Co-morbidity of Migraine and Temporomandibular Disorders: From Clinical side to the Bench

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Disclosures

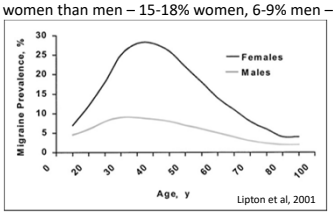
Consultant/Honoraria for:

- Kallyope
- Finnegan Law – Medicolegal Work
- Allergan/AbbVie

2

Migraine

- It is the most prevalent and disabling of all neurological diseases - approx. 12-15% of the population globally. Over 30 million US residents, and over 1 billion adults globally
- Ranks the 6th most prevalent of all disorders, and 2nd most disabling (years lived with disability – YLD), after low-back pain (Global Burden of Disease, 2015)
- Huge socio-economic problem – cost US economy more than $20 billion a year (2004)
- More prevalent in women than men – 15-18% women, 6-9% men – 2.5-3:1 ratio



Lipton et al, 2001

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The International Classification of Headache Disorders

Migraine without aura

A. At least 5 attacks fulfilling B through D
B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)
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
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

Headache Classification Committee of the International Headache Society (IHS). 3rd Edition, Cephalalgia, 2018, 38 (1): 1-211.

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Migraine – associated symptoms

- Extracranial and extracephalic cutaneous allodynia and hyperalgesia
- Cranial autonomic symptoms – lacrimation, nasal congestion, conjunctival injection
- Food craving
- Yawning
- Urination
- Tiredness
- Cognitive dysfunction – difficulty concentrating, fuzzy
- Affective dysfunction – sad or euphoric mood

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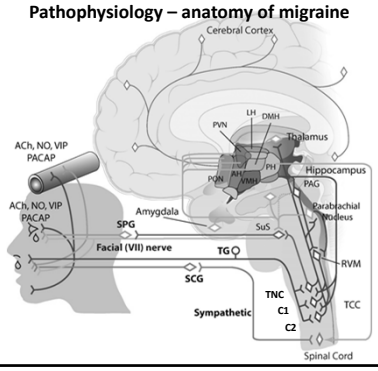
Pathophysiology – anatomy of migraine



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Temporomandibular disorders (TMD)

- Constellation of clinical problems involving the masticatory musculature and/or TMJ and associated structures (Romero-Reyes and Uyanik, 2014, J Pain Res; Okeson, 2014, Bell's Oral and Facial Pain).
- Symptoms: Pain with mastication, headache, earache, jaw ache or pre auricular pain or joint pain, joint sounds and limitation of opening
- Prevalence of TMD is 5-12% (NIDCR) with an incidence 3.9% per annum (Slade GD et-al, 2013 OPERRA study), at least 10 million people in the US. The most prevalent of the chronic orofacial pains.

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International Classification of Orofacial Pain

Primary Myofascial Pain

A. Myofascial pain fulfilling criteria B-D
B. Occurring in one or more episodes,1 or unremitting
C. Reported in the jaw, temple, ear and/or in front of ear, with both of the following:
   1. confirmation on examination of location(s) in the temporalis and/or masseter muscle(s)
   2. provoked by either or both of:
      a) palpation of the temporalis and/or masseter muscle(s)
      b) maximum unassisted or assisted jaw opening
D. Modified by jaw movement, function or parafunction (e.g. tooth-grinding or clenching)
E. Not better accounted for by another ICHD-3 diagnosis

International Classification of Orofacial Pain (ICOP). 1st Edition, Cephalalgia, 2020, 40 (12): 129-221.

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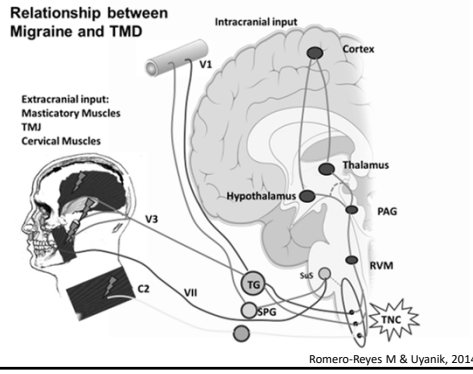
Relationship between Migraine and TMD



Romero-Reyes M & Uyanik, 2014

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Migraine Co-morbidities

Migraine is commonly co-morbid with other pain disorders

1. Temporomandibular Disorders (TMDs)
2. Inflammatory bowel disorders (IBDs)
3. Fibromyalgia

These are all more common in women

Migraine is commonly co-morbid with brain disorders (neurological/psychiatric)

1. Depression
2. Anxiety
3. PTSD and other stresses

4. Epilepsy
5. Sleep disorders

Certain things can also exacerbate migraine headache

1. TMDs
2. Traumatic brain injury
3. Sex (more common in females)

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CGRP, migraine, TMD and its role in the co-morbidity of migraine and TMD

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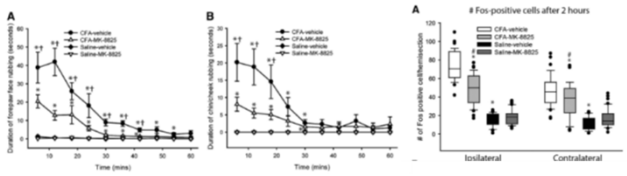
Calcitonin gene-related peptide (CGRP) and TMD

Rodents

- Spontaneous nociceptive facial grooming behaviours and neuronal activation in the Sp5 mediated by masseteric-CFA are attenuated by a rodent specific CGRP receptor antagonist (Romero-Reyes et al, 2015 Exp Neurol)



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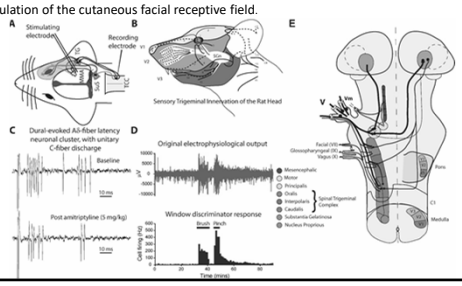
Methodology

Electrophysiology, behaviour, immunohistochemistry, biochemistry:

- Measure changes to ongoing neuronal firing in the trigeminocervical complex
- In response to dural stimulation (electrical, mechanical or chemical (inflammatory soup)) and noxious and innocuous stimulation of the cutaneous facial receptive field.



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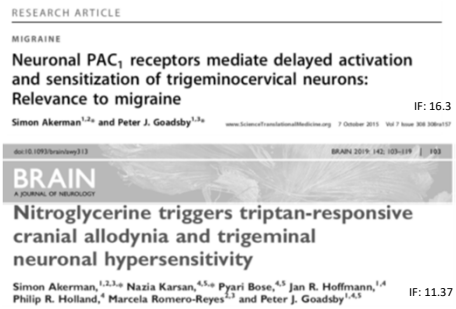
Translation of migraine triggers in preclinical studies


RESEARCH ARTICLE

MIGRAINE

Neuronal PAC_1 receptors mediate delayed activation and sensitization of trigeminocervical neurons: Relevance to migraine

IF: 16.3

Simon Akerman[1,2]* and Peter J. Goadsby[1,3]*

www.ScienceTranslationalMedicine.org 7 October 2015 Vol 7 Issue 308 308ra157

doi:10.1093/brain/awy313 BRAIN 2019; 142; 103–119 | 103

BRAIN
A JOURNAL OF NEUROLOGY

Nitroglycerine triggers triptan-responsive cranial allodynia and trigeminal neuronal hypersensitivity

Simon Akerman,[1,2,3,6] Nazia Karsan,[4,5,6] Pyari Bose,[4,5] Jan R. Hoffmann,[1,4] Philip R. Holland,[4] Marcela Romero-Reyes[2,3] and Peter J. Goadsby[1,4,5]

IF: 11.37

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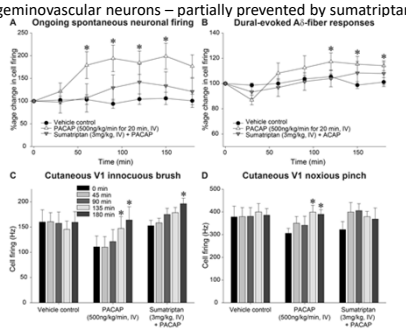
Pituitary adenylate cyclase-activating peptide mediates activation and sensitisation of dural-trigeminovascular neurons – partially prevented by sumatriptan



Akerman and Goadsby, 2015, STM; Akerman and Romero-Reyes unpublished

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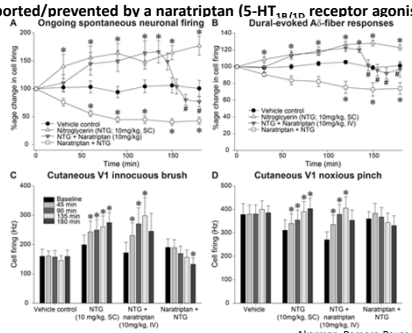
Nitroglycerin mediates activation and sensitisation of dural-trigeminovascular neurons – aborted/prevented by a naratriptan (5-$HT_{1B/1D}$ receptor agonist)



Akerman, Romero-Reyes et al, 2019, Brain

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Translation of nitroglycerin (NTG) in patients

- NTG (0.5 μg/kg/min, IV for 20 min) triggered migraine in 44 of 53 patients (83%)
- In patients that reported migraine associated cranial allodynia (CA), NTG triggered CA in 13/20 patients
- First NTG response 14/17 (82%) patients with CA responded to treatment
  - Aspirin (5/5, 100% patients)
  - Sumatriptan (9/12, 75% patients)

NTG triggers migraine-associated CA in a significant proportion of patients, which is highly responsive to treatment, including triptans

	Migraine-like headache triggered	Headache associated CA triggered	Reproducibility of NTG-headache	Reproducibility of NTG-CA
CA reported with spontaneous migraine	20	13 (65%)	11/12	8/10
CA not reported with spontaneous migraine	24	4 (16%)	12/12	2/2
Total	44	17	23	10

Akerman, Romero-Reyes et al, 2019, Brain

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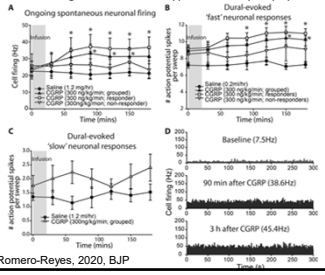
CGRP on central trigeminovascular neurons

- Using a critical ratio of 30% - 9/15 rats CGRP causes delayed activation and sensitization of central dural-trigeminovascular neurons.
- This manifests as delayed hypersensitive neuronal responses to noxious intracranial dural-vascular stimulation – indicative of migraine-like throbbing headache, and hypersensitivity to physical activity.



Akerman and Romero-Reyes, 2020, BJP

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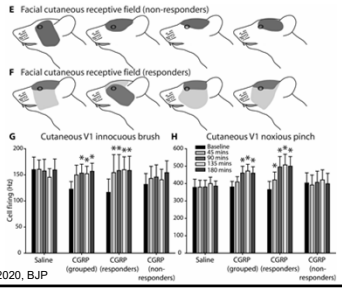
CGRP on central trigeminovascular neurons

- This also manifests as expansion of receptive field and delayed hypersensitive neuronal responses to innocuous and noxious extracranial cutaneous facial stimulation



Akerman and Romero-Reyes, 2020, BJP

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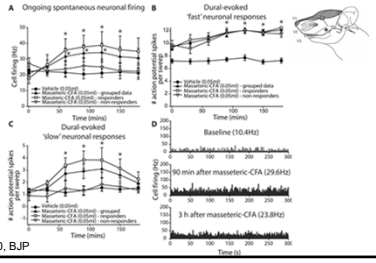
Masseteric-CFA on dural-central trigeminovascular neurons

- In 7/12 rats complete Freund's adjuvant (CFA) injection in the masseter muscle (V2 trigeminal division) causes delayed activation and sensitization of central trigeminovascular neurons.
- This manifests as delayed hypersensitive neuronal responses to noxious intracranial dural-vascular (V1 trigeminal division) stimulation.



Akerman and Romero-Reyes, 2020, BJP

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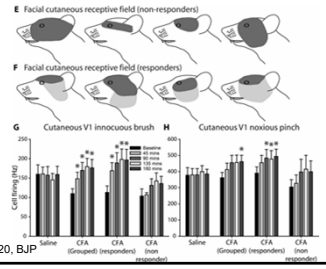
Masseteric-CFA on dural-central trigeminovascular neurons

- This also manifests as expansion of cutaneous receptive field and delayed hypersensitive neuronal responses to innocuous and noxious extracranial cutaneous facial stimulation in the V1 regions – indicative of facial cutaneous allodynia and hyperalgesia.



Akerman and Romero-Reyes, 2020, BJP

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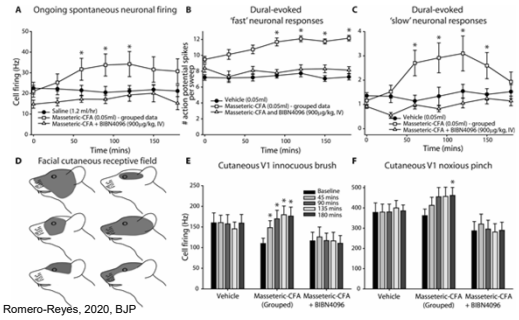
Masseteric-CFA on dural-central trigeminovascular neurons

- CGRP receptor antagonist (BIBN4096-olcegepant) prevents these changes.



Akerman and Romero-Reyes, 2020, BJP

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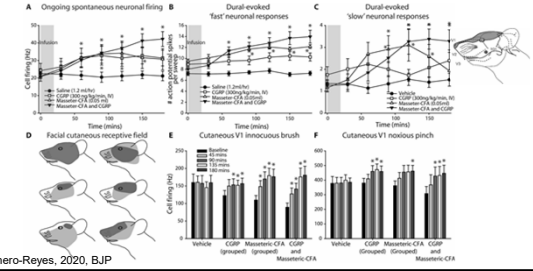
Co-morbidity of masseteric-CFA/CGRP on dural-central trigeminovascular neurons

- Combined masseter-CFA and CGRP causes delayed activation and sensitization of central trigeminovascular in all rats (10/10).
- This manifests as delayed hypersensitive, and exacerbated, neuronal responses to noxious intracranial dural-vascular (V1 trigeminal division) and extracranial cutaneous stimulation.



Akerman and Romero-Reyes, 2020, BJP

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Co-morbidity of masseteric-CFA/CGRP on dural-central trigeminovascular neurons

RESEARCH PAPER

Preclinical studies investigating the neural mechanisms involved in the co-morbidity of migraine and temporomandibular disorders: the role of CGRP

Simon Akerman | Marcela Romero-Reyes

IF: 7.73

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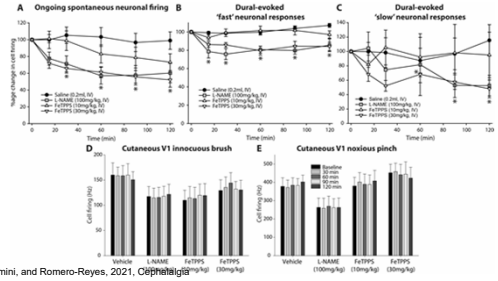
RNOS – acute migraine-like dural trigeminovascular activation

- A nitric oxide synthase inhibitor (L-NAME) and a PN decomposition catalyst (FeTPPS), both inhibit migraine-like dural nociceptive responses
- There is no effect of normal somatosensory responses



Akerman, Salvemini, and Romero-Reyes, 2021, Cephalalgia

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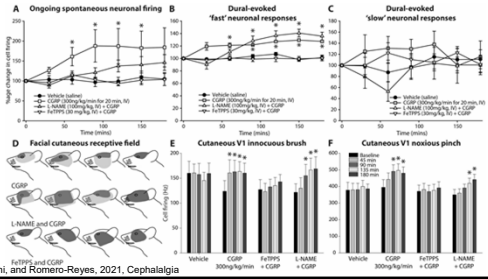
RNOS – acute migraine-like dural trigeminovascular activation

- FeTPPS prevents CGRP-mediates activation and sensitisation of migraine-like dural nociceptive responses, and cranial somatosensory hypersensitivity
- L-NAME has no significant effect



Akerman, Salvemini, and Romero-Reyes, 2021, Cephalalgia

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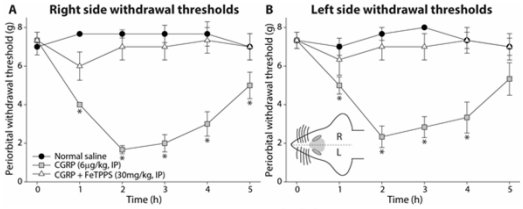
RNOS – acute migraine-like dural trigeminovascular activation

- Neuronal responses to FeTPPS translate to reduction of periorbital withdrawal thresholds



Cephalalgia

Original Article

Targeting reactive nitroxidative species in preclinical models of migraine

Simon Akerman[1], Daniela Salvemini[2] and Marcela Romero-Reyes[1]

IF: 6.292

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Thank you

Co-morbidities Project

Dr. Marcela Romero-Reyes

Molecular mechanisms-Drug Discovery – Peroxynitrite

Dr. Marcela Romero-Reyes

Dr. Daniela Salvemini (SLU)

Funding: Department of Defense grant (W81XWH2110485)

NIH-NINDS (R01 NS120930-01A1)

UNIVERSITY of MARYLAND
CENTER TO ADVANCE CHRONIC PAIN RESEARCH

NIH National Institute of Neurological Disorders and Stroke

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

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