NSAIDs & Triptans in Headache

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南區讀書會

I. NSAIDs

NSAIDs: a historical review (1)

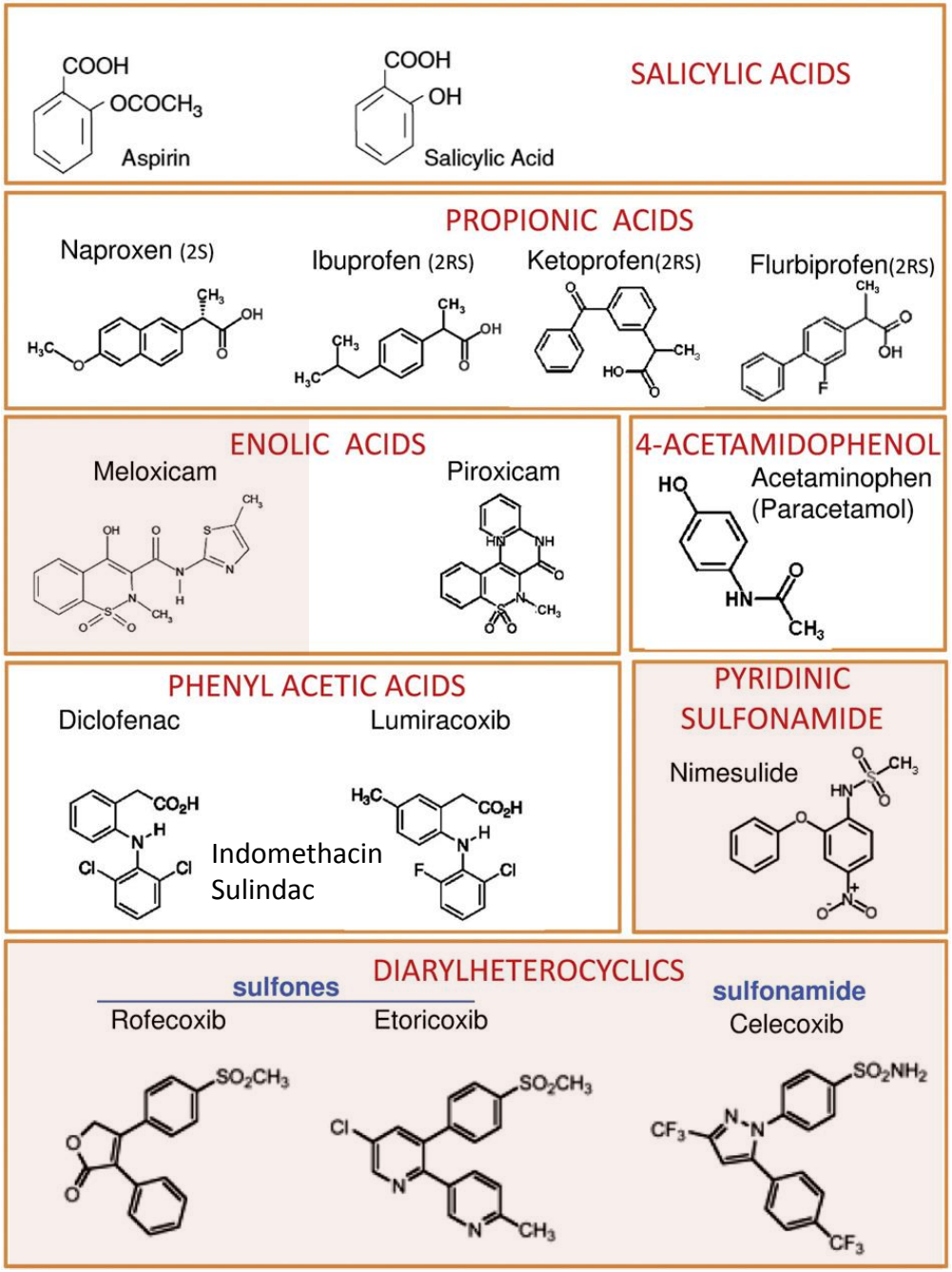
- Salicylic acid: a natural compound with known analgesic activity since antiquity.
- 1763: Na salicylate was discovered by Edward Stone
- 1897: the chemical modification of salicylic acid by Bayer
  → acetylsalicylic acid (aspirin)
- phenylbutazone (1940s) Bone maroow toxicity
  fenamates (1950s)
  indomethacin (1960s)
  proprionates (1970s)
  oxicams, tetrahydropyranoindole, sulphonanilide (1980s) Less GI irritation

NSAIDs: a historical review (2)

- 1970s: the ability of aspirin to inhibit prostaglandin (PG) production by the cyclooxygeniase (COX) enzyme was identified as the basis of its therapeutic action.
- 1988: Purificaiton of COX
- 1992: the discovery of COX1 and COX2
- 1999: rofecoxib (liscenced for OA)
  2000: celecoxib

NSAIDs (nonsteroidal anti-inflammatory drugs)

- NSAIDs possess anti-inflammatory, analgesic and anti-pyretic proprieties
- Main effect: blocking cyclooxygenase (COX): ↓**prostaglandins (PGs)** synthesis from arachidonic acid
  - COX-1 is widely distributed and is involved in homeostatic mechanisms
  - COX-2 is chiefly expressed in areas of inflammation
- **PGs** are implicated in sensitization of peripheral nociceptors associated with tissue damage or inflammation
- The main action of conventional NSAIDs is the non-selective inhibition of both COX isoforms
- However, they do exhibit some differences in their response as treatments and mechanism



Biochimica et Biophysica Acta 1851 (2015) 422–432

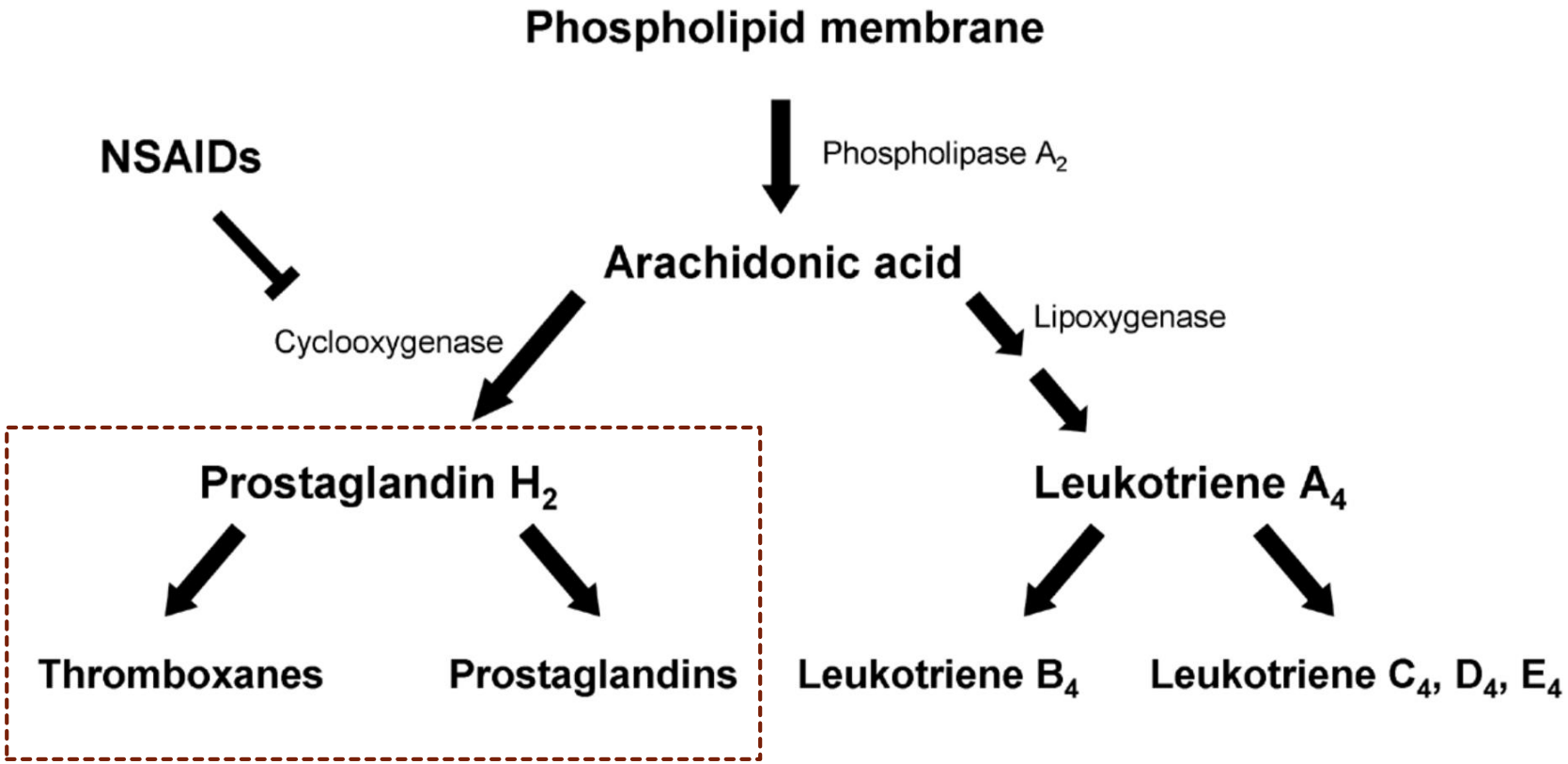
Chemical structures of NSAIDs

As a group, the NSAIDs are structurally diverse, with most being carboxylic acids (羧酸).

- Salicylates
- Propionic acids
- Enolic acids (oxicams)
- Acetic acids
- Pyridinic sulfonamide: nimesulide
- Diarylheterocyclics (coxibs)
- Fenamates
- Naphthylalkanone: nabumetone

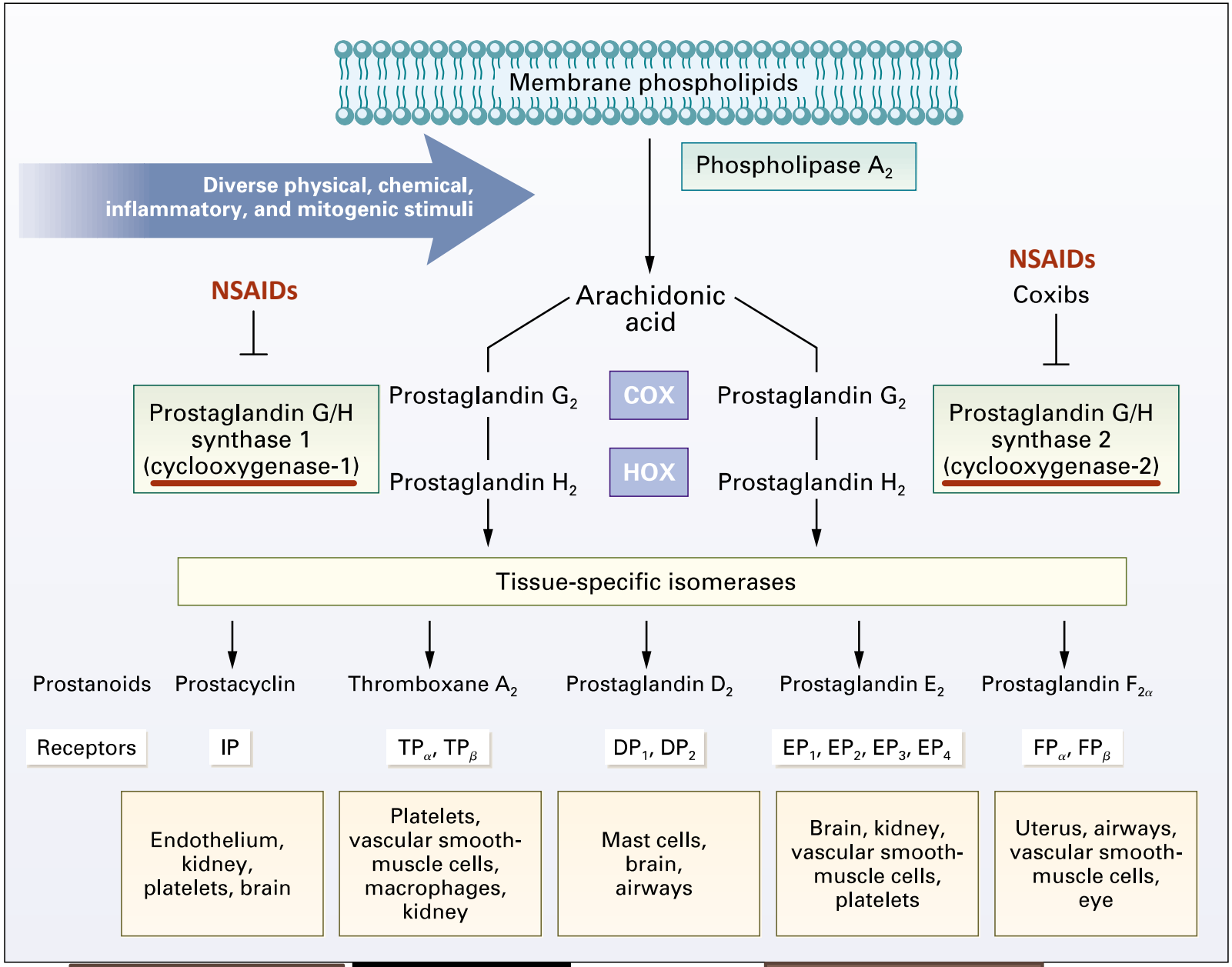
….

Main biochemical pathways of arachidonic acid



NSAIDS have Little or no effect on lipoxygenase (leukotriene synthesis intact)

Pharmaceuticals 2010, 3, 1966-1987



N Engl J Med. 2001 Aug 9;345(6):433-42.

COX1, COX2, COX3

COX-1: expressed in most tissues (with variability).

- A “housekeeping” enzyme, regulating normal cellular processes*, and is stimulated by hormones or growth factors.

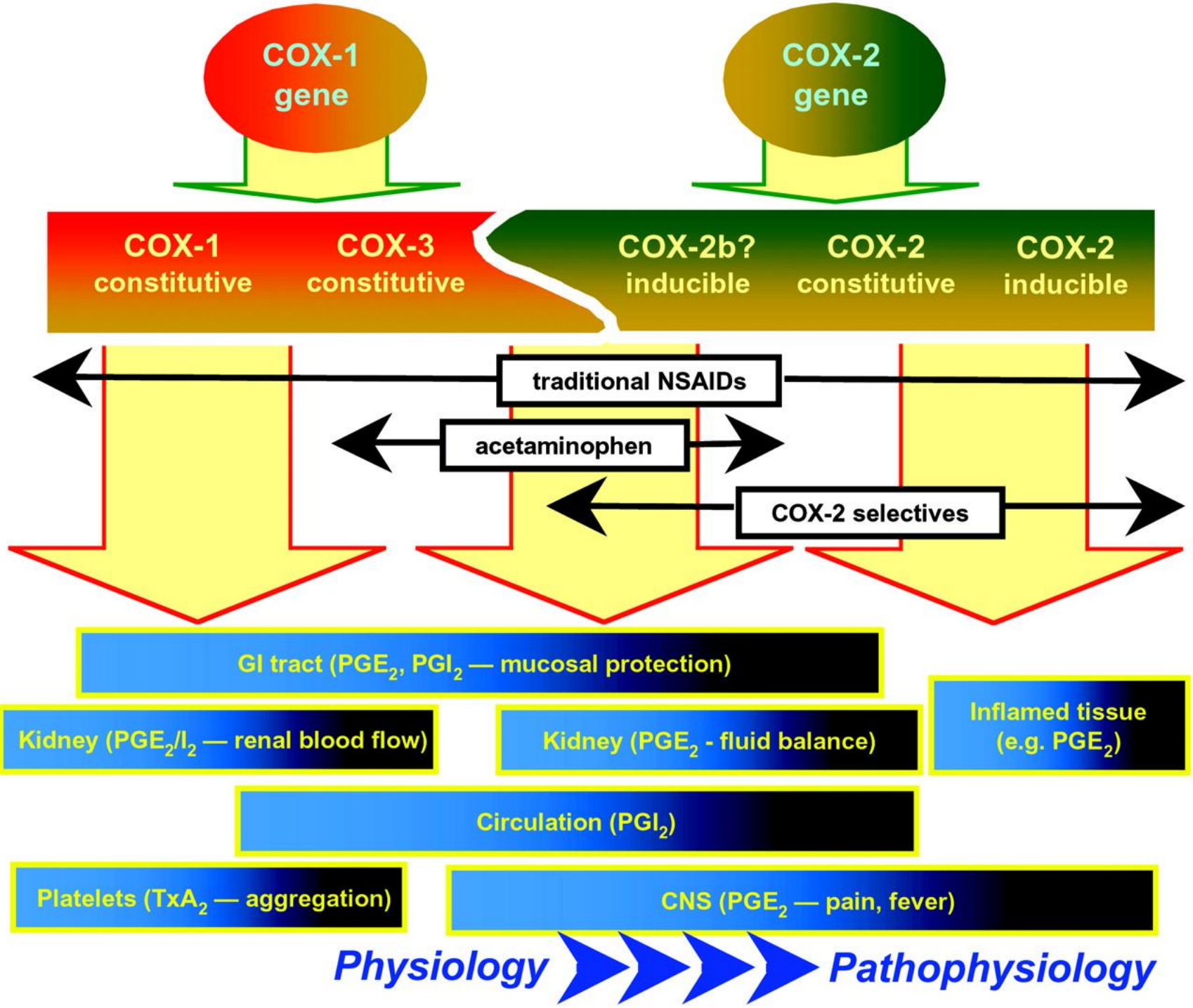
COX-2: usually undetectable in most tissues.

- ↑expression during inflammation or in response to mitogenic stimuli.
- Constitutively expressed in the brain, kidney, bone, and female reproductive system.

COX-3: expressed at a high level in the CNS, and the heart.

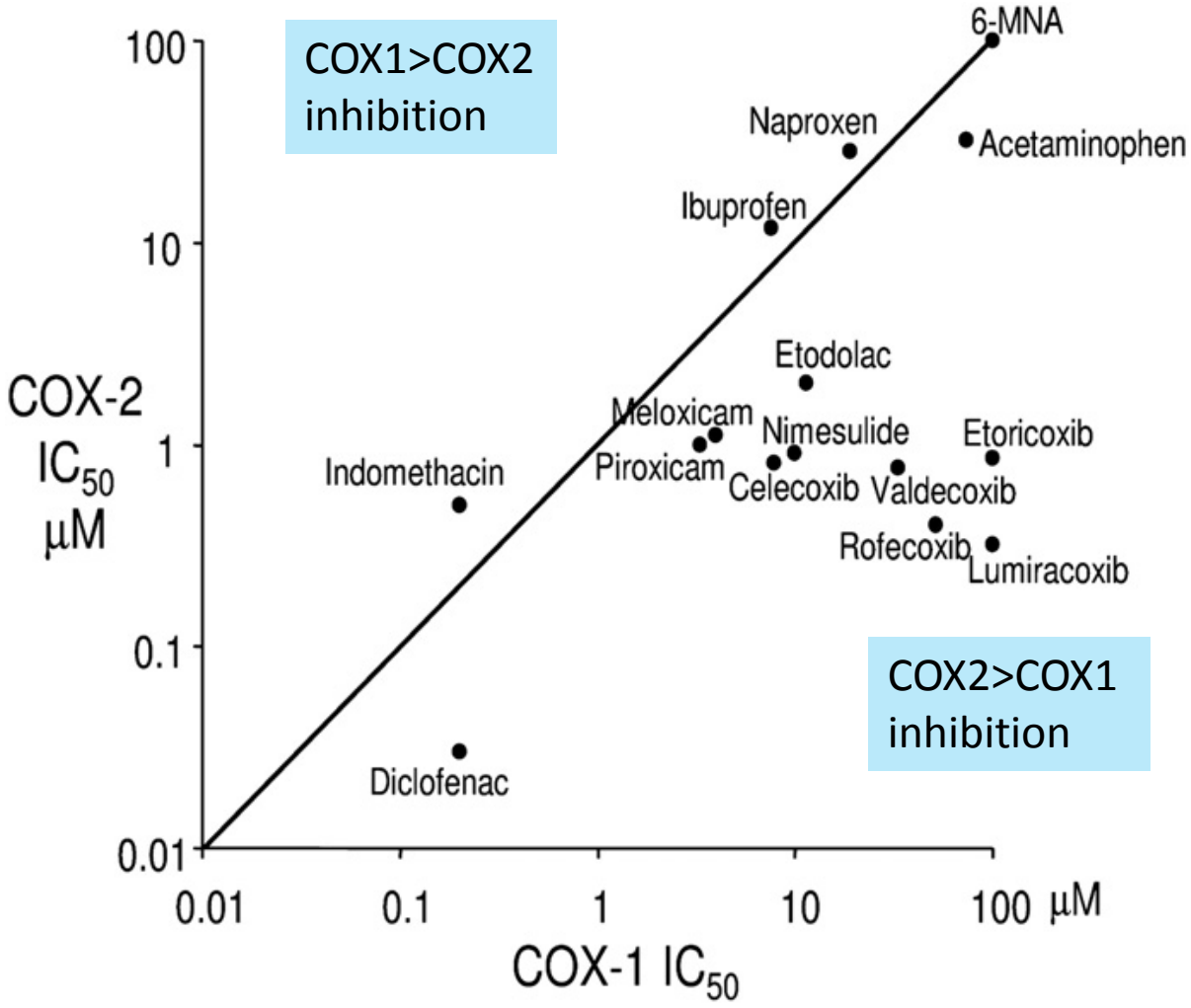
- Modulatin of pain, fever

*gastric cytoprotection, vascular homeostasis, platelet aggregation, kidney function


COX-1 gene
COX-2 gene
COX-1 constitutive
COX-3 constitutive
COX-2b? inducible
COX-2 constitutive
COX-2 inducible
traditional NSAIDs
acetaminophen
COX-2 selectives
GI tract (PGE2, PGI2 — mucosal protection)
Kidney (PGE2/I2 — renal blood flow)
Kidney (PGE2 - fluid balance)
Inflamed tissue (e.g. PGE2)
Circulation (PGI2)
Platelets (TxA2 — aggregation)
CNS (PGE2 — pain, fever)
Physiology
Pathophysiology

COX1/COX2 selectivity

- All NSAIDs are COX-2 inhibitors with some degree of COX-1 inhibition as a “side-effect”
- COX-2 selectivity can be described as the variable probability of sparing COX-1 activity (e.g., in the GI mucosa and platelets) at therapeutic drug concentrations of the NSAID
  - Low COX-2 activity (e.g., paracetamol)
  - Intermediate COX-2 activity (nimesulide, meloxicam, diclofenac)
  - High COX-2 activity (rofecoxib, etoricoxib, lumiracoxib).



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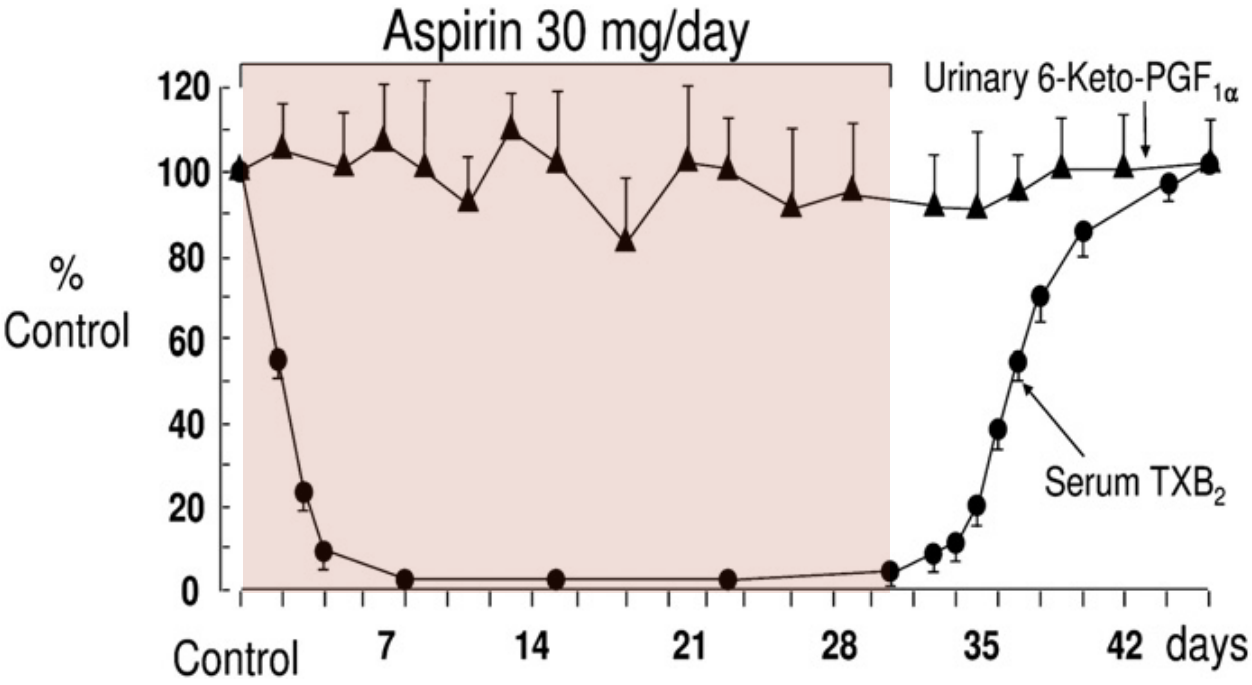
- COX-2 selectivity is a continuous variable with overlap between some tNSAIDs (i.e., nimesulide and diclofenac) and some first-generation coxib (i.e., celecoxib).



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Aspirin:

- In vivo, low- dose aspirin (75–100 mg daily) is a relatively selective inhibitor of platelet COX-1, with transient inhibition of COX-1 and COX-2 in extraplatelet cellular targets (Figure)

- At higher dosage (≥ 160 mg): aspirin has some dose-dependent inhibition of COX-1 and COX-2 as a “side-effect”, as exemplified by inhibition of PGI2 biosynthesis

The mechanisms of NSAIDs in migraine treatment

- 1. NSAIDs and peripheral nociceptors in the trigeminovascular system
- 2. NSAIDs and 2nd order trigeminal nociceptors
- 3. NSAIDs and migraine ''generators''
- 4. NSAIDs and cortical spreading depression (CSD)
- 5. NSAIDs and cortex

1. NSAIDs and peripheral nociceptors in the trigeminovascular system

- Both COX-1 and COX-2 isoforms are present in the dura mater.
  - COX-1: in dural mast cells, endothelium, and small to medium (esp. meningeal) vessels
  - COX-2: in dural macrophages and some CGRP-containing axons
- It is likely **only COX-2 inhibition** contributes to ↓PGs in the brain & spinal cord to reduce pain
  - PGE2 was detected <1 h of migraine onset in jugular vein samples in migraine pts [1]
  - PGE2 can cause an immediate migraine-like headache in the majority of patients; [2] PGI2 produced headache and delayed migraine-like Sx in a proportion of patients [3]

1. Cephalalgia 20(10), 907–918 (2000).
2. Cephalalgia 32(11), 822–833 (2012).
3. Cephalalgia 30(2), 179–190 (2010).

1. NSAIDs and peripheral nociceptors in the trigeminovascular system

- After chemical or electrical stimulation: PGE2 is released from the rat dura mater.
- ASA Tx: ↓meningeal nociception in rats.
- Naproxen: ↓dural nociceptor activation and ↓peripheral nociceptive sensitization.
- ASA, indometacin or parecoxib: ↓ PPE in the dura mater after electrical stimulation of the gasserian ganglion.
- These results suggest the importance of the COX system in TGV, and NSAIDs can be effective in migraine Tx via an action on these peripheral nociceptors.
- However, where in the TVS they exactly act is not completely clear.

PPE = plasma protein extravasation

1. Pain 1999, 81, 7–14.
2. Eur. J. Neurosci. 2008, 27, 917–922
3. Eur. J. Pharmacol. 1989, 165, 251–258.
4. Headache 2006, 46, 276–285.

2. NSAIDs and 2nd order trigeminal nociceptors

- CGRP release from the central terminals of the trigeminal sensory neurons is modulated by PGE2. [1]
- Both COX-1 and COX-2 are expressed in the spinal cord, and COX-2 is enhanced after inflammatory stimuli.
- ASA: ↓activation of second order trigeminal neurons in the cat after electrical stimulation of the superior sagittal sinus. [2]
- Parecoxib: ↓c-fos activation in the TNC after electrical stimulation of the Gasserian ganglion. [3]

1. Neurosci. Lett. 2004, 366, 241–244.
2. Headache 1993, 33, 541–544.
3. Headache 2006, 46, 276–285.

2. NSAIDs and 2nd order trigeminal nociceptors (2)

- After systemic administration of NTG:
  - ↑COX-2 in hypothalamus and lower brain stem. [1]
  - The NTG-induced c-fos expression in rat TNC: ↓by indomethacin. [2]
  - the NTG-induce neuronal nitric oxide synthase (nNOS): ↓by ASA. [3]
  - NTG- induced overexpressions of nNOS and calmodulin-dependent protein kinase II (CAMK-II) in TNC: attenuated by COX-2 but not by COX-1 inhibitors.
- Intrathecal administration of COX inhibitors reduced allodynia induced by trigeminal ganglion compression. [4]

1. Int. Rev. Neurobiol. 2007, 82, 373–382.
2. Neuropharmacology 1997, 36, 1417–1424.
3. Cephalalgia 2004, 24, 439–445.
4. Biol. Psychiatry 2009, 33, 589–595.

3. NSAIDs and migraine “generators”

- Migraine attack is associated with activation of brainstem areas: DRN, NRM, LC, and PAG.
- COX-1 is present in the **PAG**.
  COX-2 can be found in **LC** and **DRN**.
- In **PAG** neurons, COX-2 is an important modulator of glycine- and glutamate-induced ion currents, suggesting its role in pain control.
- COX inhibitors can potentiate opioid inhibition in the **PAG**.
- There is also evidence that COX-1 in the **PAG** can explain a central component in the antinociceptive effects of NSAIDs.

DRN = dorsal raphe nucleus; NRM = nucleus raphe magnus; LC = locus coeruleus; PAG = periaqueductal grey matter

4. NSAIDs and CSD

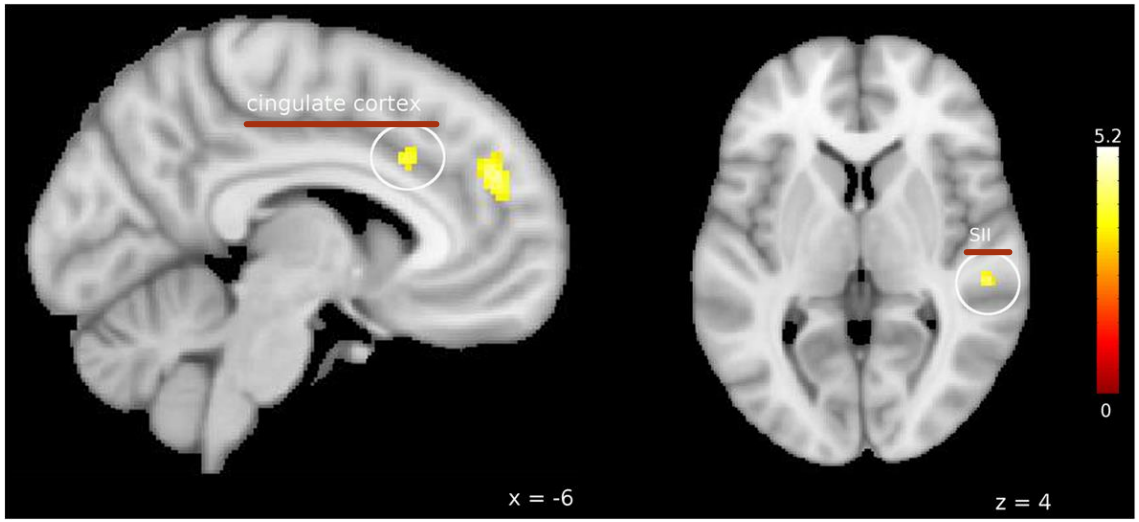
- Whether COX modulates CSD is controversial:
  - In one experiment: ASA failed to modulate CSD in the cat brain [1]
  - Another work: ASA and paracetamol effectively ↓retinal CSD [2]
  - Many other studies found a positive correlation between CSD and the expression of COX-2 in the brain.
- Pial arteriolar constriction during CSD is mediated by prostanoids in the rabbit.
- PGs play an essential role in the downstream events of CSD, ie, the vascular changes after CSD.

1. Eur. Neurol. 1994, 34, 30–35.
2. Naunyn Schmiedebergs Arch. Pharmacol. 1996, 353, 552–556

5. NSAIDs and cortex

- In the acute migraine attack, acetylsalicylic acid (ASA) could attenuate accompanying symptoms like nausea or photophobia.
- ASA exhibits an inhibitory effect on the activation of central trigeminal neurons after sagittal sinus stimulation.
- A high binding affinity of ASA to the dorsal horn and nuclei in the brainstem.
- Following ASA: ↓activation of the primary and secondary somatosensory cortex, and a slight ↓in the anterior cingulate cortex could be revealed in the acute pain model

Central effects of acetylsalicylic acid on trigeminal-nociceptive stimuli



Increased BOLD signal intensity in the anterior cingulate cortex (left) and secondary somatosensory cortex (right) during nociceptive input (ammonia > air puffs) after saline treatment compared to ASA condition.

J Headache Pain. 2014 Sep 9;15:59

II. Triptans

Serotonin & migraine (1)

- During migraine attacks: ↑in brain serotonin (5-HT) synthetic rate, ↓platelet 5-HT levels
- 5-HT, ergotamine, N.E.→ vasoconstriction → ↓migraine attacks
- Exogenous serotonin causes both vasoconstriction and marked arteriolar dilation of cerebral vessels: cerebral vessels respond to exogenous serotonin in a dramatic and complex manner. [1]
- 5-HT and NO are colocalized and maybe coreleased from the rat trigeminal ganglion neurons. [2] Depletion of serotonin would leave the vasodilator NO unopposed, and hence pain is perceived.

1. MacKenzie E T, Edvinsson L. (Amsterdam) 1980. Cerebral circulation and neurotransmitters, in Excerpta Medica; 163 pp.
2. Neurosci Lett. 2010 Nov 5;484(3):192-6.

Serotonin & migraine (2)

- The serotonin agonists selectively brings the elevated serum levels of **CGRP** (a vasodilatator) to normal ranges.
- activation of the endogenous 5-HT1 receptor → calcium signaling pathways → inhibition of **CGRP** gene transcription. [1]
- Older anti-migraine medications (ie, the ergot alkaloids):
  - strong affinity for the "anti-migraine" 5-HT_{1B} and 5-HT_{1D} receptors
  - also affinity for other 5-HT, adrenergic and DA receptor subtypes
  - unwanted nausea, dysphoria, asthenia and vascular effects
- As 5-HT itself could not be researched, efforts were focused on the receptors of 5-HT, leading to discovery of several types and subtypes of 5-HT receptors

1. J Neurosci. 1997;17(24):9545–9553

5-HT receptor	Locus	Aminoacid length	Human brain regions	Putative functions	Related clinical interests	Ref
5-HT1A	5q11.2-q13	422	Raphe n hyp, hip, amy, CPu, Cx, Fcx	5-HT activity, thermoregulation, feeding, stress, pain, mood, emotion, cognition, learning, memory…	Anxiety/depression, neurodegenerative disorders, schizophrenia	25,147,171
5-HT1B (5-HT1Dß)	6q13	390	SN /VTA, ACN, CPu, ventral pallidum, Cx	5-HT activity,mood, feeding	Anxiety/depression, migraine	131,138,172
5-HT1D	1p36.3-34.3	343	CPu, , ventral pallidum, Fcx	5-HT activity, mood, feeding	Anxiety/depression, migraine	173
5-HT1E	6q14-q15	365	CPu, Hyp, Cx	(?)	(?)	See 174
5-HT1F	3p13-p14.1	366	Ce, Hip, Cx	Mood, emotion	Migraine	175
5-HT2A	13q14-q21	471	Dorsal vagal complex, hypoglossal n, inferior olvary complex, Thal, CPu, Cx, FCx	Mood, respiratory control, feeding, nociception	Schizophrenia, anxiety/ depression, Tourette's syndrome, Alzheimer's didease, anorexia/ bulimia, drug abuse, pain	110,160,176
5-HT2B	2q36.3-q37.1	481	Ce (?), LS (?), Hyp (?) Cx (?)	Brain development (?), feeding (?)	Drug abuse, anxiety (?)	177
5-HT2C	Xq24	458°	Choroid plexus, Ce, DRN, SN, Hyp, Amy, Hip, CPu, ACN, Cx	Mood, impulsivity, feeding, locomotor activity	Anxiety/depression, schizophrenia, drug abuse, obesity	178
5-HT3A-E subunits	11q23.1-27.1	510* (5-HT3A)	Dorsal vagal complex, Hip, Amy, CPu	Vomiting reflex, mood,	Nausea, anxiety/depression	103,104
5-HT4	5q34-q36	402*	Hyp, Hip, ACN, CPu	Feeding, reward, cognition	Anorexia, drug abuse, Alzheimer's disease	139,171, 179,180
5-HT5A	7q34-q36	357	Ce, Hyp, Thal, Hip, Cx	Circadian rhythm, sleep, mood, cognition	Schizophrenia (?) anxiety/depression (?)	181
5-HT6	1p36-p35	440	Hip, CPu, Cx, olfactory tubercle	Cognition, learning, memory, feeding	Alzheimer's disease, dementia, obesity	171,182
5-HT7	10q21-q24	479*	Raphe n., Hyp, Tha, Hip, Amy, Cx	Mood, sleep, cognition	Anxiety/depression, schizophrenia.	183

Table I. Serotonin (5-HT) receptors in the human brain: distribution, putative functions, and related pathologies. Pre-RNA *splicing and ° editing variants. For review see also refs 98 to100. X, dorsal motor n of the vagus nerve; ACN, accumbens n; Amy, amygdala; cc, corpus callosum; Ce, cerebellum; CPu, caudate-putamen; Cx, cortex; DRN, dorsal raphe n; Fcx, frontal cortex; Hip, hippocampus; Hyp, hypothalamus; LS, lateral septum; MRN, n, nucleus; SN, subtantia nigra; Tha, thalamus; VTA, ventral tegmental area

Dialogues Clin Neurosci. 2010;12:471-487.

Triptans: "2nd generaion ergot alkloids"

- The 1st triptan (5-$HT_{1B/1D}$ agonist), sumatriptan, was developed by Pat Humphrey et al.
- 1991: Sumatriptan was first launched in Europe
  1993: launched in the US
- The receptor specificity profile of the triptan agents is broadly similar, though their individual potencies at 5-HT_{1B} and 5-HT_{1D} receptors varies.
  - Sumatriptan, zolmitriptan, rizatriptan, naratriptan, almotriptan, and frovatriptan binds to 5-$HT_{1B/1D}$ receptors
  - Eletriptan binds to 5-$HT_{1B/1D/1F}$ receptors.
- The 5-HT_{1B} receptor reserve of coronary vessels is low and the triptans lack activity of 5-HT_{2A}* → good cardiovascular safety profile

*5-HT2A receptors mediate most of the serotonergic contraction in coronary blood vessels

Pharmacological activity of dihydroergotamine (DHE), ergotamine, sumatriptan, and methysergide at animal or human monoaminergic receptors

Receptor	DHE	Ergotamine	Sumatriptan	Methysergide
5-HT_{1A}	+++	+++	++	++*
5-HT_{1B}	+++	+++	+++	++*
5-HT_{1D}	+++	+++	+++	++*
5-HT_{1E}	+	+	+	N.D.
5-HT_{1F}	+	+	++	N.D.
5-HT_{2A}	++	N.D.	0	+*
5-HT_{2C}	+++	N.D.	0	N.D.
5-HT_3	0	0	0	N.D.
5-HT_4	+	+	0	N.D.
α_{1a}	++	++	0	0**
α_{1b}	++	++	0	N.D.
α_{2a}	+++	N.D.	0	0**
α_{2b}	+++	N.D.	0	N.D.
α_{2c}	+++	N.D.	0	N.D.
β_1	0	N.D.	0	N.D.
β_2	0	N.D.	0	N.D.
β_3	+	N.D.	0	N.D.
D_2	+++	+++	0	+**
D_3	++	+++	0	N.D.
D_4	++	+++	0	N.D.

Neurol Sci (2012) 33 (Suppl 1):S193–S198

The triptan family

Group 1- Fast onset, high potency:

- Sumatriptan (IMIGRAN, IMITREX)
- Zolmitriptan (ASCOTOP, ZOMIG, ZOMIGON)
- Rizatriptan (MAXALT)
- Almotriptan (ALMOGRAN, AXERT)
- Eletriptan (RELPAX)

Group 2- Slow onset, lower potency:

- Naratriptan (NARAMIG, AMERGE)
- Frovatriptan (MIGARD, FROVA)

Table 4. Quality of evidence and clinical impression of the triptans[85].

Drug	Quality of evidence	Scientific effect	Clinical impression of effect	Adverse effects
Oral triptans				
Almotriptan	A	+++	++	Infrequent
Eletriptan	A	+++	+++	Occasional
Frovatriptan	A	++	++	Infrequent
Naratriptan	A	++	++	Infrequent
Rizatriptan	A	+++	+++	Occasional
Sumatriptan	A	+++	+++	Occasional
Zolmitriptan	A	+++	+++	Occasional
Nasal triptans				
Sumatriptan nasal spray	A	+++	+++	Occasional
Zolmitriptan nasal spray	A	+++	+++	Occasional
Injectable triptans				
Sumatriptan SC	A	+++	+++	Frequent
Triptan combination				
Sumatriptan plus naproxen sodium fixed-dose combination	A	+++	+++	Occasional

The mechanisms of triptans in migraine treatment

- 1. Peripheral mechanisms
- 2. CNS mechanisms

Vascular mechanisms of triptans (1)

- Traiptans (selective serotonin$_{1B/1D}$ receptor agonists) are the first class of molecules designed specifically for the acute migraine treatment
- The peripheral hypothesis of migraine: vasodilatation → plasma protein extravasation → neurogenic inflammation → TVS activation → headache
- Sumatriptan may be acting by constricting the dilated blood vessels:
  - 5-HT$_{1B}$ receptors exists on human intracranial arteries [1]
  - 5-HT$_{1B}$ receptor activation → arterial vasoconstriction [2]
  - sumatriptan inhibits neurogenic dural inflammation in animals [3]

1. Cephalalgia 17(8), 833–842 (1997).
2. Br. J. Clin. Pharmacol. 47(1), 75–82 (1999).
3. Br. J. Pharmacol. 99(1), 202–206 (1990).

Vascular mechanisms of triptans (2)

- PPE inhibitors were developed that are without cardiovascular side effects at doses that do not activate 5-$HT_{1B/1D}$ receptors.[51]
- These molecules could blcok neurogenic dural inflammation in clinical assays,[1] but failed in clinical trial.[2]
- These data indicated that:
  - the therapeutic mechanism of action of triptans was not by inhibiting PPE but by a different mechanism of action
  - PPE is not relevant to migrainogenesis

* PPE = plasma protein extravasation

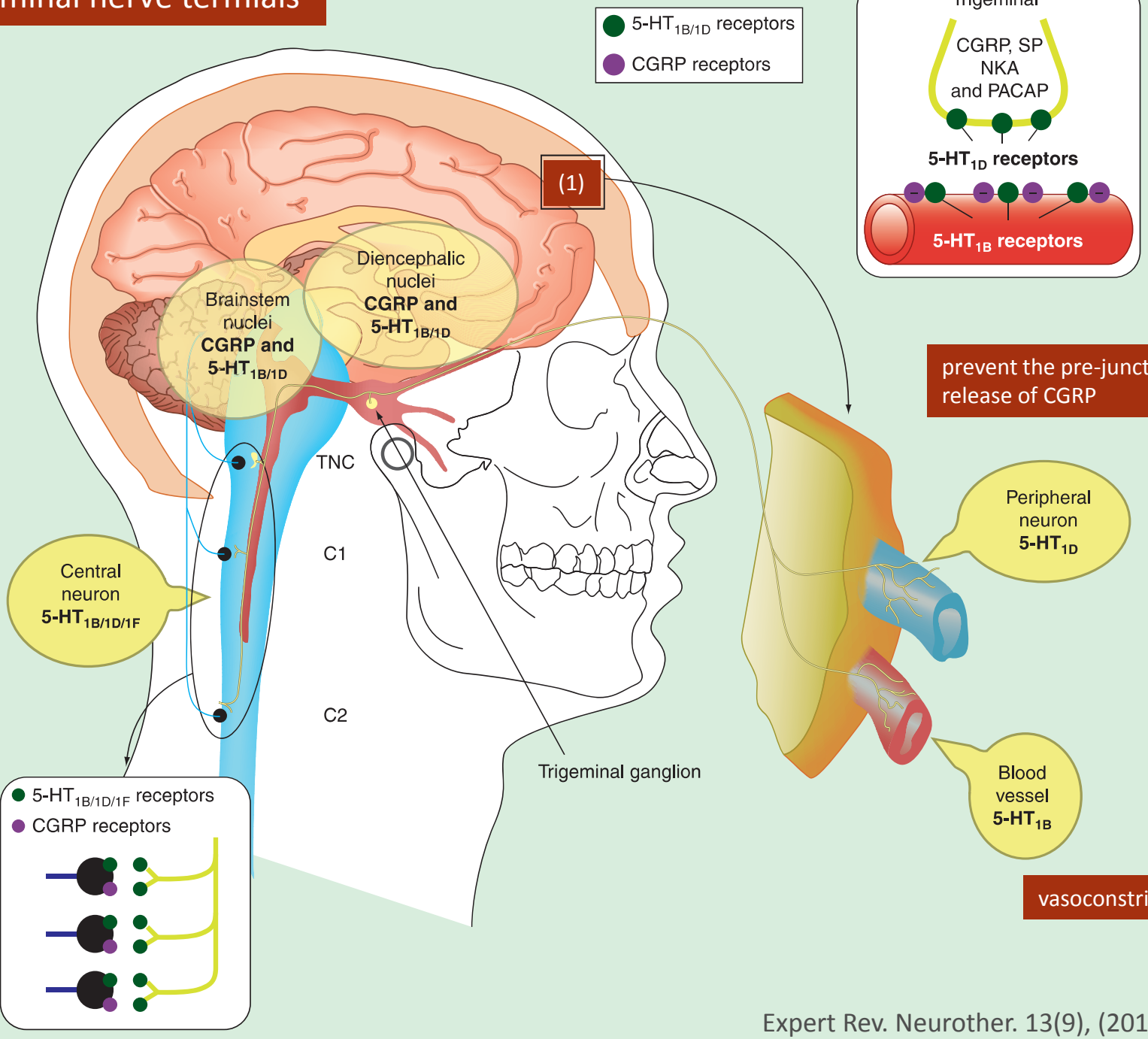
1. Brain Res. 626(1–2), 303–305 (1993).
2. Ann. Neurol. 47(2), 238–241 (2000).

Neural mechanisms of triptans (3)

- The presence of 5-HT_{1D} receptors on peripheral trigeminal **nerve** fibers [1,2]
- The presence of 5-$HT_{1B/1D}$ receptors on trigeminal **ganglion** cells in humans and rats [3–5]
- The presence of 5-$HT_{1B/1D}$ receptors on **central** trigeminal **neurons** in humans [1,6,7]
- Specific binding of ^{3H}sumatriptan in the **TCC** in human [8], cat and guinea pig, and ^{3H}zolmitriptan in the cat
  → demonstrates a locus of action of 5-$HT_{1B/1D}$ receptor agonists

1. Cephalalgia 17(8), 833–842 (1997).
2. Br. J. Clin. Pharmacol. 47(1), 75–82 (1999).
3. Neuroreport 12(8), 1589–1591 (2001).
4. Eur. J. Neurosci. 13(11), 2099–2104 (2001).
5. J. Neurosci. Methods 80(2), 155–161 (1998).
6. Cephalalgia 22(6), 424–431 (2002).
7. Neuropharmacology 36(4–5), 535–542 (1997).
8. Eur. J. Pharmacol. 295(2–3), 271–274 (1996).

(1) At the trigeminal nerve termials



prevent the pre-junctional release of CGRP

vasoconstriction

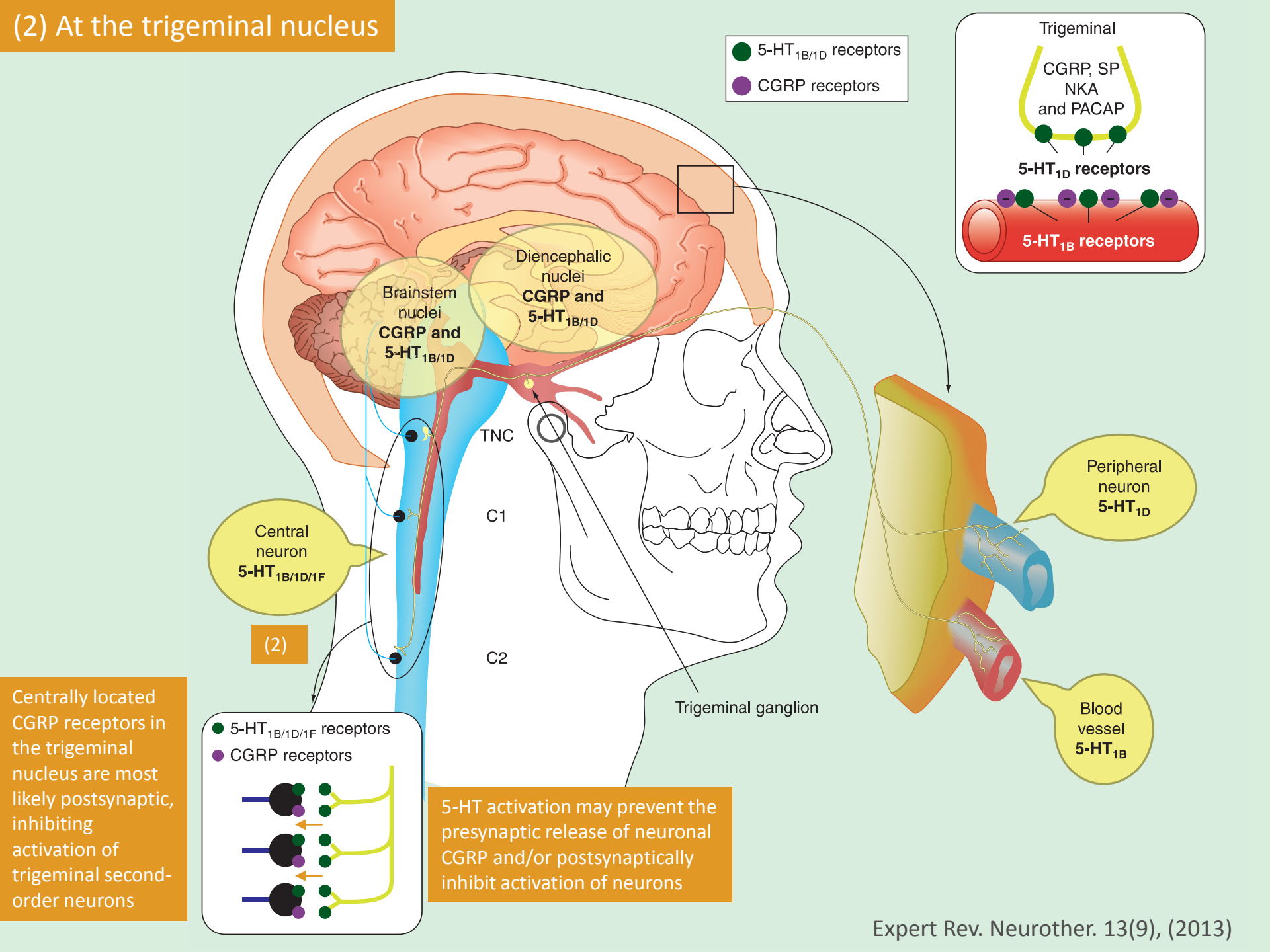
Expert Rev. Neurother. 13(9), (2013)

Neural mechanisms of triptans (4)

- inhibitory 5-HT_{1D} receptors on trigeminal nerve terminals projecting peripherally to the dural vasculature and centrally to the brain stem trigeminal nuclei. [1,2]
- Activation of 5-HT_{1D} pre-junctional receptors on nerve terminals downregulates CGRP release.
- Co-localization of 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors on glutamate positive trigeminal neurons mean that triptans could ↓glutamate release via these receptors. [3]
- 5-HT_{1D} receptor agonist: a potent inhibitor of neurogenic dural inflammation and capsaicin-induced Fos expression in the TCC, with no vascular effects
  - However, PNU-142633 is **ineffective** in the acute migraine treatment in a clinical trial. [4]

1. Trends Pharmacol Sci 1991;12:444-446.
2. Eur Neurol 1991;31:282-290.
3. CNS Spectr 2003;8:446-449.
4. Cephalalgia 21(7), 727–732 (2001).

(2) At the trigeminal nucleus



Centrally located CGRP receptors in the trigeminal nucleus are most likely postsynaptic, inhibiting activation of trigeminal second-order neurons

5-HT activation may prevent the presynaptic release of neuronal CGRP and/or postsynaptically inhibit activation of neurons

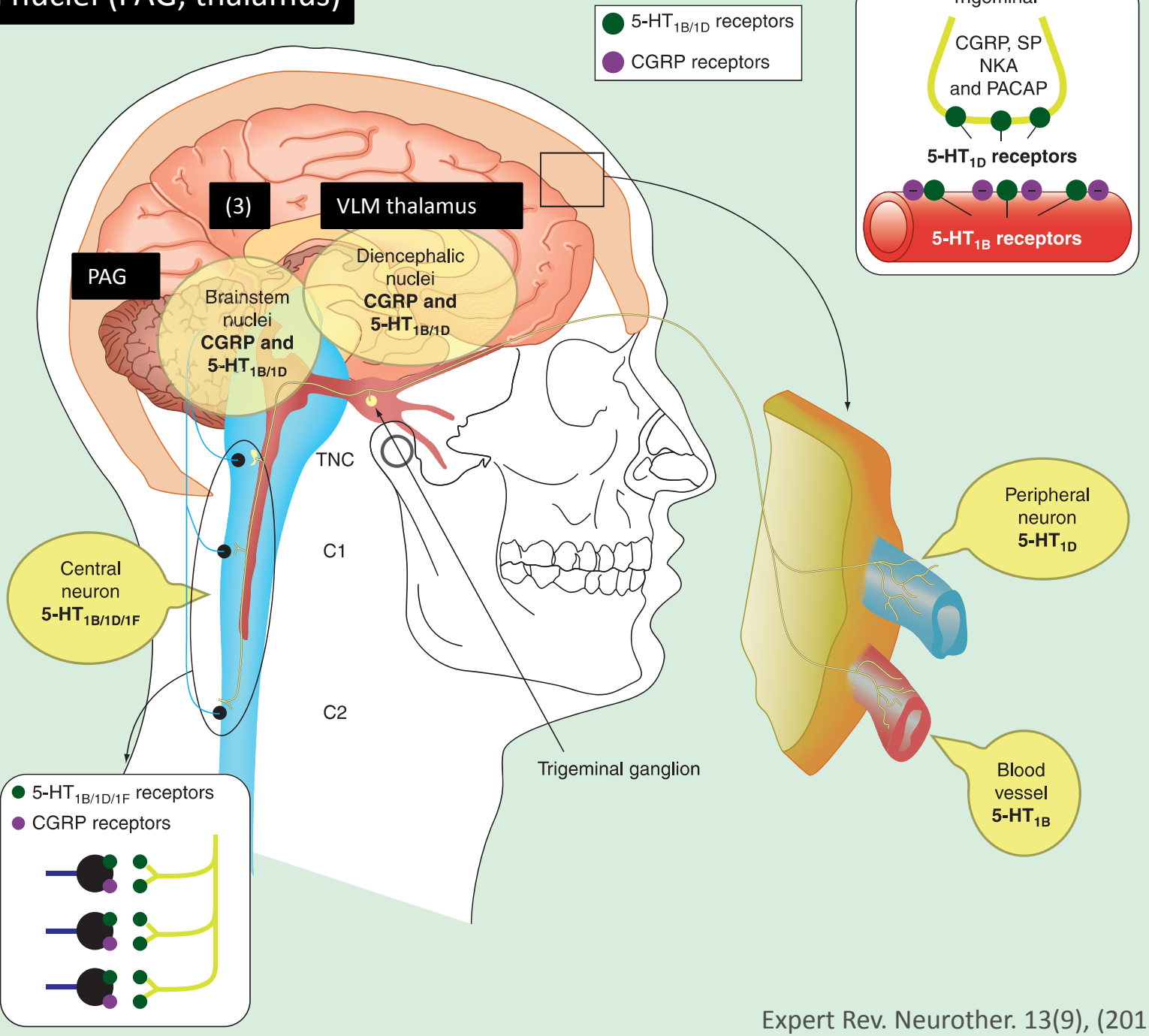
Expert Rev. Neurother. 13(9), (2013)

Neural mechanisms of triptans (5)

- The central actions of triptans is also suggested by their adverse events profile, such as asthenia, dizziness, somnolence, throat tightness and dysasthesia.
- Direct microiontophoresis of triptans on dural-evoked neurons of the TCC results in reversible inhibition of these neurons. [1,2]
- Similar effects of triptans on ventrolateral periaqueductal gray [3] and the ventroposteromedial (VPM) thalamic nucleus.[4]

1. Brain 120(Pt 12), 2171–2177 (1997)
2. Ann. Neurol. 50(6), 804–807 (2001)
3. Ann. Neurol. 56(3), 371–381 (2004)
4. Neurobiol. Dis. 23, 491–501 (2006)

(3) In the brain nuclei (PAG, thalamus)

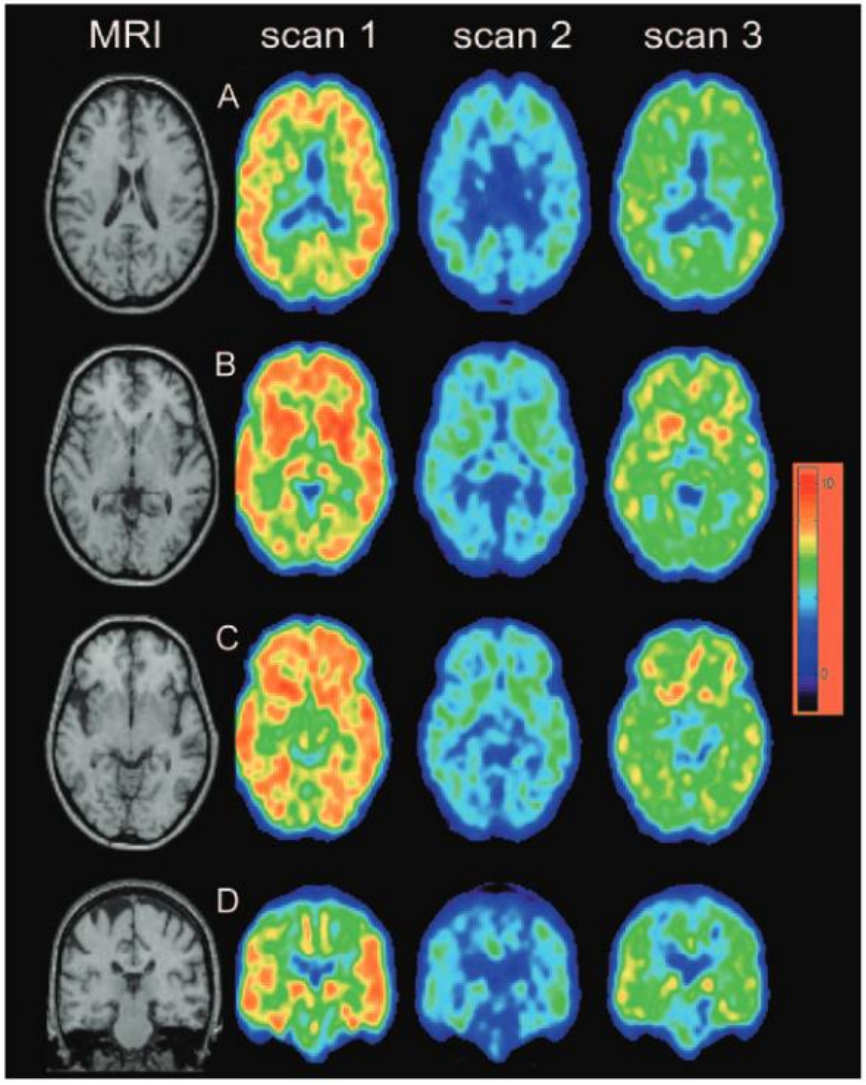


Expert Rev. Neurother. 13(9), (2013)

migraine After triptan Interictal state

PET scan

Figure 1 PET visualization of changes in brain serotonin synthetic rate in patients with migraine



A set of representative MRIs (column 1) at the same cross-sectional level as those of PET images (Scans 1, 2, and 3) shows the average K^* values (μL/g/minute) for all subjects during the headache phase (Scan 1; column 2), after sumatriptan (Scan 2; column 3), and interictally at the time of no pain (Scan 3; column 4). The color-coded bar on the side identifies associations between different colors and the values of K^* (μL/g/minute).

PET scan with ^{11C}methyl-L-Tryptophan as a surrogate marker for brain 5-HT synthetic rate.

Brain 5-HT synthesis was highest during attacks, lowest after sumatriptan, and intermediate at the interictal period.

Triptans exert a negative feedback regulation of brain serotonin synthesis along with modulation of pain pathways.

Neurology. 2008 Feb 5;70(6):431-9.

Neural mechanisms of triptans (6)

- However, sumatriptan is not a brain epentrant:
  - It does not inhibit trigeminal neurons when activated by dural electrical stimulation, unless the BBB is disrupted.[1]
  - How it gains access to the brain, and whether it acts on specifically the TCC and other brain structures, is still to be determined.
  - Maybe lipophilic triptans can affect central structures throughout the brain in areas thought to be important in migraine, and the TCC is an ideal and likely target for drug action in migraine therapy.

1. Br. J. Pharmacol. 109(3), 788–792 (1993).

Conclusion:

- Both NSAIDs and triptans have peripheral and central mechanisms of action on migraine treatment.
- Synergic action if combing NSAIDs and triptans.