One Hundred Years of Migraine Research

Major Clinical and Scientific Observations From 1910 to 2010

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New era of migraine (1980-1990)

All images have been obtained from freely available internet sites

- **A new headache classification**

  Classification Committee of the IHS, 1988

- **A new drug for migraine- the discovery of Sumatriptan**

  Humphrey et al, 1988

- **Migraine and calcitonin gene-related peptide**

  Goadsby and Edvinsson, 1990

Development of ICHD

1962 Ad Hoc Committee on Classification of Headache.

1978 Olesen proposed a diagnostic classification of headache disorder.

1988 The ICHD was published.

- Operational diagnostic criteria.

1992 The ICHD was adopted by WHO into ICD-10.

2004 The ICHD-II was published.

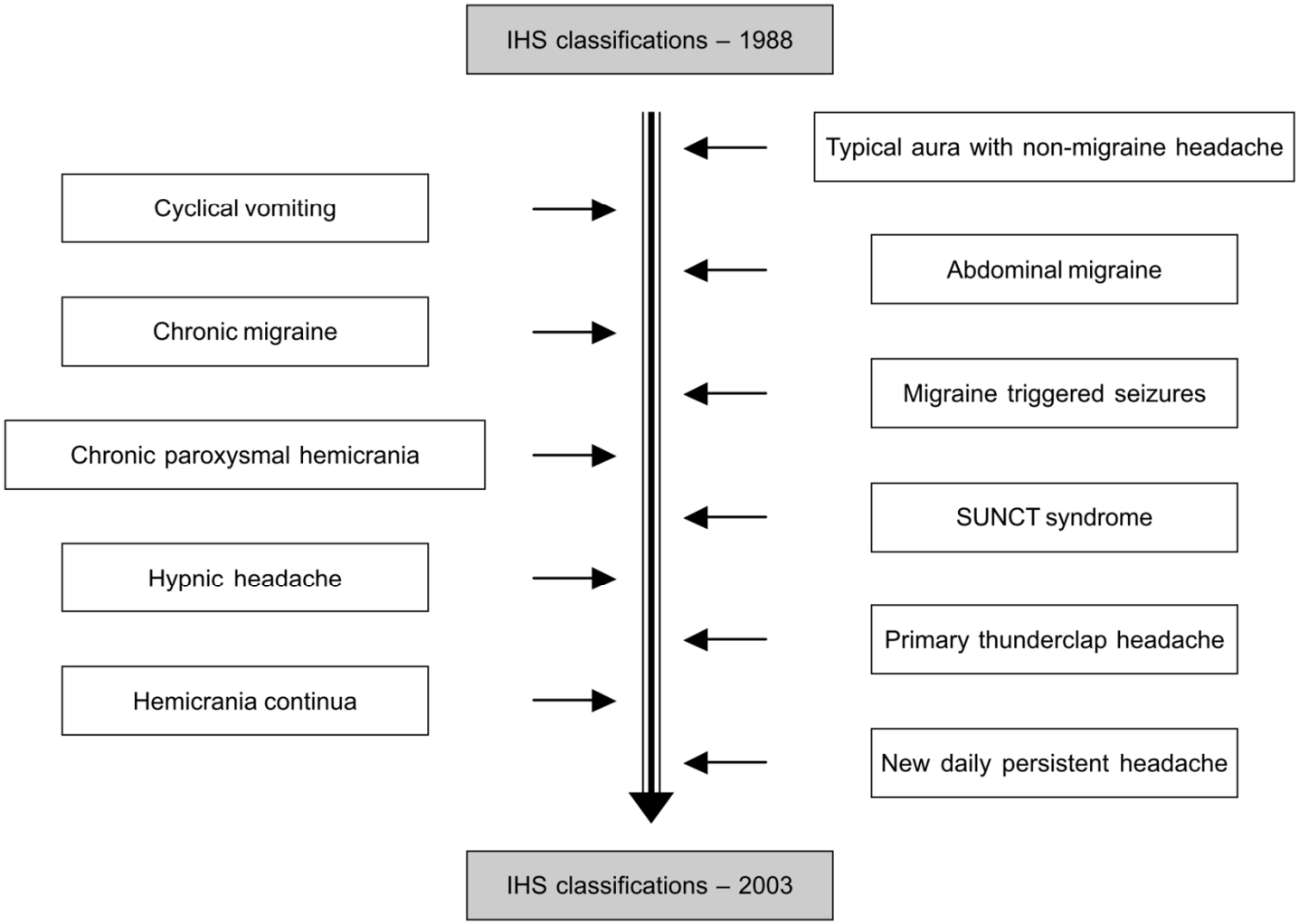
- Typical aura could be followed by either migraine headache or just headache.
- Sporadic hemiplegic migraine as a new subtype of migraine with aura.
- Chronic migraine as a complication of migraine.

2006 The criteria for chronic migraine revised.

Table 1
Criteria diagnosis for migraine from 1988 to 2003 classification

1988 – Classification	2003 – Classification
1.1 Migraine without aura	1.1 Migraine without aura
1.2 Migraine with aura 1.2.1 Migraine with typical aura 1.2.2 Migraine with prolonged aura 1.2.3 Familial hemiplegic migraine 1.2.4 Basilar migraine 1.2.5 Migraine aura without headache 1.2.6 Migraine with acute onset aura	1.2 Migraine with aura 1.2.1 Typical aura with migraine headache 1.2.2Typical aura with non-migraine headache 1.2.3 Typical aura without headache 1.2.4 Familial hemiplegic migraine 1.2.5 Sporadic hemiplegic migraine 1.2.6 Basilar type migraine
1.5 Childhood periodic syndromes that may be precursors to or associated with migraine 1.5.1 Benign paroxysmal vertigo of childhood 1.5.2 Alternanting hemiplegia of childhood	1.3 Childhood periodic syndromes that are commonly precursors of migraine 1.3.1 Cyclical vomiting 1.3.2 Abdominal migraine 1.3.3 Benign paroxysmal vertigo of childhood
1.4 Retinal migraine	1.4 Retinal migraine
1.6 Complications of migraine 1.6.1 Status migranosus 1.6.2 Migrainous infarction	1.5 Complications of migraine 1.5.1 Chronic migraine 1.5.2 Status migranosus 1.5.3 Persistent aura without infarction 1.5.4 Migrainous infarction 1.5.5 Migraine triggered seizures
1.7 Migrainous disorder not fulfilling abore criteria	1.6 Probable migraine 1.6.1 Probable migraine without aura 1.6.2 Probable migraine with aura
1.3 Ophthalmoplegic migraine	It was excluded.

Table 8
Headaches that were included in the new classifications



A New Drug for Migraine
The Discovery of Sumatriptan

Serotonin, triptans and migraine

1960	Intravenous serotonin (5-HT) was effective in the treatment of migraine, but many adverse events.
1967	Serotonin depletion from blood platelets during migraine attacks.
1980+	Identification of an unknown serotonin receptor type (now called 5-HT1B) that is largely located in cranial rather than peripheral blood vessels.
1984	Development of the first 5-HT1B agonists– sumatriptan.

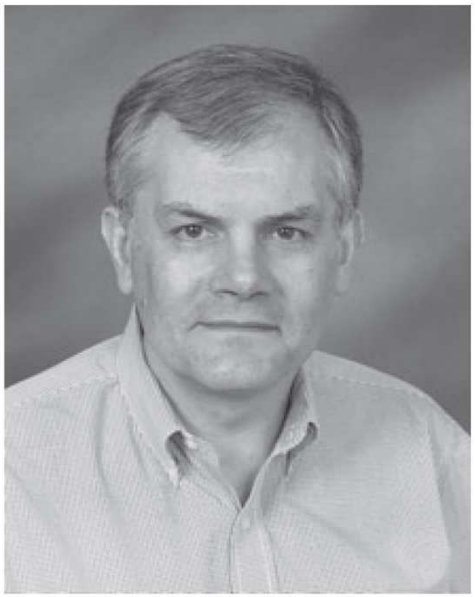
ISSN 0017-8748
Published by Wiley-Blackwell Publishing, Inc.

The Discovery and Development of the Triptans, a Major Therapeutic Breakthrough

Patrick P.A. Humphrey, PhD, DSc, OBE

The drug discovery programs that led to the development of the triptans were determined by the membership of the American Headache Society to be the most important breakthrough in headache medicine in the last 50 years. Dr. Humphrey, who spearheaded the drug discovery, recounts the pioneering work that took place and examines its therapeutic impact.

Headache; 48:685-687



Dr. Humphrey was until recently the Executive Vice President of Research at Theravance Inc., South San Francisco, California. Dr. Humphrey's pioneering drug discovery work led to the development of sumatriptan.

The triptans are a class of drug specifically designed and developed for the acute treatment of migraine. All

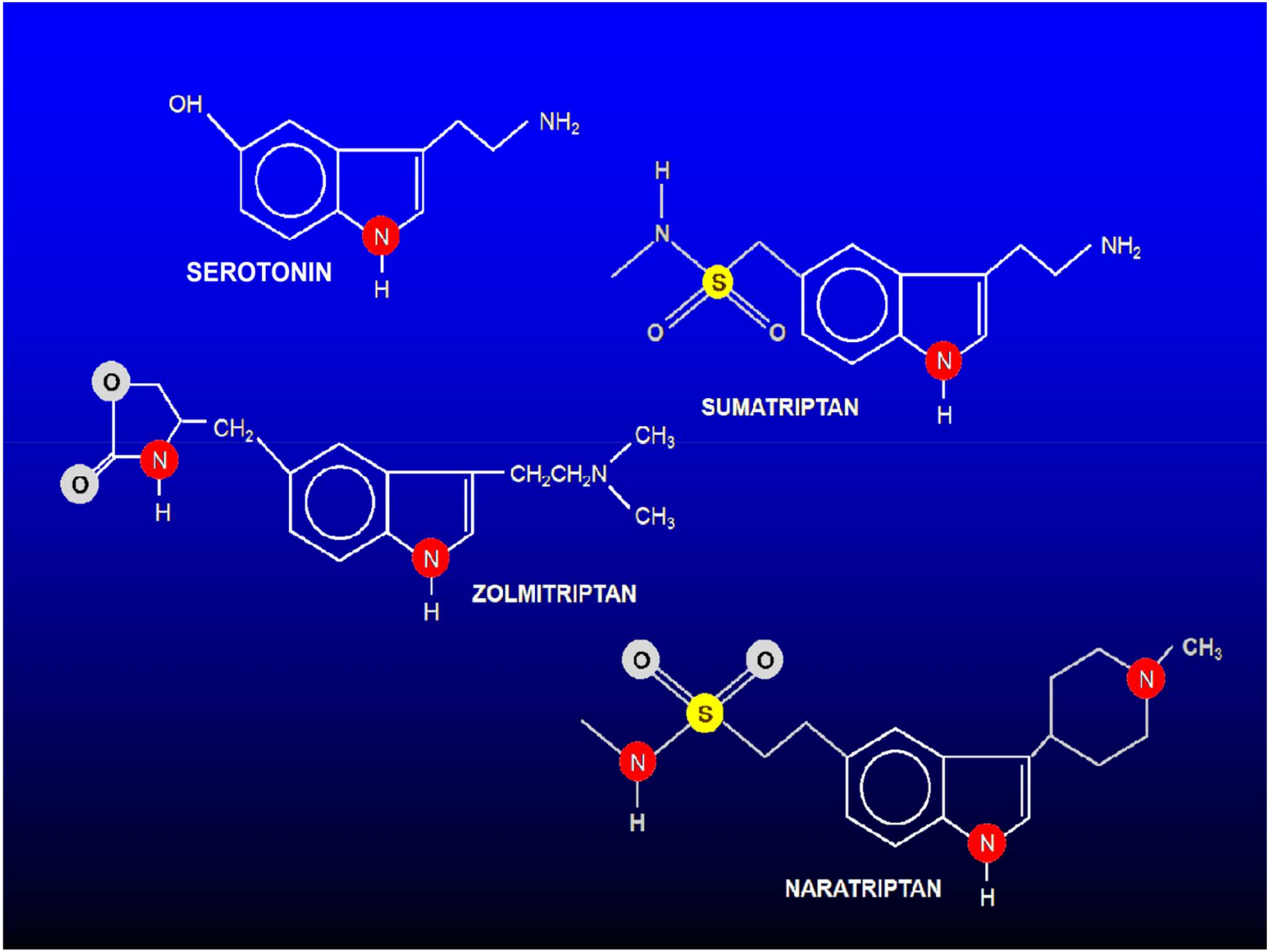
tively continue with their endeavors, without the previously inevitable day-off sick. Sumatriptan also proved to be

Role of serotonin

- serotonin (released from brainstem serotonergic nuclei) plays a role in the pathogenesis of migraine,
  - perhaps mediated by its direct action upon the cranial vasculature,
  - by its role in central pain control pathways,
  - or by cerebral cortical projections of brainstem serotonergic nuclei.
- tricyclic antidepressants, which block serotonin reuptake, are effective antimigraine prophylactic agents.
- more SSRIs are not very effective in migraine prevention.
- low serotonin state may result in a deficit in the serotonin descending pain inhibitory system, facilitating activation of the trigeminovascular nociceptive pathways in conjunction with cortical spreading depression.

Serotonin, methyergide and triptan

- Serotonin- vasoconstrictor for all vessels.
- Methyergide- selectively constrictor effect in the dog carotid bed and femoral vein. The “atypical” 5-HT receptor (5-HT$_{1B}$) was suggested.
- Ketanserin (5-HT$_2$ antagonist) did not antagonize the effect of 5-CONH$_2$T (5-hydroxaminotryptamine, a potent selective 5-HT agonist) in dog saphenous vein.
- 5-CONH$_2$T has only a weak effect on rabbit isolated aorta, but was a potent agonist in dog saphenous vein.
- The triptans are relatively cranioselective when compared the effect on coronary arteries.


OH
NH2
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H
SEROTONIN
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NH2
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SUMATRIPTAN
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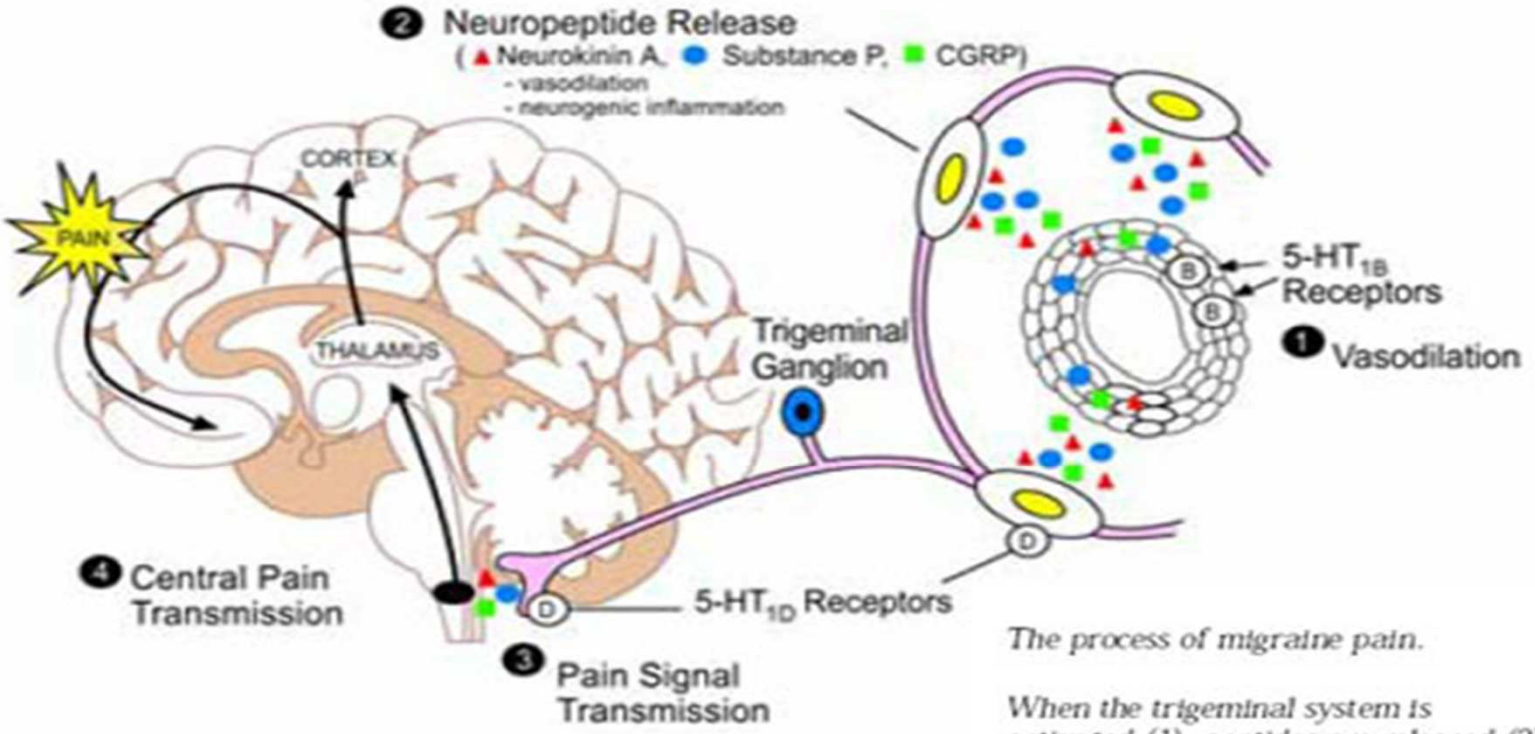
The process of migraine pain



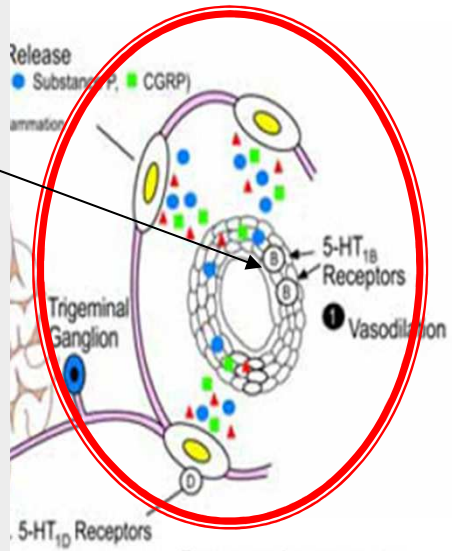
The process of migraine pain.

When the trigeminal system is activated (1), peptides are released (2) prompting an inflammatory reaction. This increases flow of sensory traffic through the brain stem (3), the thalamus and ultimately the cortex (4).

Triptans (serotonin 1B/1D agonist)

"specific" therapies for acute migraine

- Triptans inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem
- Triptans inhibit transmission in the trigeminal nucleus caudalis (TNC), thereby blocking afferent input to second order neurons; this effect is probably mediated by reducing the levels of calcitonin gene related peptide (CGRP).
- Triptans may also activate serotonin receptors in descending brainstem pain modulating pathways and thereby inhibit dural nociception.



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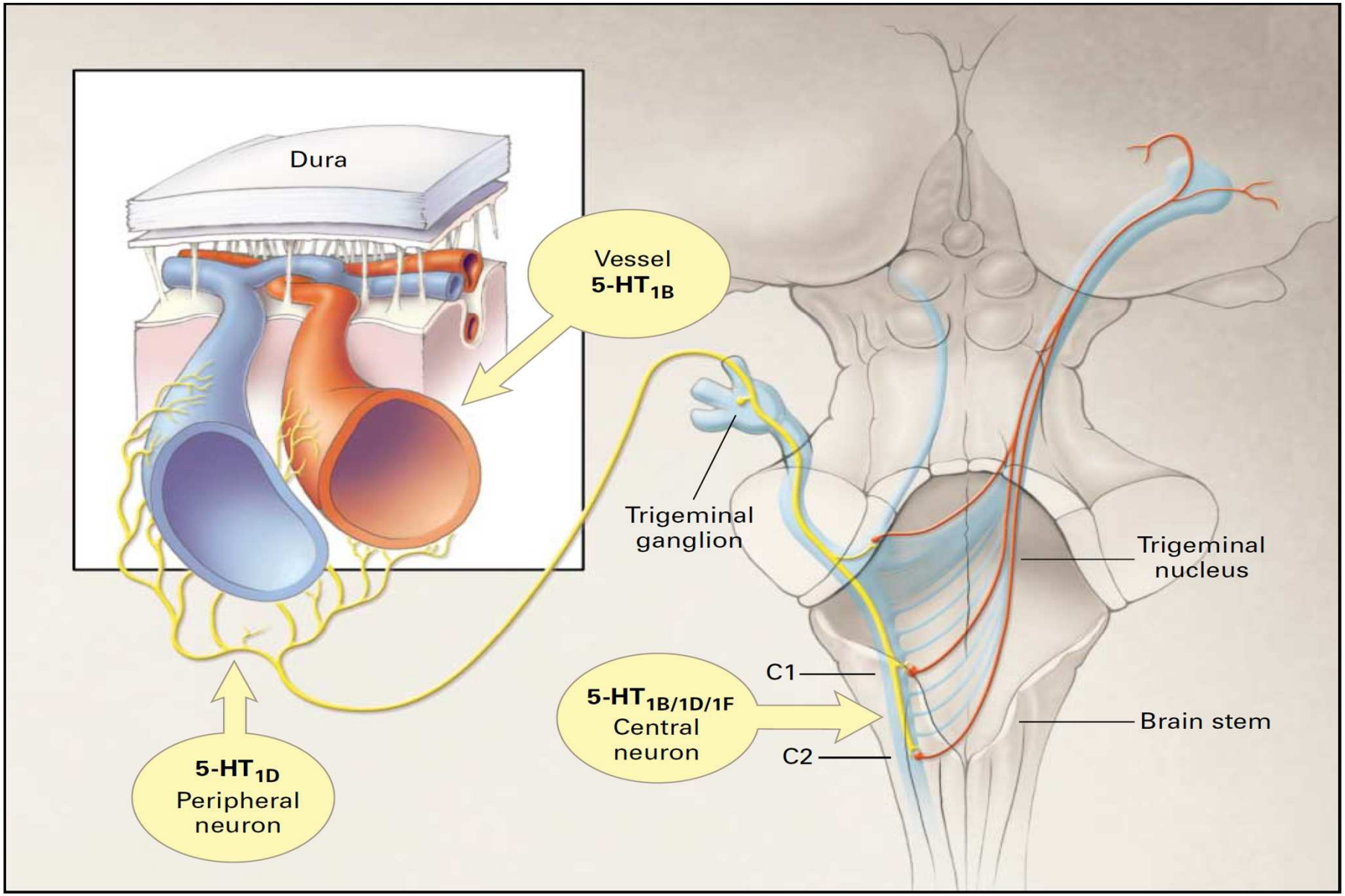
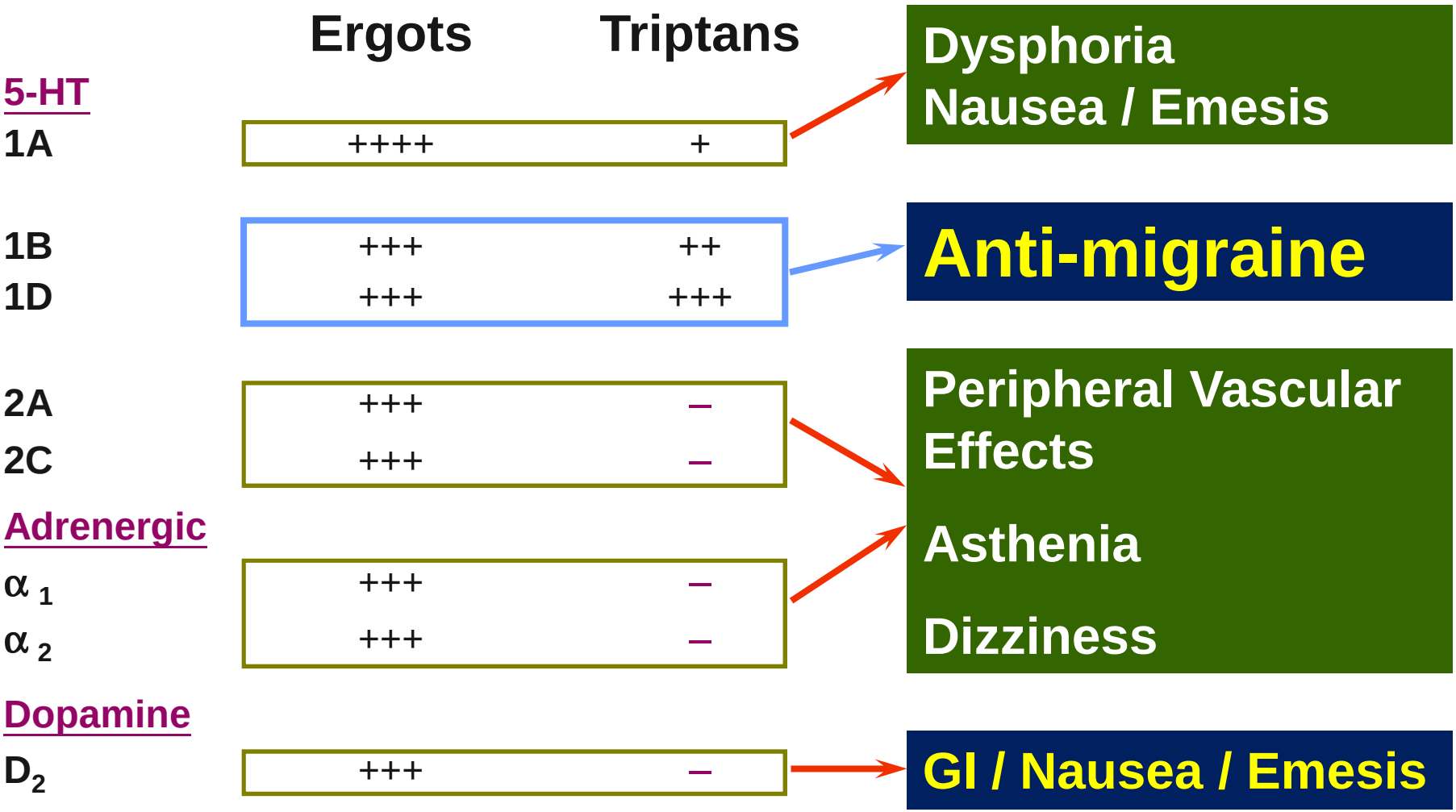


Figure 2. Possible Sites of Action of Triptans in the Trigeminovascular System.

Goadsby PJ, Lipton RB and Ferrari MD, NEJM 2002;346:257-270

Ergots vs. Triptans



Triptan/Ergot
Contraindication and Adverse Events

- Contraindication
  - ischemic heart disease
  - uncontrolled HTN
  - basilar or hemiplegic migraine
  - pregnancy
  - MAO-I use
- Adverse Events
  - paresthesia, tingling
  - flushing, burning, or warm/hot sensation
  - dizzy, somnolence, fatigue, heaviness

Cardiovascular Safety of Triptans

- Incidence of serious cardiovascular events is extremely low.
- Risk-benefit profile favors use in the absence of vascular risk factors.
  - Triptan cardiovascular safety expert panel of the American Headache society – consensus statement

    Headache 44(5):414, 2004

Migraine and Calcitonin Gene-Related Peptide (CGRP)

calcitonin gene-related peptide (CGRP)

- Widely expression in
  - Heart
  - Blood vessels
  - Pituitary
  - Thyroid
  - Lung
  - GI tract
- Biological effect
  - Neuromodulation
  - Vasodilatation
  - Cardiac contractility
  - Bone growth
  - Mammalian development

- Released from motor neurons at the neuromuscular junction and sensory neurons of spinal cord.
- 2 isoforms:
  - α CGRP is present in the sensory neurons
  - β CGRP is mainly present in the enteric nervous system.

Role of calcitonin gene-related peptide (CGRP)

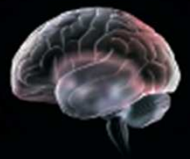
- CGRP- A neuropeptide, present in perivascular nerves of cerebral arteries and trigeminal ganglia nerves, is a potent vasodilator of cerebral and dural vessels.
- Stimulation of the trigeminal ganglion induces the release of CGRP, substance P & VIP and CGRP infusion can trigger a migraine attack in migraineurs.
- CGRP may mediate trigeminovascular pain transmission from intracranial vessels to the central nervous system, as well as the vasodilatory component of neurogenic inflammation. However, the evidence is conflicting.
- Although one study found elevation of CGRP levels in EJV during migraine attack, this result was not reproduced in a subsequent study. In addition, CGRP did not activate or sensitize meningeal nociceptors in an animal model.
- Elevated CGRP levels are normalized in patients with migraine following administration of the sumatriptan, suggesting that triptans may control migraine at least in part by blocking the release of CGRP.

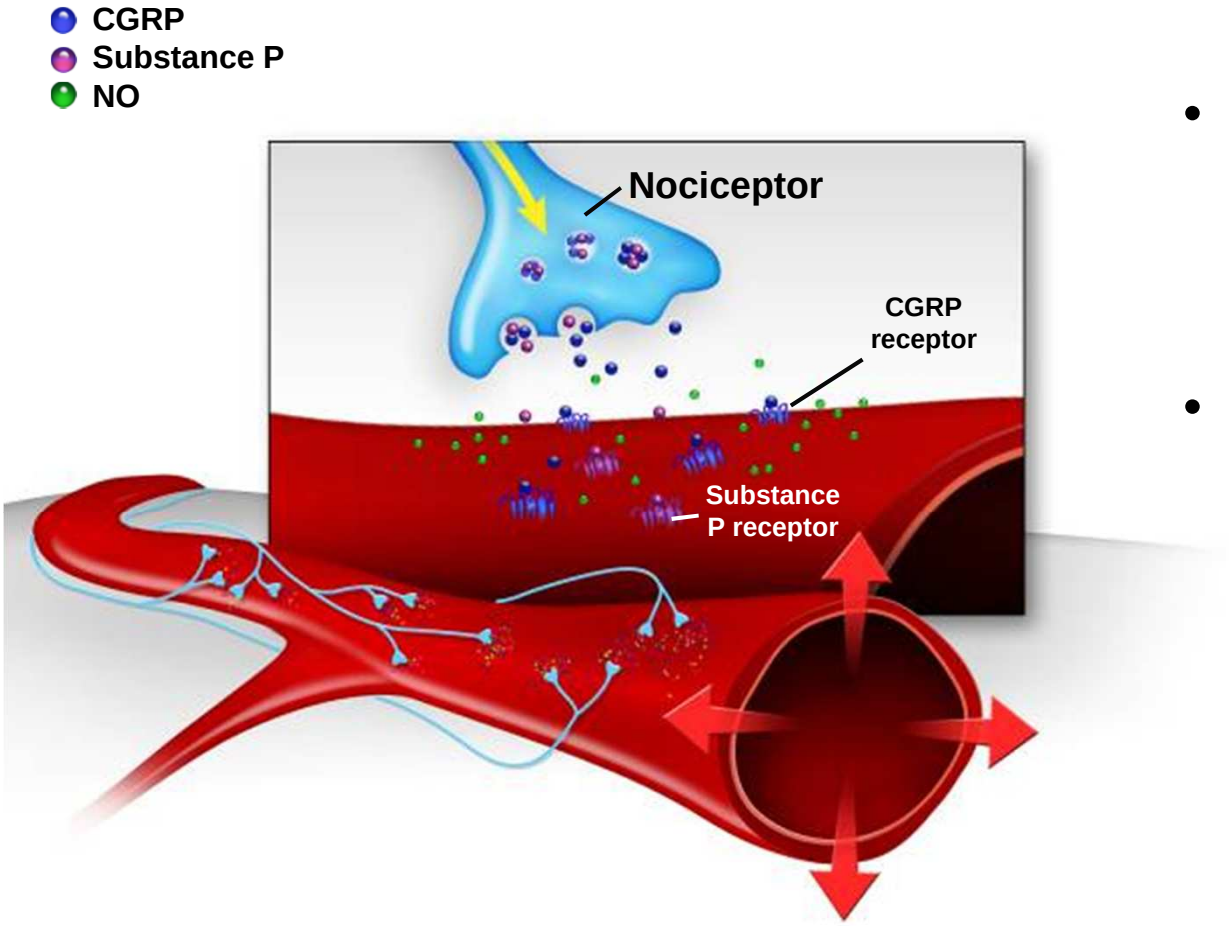
VIP: vasoactive intestinal peptide; EJV: external jugular vein.

CGRP: Central role in migraine

- Highly expressed in both the peripheral and central nervous systems
- Contained in nerve fibers innervating all organs and tissues, including vasculature, skin, muscles
  - Olfaction, audition, learning, feeding, autonomic functions, motor activity, nociception, and vasodilation
- Originally thought to contribute to migraine strictly through its vasodilatory actions
  - Early theories viewed migraine as a vascular disorder
- Then speculated to be involved in peripheral inflammation
  - The neurogenic inflammation theory of migraine
- Currently considered to be a neuropeptide involved in the transmission of migraine pain and induction of the pronociceptive stage
  - The neuronal origin of migraine.

CGRP First Identified as a Potential Mediator of Trigeminal Inflammation

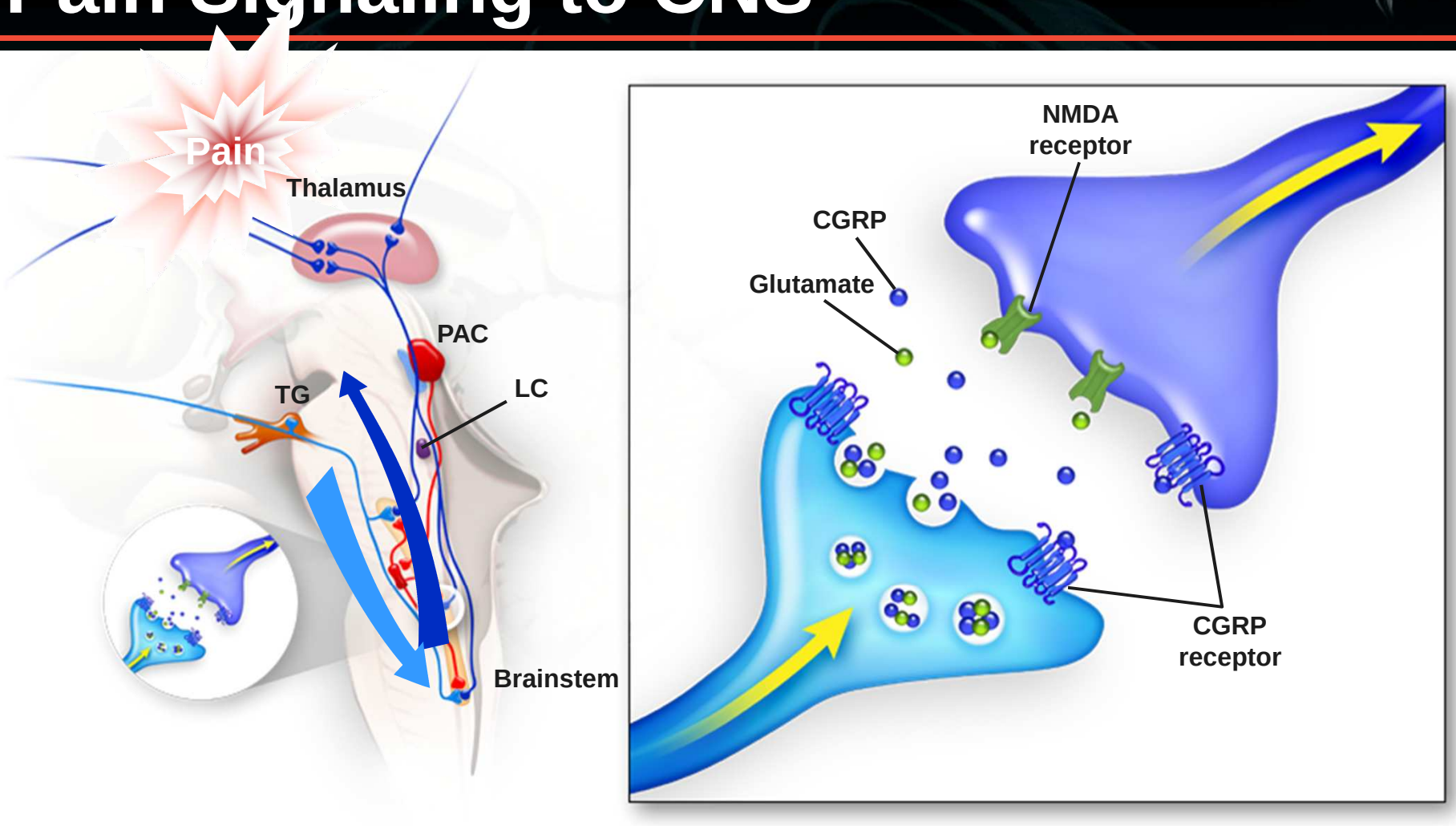




- CGRP, a 37-amino-acid peptide, was first discovered as a potent vasodilator
- Initially considered important in migraine because of its potential peripheral actions:
  - Vasodilation
  - Neuroinflammation

Brain SD et al. *Nature*. 1985;313:54-56; Edvinsson L et al. *Brain Res Rev*. 2005;48:438–456; McCulloch J et al. *Proc Natl Acad Sci USA*. 1986;83:5731–5735; Moskowitz MA. *Neurol Clin.* 1990;8:801–815.

Pain Signaling to CNS

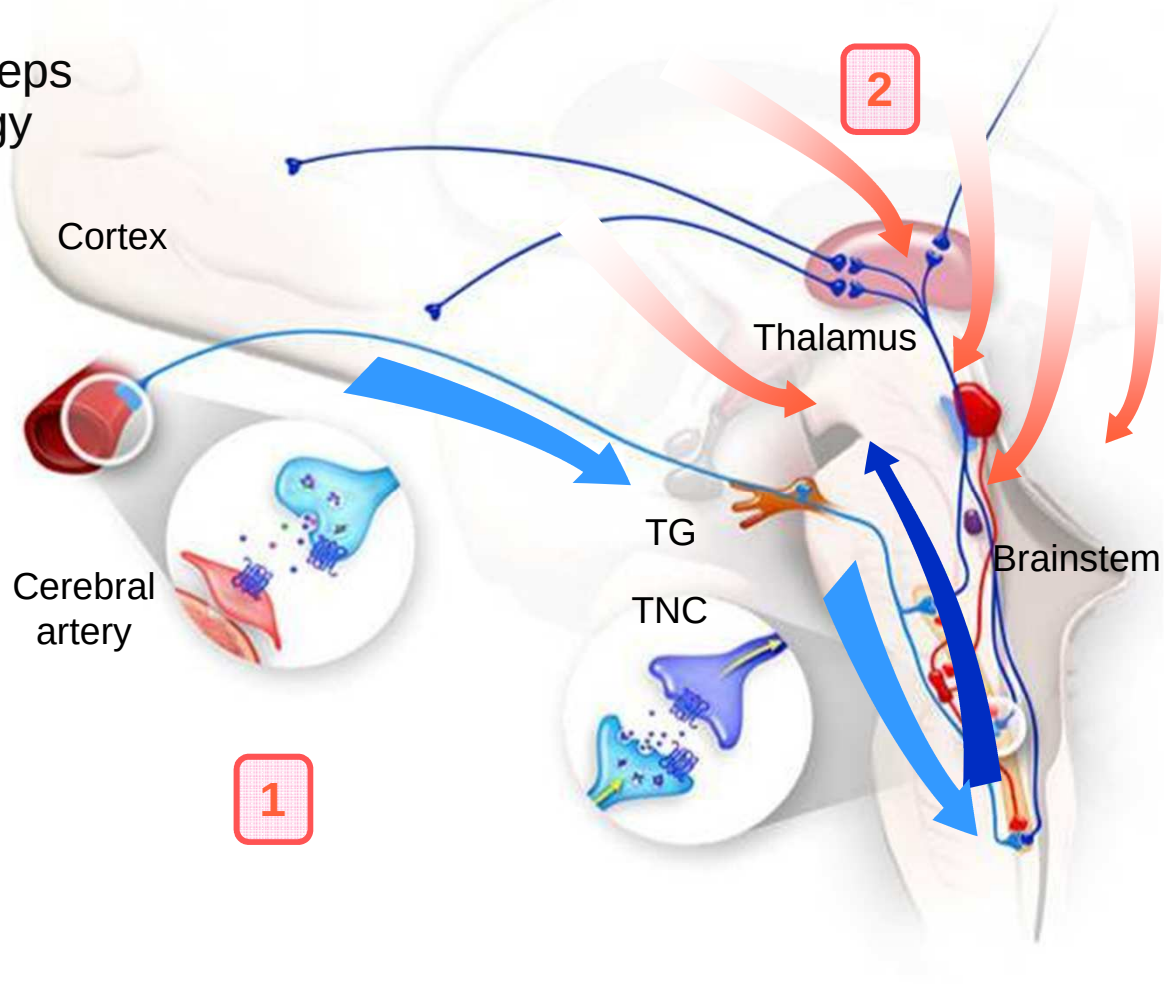


Dodick D et al. *Headache*. 2006;46(suppl 4):S182–S191; Ramadan NM et al. *Pharmacol Ther*. 2006;112:199–212; Storer RJ et al. *Neuroscience*. 1999;90:1371–1376; Storer RJ et al. *Br J Pharmacol*. 2004;142:1171–1181.

CGRP: Central Role in Migraine

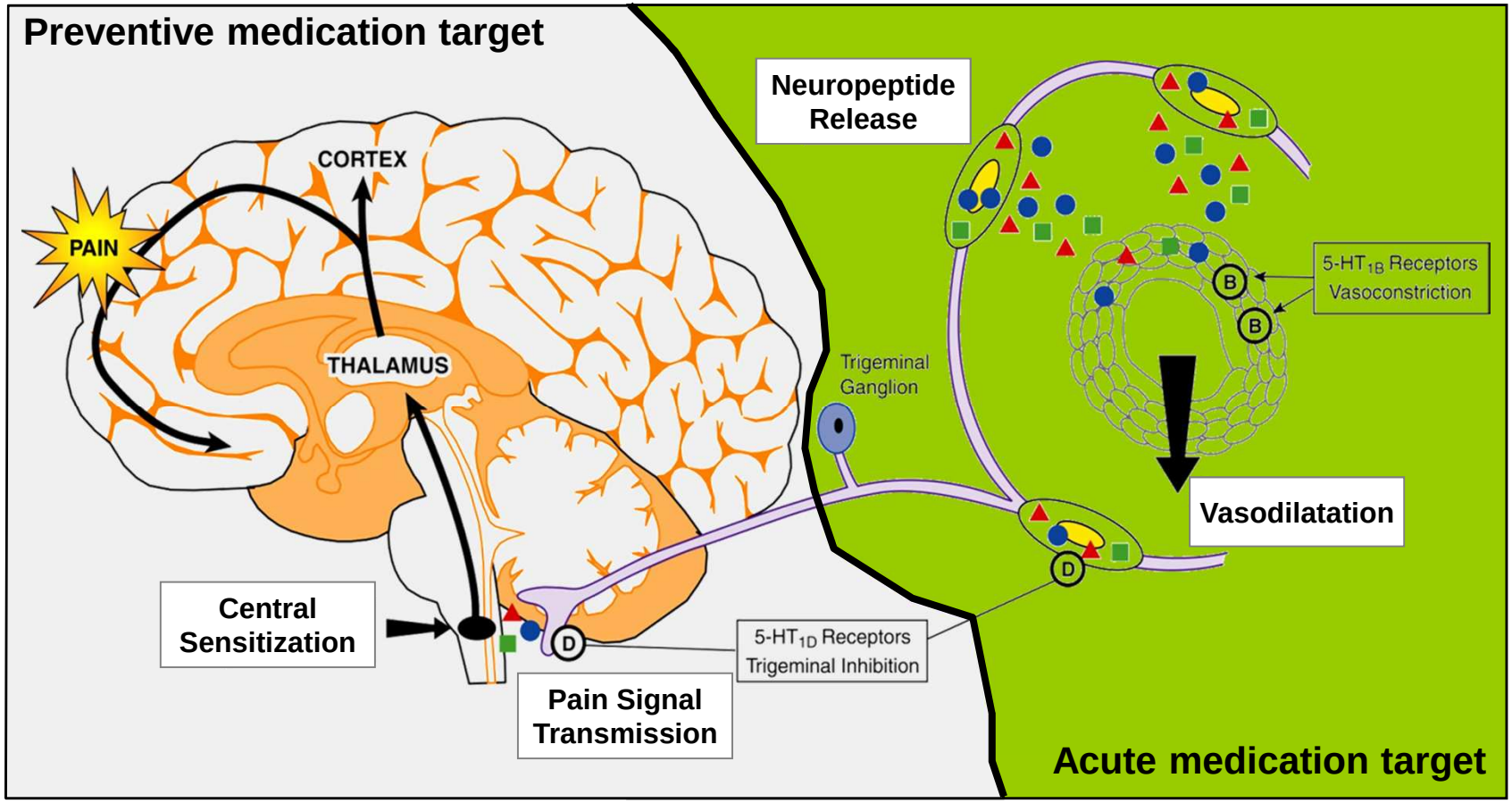
- CGRP involved in many steps of migraine pathophysiology

1. Pain transmission and induction of the pronociceptive state
   - At the ganglion
   - At the caudalis
2. Potential actions at many other sites of the brain
3. Peripherally: inflammation and vasodilation



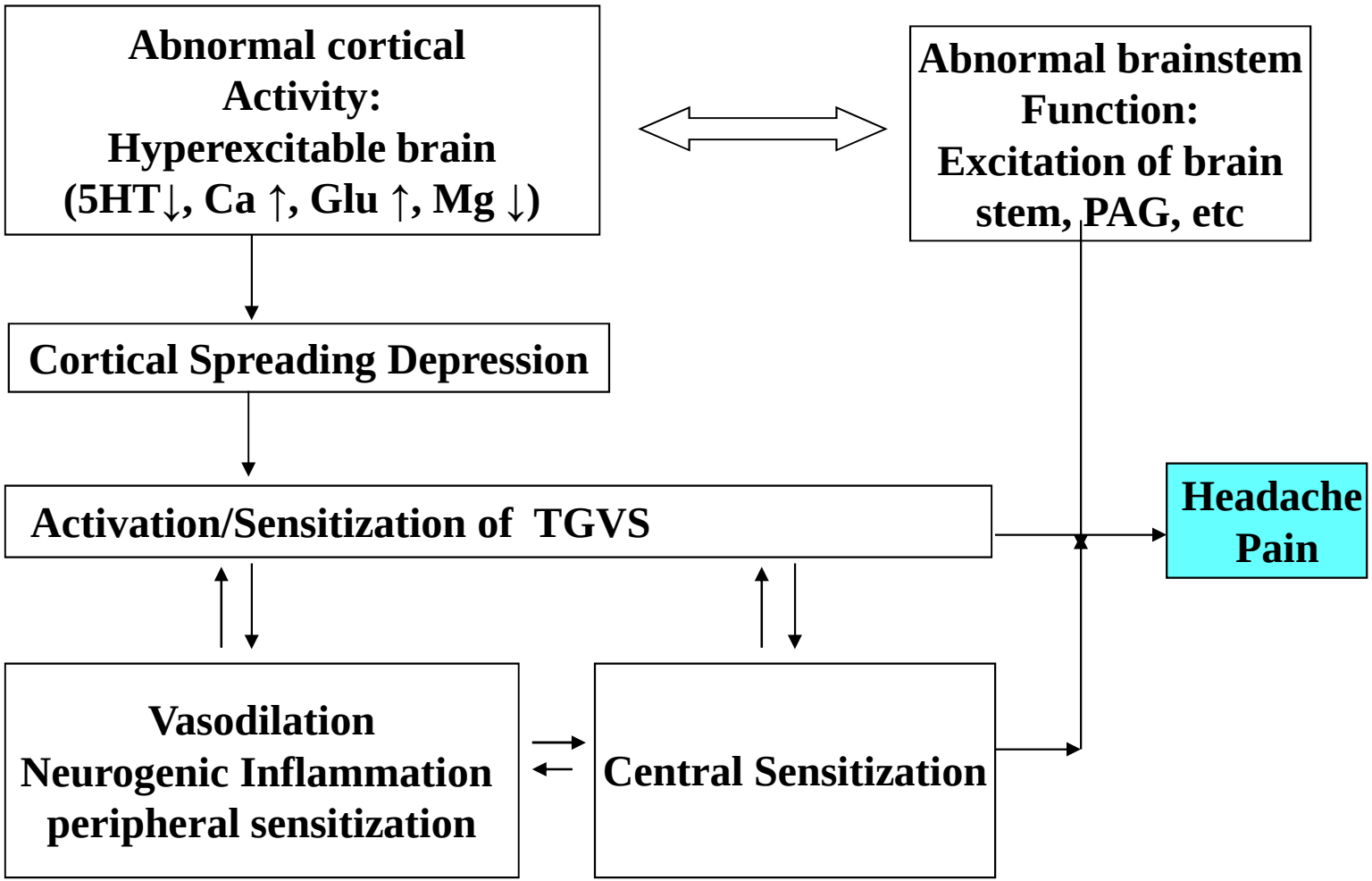
Goadsby PJ et al. *Ann Neurol*. 1988;23:193–196; Goadsby PJ et al. *Ann Neurol.* 1990;28:183–187; Jenkins DW et al. *Neurosci Lett*. 2004;366:241–244; Moskowitz MA. *Neurol Clin*. 1990;8:801–815; Storer RJ et al. *Br J Pharmacol*. 2004;142:1171–1181; Theoharides TC et al. *Brain Res Rev*. 2005;49:65–75.

Trigeminovascular Migraine Pain Pathway



Hargreaves RJ, Shepheard SL. *Can J Neurol Sci.* 1999;26(suppl 3):S12-S19.

Proposed Mechanisms of Migraine



TGVS=trigeminal vascular system.

Adopted from Pietrobon D. Striessing J. Nat Neurosci.2003;4:386-398.

- **Development of migraine headache depends on the activation of these afferents**
- **Activation of the meningeal trigeminovascular afferents leads to activation of second-order dorsal horn neurons in the trigeminal nucleus pars caudalis (TNC).**
- **Impulses are then carried rostrally to brain structures that are involved in the perception of pain, including several thalamic nuclei and the ventrolateral area of the caudal periaqueductal grey region (PAG)**

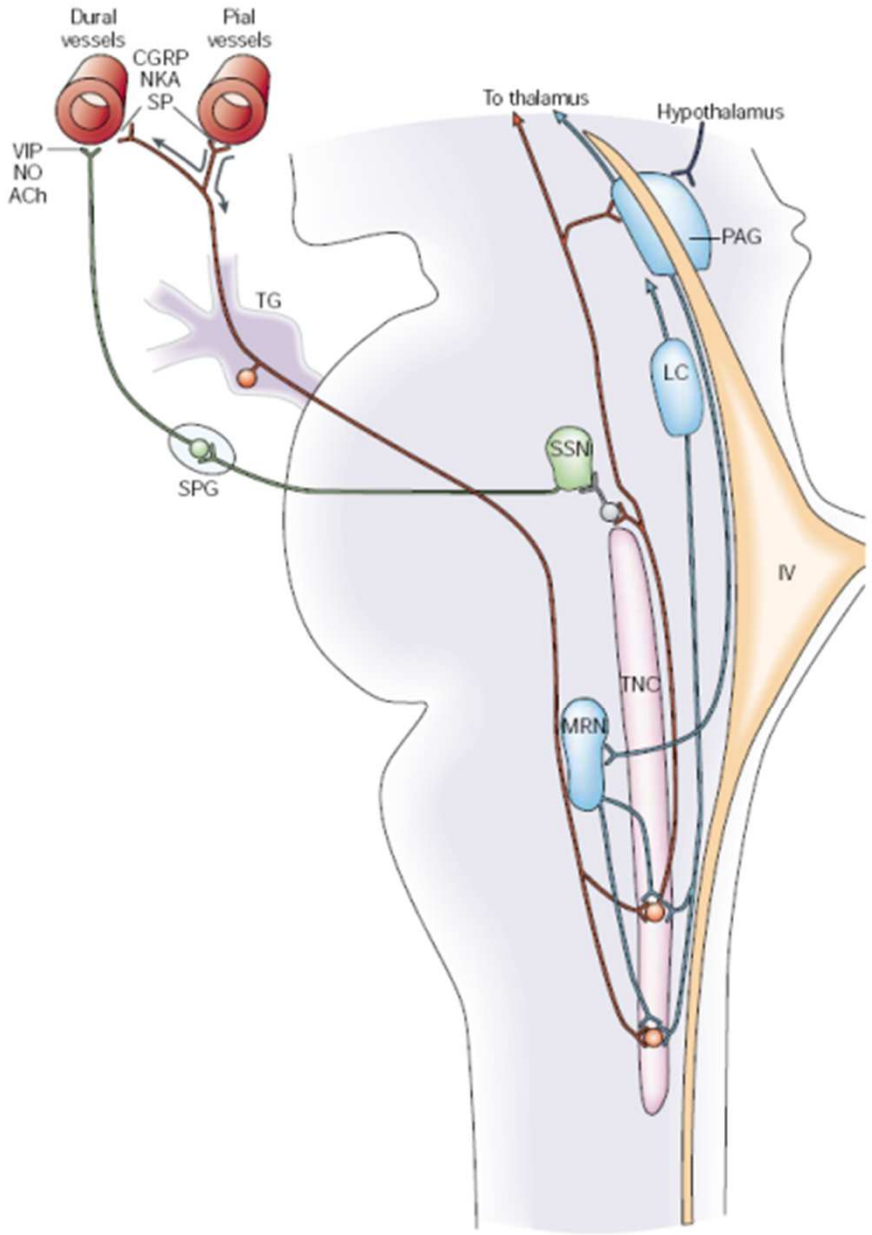


Figure 1 | **Neuronal pathways involved in trigeminovascular activation and pain processing.** IV, fourth ventricle; ACh, acetylcholine; CGRP, calcitonin gene-related peptide; LC, locus coeruleus; PAG, periaqueductal grey region; MRN, magnus raphe nucleus; NKA, neurokinin A; NO, nitric oxide; SP, substance P; SPG, superior sphenopalatine ganglion; SSN, superior salivatory nucleus; TG, trigeminal ganglion; TNC, trigeminal nucleus pars caudalis; VIP, vasoactive intestinal peptide.

New drugs for acute migraine

Table 1. Emerging therapies for acute migraine

Compounds	Treatment class	Clinical phase
COL-144	5-HT_{1F} receptor agonist	Phase II–complete
Telcagepant (MK-0974)	CGRP receptor antagonist	Phase III–complete
BI 44370	CGRP receptor antagonist	Phase II–complete
BGG492	AMPA receptor antagonist	Phase II
Tezampanel (LY-293558)	AMPA and kainate receptor antagonist	Phase II
LY466195[a]	GLUK5 kainate receptor antagonist	Phase II
SB-705498	TRPV1 receptor antagonist	Phase II–complete
NXN-188	Neuronal nitric oxide synthase (nNOS) inhibition & 5-$HT_{1B/D}$ agonist	Phase II
GW274150	Inducible nitric oxide synthase inhibition	Phase II–complete
BGC20-1531	Prostanoid EP4 receptor antagonist	Phase II, phase I

[a]Not yet listed on the *ClinicalTrials.gov* website

AMPA α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid, *CGRP* calcitonin gene-related peptide, *TRPV1* transient receptor potential vanilloid subfamily member 1

Thank you

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