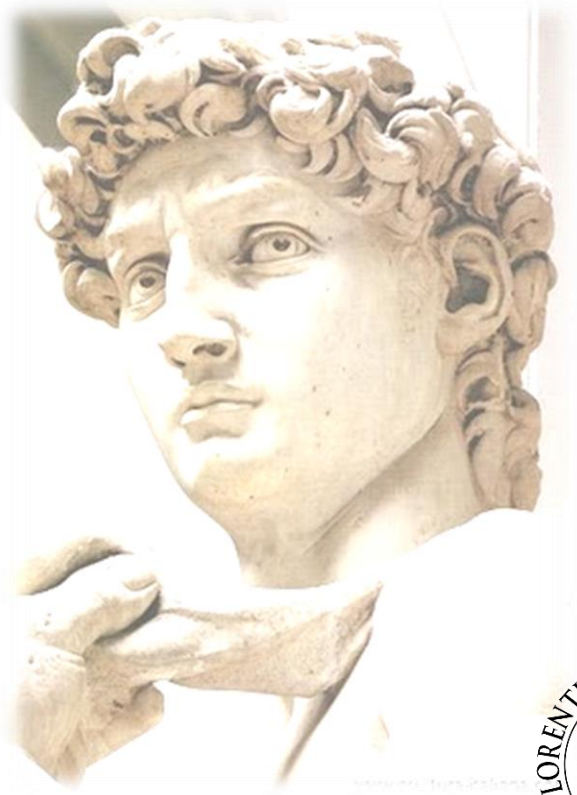
Innovazioni terapeutiche per l' emicrania



Pierangelo Geppetti

Headache Center

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University Hospital Careggi

UNIVERSITÀ DEGLI STUDI FIRENZE

DSS DIPARTIMENTO DI SCIENZE DELLA SALUTE

Faculty Disclosure

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Novartis	X	X	X					
Allergan	X		X					
Sanofi-Aventis	X	X						
Eli Lilly			X					
TEVA		X	X					
IBSA	X		X					
Chiesi			X					
Electrocore	X	X	X					

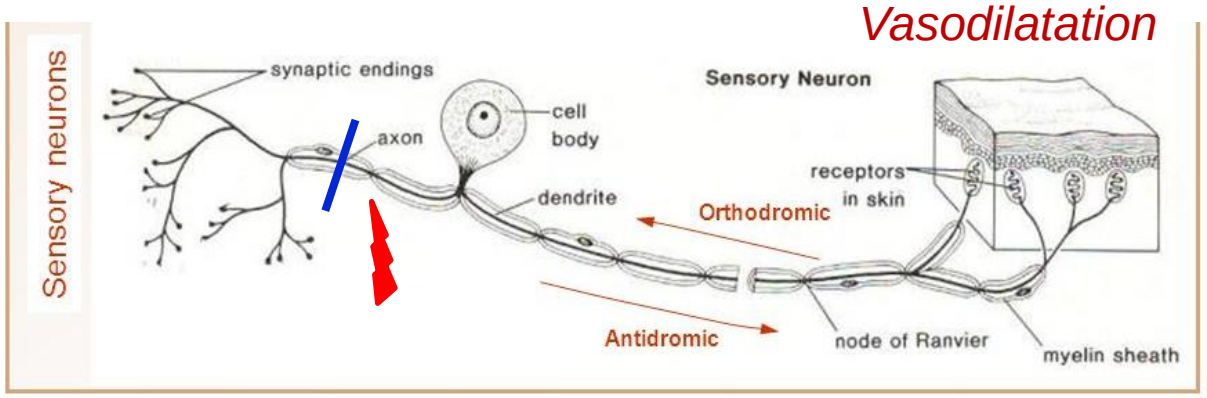
Question?

Why Calcitonin Gene Related Peptide is essential in migraine?

Neurogenic Inflammation
William Bayliss, J Physiol, 1901

- '*There are nerve-fibres in the posterior roots of the 5th, 6th, and 7th lumbar and 1st sacral nerves, excitation of which, when cut away from the spinal cord, gives rise to vascular dilatation in the hind-limb of the same side.*'

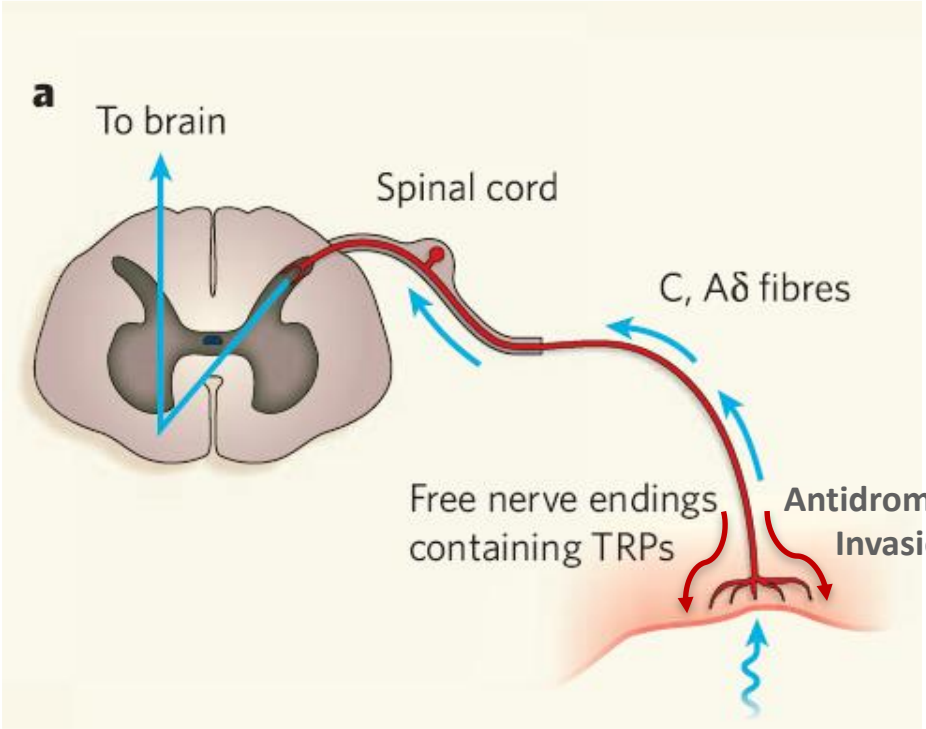
- '*They are, in fact, identical with the ordinary sensory afferent posterior root-fibres; the name "antidromic" is suggested …….*



Sir Thomas Lewis (Clin Sci 1936)

Postulated :

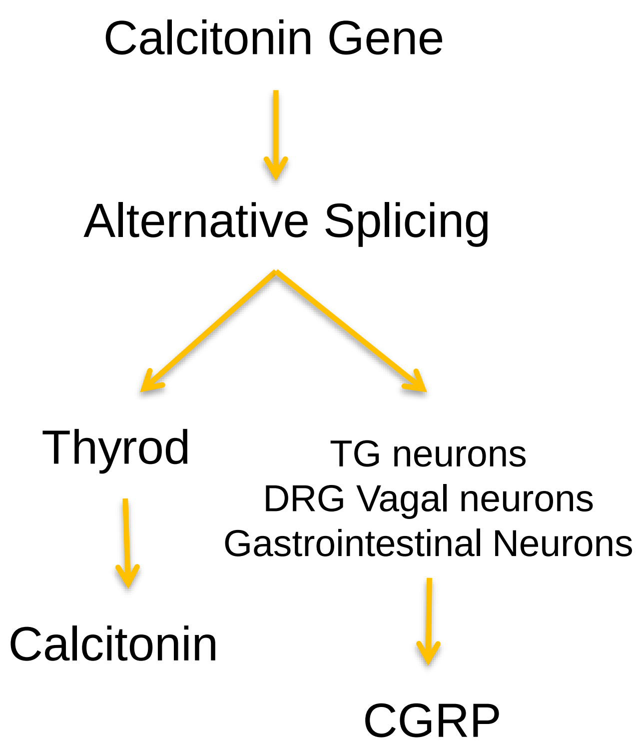
1. *that one portion of a widely branching sensory fiber responded to the injury, and that*
2. *action potentials were carried, antidromically to other branches of the fiber where*
3. *they liberated a chemical substance that*
4. *caused the flare and*
5. *enhanced sensitivity of other sensory axons responsible for pain*



Isaac Newton:

If I have seen further, it is by standing on the shoulders of giants.

Calcitonin Gene Related Peptide and its Family of Peptides



Calcitonin
Calcitonin gene related peptide
Amylin
Adrenomedullin

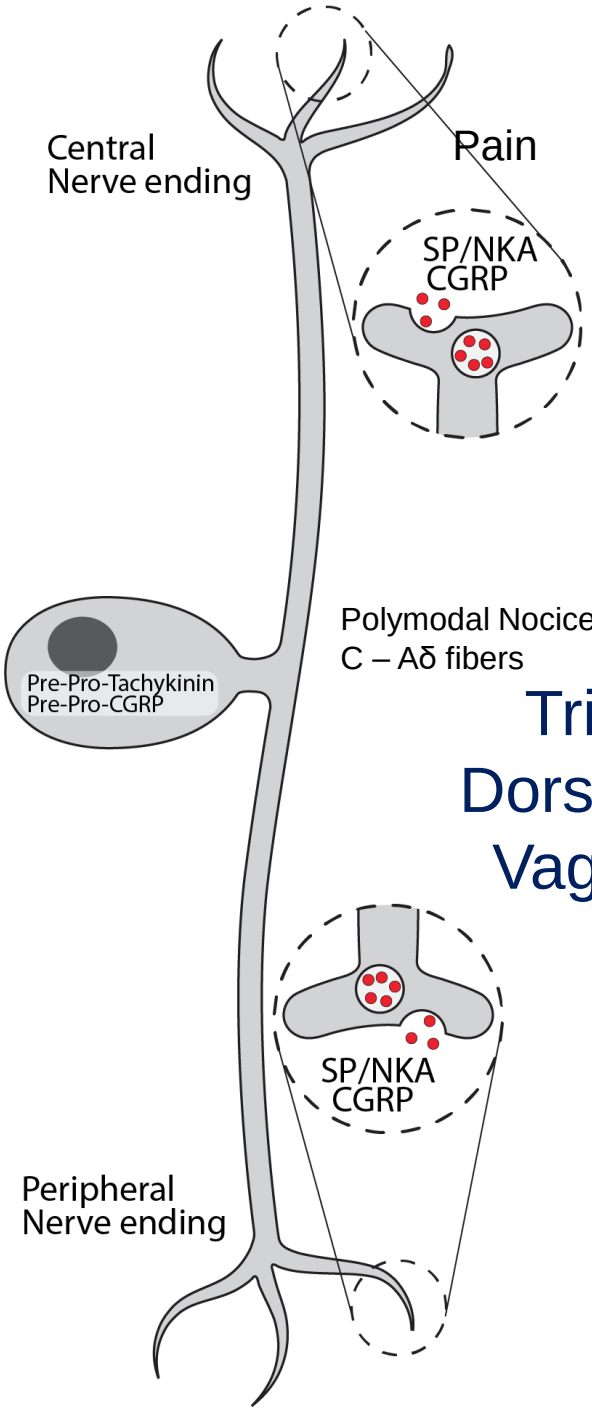
Structures CGRP, amylin, adrenomedullin, and calcitonin

hαCGRP	A C D T A T C V T H R L A G L L S R S G G V V K N N F V P T N V G S K A F
rαCGRP	S C N T A T C V T H R L A G L L S R S G G V V K D N F V P T N V G S E A F
hβCGRP	A C N T A T C V T H R L A G L L S R S G G M V K S N F V P T N V G S K A F
rβCGRP	S C N T A T C V T H R L A G L L S R S G G V V K D N F V P T N V G S K A F
hAMY	K C N T A T C A T Q R L A N F L V H S S N N F G A I L S S T N V G S N T Y
rAMY	K C N T A T C A T Q R L A N F L V R S S N N L G P V L P S T N V G S N T Y
hAM	G C R F G T C T V Q K L A H Q I Y Q F T D K D K D N V A P R N K I S P Q G Y
rAM	G C R F G T C T M Q K L A H Q I Y Q F T D K D K D G M A P R N K I S P Q G Y
hCT	C G N L S T C M L G T Y T Q D F N K F H T F P Q T A I G V G A P
sCT	C S N L S T C V L G K L S Q E L H K L Q T Y P R T N T G S G T P

Disulfide bond — α-helix

h, human; r, rat; s, salmon.
hAM is the structure of the 15–52 fragment; the N-terminal amino acids are YRQSMNNFQGLRSF. rAM shows the structure of the 13–50 fragment; the N-terminal amino acids are YRQSMNQGSRST.

Primary Sensory Neuron

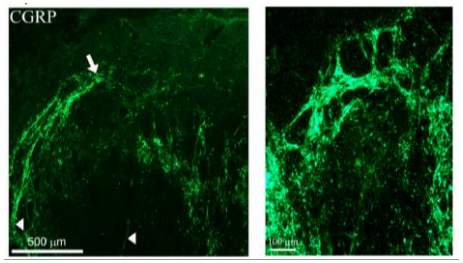


Polymodal Nociceptor
C – Aδ fibers

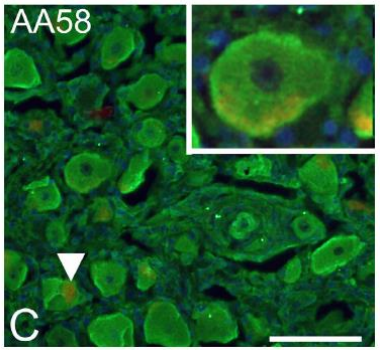
Trigeminal, Dorsal Root and Vagal Ganglia

Edvinsson et al.,
J Blood Flow Metab. 1987.

Spinal Trigeminal Nucleus



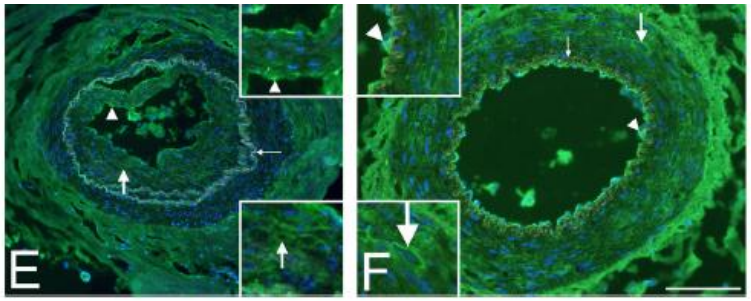
Trigeminal Ganglion



CGRP Staining
in Human Tissues

Dural Artery

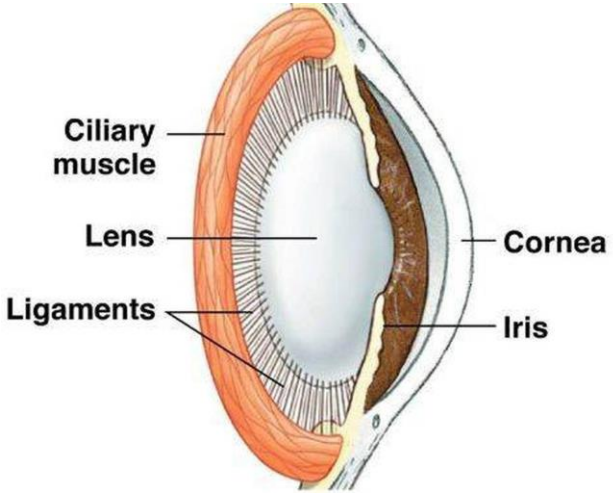
Subcutaneous Artery



Miller et al, Neuroscience 2016

CGRP, but not Substance P, is released from **Human Trigeminal Neurons**

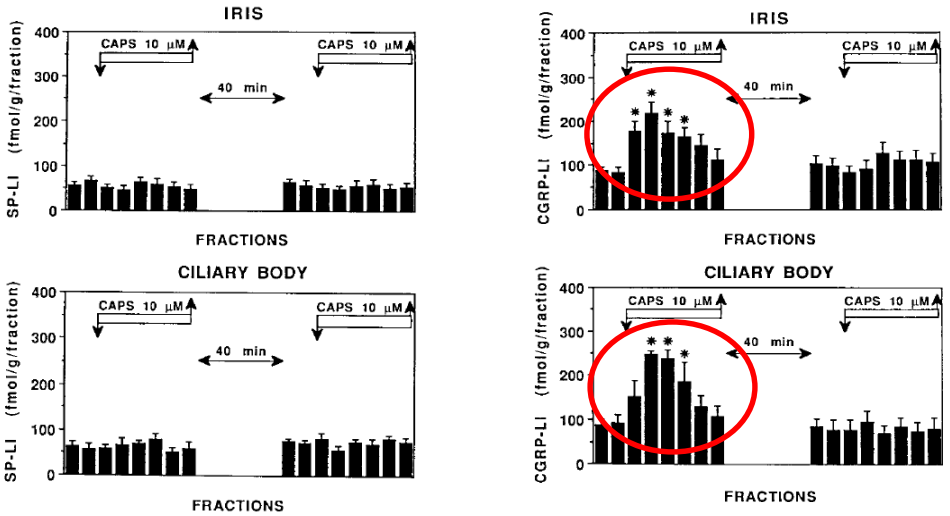
Trigeminal Innervation Of the Human Eye



Capsaicin releases calcitonin gene-related peptide from the human iris and ciliary body in vitro

Regulatory Peptides, 41 (1992) 83–92

Pierangelo Geppetti[a], Elena Del Bianco[a], Roberto Cecconi[a], Manuela Tramontana[a], Andrea Romani[b] and Elvar Theodorsson[c]



CGRP Mediates Neurogenic Vasodilatation

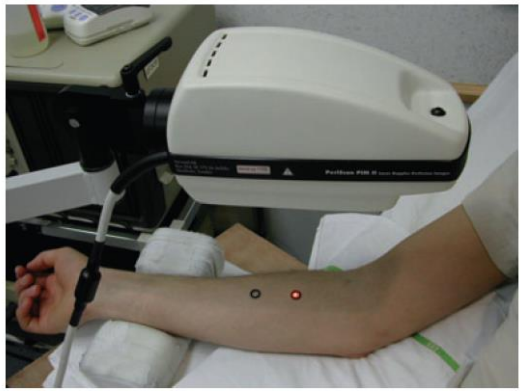


Figure 1

Assessment of dermal blood flow using laser Doppler following application of topical capsaicin to human forearm

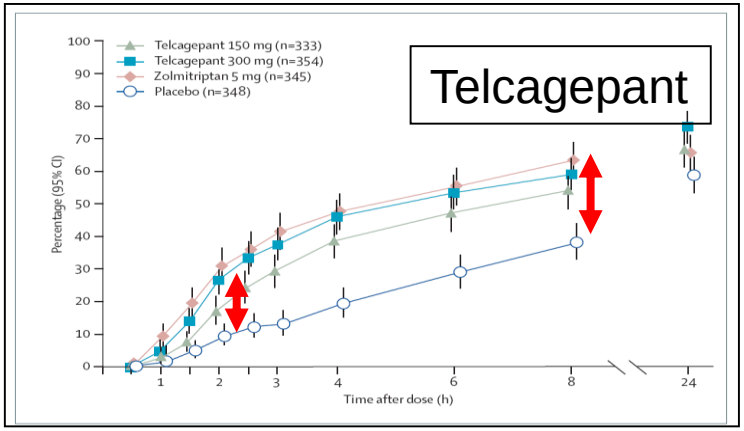


Table 3

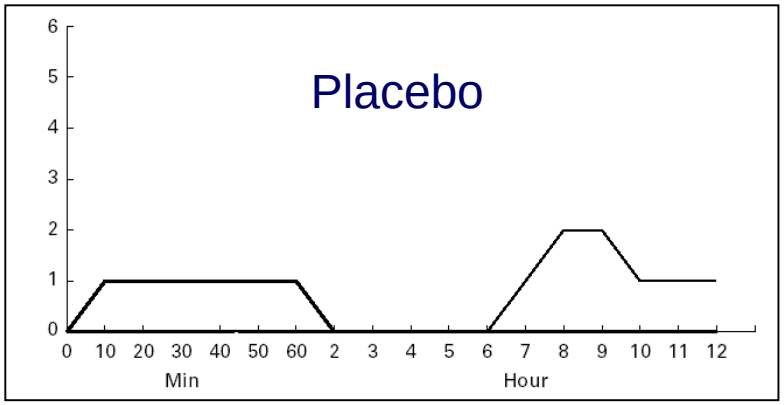
Capsaicin-induced dermal blood flow following telcagepant or placebo ($n = 12$)

Time	Telcagepant dose, mg	Capsaicin dose	Mean perfusion (volt) Geometric mean*
1 h	Placebo	300 µg per 20 µl	1.19
	300		0.56
	800		0.47
	Placebo	1000 µg per 20 µl	1.67
	300		0.69
	800		0.53
4 h	Placebo	300 µg per 20 µl	1.00
	300		0.62
	800		0.52
	Placebo	1000 µg per 20 µl	1.44
	300		0.86
	800		0.62

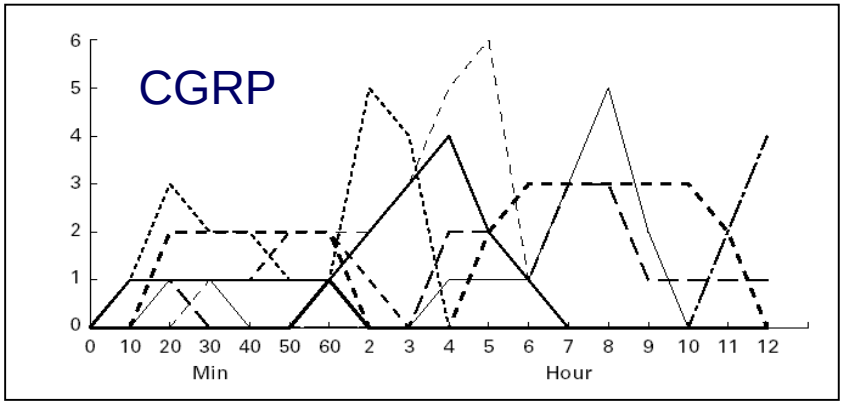
*Geometic mean ratio (GMR), computed from least squares estimates from ANOVA performed on the natura
†Transformed from mean perfusion GMR.

Sinclair et al., Br J Clin Pharmacol, 2009

CGRP Provokes Migraine-Like Attacks and Periorbital Allodynia in Mice

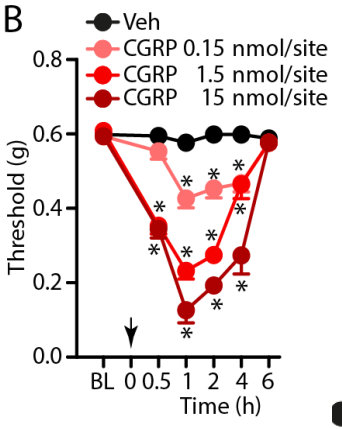


Lassen, Cephalalgia 2002, 22 54-61

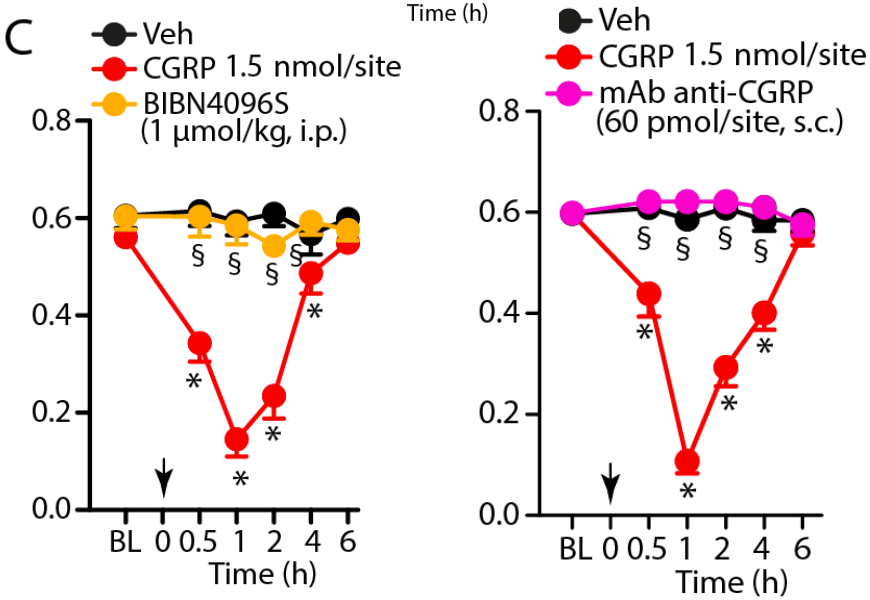


CGRP evokes migraine-like attacks

Priorbital allodynia in Mice

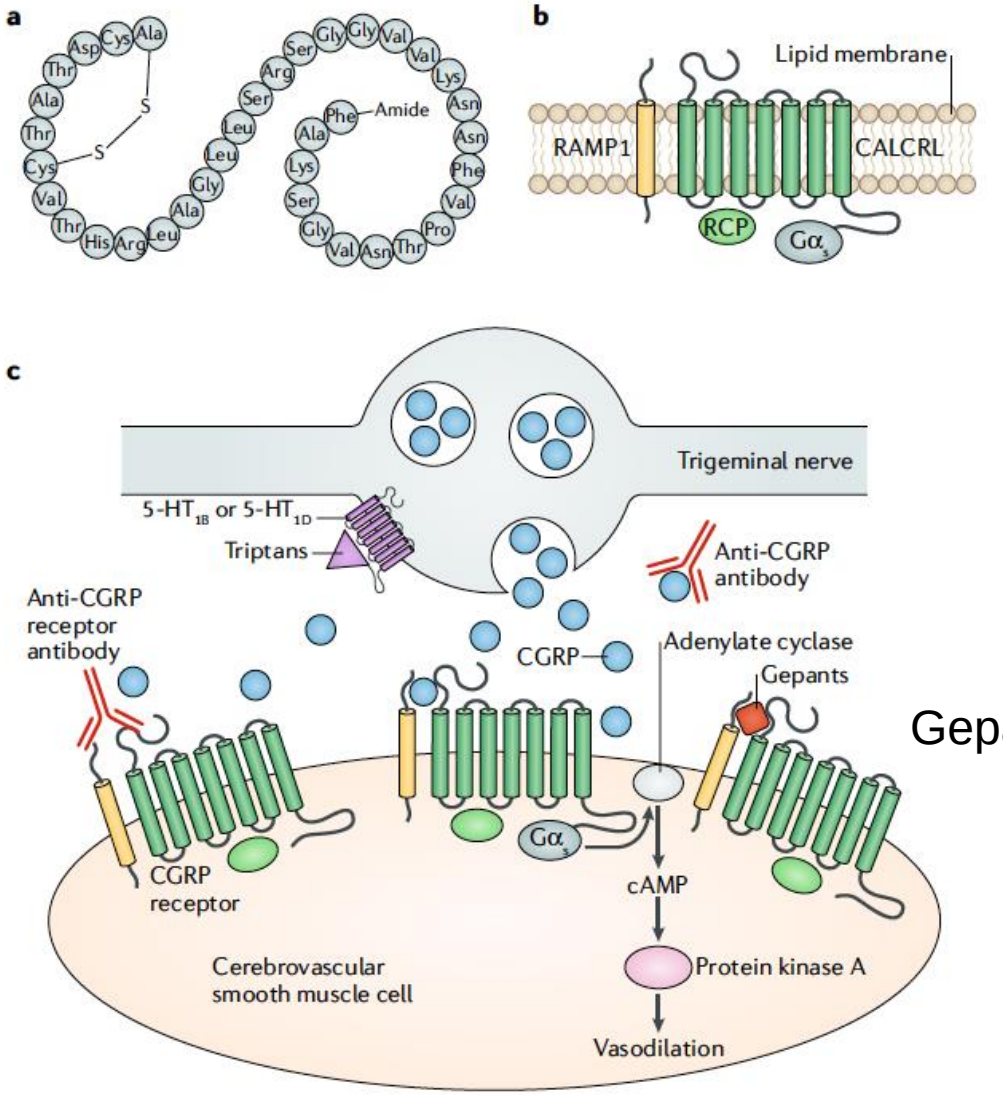


De Logu et al, J Head Pain 2019



How do Anti-CGRP drugs act?

Erenumab



Fremanezumab
Galcanezumab
Eptinezumab

Gepants

CGRP-R Antagonists are Effective in Migraine

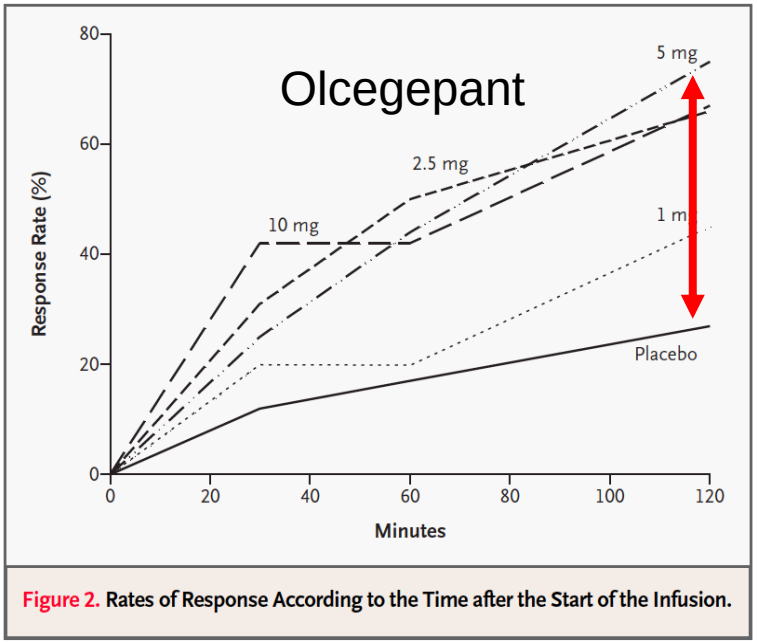
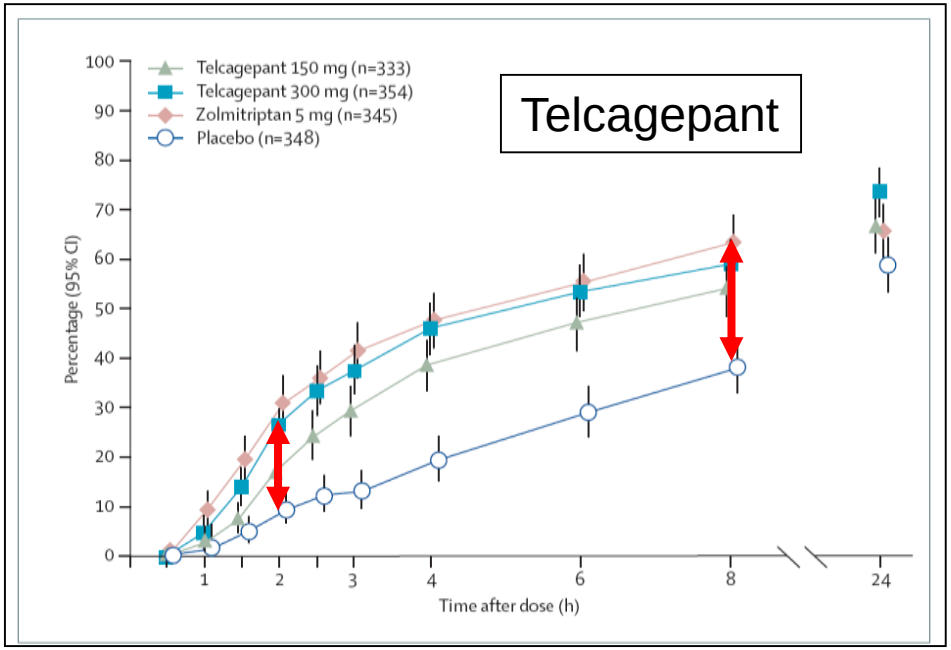


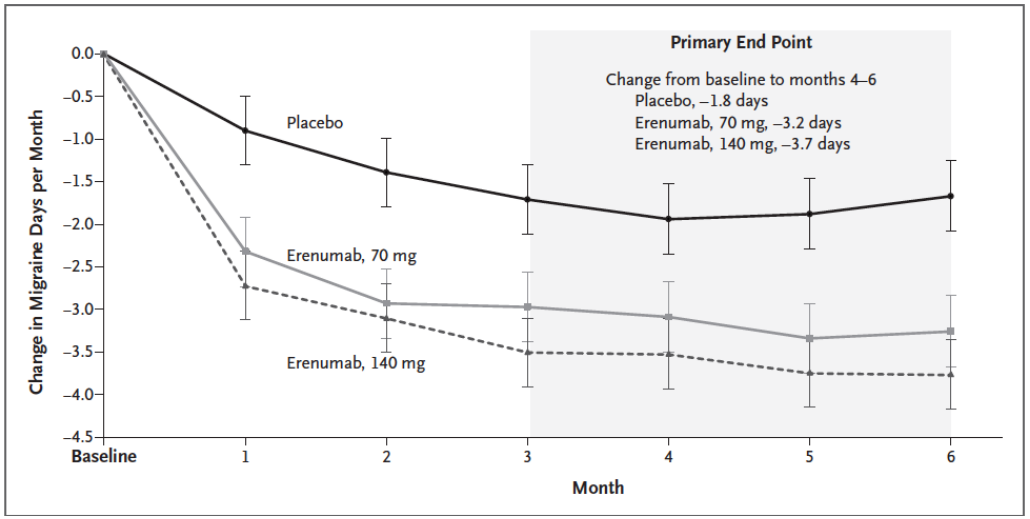
Figure 2. Rates of Response According to the Time after the Start of the Infusion.



Olesen J, Diener HC, Husstedt IW, Goadsby PJ, Hall D, Meier U, Pollentier S, Lesko LM; BIBN 4096 BS Clinical Proof of Concept Study Group. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. **N Engl J Med** 2004, 350:1073-1075

Ho TW, Ferrari MD, Dodick DW, Galet V, Kost J, Fan X, Leibensperger H, Froman S, Assaid C, Lines C, Koppen H, Winner PK. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. **Lancet.** 2008 Dec 20;372(9656):2115-23

Anti-CGRP/R mabs are Effective in Migraine

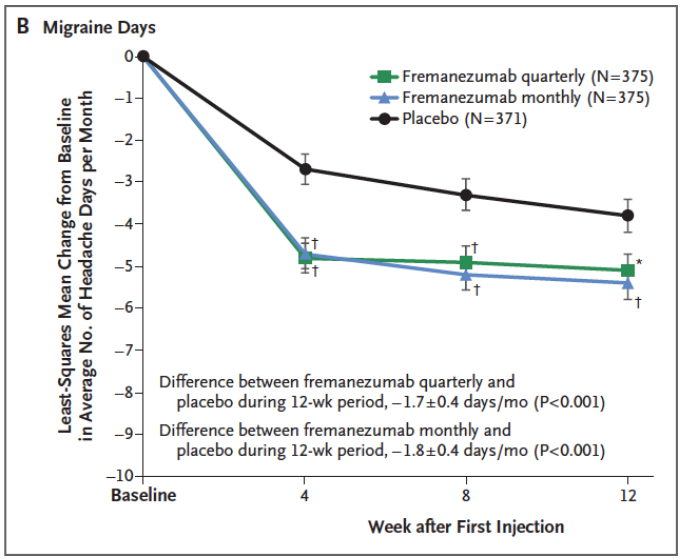


The NEW ENGLAND JOURNAL of MEDICINE

A Controlled Trial of Erenumab for Episodic Migraine

Peter J. Goadsby, M.D., Ph.D., Uwe Reuter, M.D., Yngve Hallström, M.D., Gregor Broessner, M.D., Jo H. Bonner, M.D., Feng Zhang, M.S., Sandhya Sapra, Ph.D., Hernan Picard, M.D., Ph.D., Daniel D. Mikol, M.D., Ph.D., and Robert A. Lenz, M.D., Ph.D.

NOVEMBER 30, 2017



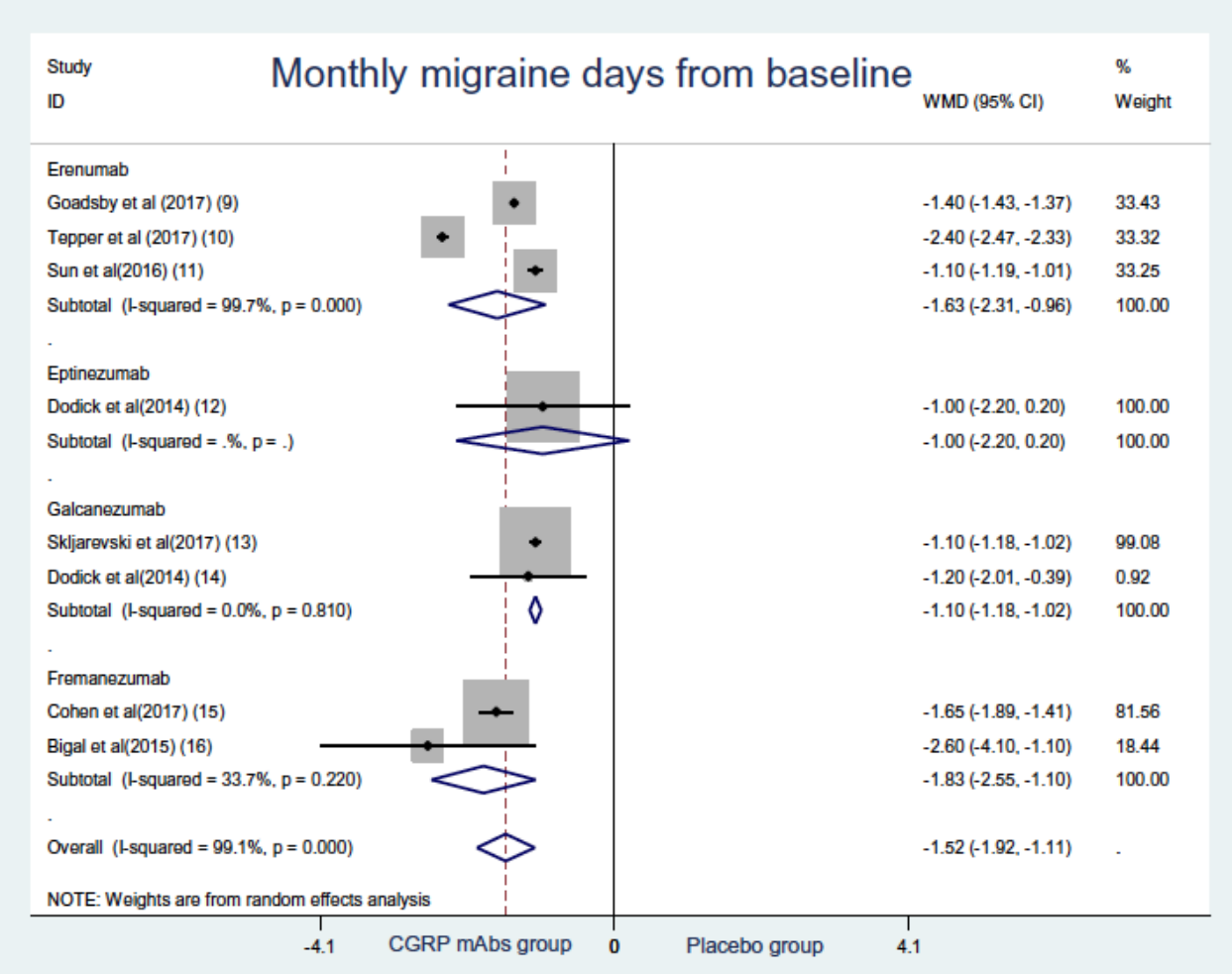
The NEW ENGLAND JOURNAL of MEDICINE

Fremanezumab for the Preventive Treatment of Chronic Migraine

Stephen D. Silberstein, M.D., David W. Dodick, M.D., Marcelo E. Bigal, M.D., Ph.D., Paul P. Yeung, M.D., M.P.H., Peter J. Goadsby, M.D., Ph.D., Tricia Blankenbiller, M.A., Melissa Grozinski-Wolff, B.S., Ronghua Yang, Ph.D., Yuju Ma, M.S., and Ernesto Aycardi, M.D.

NOVEMBER 30, 2017

Efficacy of anti-CGRP/R mABs



Zhu et al, Neurol Sci 2018

One Year Efficacy

Phase-3 Studies
Between 40% and 50% of the patients report >50% reduction from baseline

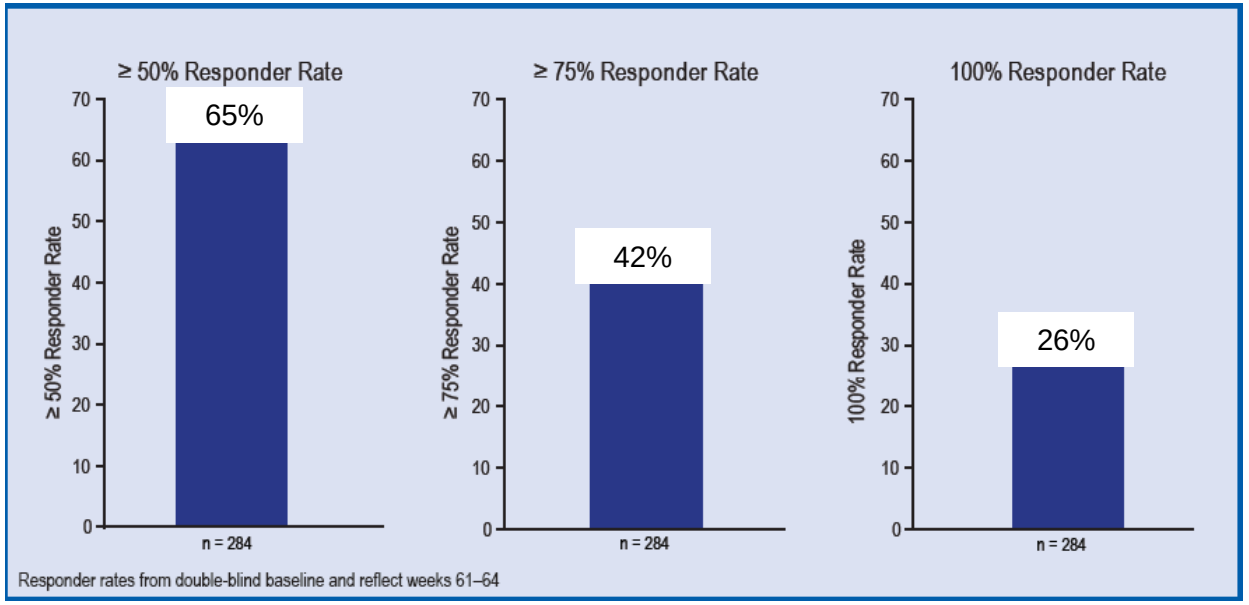
Erenumab (AMG 334) in episodic migraine

Ashina et al., *Neurology® 2017;89:1-7*

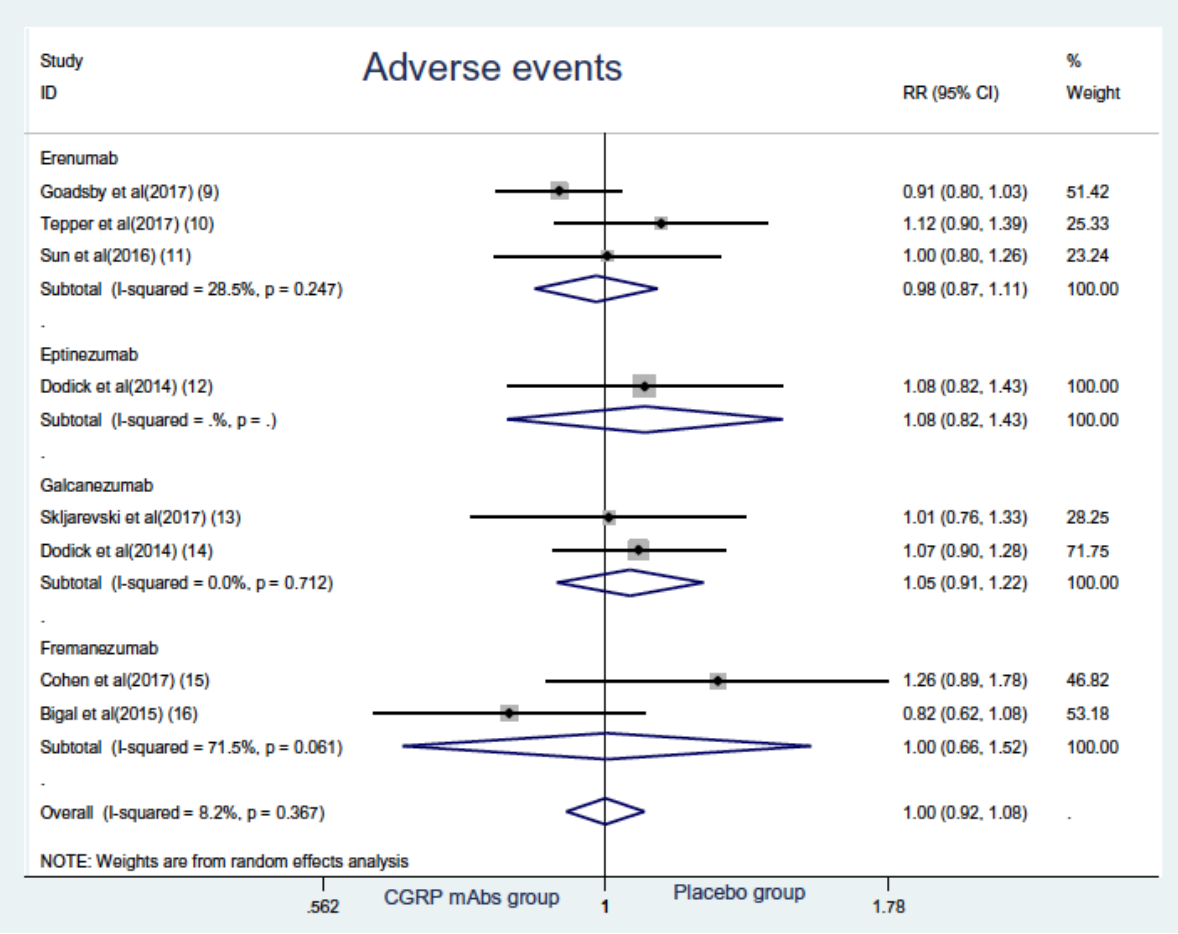
Interim analysis of an ongoing open-label study

One year treatment

Responder rate at week 64

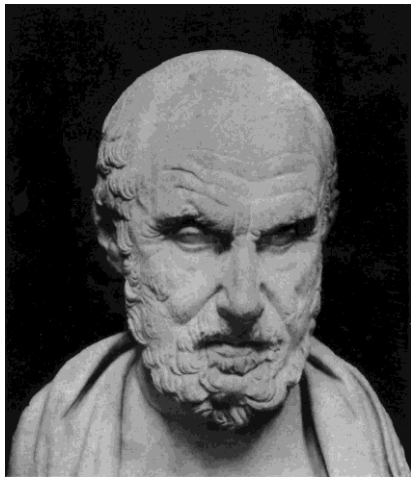


Safety of anti-CGRP/R mABs

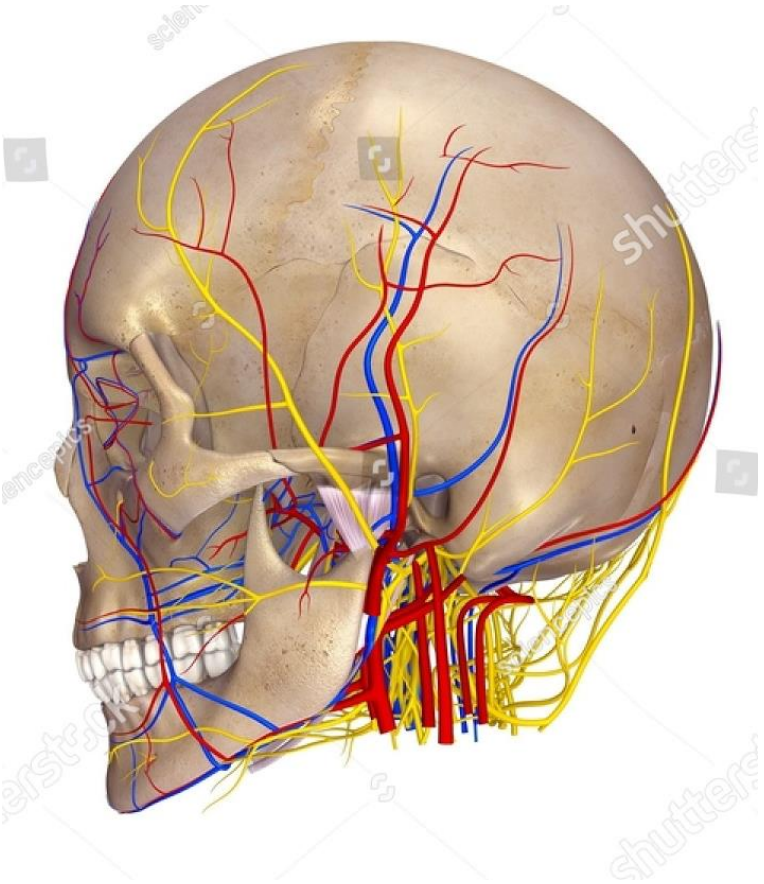


Zhu et al, Neurol Sci 2018

Hemicrania (half-head)



Aelius Galenus
of Pergamon (129-216, AD)



Word cloud of the Gene Ontology, Kyoto Encyclopedia of Genes and Genomes(KEGG)and Reactomepathways enriched in the 37 genes implicated in migraine

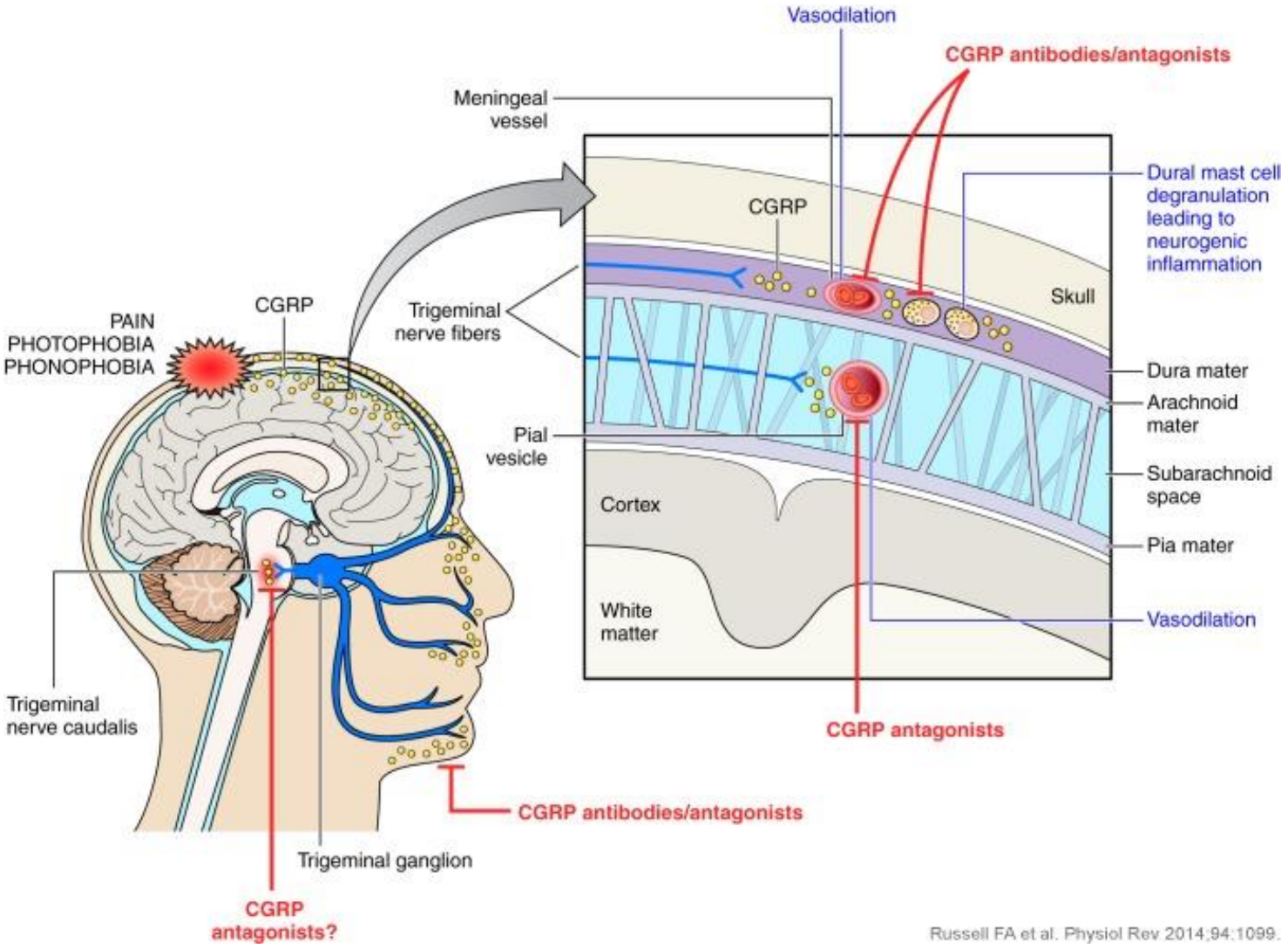
Migrainomics — identifying brain and genetic markers of migraine

Dale R. Nyholt[1], David Borsook[2,3] and Lyn R. Griffiths[1]

NATURE REVIEWS | NEUROLOGY

doi:10.1038/nrneurol.2017.151
Published online 17 Nov 2017

CGRP and Meningeal Arteries



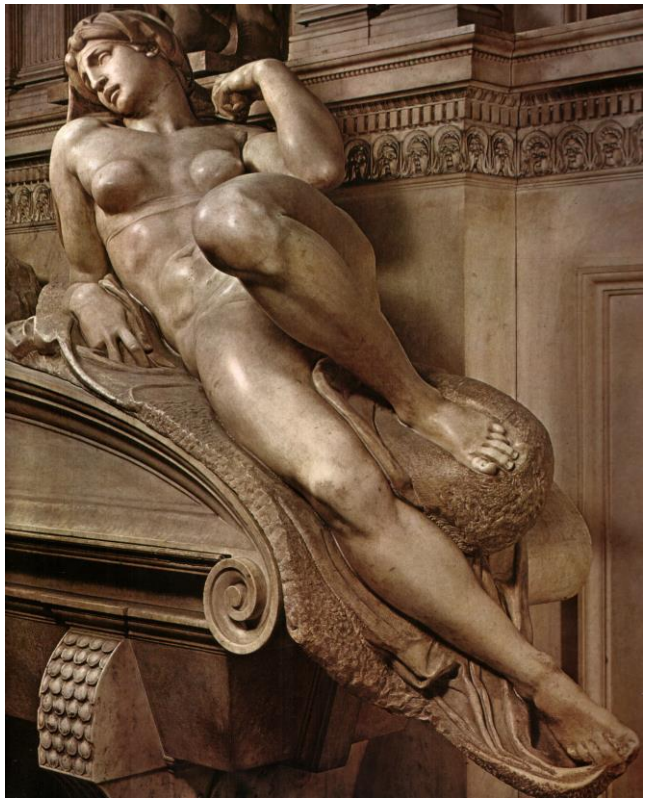
Russell FA et al. Physiol Rev 2014;94:1099.

Conclusions

CGRP:

- belongs to a family of regulatory peptides
- is a local vasodilator neuropeptide with local pro-algesic actions
- is released from human sensory nerves locally
- provokes migraine pain via a delayed mechanism, probably non-involving vasodilatation
- is the main, but probably not the sole, mediator implicated in migraine pain
- acts at peripheral targets outside the blood brain barrier
- affecting proinflammatory, but not homeostatic functions, can be blocked without causing severe side effects

Grazie dell'Attenzione



Aurora
Cappelle Medicee, Firenze