Migraine 100 years
Recent Advance in Migraine (1990~)

100/12/10

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Outline

- The Brainstem "Migraine Generator"- PET Studies in Migraine (1995)
- Migraine as a Channelopathy? Research From the Genetic Perspective (1996)
- Meningeal Sensitization, Central Sensitization, and Allodynia in Migraine(1996)
- Summary & Conclusion

The Brainstem "Migraine Generator"- PET Studies in Migraine (1995)

9 patients with right-sided migraine without aura
while attack (<6hr), after sc triptan
during attack– after headache free= Left PAG lesion

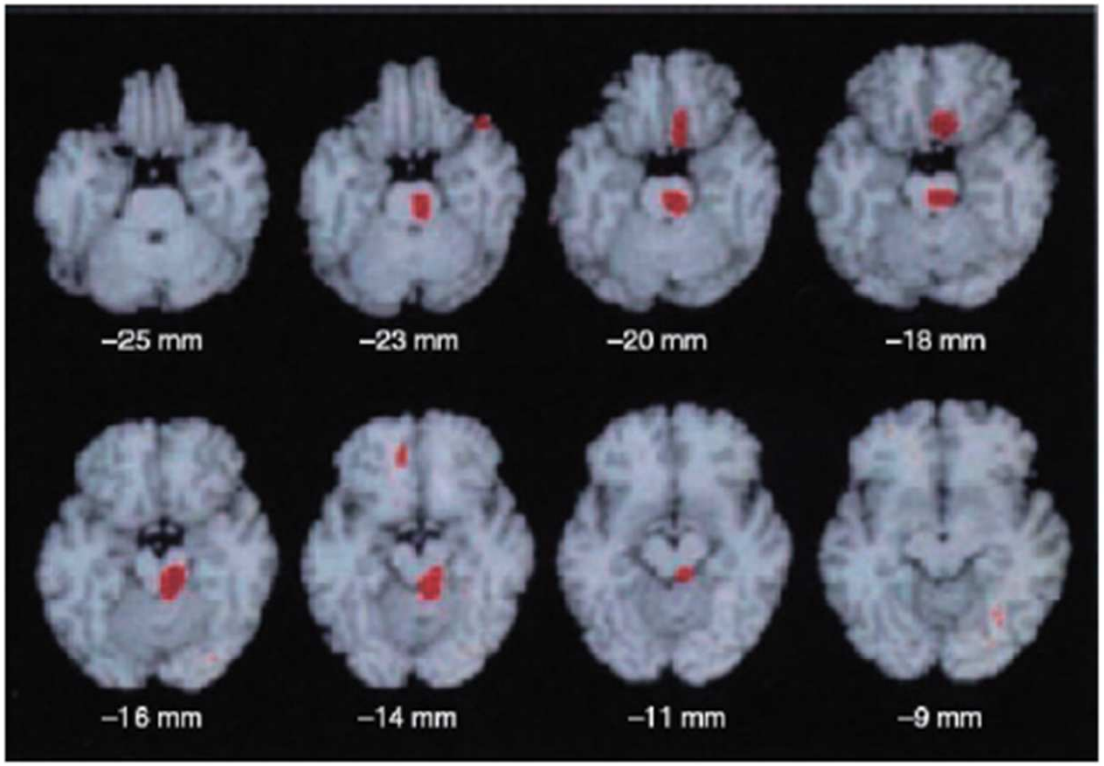


Fig 9.—Regional cerebral blood flow (rCBF) PET measurements in 9 migraine patients.[18] Data were calculated by subtracting rCBF during the headache-free phase from the migraine attack. Note the increase in rCBF in the brain stem. The activation in the singulum is unspecific. This brain stem activation persisted after subcutaneous sumatriptan 6 mg had induced complete relief from headache and phono- and photophobia. It has been suggested that this brain stem activation could be a "migraine generator."[157]

Nat Med. 1995;1:658-660

PET Study

- During the attacks, ↑ blood flow in cerebral heimspheres in the cingulate, auditory, and visual association cortices, brainstem; Slightly lateralized to left
- Only the brainstem activation persisted after sc sumatriptan 6mg
- The pattern of increased blood flow does not follow a neurovascular distribution

PET study

- NTG induced migraine without aura

  Tx by triptan: same results
- Spontaneous migraine without aura: contralateral hypothalmus+ brainstem

➔ The lateralization of pain in migraine was due to lateralized brain dysfunction

➔ Brainstem as the migraine generator

Migraine as a Channelopathy? Research From the Genetic Perspective (1996)

Channelopathy/Gene

Probands / 1st degree relatives	Migraine without aura	Migraine with aura
Migraine without aura	1.9	no increased
Migraine with aura	1.4	4.0

Migraine with and without aura

- 2 forms?
- Different phenotype
- Different functional image
- Different gene study results

→ However, some investigators suggest that there is migraine continuum

Channelopathy/Gene

- 1993 Paris, linkage of monogenic FHM to chromosome 19p13
- Gene heterogeneity , because only 50% of FHM families linked to this locus
- Subsequent repeated study: conflicts
- 1996, Leiden group: 80K-H gene

  → later, 1996 Cell:

  Voltage gated P/Q Ca2+ channel (CACNA1A) in FHM was found

Channelopathy/Gene

- 16 patients VS 50 Controls
- Exon trap experiments, cDNA sequence, Northern blot analysis,
- Genomic DNA was used as template to generate PCR products for single-strand conformational polyymorphism analysis and denaturing high performance liquid chromatography

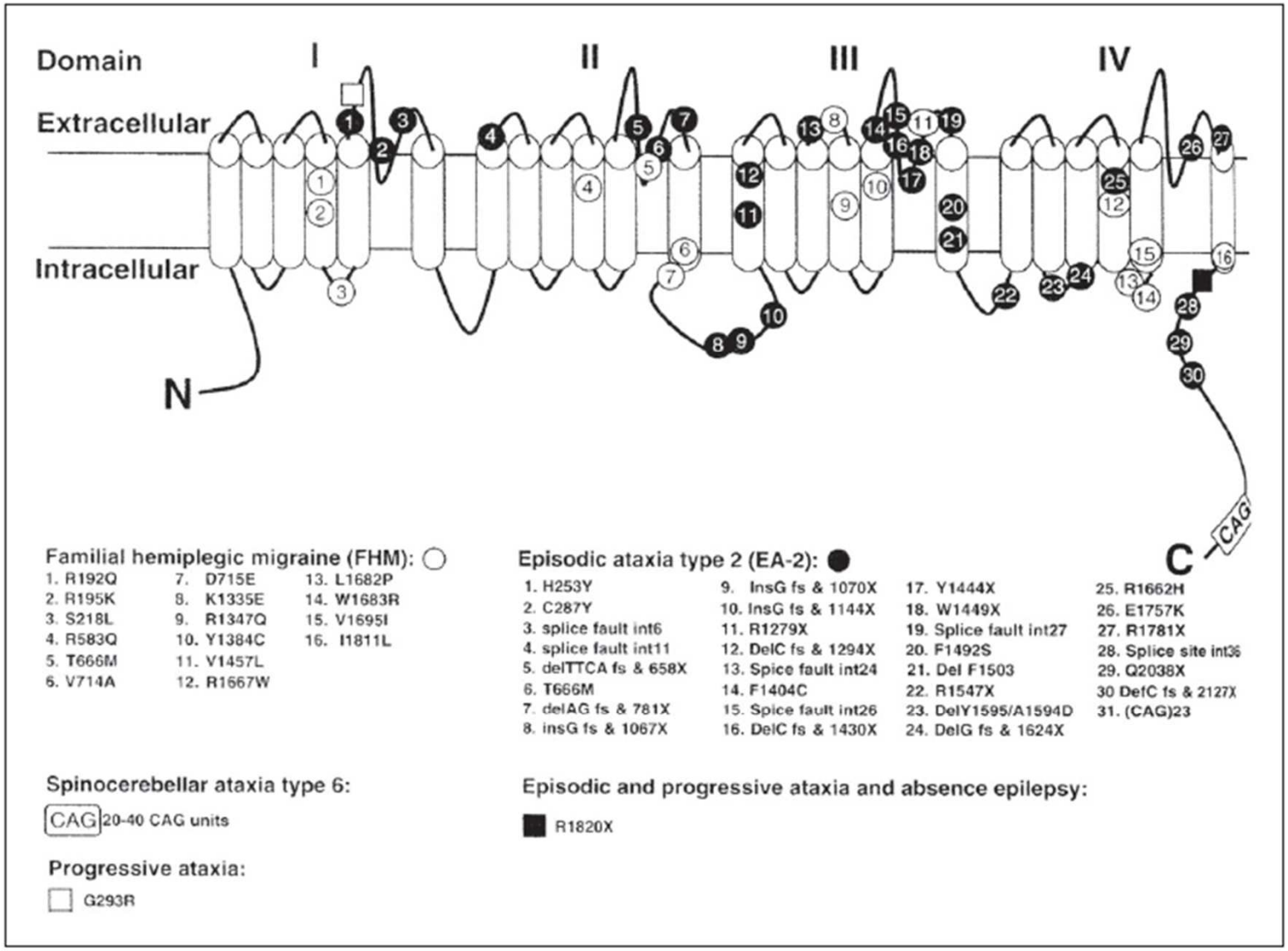
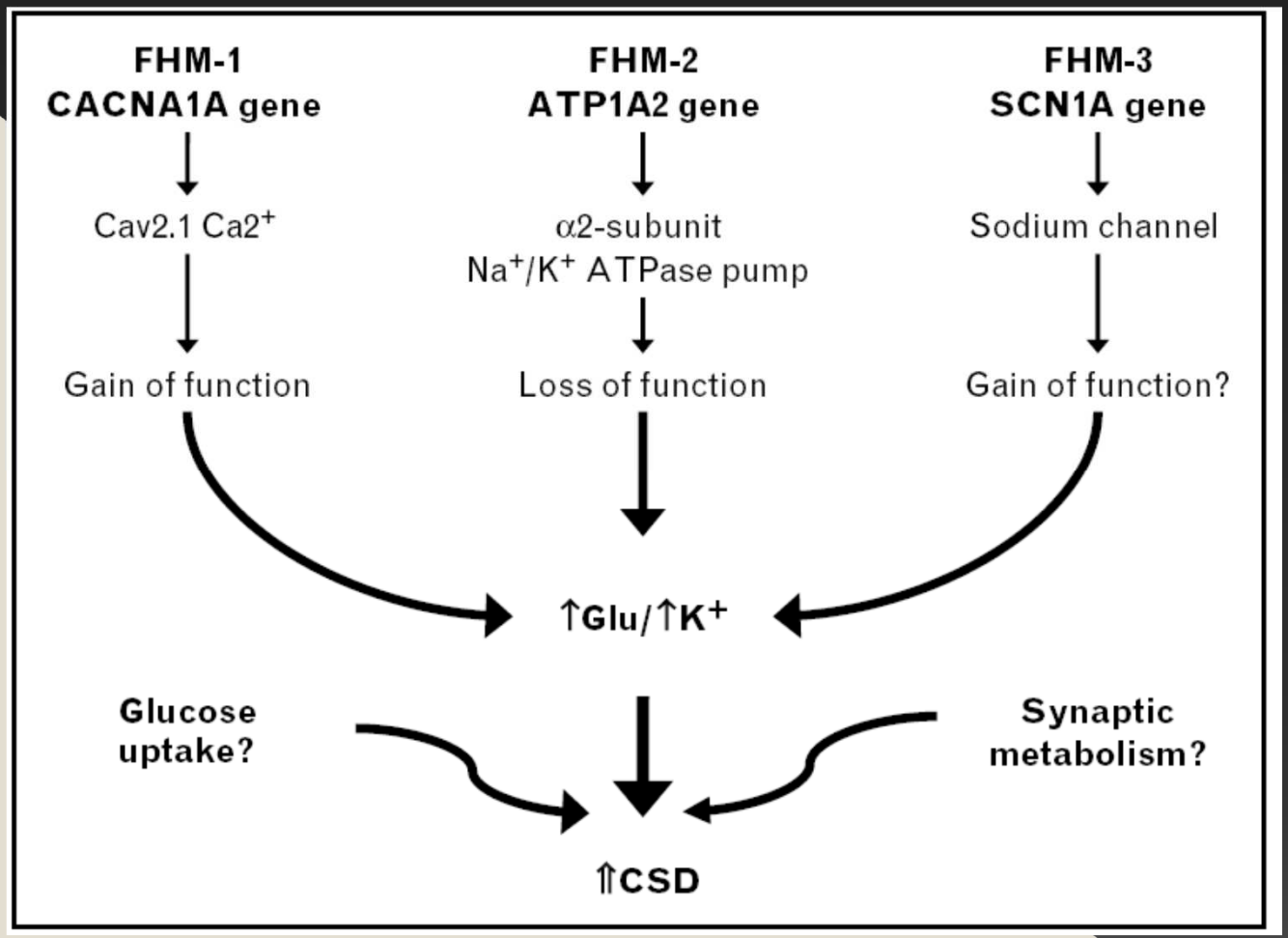


Fig 10.—Membrane topology of α_{1A} subunit of the P/Q-type Ca^{2+} channel, CACNA1A. The location and amino acid substitutions are indicated for mutations that cause familial hemiplegic migraine (FHM), episodic ataxia type 2 (EA-2), tottering mouse (tg), and spinocerebellar ataxia type 6 (SCA6).[19]

Channelopathy/Gene

- 19p13.1→ EA2 and FHM→ FHM1
- ATP1A2 gene, chromosome 1q23→ FHM2
- SCN1A, chromosome 2q24→ FHM3

→ gene studies toward for migraine with and without aura, but fails



Curr Opin Neurol.2006;19:294–298

Channelopathy/Gene

- 827 Typical migraine and 765 controls: found a single gene
- 949 patients and 648 controls: can't replicate this results
- FHM1/FHM2 didn't show hypersensitivity to NI

Candidate genes and polymorphisms associated with migraine in studies published since 2000 and including at least 200 patients and 200 controls

Gene	Chr	Polymorphism	Study size	Population	Associated allele/ genotype, p value, OR	Associated phenotype	Notes
Oestrogen receptor 1 (*ESR1*)	6q25.1	G594A (exon 8; rs2228480)	I) 275 patients (139 MA, 85 MO), 275 controls II) 300 patients (221 MA, 39 MO), 300 controls	Australian	594A, I) p=0·003; II) $p=8x10^{-6}$, OR for A allele carriers 1·96	Migraine	Independent replication
		G325C (exon 4)	367 patients, 232 controls	Spanish	C325, p=0·008, OR for C/C 3·24	Migraine, females only	
Progesterone receptor (*PGR*)	11q22–23	PROGINS Alu insertion within intron 7	I) 275 patients (139 MA, 85 MO), 275 controls II) 300 patients (221 MA, 39 MO), 300 controls	Australian	PROGINS, I) p=0·02; II) p=0·003, OR for PROGINS allele carriers 1·77		Independent replication; possible interaction with ESR1 594A allele
Insulin receptor (*INSR*)	19p13.3–13.2	5 SNPs within the gene	I) 827 patients (377 MA, 450 MO), 765 controls II) 275 patients, 275 controls	North American (white) Australian	SNP84 (intron 15), I) p=0·005; II) p=0·016	I) MA, females only; II) MO	Independent replication but in different subgroups[a]
Methylenetetra-hydrofolate reductase (*MTHFR*)	1p36.3	C677T	270 patients (170 MA, 100 MO), 270 controls	Australian	677T, p=0·017, OR for T/T 2·54	MA	Independent replication in family sample (OR for T/T 1·88)
			413 patients (187 MA, 226 MO), 1212 controls	Dutch	T/T, p<0·006, OR 2·05	MA	
Tumour necrosis factor α (*TNFα*)	6p21.3	–308 G/A	299 patients (38 MA, 261 MO), 306 controls	Italian	G/G, p<0·001, OR 2·85	Migraine (especially MO)	More common allele (0·8)
Angiotensin-converting enzyme (*ACE*)	17q23	ACE-D (insertion/ deletion)	302 MO, 201 controls	Sicilian	DD, p<0·05	MO	
Low-density lipoprotein receptor (*LDLR*)	19p13.2	Triallelic TA repeat in the 3′ UTR	360 patients (140 MA, 220 MO), 200 controls	Italian	Allele 4 (ten repeats), p=0·033	MO	
HLA-DRB1	6p21.3	HLA-DRB1*16	255 patients (41 MA, 214 MO), 325 controls	Italian	DRB1*16, p=0·02	MO	

Chr=chromosome. MA=migraine with aura. MO=migraine without aura. OR=odds ratio. SNP=single-nucleotide polymorphism. UTR=untranslated region.

Lancet Neurol 2007; 6: 521–32

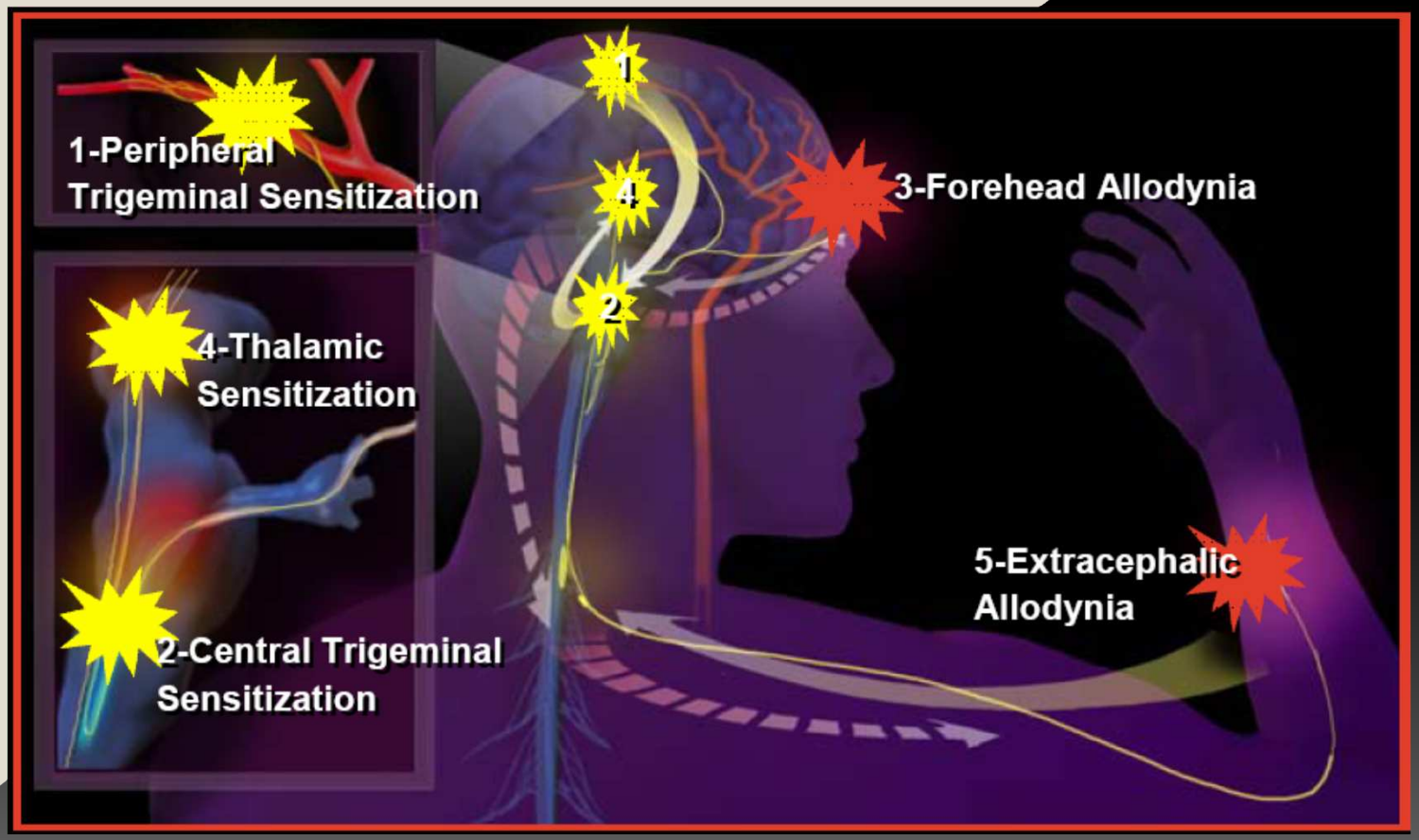
	Study population	Chromosome	Gene	Reference
FHM1	European/American	19p13	*CACNA1A*	34
FHM2	Italian	1q23	*ATP1A2*	66
FHM3	European	2q24	*SCN1A*	79
MA	Finnish	4q24	Unknown	131
MA	Canadian	11q24	Unknown	133
MO	Icelandic	4q21	Unknown	132
MO	Italian	14q21.2–22.3	Unknown	134
MA, MO	Swedish	6p12.2–21.1	Unknown	130
LCA-severe	Australian	3q29	Unknown	136
LCA-severe	Australian	5q22.1	Unknown	137
Pulsation trait	Finnish	17p13	Unknown	138

FHM=familial hemiplegic migraine. MA=migraine with aura. MO=migraine without aura. LCA=latent class analysis.

Table 2: **FHM genes and loci identified in genome-wide scans in common types of migraine**

Lancet Neurol 2007; 6: 521–32

Meningeal Sensitization, Central Sensitization, and Allodynia in Migraine(1996)



Central Sensitization

- Brief Inflammatory soup on animal:

  → 1. prolonged primary meningeal afferent nerves stimulation

  → 2. more sensitization to following outer simulation

- Sensitization of central trigeminal neurons that receive convergent input form the dura and the skin (allodynia)

Central Sensitization

- 11388 patients: central sensitization: 63%, severe cutaneous allodynia: 20%
- Pain threshold: heat, cold, mechanical stimuli → compared during and outside the attack
- Bil. perioribal and ventral forearm
  → 33/42 allodynia while migraine attack
- 28 patient had allodynia beyond the ipsilateral side of the head→ sensitization of third-order neuron

Central Sensitization/Triptans

- Allodynia or not
- Triptan oral VS sc
- Early or late Tx : within 2-4 hours after attack

Central Sensitization/Triptans

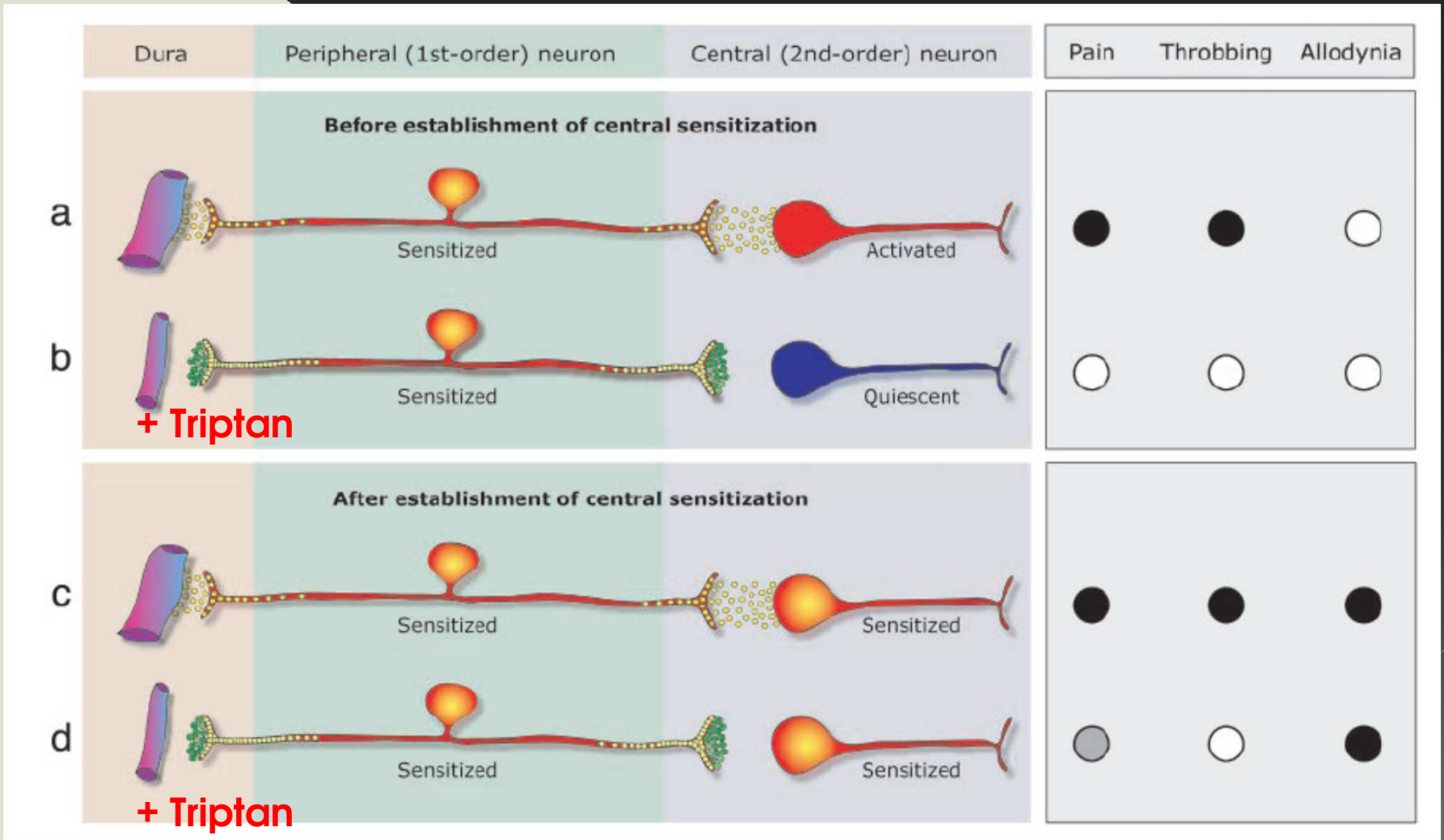
- Triptan response- Pain Free (PF) rate after early triptan therapy in 2 hours:

  5/34 (15%) in allodynia group

  25/27 (93%) in non-allodynia group

  ➔ triptan therapy is vigilantly timed to precede any signs of allodynia
- Animal study: triptan disrupted communication between peripheral and central trigeminovascular neurons
- Early treatment with triptan

Cutaneous Allodynia Predicts Effect of Triptans



PNAS 2004; 101: 4274-4279

Central Sensitization/Triptans

- 28 patients with allodynia, treated by sc sumatriptan 4 hours after migraine attack: ½ failure
- Thereafter Keto iv in each group: 71% and 64%
- Animal study, Keto, naposin, indomethacin use could inhibit central sensitization

Central Sensitization/Triptans

- sc Sumatriptan in migraneurs with allodynia:

  Early group: 62% PF in 2 hours

  Late group: 55% PF in 2 hours
- Unpublished RCT study (n=90), sc Sumatriptan 6mg: 80% PF in both early and late group
- Sc Naratriptan 10mg in another RCT:

  88% PF (> half were Tx after 4 hours)

Paraenteral triptans are equally effective for migraine no matter early or late used.

Central Sensitization

- RCT trial; Almotriptan 12.5mg:
  early and mild grouped: 53% PF
  moderate or severe headache: 38% PF
- Good way to circumvent the problem of allodynia: Tx early!

Summary & Conclusion

Table 1.—Major Clinical and Scientific Observations in Migraine Research From 1900 to 2000

Subjects	References
Isolation and clinical introduction of ergotamine	Stoll, 1918[6]
Further establishing the vasodilation in migraine and the constrictive action of ergotamine	Graham and Wolff, 1938[7]
Pain-sensitive structures in the head	Ray and Wolff, 1940[8]
Lashley's description of spreading scotoma	Lashley, 1941[9]
Cortical spreading depression (CSD) of Leão	Leão, 1944[10]
Serotonin and the introduction of methysergide	Sicuteri, 1959[11]
Spreading oligemia in migraine with aura	Olesen et al, 1981[12]
Oligemia in the wake of CSD in rats	Lauritzen et al, 1982[13]
Neurogenic inflammation theory of migraine	Moskowitz, 1984[14]
A new headache classification	Classification Committee of the International Headache Society, 1988[15]
A new drug for migraine – the discovery of sumatriptan	Humphrey et al, 1988[16]
Migraine and calcitonin gene-related peptide	Goadsby and Edvinsson, 1990[17]
The brainstem "migraine generator" – PET studies in migraine	Weiller et al, 1995[18]
Identification of the gene for familial hemiplegic migraine	Ophoff et al, 1996[19]
Meningeal sensitization, central sensitization and allodynia	Burstein et al, 1996[20]