2).**

These areas are concerned mainly with the reception of tactile and proprioceptive stimuli and with discriminative sensory function, including pain. The extend to which either area is activated by thermal and painful stimuli is uncertain. Stimulation of these cortical areas in a normal, alert human does not produce pain. Some pain afferents project to subcortical structures, e.g. amygdaloid nuclei, the hypothalamus, and the limbic brain.

ENDOGENOUS PAIN CONTROL MECHANISMS

There exists an **endogenous neuronal system for analgesia**, which can be activated by the administration of **opiates** or by naturally occurring brain substances with the pharmacological properties of opiates.

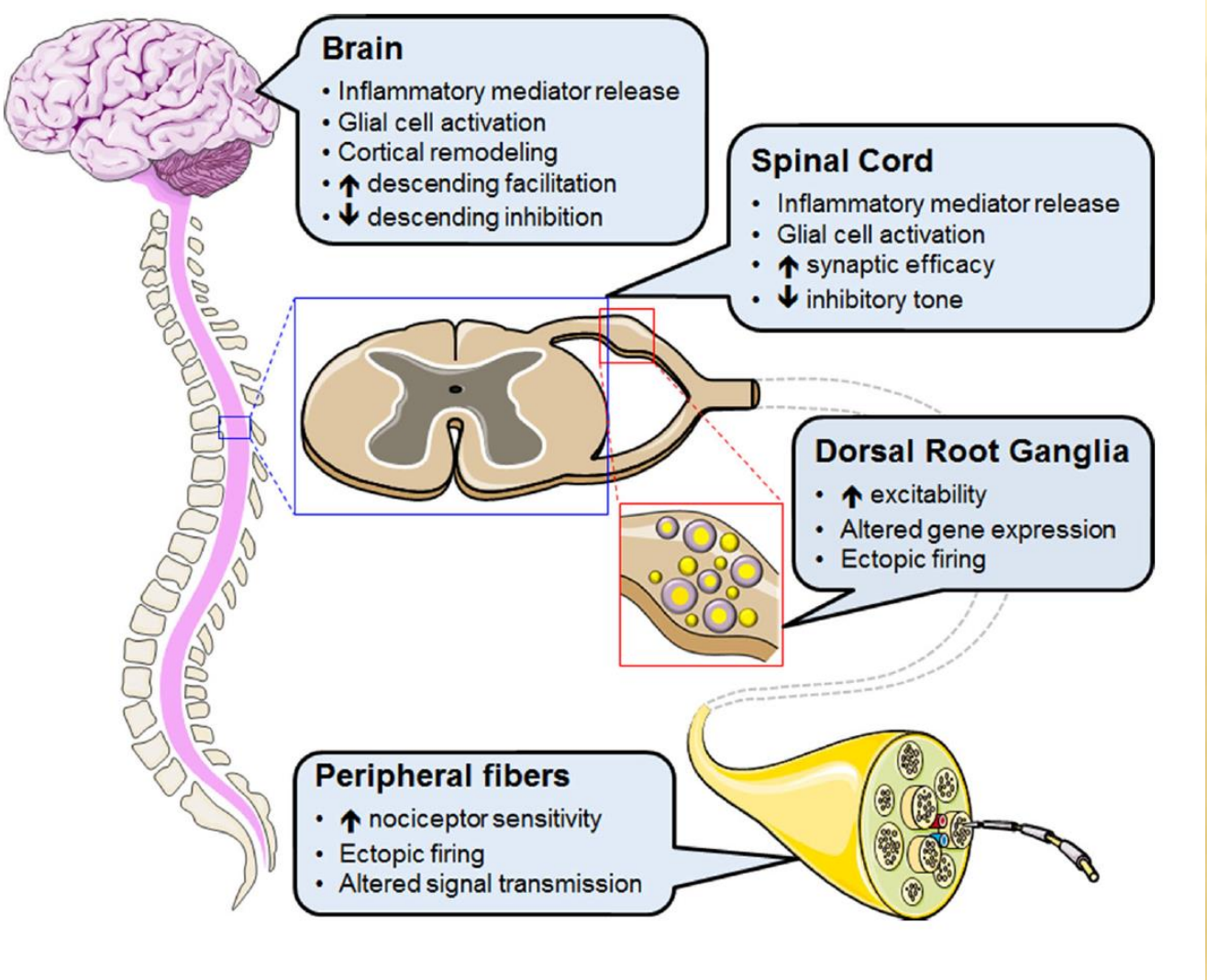
This endogenous analgesia system was first demonstrated by Reynolds in 1969, who found that stimulation of ventrolateral periaqueductal gray matter produced a profound analgesia without altering behavior or motor activity. **Stimulation produced analgesia** (SPA) produces its effect by inhibiting the neurons of laminae I and V of the dorsal horn, i.e., the neurons that are activated by noxious stimuli. Opiates act at several loci in the brainstem, as well as on the neurons of the dorsal horn, suppressing the input from both the A-delta and C fibers. It appears that their sites of action correspond with the sites that produce analgesia when stimulated electrically.

ENDOGENOUS PAIN CONTROL MECHANISMS

The endogenous, morphine-like compounds are generically referred to as "**endorphins**", meaning "the morphine within". Spinal interneurons containing enkefalin synapse with the terminals of pain fibers and inhibit the release of the presumptive transmitter, substance P. A deficiency of endorphins in a particular region would explain persistent or excessive pain.

Beta-endorphins not only relieve pain, but suppress **withdrawal symptoms.** The mysterious effects of **placebos** and perhaps of **acupuncture** are due to activation of an endogenous system that shuts off pain through the release of endorphins. The descending pain control systems probably contain **noradrenergic** and **serotoninergic** as well as endorphin-producing links.

Peripheral and central mechanisms of neuropathic pain Meacham et al. 2017



TERMINOLOGY

Pain can be **spontaneous** or **evoked**

Evoked pain:

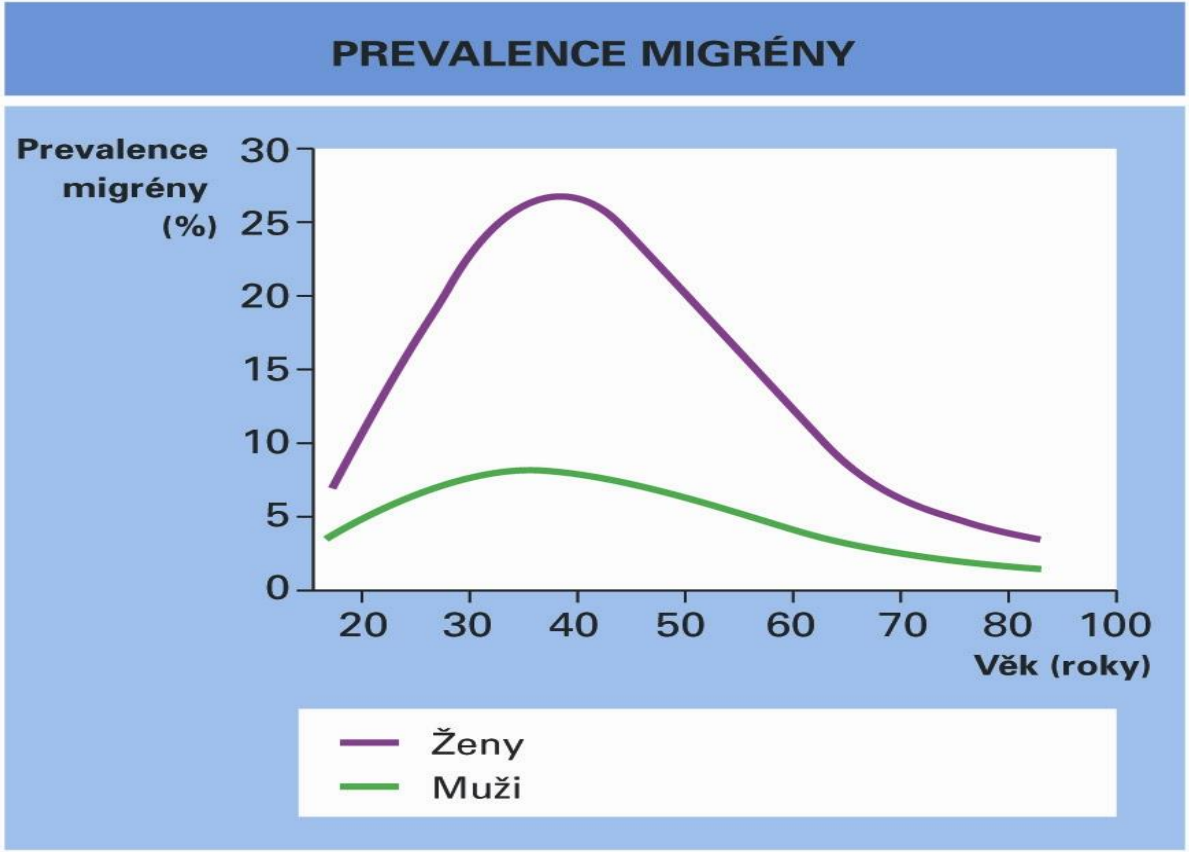
- The term **hyperalgesia** referrs to an increased sensitivity and a lowering of the threshold to painful stimuli.
- The term **allodynia** referrs to pain evoked by a stimulus that usually doesnot evoke pain (i.e. light touch).

HEADACHE - EPIDEMIOLOGY

- Migraine is one of the most prevalent and disabling medical illnesses in the world.
- WHO ranks migraine as the **third most prevalent medical condition** and the **second most disabling neurological disorder** in the world.
- The 1-year prevalence of migraine in the general population is 12%.
- The annual and lifetime prevalence are 18% and 33% in women, respectively, and 6% and 13% in men.
- Migraine affects approximately 10% of school-aged children (5–18 years), and at prepubertal ages (<13 years) the rate of onset of migraine is slightly higher in boys than in girls.
- Although, for half of patients with migraine onset occurs before age 20 years, onset can occur at an early age—eg, infantile colic has emerged as perhaps the earliest manifestation of migraine.

HEADACHE - EPIDEMIOLOGY

Migraine is most prevalent between the ages of 25 and 55 years, and the prevalence rises through early adult life
and then falls after midlife (ie, 55 years).



CLASSIFICATION OF HEADACHE

Cephalalgia
An International Journal of Headache
International Headache Society

Cephalalgia
2018, Vol. 38(1) 1–211

DOI: 10.1177/0333102417738202
journals.sagepub.com/home/cep
SAGE

Headache Classification Committee of the International Headache Society (IHS)

The International Classification of Headache Disorders, 3rd edition

https://ichd-3.org/

3rd INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS (2018)

1. Migraine
2. Tension type headache
3. Trigeminal autonomic cephalalgias (incl. Cluster headache)
4. Other primary headache disorders
5.-12. Secondary headaches
13. Painful lesions of the cranial nerves and other facial pain (incl. Trigeminal neuralgia)
14. Other headache disorders

CLASSIFICATION OF MIGRAINE

1. Migraine

1.1 Migraine without aura

1.2 Migraine with aura

- 1.2.1 Migraine with typical aura
  - 1.2.1.1 Typical aura with headache
  - 1.2.1.2 Typical aura without headache
- 1.2.2 Migraine with brainstem aura
- 1.2.3 Hemiplegic migraine
  - 1.2.3.1 Familial hemiplegic migraine (FHM)
    - 1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)
    - 1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)
    - 1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)
    - 1.2.3.1.4 Familial hemiplegic migraine, other loci
  - 1.2.3.2 Sporadic hemiplegic migraine (SHM)
- 1.2.4 Retinal migraine

CLASSIFICATION OF MIGRAINE

1.3 Chronic migraine
1.4 Complications of migraine
- 1.4.1 Status migrainosus
- 1.4.2 Persistent aura without infarction
- 1.4.3 Migrainous infarction
- 1.4.4 Migraine aura-triggered seizure

1.5 Probable migraine
- 1.5.1 Probable migraine without aura
- 1.5.2 Probable migraine with aura

1.6 Episodic syndromes that may be associated with migraine
- 1.6.1 Recurrent gastrointestinal disturbance
  - 1.6.1.1 Cyclical vomiting syndrome
  - 1.6.1.2 Abdominal migraine
- 1.6.2 Benign paroxysmal vertigo
- 1.6.3 Benign paroxysmal torticollis

DIAGNOSTIC CRITERIA FOR MIGRAINE

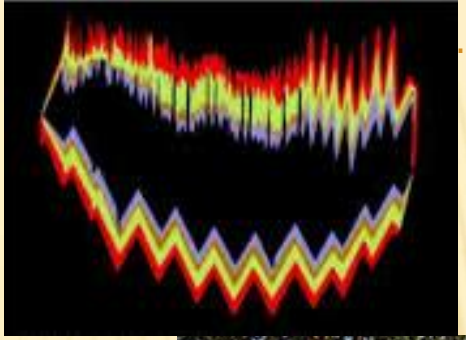
I.1 Migraine without aura

A. At least five attacks[1] fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)[2,3]
C. Headache has at least two of the following four characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

I.2 Migraine with aura

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   1. visual
   2. sensory
   3. speech and/or language
   4. motor
   5. brainstem
   6. retinal
C. At least three of the following six characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes
   2. two or more aura symptoms occur in succession
   3. each individual aura symptom lasts 5–60 minutes[1]
   4. at least one aura symptom is unilateral[2]
   5. at least one aura symptom is positive[3]
   6. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis.

VISUAL MIGRENOUS AURA



Positive symptoms:

- Photopsia
- Teichopsia (fortification spectra)

Negative symptoms:

- Scotoma

Combined:

- Scotoma scintillans

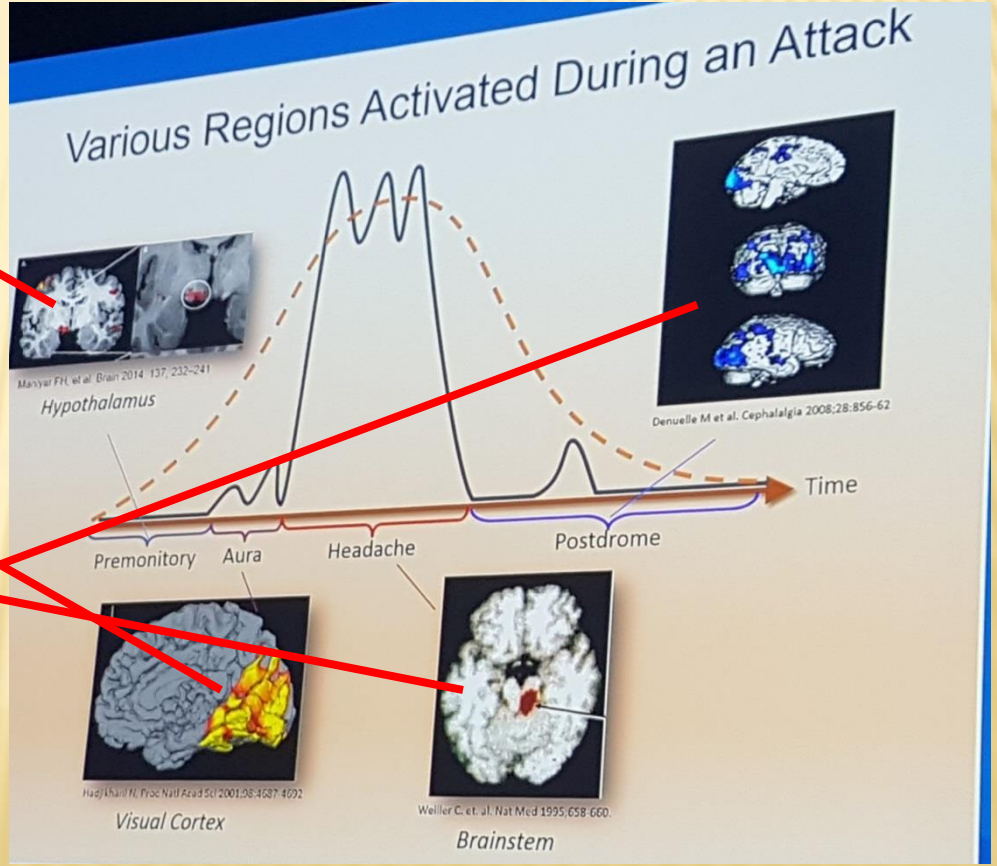
PHASES OF MIGRAINE AND CHANGES OF BRAIN ACTIVITY

Premonitory:
Fatigue,
Cognitive difficulty,

Aura:
Scotoma,
Fortification spectrum,
Paresthesia,
Weakness,
Vertigo

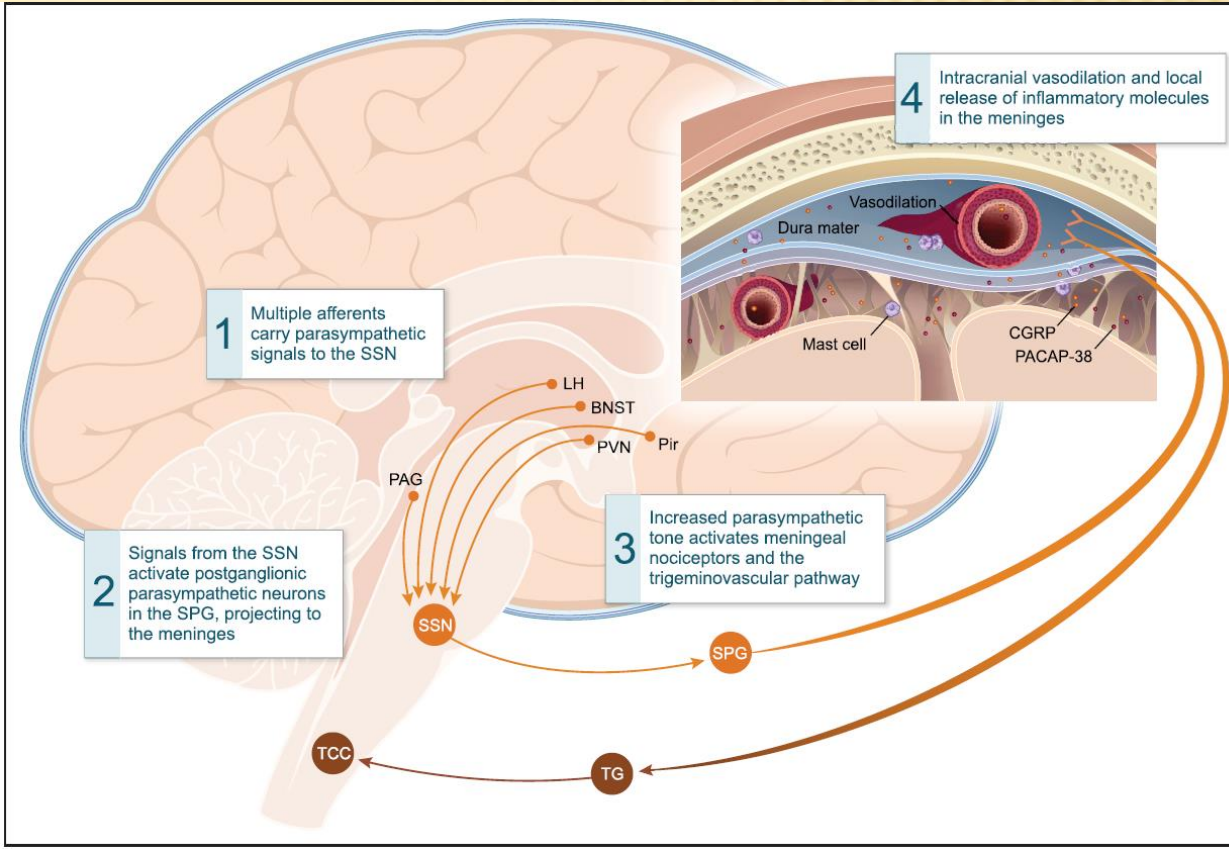
Headache phase:
Headache,
Nausea and vomiting,
Photophobia,

Postdrome:
Fatigue,
Cognitive difficulty,
Heightened sensory awareness,
Food craving



PREMONIOTORY: ACTIVATION OF MENINGEALS NOCICEPTORS BY INCREASED PARASYMPATHETIC TONE

Dodick: Headache 2018



MECHANISM OF AURA

8.11.2019

Dodick: Headache 2018

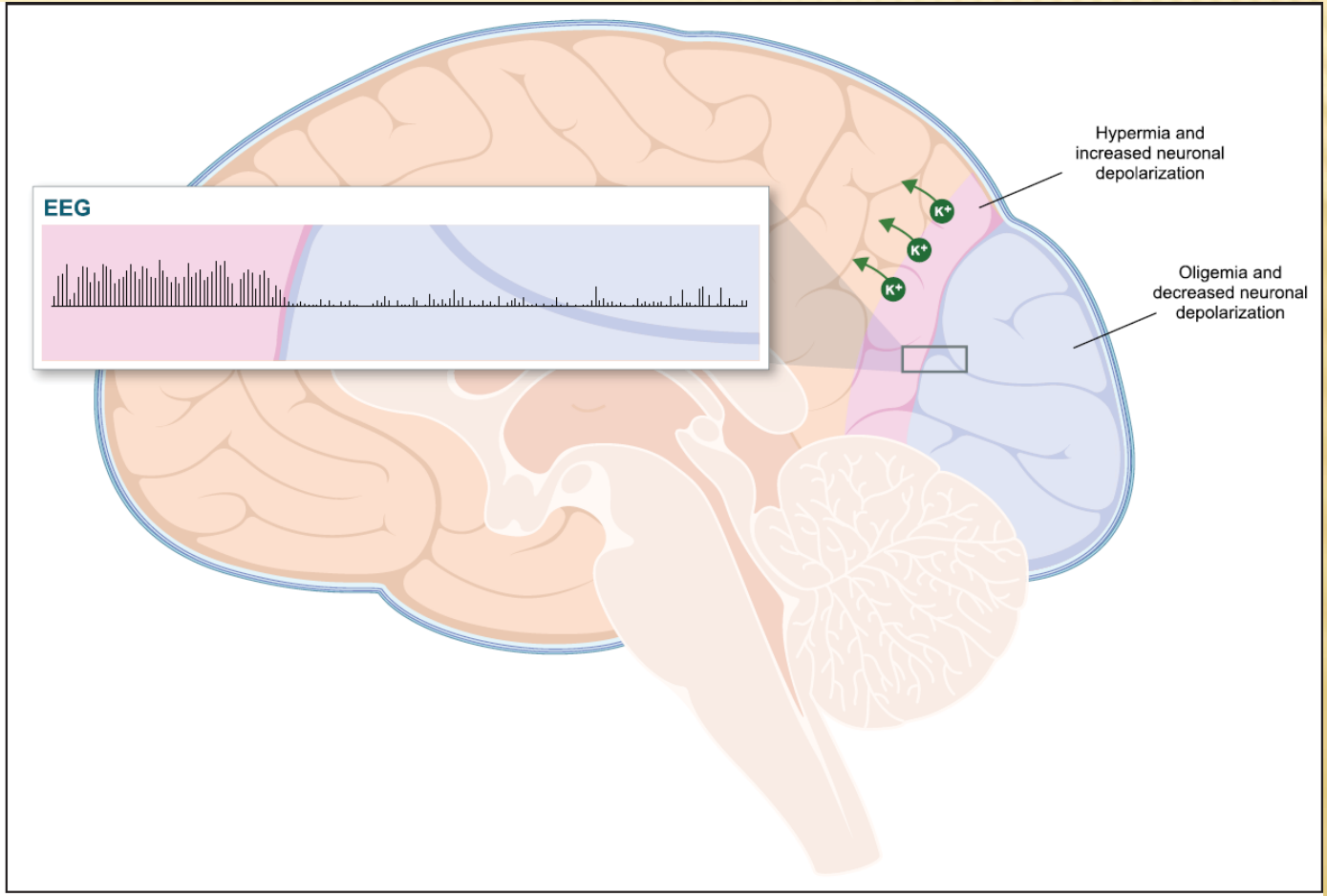
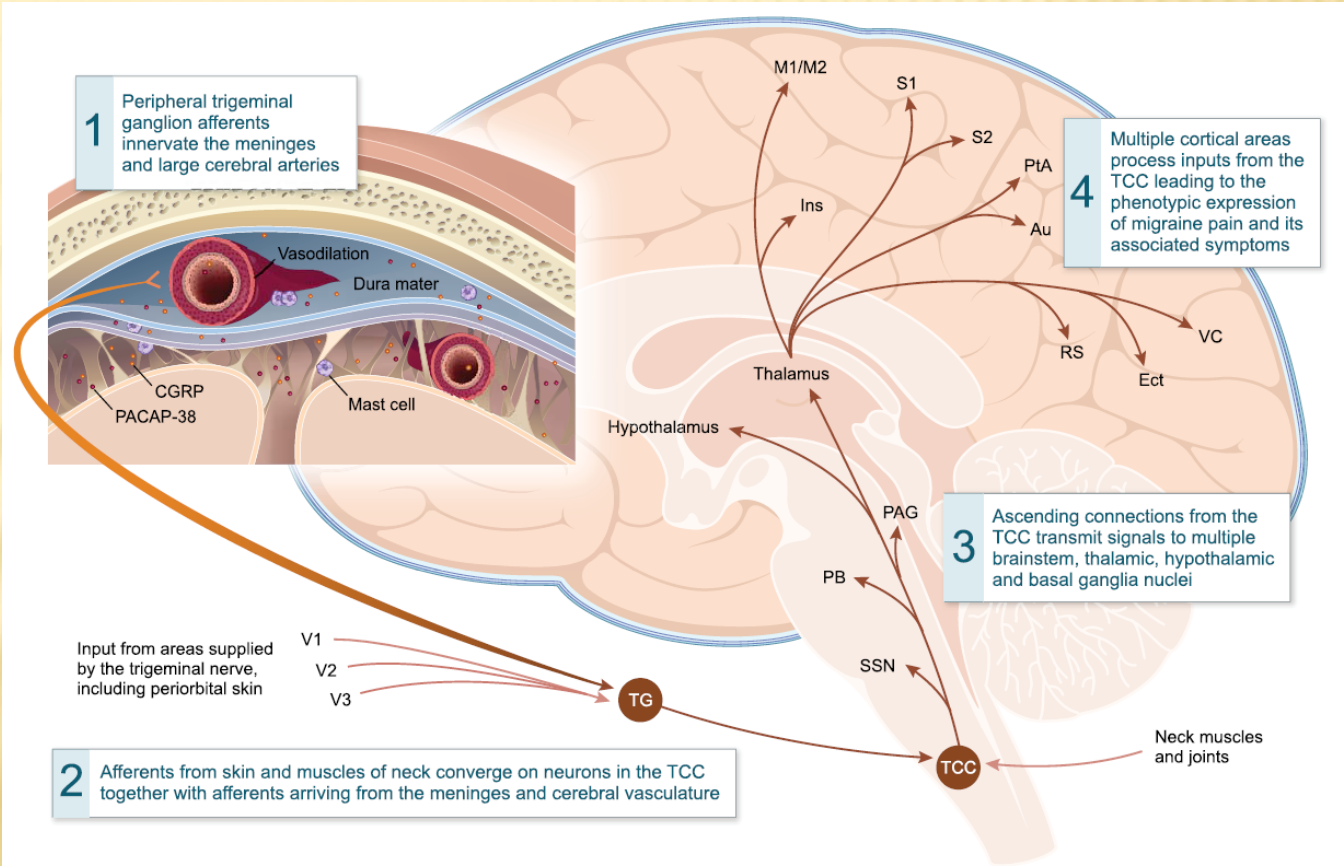


Fig. 2.—Cortical spreading depression. EEG = electroencephalogram; K^+ = potassium.

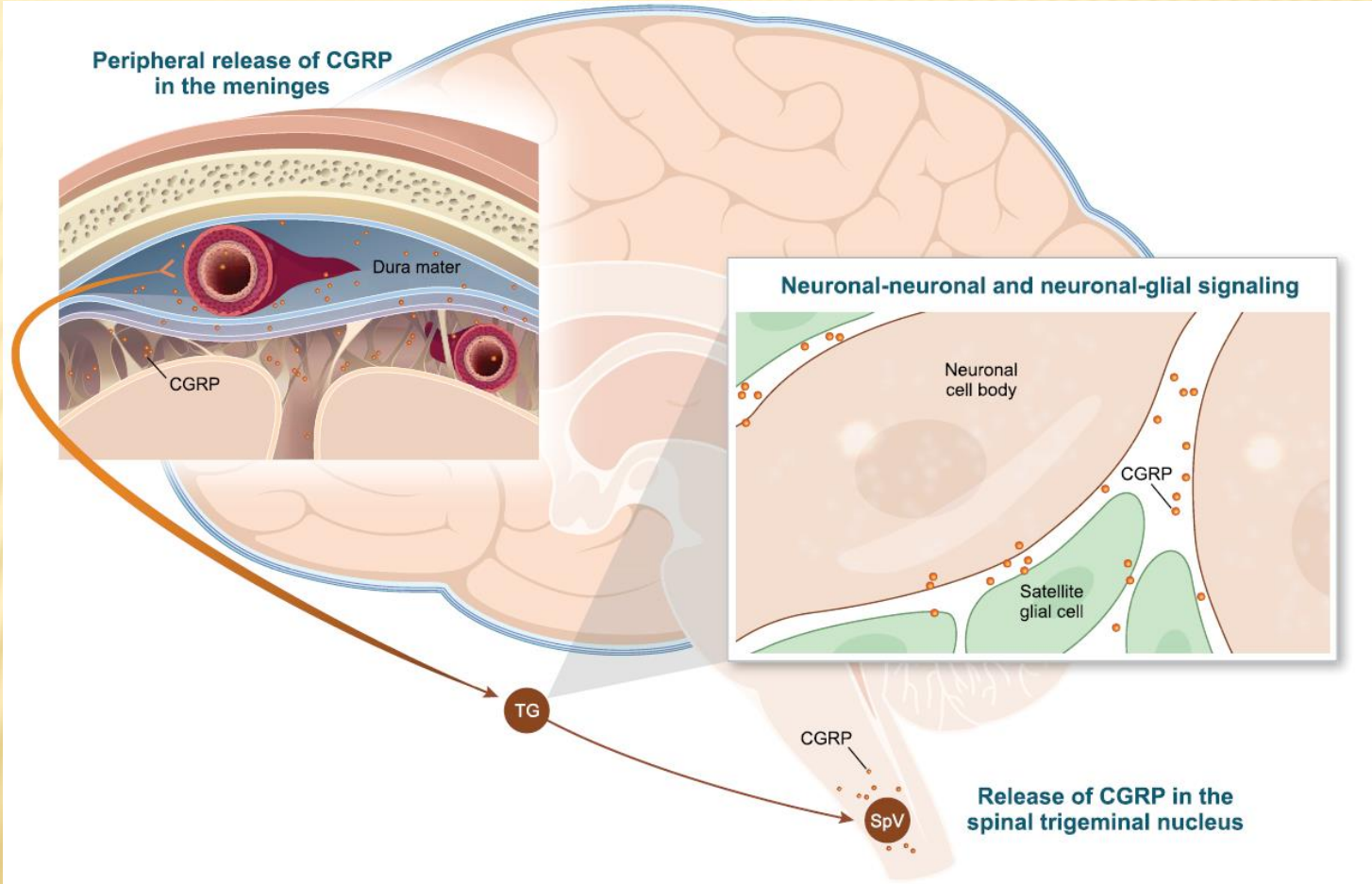
TRIGGERING OF PAIN VIA ACTIVATION OF TRIGEMINOVASCULAR PATHWAY

Dodick: Headache 2018

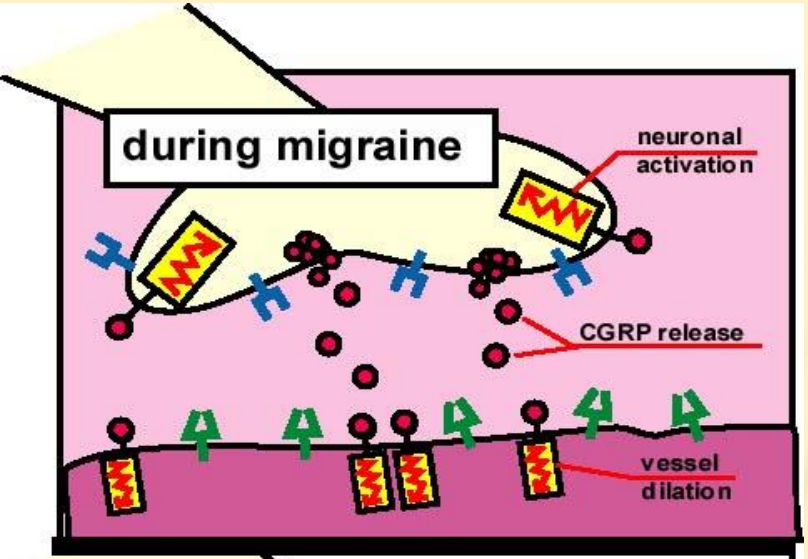


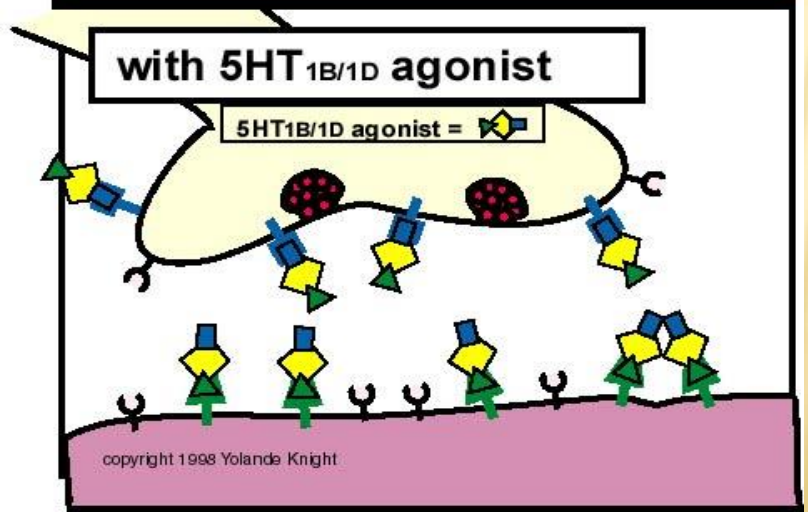
CRGP SIGNALLING IN THE TRIGEMINOVASCULAR SYSTEM

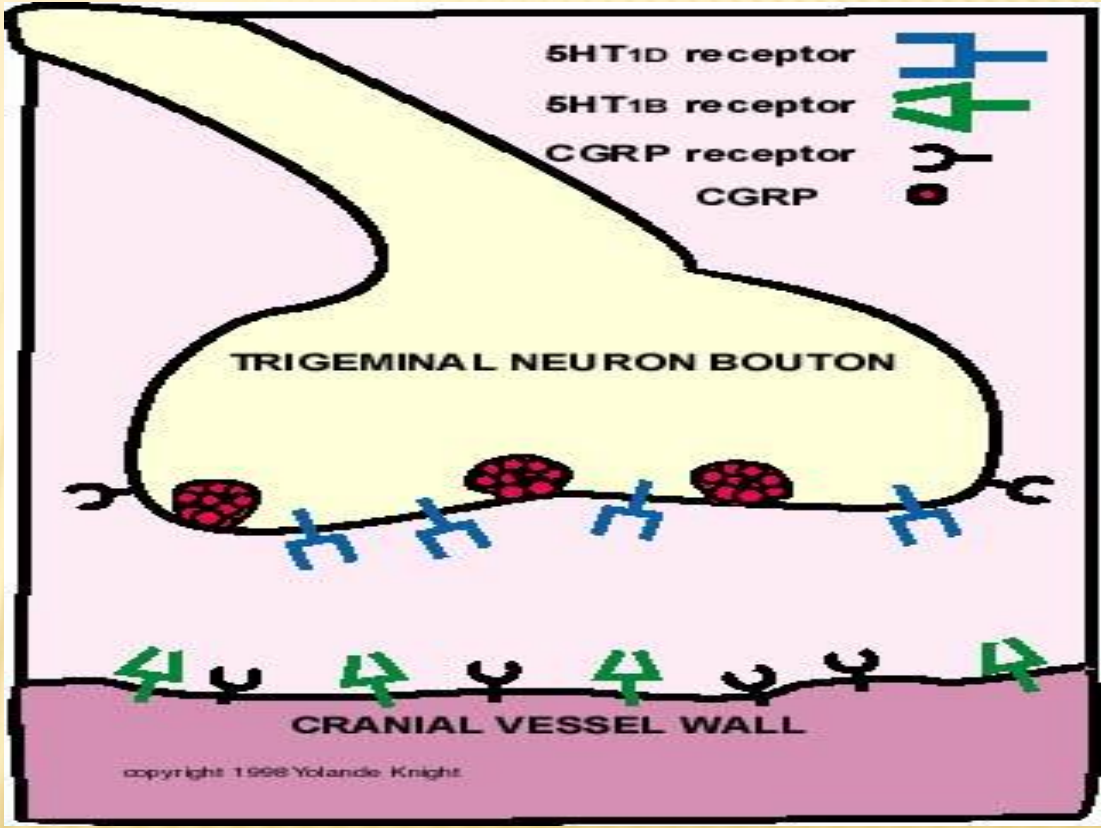
Dodick: Headache 2018



SEROTONINE RECEPTORS AND TRIPTANS

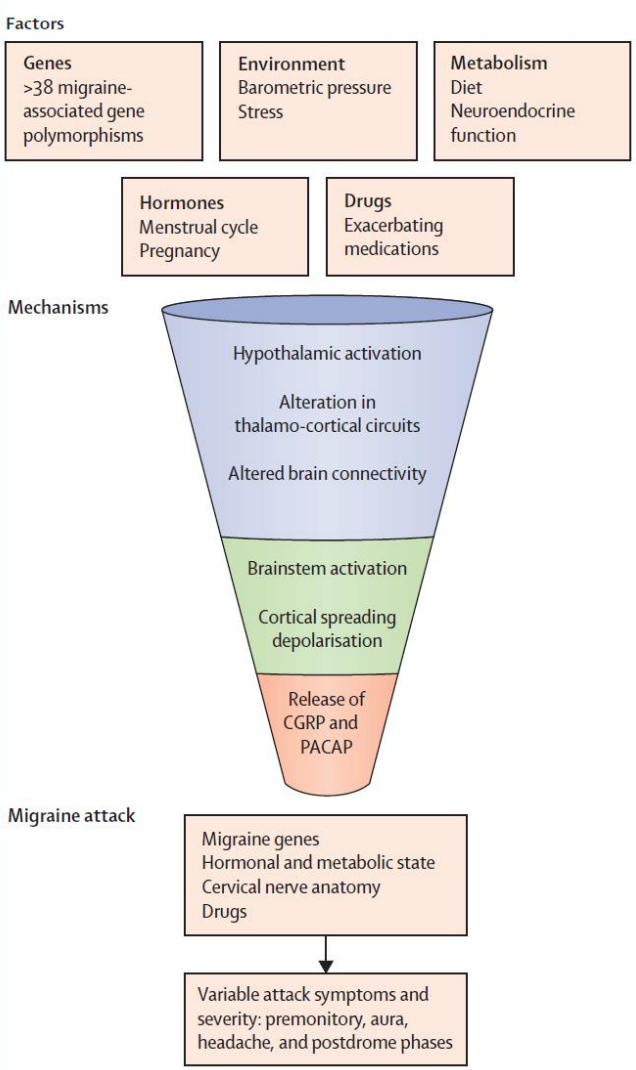






COMPLEX PATHOPHYSIOLOGY OF MIGRAINE

Charles: Lancet Neurol 2018



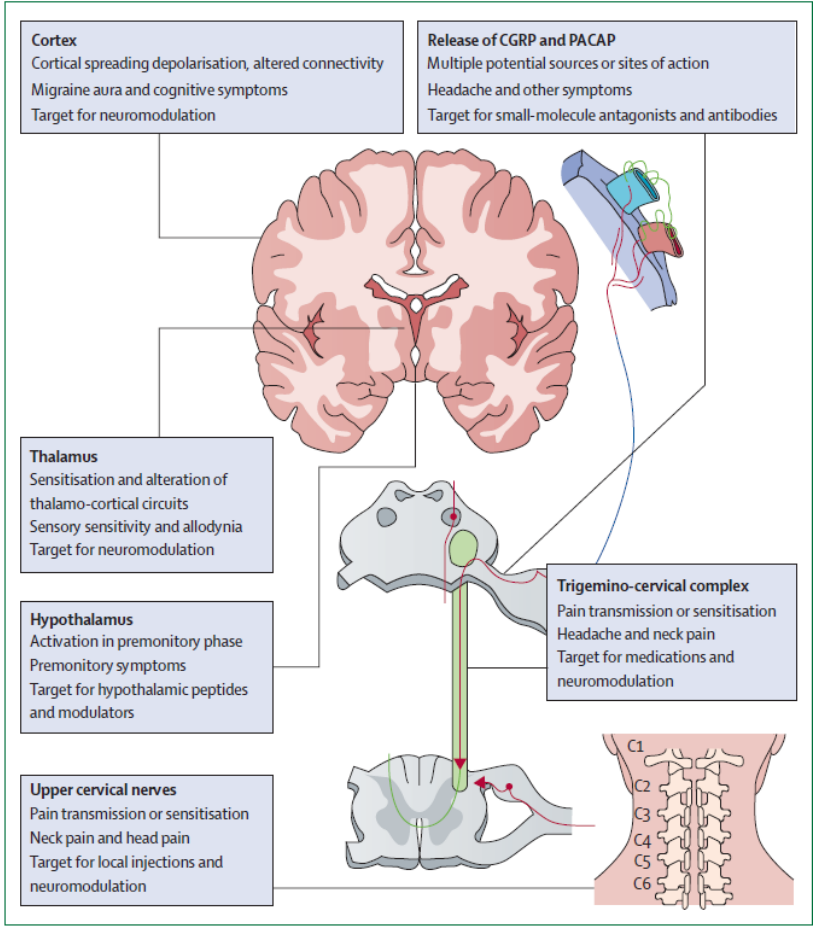


***Figure 2*: Anatomical sites of migraine mechanisms, symptoms, and therapeutic targets**
Migraine involves the simultaneous alteration in function of multiple components of the CNS and peripheral nervous system, some of which are represented in this diagram. Each of these components could be responsible for different symptoms of migraine, and each could represent a specific therapeutic target in individual patients. Red arrows indicate sensory inputs from the trigeminal nerve and upper cervical nerve roots, which converge in the trigemino-cervical complex. CGRP=calcitonin gene-related peptide. PACAP=pituitary adenylate cyclase-activating

PET FINDINGS

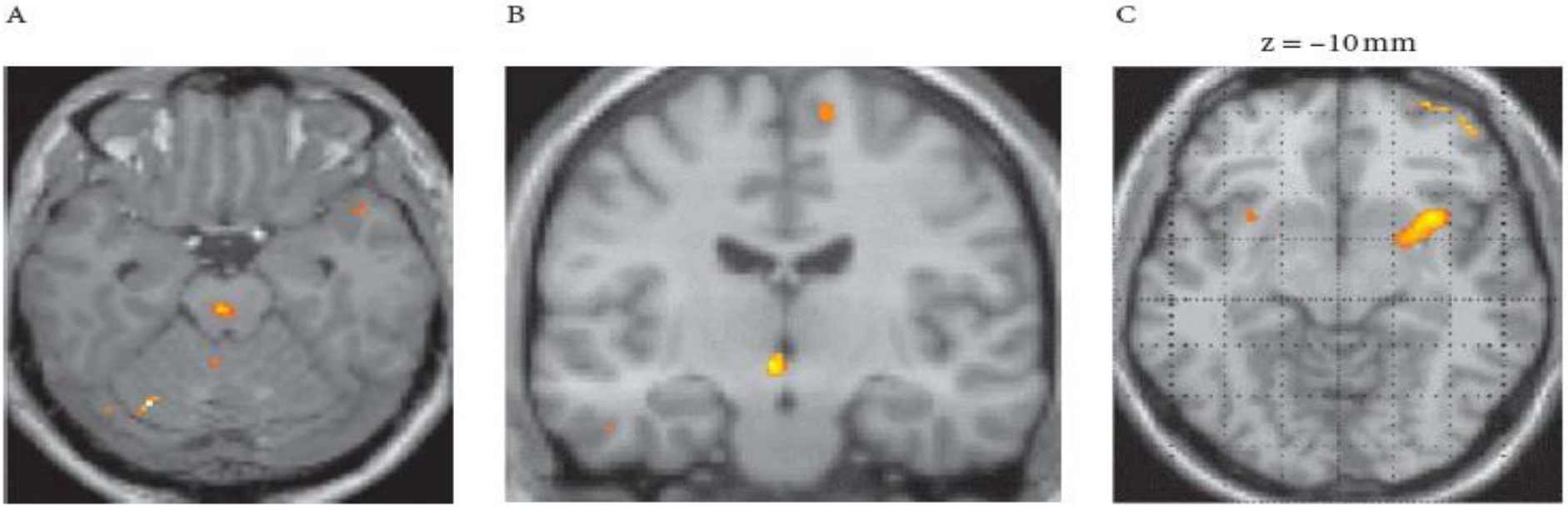
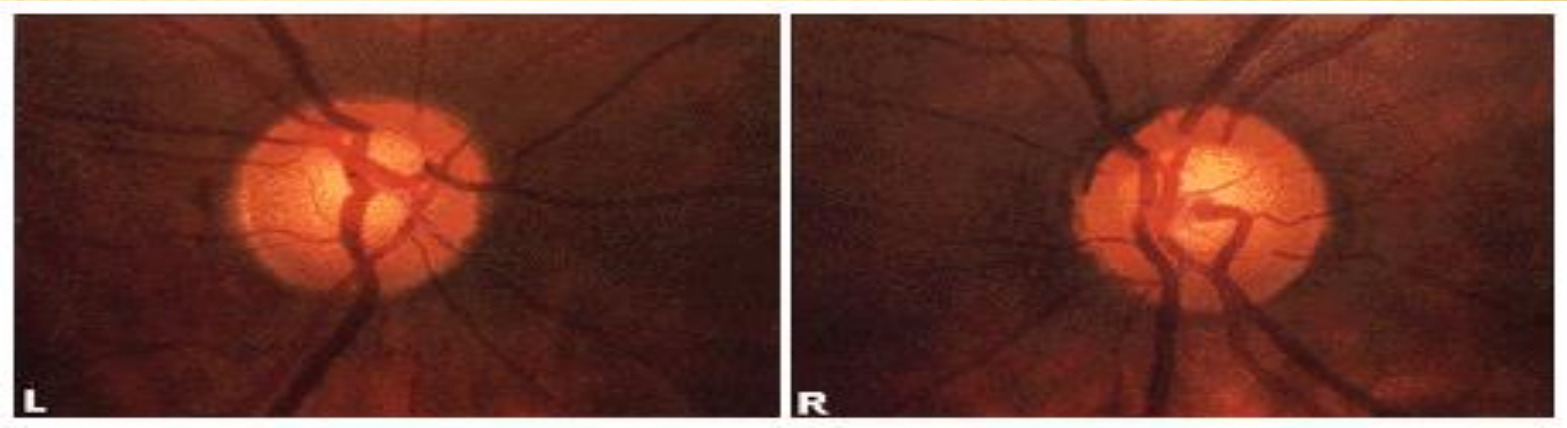


Fig. 1 Positron emission tomography (PET) findings in Migraine [2] (**A**), Cluster Headache [43] (**B**) and experimental head pain [44] (**C**). Activation of rostral brainstem structures in migraine, and posterior hypothalamic grey matter in clusters headache seem relatively specific for the syndromes, as neither are seen in experimental ophthalmic (first) division head pain. The findings support the view that primary neurovascular headaches, migraine and cluster headache, are fundamentally disorders of the nervous system

Migraine is a brain disease, maybe progressive

OPHTHALMOSCOPIC FINDING IN RETINAL MIGRAINE



TREATMENT OF MIGRAINE

I. Non-pharmacological treatment of migraine

The avoidance of identified aggravating (long-term effect) or triggered (short-term < 48 hours) factors:

- **stress**
- **the menstrual cycle**
- **certain foods**
- **trauma**
- **caffeine withdrawal**

- If there is a reproducible trigger than its elimination will reduce the frequency of headaches. Unfortunately, this is often not possible because of the lack of a single reproducible trigger.
- Other non-pharmacological treatments has been suggested for migraine patients, including relaxation exercises, biofeedback, massage, acupuncture, chiropractic, osteopathy, and naturopathy, but their effect is not proven.

TREATMENT OF MIGRAINE

I. Non-pharmacological treatment of migraine

Coppola et al.: Cephalalgia 2015

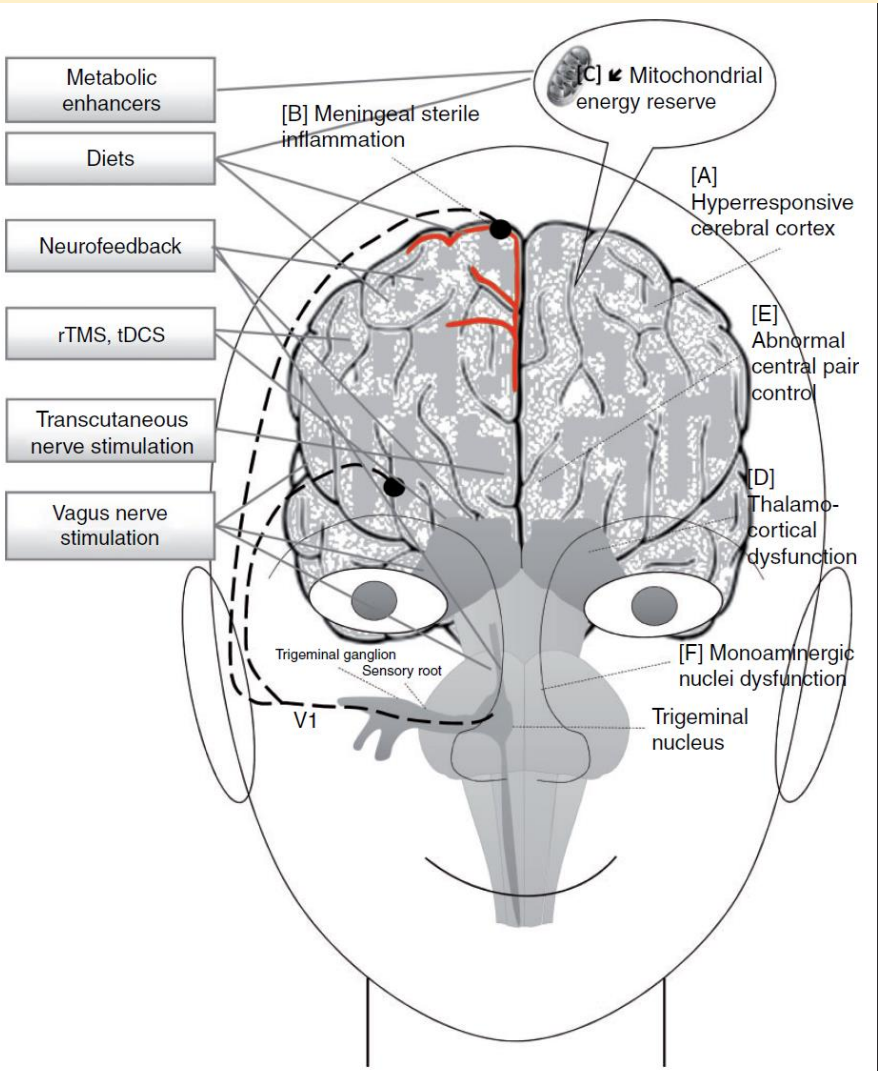


Figure 1. Scheme of migraine pathophysiological targets in migraine for non-pharmacological interventions. Diets could act by modulating neuronal excitability (a), mitigating sterile inflammation at the level of the trigeminovascular system (b) or enhancing mitochondrial energy metabolism (c). Nutraceuticals enhancing oxidative phosphorylation can augment the activity of mitochondrial complexes 1 and 2 (c). rTMS and tDCS are able to modify cortical responsivity (a) and thalamocortical circuits (d). Transcutaneous nerve stimulation may act by inducing long-term plasticity changes in central pain control centers (e). Vagus nerve stimulation is able to modulate the thalamus (d), the brainstem monoaminergic nuclei (f) and the cerebral cortex (a). Neurofeedback may act via neuroplastic changes in interconnected cerebral areas, such as the thalamus (d), brainstem (f) and various cortical networks (a), including executive, salient and attentional networks.
rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation.

TREATMENT OF MIGRAINE

II. Drug treatment

A. Preventive treatment

- beta blockers (propranolol, metoprolol, atenolol
- calcium blockers (verapamil, flunnarizine)
- anticonvulsants (gabapentin, topiramate, valproic acid)
- antidepressants (tricyclic antidepresants, venlafaxin)
- angiotensin converting enzyme inhibitors or angiotensin receptor blockers (lisinoprin, candesartan, cyproheptadine, ibuprofen, ketoprofen, naproxen)

- No one drug is superior to the other; the choice of suitable treatment is often a case of selecting from drugs on the basis of their side effects.

TREATMENT OF MIGRAINE: PREVENTIVE

	Level of evidence	Daily dose
β blockers		
Atenolol	B	50–200 mg once a day
Metoprolol	A	50–200 mg once a day for long-acting formulation
Nadolol	B	20–160 mg once a day
Propranolol	A	40–240 mg once a day for long-acting formulation
Antidepressants		
Timolol	A	20–60 mg once a day
Amitriptyline	B	10–50 mg before bed
Nortriptyline	..*	10–150 mg before bed
Venlafaxine	B	75–225 mg once a day for long-acting formulation
Calcium-channel blockers and anticonvulsants		
Verapamil	U	120–960 mg in divided doses for long-acting formulation
Flunarizine	A	5–10 mg once a day
Gabapentin	U	600–3600 mg in two–three divided doses
Topiramate†	A	50–200 mg twice a day or before bed
Valproic acid–divalproex†	A	500–2000 mg once a day or in two divided doses
Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers		
Lisinopril	C	10–40 mg once a day
Candesartan†	C	16–32 mg once a day
Cyproheptadine	C	4–16 mg before bed
Ibuprofen	B	200 mg twice a day
Fenoprofen	B	200–600 mg twice a day
Ketoprofen	B	50 mg three times a day
Naproxen	B	500–1100 mg once a day
Naproxen sodium	B	550 mg twice a day

TREATMENT OF MIGRAINE

II. Drug treatment

B. Treatment of acute attacks

1. Non-specific treatment

- Analgesic drugs
  - paracetamol
  - codeine phosphate
- Anti-inflammatory drugs
  - acetylosalicylic acid
  - ibuprofen
  - diclofenac
  - naproxen
  - ketorolac
- Anti-emetics
  - metoclopramide

2. Specific antimigraine treatment

- Ergotamines
  - ergotamine
  - dihydroergotamine
- Agonists of 5-HT_{1B} and 5-HT_{1D}
  - sumatriptan
  - zolmitriptan
  - naratriptan
  - rizatriptan
  - eletriptan
  - almotriptan
  - frovatriptan

TREATMENT OF MIGRAINE: ACUTE

	Route	Number needed to treat (2 h pain free)
Sumatriptan 6 mg	Subcutaneous	2·3
Sumatriptan 20 mg	Intranasal	4·7
Zolmitriptan 5 mg	Intranasal	4·6
Almotriptan 12·5 mg	Oral	4·3
Eletriptan 20 mg	Oral	10
Eletriptan 40 mg	Oral	4·5
Frovatriptan 2·5 mg	Oral	8·5
Naratriptan 2·5 mg	Oral	8·2
Rizatriptan 10 mg	Oral	3·1
Sumatriptan 50 mg	Oral	6·1
Sumatriptan 100 mg	Oral	4·7
Zolmitriptan 2·5 mg	Oral	5·9

Migraine attacks were treated at moderate or severe intensity. Numbers needed to treat might be lower than indicated in the table when treatment is administered early while pain is mild.

CGRP TREATMENTS

Gepants: účinné, ale toxické

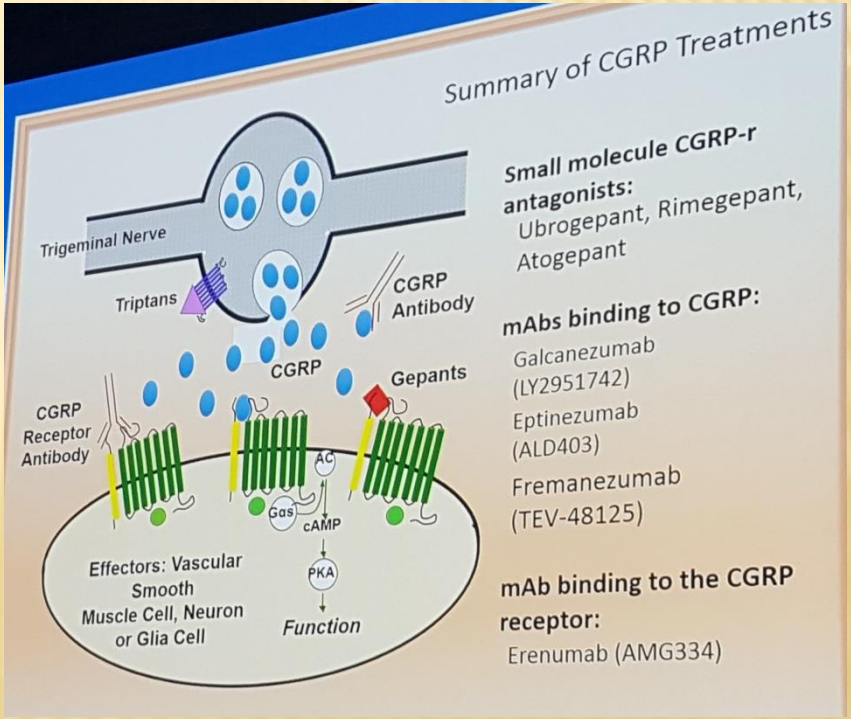
mABS bindings to CRPR:

- Galcanezumab
- Eptinezumab
- Frenezumab

mAB binding to the CGRP receptor:

- Erenumab

This mABS proved to be efficient in reduction of both number and severity of both headache attacks in recurrent migraine, and in reduction of days with headache in chronic migraine



2. Tension-type headache (TTH)

2.1 Infrequent episodic tension-type headache
- 2.1.1 Infrequent episodic tension-type headache associated with pericranial tenderness
- 2.1.2 Infrequent episodic tension-type headache not associated with pericranial tenderness

2.2 Frequent episodic tension-type headache
- 2.2.1 Frequent episodic tension-type headache associated with pericranial tenderness
- 2.2.2 Frequent episodic tension-type headache not associated with pericranial tenderness

2.3 Chronic tension-type headache
- 2.3.1 Chronic tension-type headache associated with pericranial tenderness
- 2.3.2 Chronic tension-type headache not associated with pericranial tenderness

2.4 Probable tension-type headache
- 2.4.1 Probable infrequent episodic tension-type headache
- 2.4.2 Probable frequent episodic tension-type headache
- 2.4.3 Probable chronic tension-type headache

Tension-type headache:

- **is not of pulsating quality**
- **Is not unilateral**
- **Is not aggravated by physical activity**
- **Is not of severe intensity**
- **Is not accompanied by nausea, vomitting, photofobia or phonofobia**

3. Trigeminal autonomic cephalalgias (TACs)

- 3.1 Cluster headache
  - 3.1.1 Episodic cluster headache
  - 3.1.2 Chronic cluster headache
- 3.2 Paroxysmal hemicrania
  - 3.2.1 Episodic paroxysmal hemicrania
  - 3.2.2 Chronic paroxysmal hemicrania
- 3.3 Short-lasting unilateral neuralgiform headache attacks
  - 3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
    - 3.3.1.1 Episodic SUNCT
    - 3.3.1.2 Chronic SUNCT
  - 3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)
    - 3.3.2.1 Episodic SUNA
    - 3.3.2.2 Chronic SUNA
- 3.4 Hemicrania continua
  - 3.4.1 Hemicrania continua, remitting subtype
  - 3.4.2 Hemicrania continua, unremitting subtype
- 3.5 Probable trigeminal autonomic cephalalgia
  - 3.5.1 Probable cluster headache
  - 3.5.2 Probable paroxysmal hemicrania
  - 3.5.3 Probable short-lasting unilateral neuralgiform headache attacks
  - 3.5.4 Probable hemicrania continua

Paroxysmal hemikrania: respond absolutely to indomethacin!!!

3.1 CLUSTER HEADACHE

8.11.2019

A. At least five attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)[1]
C. Either or both of the following:
   1. at least one of the following symptoms or signs, ipsilateral to the headache:
      a) conjunctival injection and/or lacrimation
      b) nasal congestion and/or rhinorrhoea
      c) eyelid oedema
      d) forehead and facial sweating
      e) miosis and/or ptosis
   2. a sense of restlessness or agitation
D. Occurring with a frequency between one every other day and eight per day[2]
E. Not better accounted for by another ICHD-3 diagnosis.

4.OTHER PRIMARY HEADACHE DISORDERS

4.1 Primary cough headache
- 4.1.1 Probable primary cough headache

4.2 Primary exercise headache
- 4.2.1 Probable primary exercise headache

4.3 Primary headache associated with sexual activity
- 4.3.1 Probable primary headache associated with sexual activity

4.4 Primary thunderclap headache

4.5 Cold-stimulus headache
- 4.5.1 Headache attributed to external application of a cold stimulus
- 4.5.2 Headache attributed to ingestion or inhalation of a cold stimulus
- 4.5.3 Probable cold-stimulus headache
  - 4.5.3.1 Headache probably attributed to external application of a cold stimulus
  - 4.5.3.2 Headache probably attributed to ingestion or inhalation of a cold stimulus

4.6 External-pressure headache
- 4.6.1 External-compression headache
- 4.6.2 External-traction headache
- 4.6.3 Probable external-pressure headache
  - 4.6.3.1 Probable external-compression headache
  - 4.6.3.2 Probable external-traction headache

4.7 Primary stabbing headache
- 4.7.1 Probable primary stabbing headache

4.8 Nummular headache
- 4.8.1 Probable nummular headache

4.9 Hypnic headache
- 4.9.1 Probable hypnic headache

4.10 New daily persistent headache (NDPH)
- 4.10.1 Probable new daily persistent headache

THE SECONDARY HEADACHES

5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial and/or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homoeostasis
11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structure
12. Headache attributed to psychiatric disorder

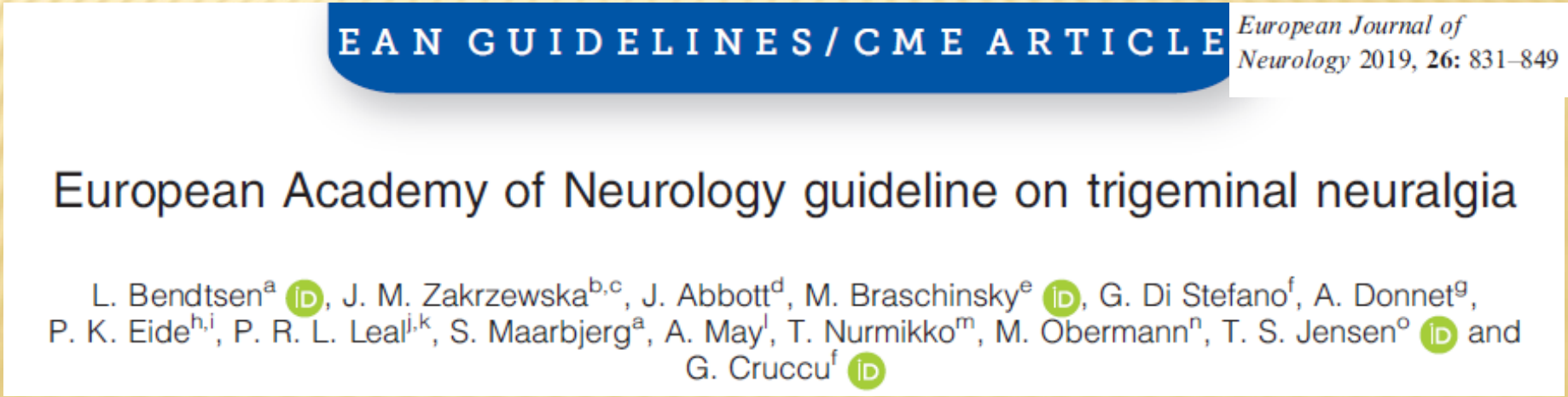
Secondary headache	
Type	*Prevalence (%)*
Systemic infection	63
Head injury	4
Drug-induced headache	3
Subarachnoid hemorrhage	<1
Vascular disorders	1
Brain tumor	0-1

Rasmussen et al. 1995

TRIGEMINAL NEURALGIA: EPIDEMIOLOGY

Prevalence is 150/milion, women:men = 3:2 (3:1), mostly > 60 years.

Arterial hypertension is established risk factor.



NEW CLASSIFICATION OF TRIGEMINAL NEURALGIA

- Etiology

1. Classical TN (neurovascular conflict – NCV - with morphological changes of trigeminal nerve due to compression)
2. Idiopathic TN (no NCV or NCV with no morphological changes of trigeminal nerve)
3. Secondary TN (other pathology or disease as a cause)

- Clinical form (phenotype):

1. Pure paroxysmal form
2. TN with concomitant continuous pain

CLASSICAL TRIGEMINAL NEURALGIA

- It involves mostly 2. and 3. trigeminal branch, 1. branch is involved in 5% only.
- Pain is sharp, lancinating, like electrique shocks, sometimes continues as ongoing dull pain.
- Pain is mostly unilateral (bilatera in 3% only).
- Trigger zone is present in 50% of patients. Pain could be triggered by chewing, cleaning the tooth, speaking, washing, yawning, laughing, blowing one‘s nose.
- There is no motor or sensory deficit in trigeminal zone.
- Remisions could last months or years.

TRIGEMINAL NEURALGIA: DIAGNOSTIC CRITERIA

Diagnostic criteria are based onthe characteristics of pain, normal neurological findings and the absence of clear cause of pain.

A. Attacks of pain lasting from a fragment of second to 2 minutes in an area of one or more trigeminal branches and complying with criteria B and C.

B. Pain has to have one of the following characteristics:

- Intense, sharp, superficial, stabbing
- Induced from a trigger zone or triggeering factors

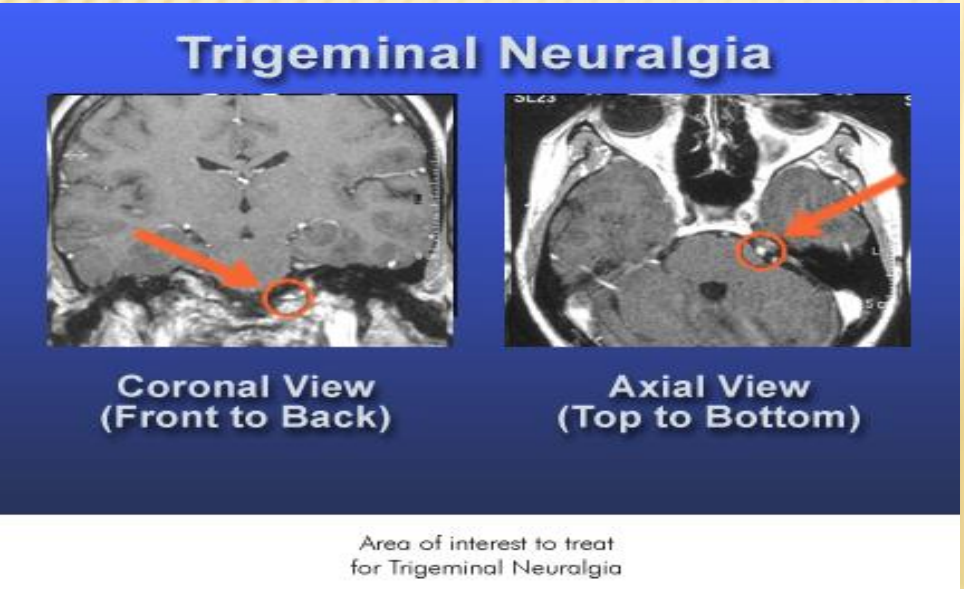
C. Atacks are stereotypic in an individual patient

D. No other pathology or disease as a cause of pain.

CLASSICAL TRIGEMINAL NEURALGIA

Neurovascular confict is a cause – a compression of trigeminal nerve by a vessel (mostly a. cerebelli superior, less frequently by a. cerebelli anterior inferior or a. basilaris) 4-6 mm after the exit from the brainstem (transitional zone from central – oligodendroglia – to peripheral – Schwann cells – myelin.

NEUROVASCULAR CONFLICT



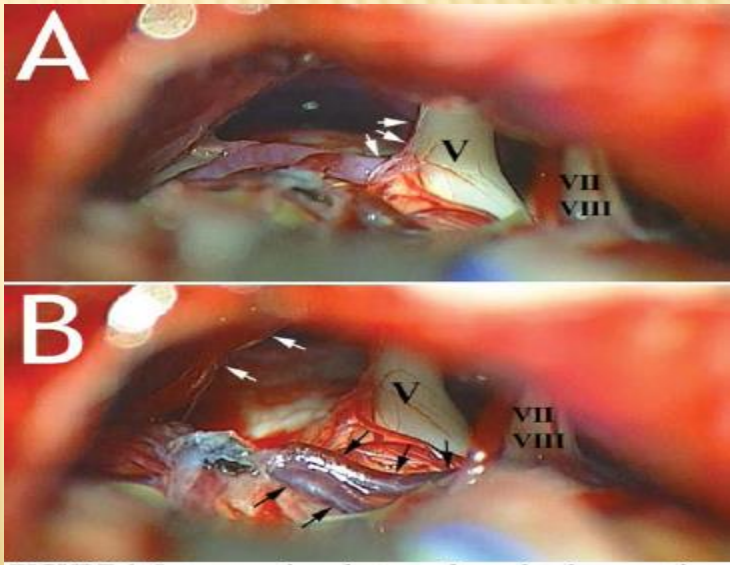
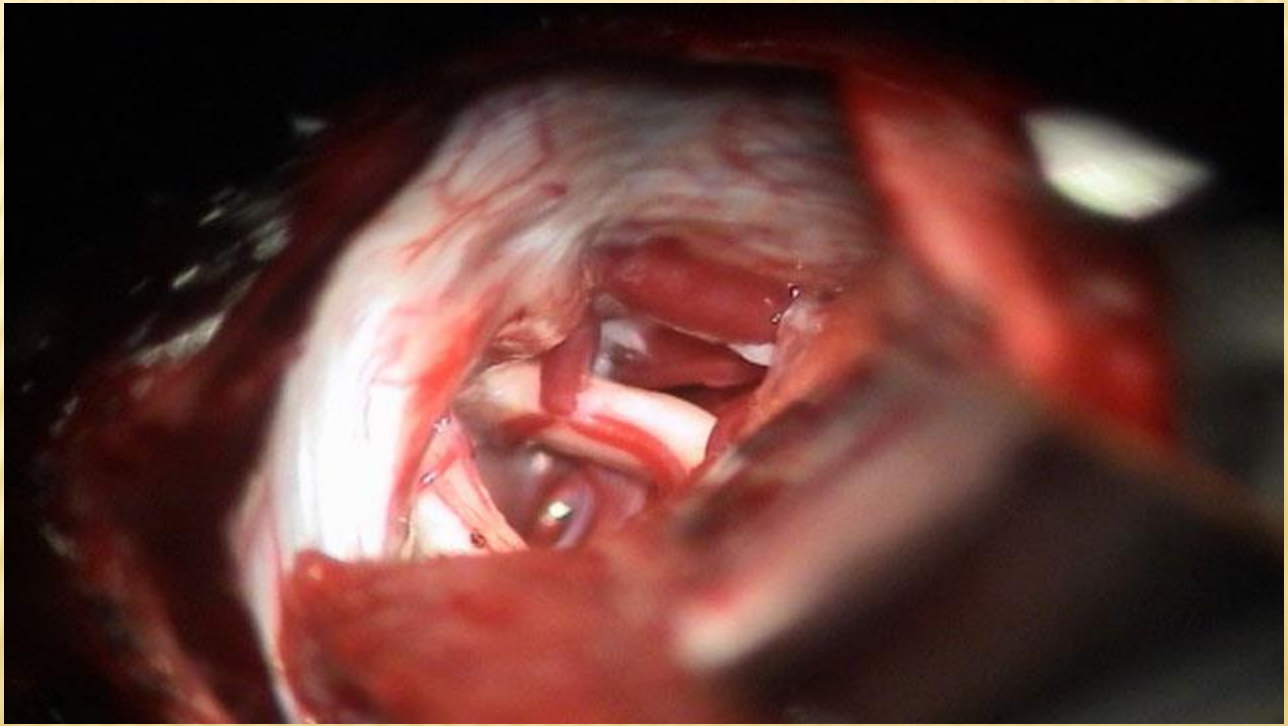


FIGURE 1: Intraoperative photographs under the operating microscope in a patient with right-sided TN showing the trigeminal nerve (V) and the seventh and eighth cranial nerve complex (VII & VIII). The trigeminal nerve is compressed from below from a loop of the superior cerebellar artery (white arrow heads in figures A and B). Once the artery is moved away and the cerebellum mobilized to show the nerve as it blends with the brain stem (Figure B), the nerve is also found to be cross-compressed from above by two veins (black arrow heads).

NEUROVASCULAR CONFLICT



SECONDARY TRIGEMINAL NEURALGIA

It is a symptom of another disease.

- Is is possible to reliably clinically distinguish secondary and classical TN?

There are samo clues to secondary TN:

- younger age
- worse therapeutical response
- involvement of 1. trigeminal branch
- sensory deficit
- According to last guideline it is NOT possible to clinically differentiate classical and secondary TN!!!

MRI focused on NCV and other causes of TN should be a part of routine diagnostic algorithm.

SECONDARY TRIGEMINAL NEURALGIA

- 3% of TN is caused by multiples sclerosis (MS), especially between 20-40 years; 1% of MS patients develop TN
- Painful ophthalmoplegia syndrome (Tolosa-Hunt) – granulomatous inflammation of the cavernous sinus)
- Compression of the trigeminal nerve in the cerebellopontine angle – schwannoma of n.VIII, V, meningeoma
- Other brainstem lesions – syringobulbia, basilar aneurysm
- Postherpetic neuralgia (herpes zoster ophthalmicus)

THERAPY OF TN

A. Acute treatment
1. I.v. phenytoin or lidocain (low evidence)

B. Chronic treatment
1. Carbamazepine, oxcarbazepine (high evidence)
2. Lamotrigine, baclofen, phenytoin, pregabalin, gabapentin, Botox (low evidence)
3. Microvascular decompression
4. Gamma knife radiosurgery
5. Ablative neurosurgical techniques

C. Causative treatment in secondary TN