

From the Bench To the Bedside

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Disclosures

- Consultant
 - Allergan, Teva, Lilly, Alder, Biohaven, Theranica
- Speaker
 - Allergan, Lilly, Amgen, Teva, Biohaven
- Research
 - Allergan

Objectives

- To recognize the unique clinical characteristics of migraine triggers
- To propose a new classification for migraine triggers
- To understand how basic science studies might explain how triggers might both activate and sensitize neurons with the trigeminal pathways
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Types of Trigger Factors

Type of Triggers	Examples
Behavioral	Stress, Fasting, Sleep, Emotions, Exercise, Travel
Environmental	Weather, Odors, Bright Lights, Allergens, Pollutants
Hormonal	Menstruation
Dietary	Caffeine, Alcohol, MSG, Nitrites
Chemical	Cleaning Solvents, Paint Fumes

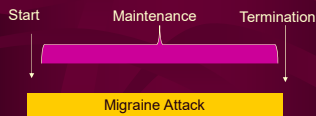
Martin V. Med Clin N Amer 2001; 911-041

How Long Does It Take for a Trigger to Precipitate a Migraine?

Trigger Factor	Duration after Exposure
Bright Sunlight	5-10 minutes (summer), 60 minutes (winter)
Flashing Photic Stimulus	<15 minutes
Odors	118 minutes
Red Wine	3 hours
Stress (after a reduction in stress)	6-24 hours
Chocolate	22 hours

Gibb C. Cephalalgia 1991; 11: 93-95; Littlewood J. Lancet 1988; 1: 550-553; Tekatas A. Eur Neurol 2013; 70: 15-16; Silva Neto R. 2017; 37: 20-28

Phases of a Migraine Attack



Time Epochs of More Frequent Headache

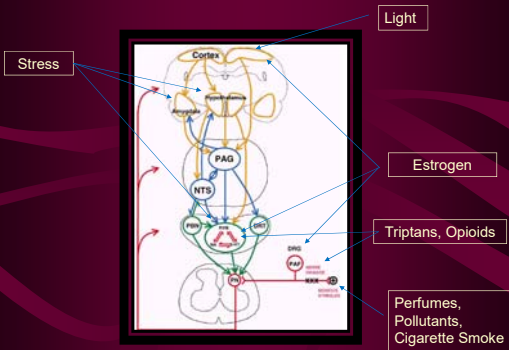


Anxiety and Depression



Sinus and Allergies

Central vs Peripheral Acting?



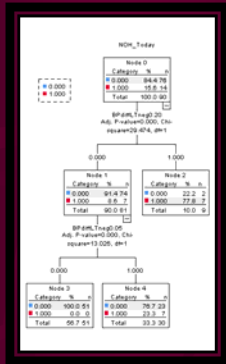
Proposed Classification for Trigger Factors

Activators

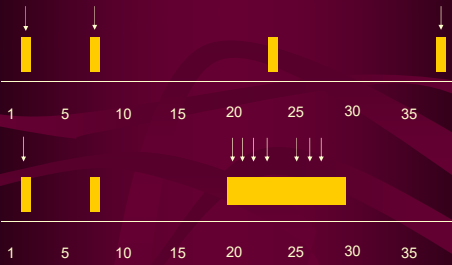
Sensitizers

Activators & Sensitizers

Quantity of Exposure



Short-lasting vs Prolonged Triggers



Short- vs Long-Acting Triggers

Short Lasting	Long Acting
Odors	Allergens
Light	Air Pollutants
Noise	Mold
Dietary	Hormones
Stress	Stress
Sleep Disturbances	Sleep Disturbances

*Short Acting <1 day exposure
 **Long Acting >1 days exposure

Female Hormones & Migraine

Central Sensitization

Menstrual Migraine

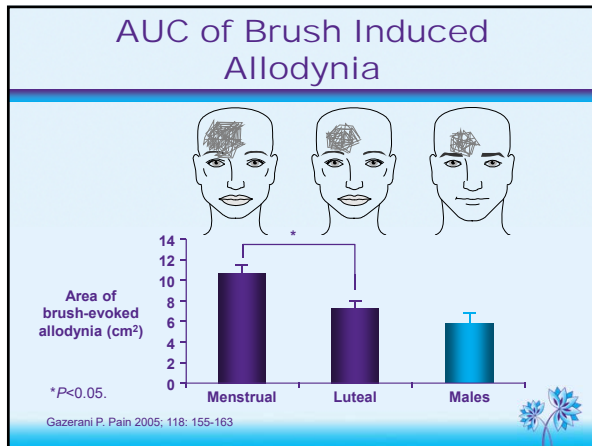
Time of Cycle	Odds Ratio
Premenstrual	
Days -1 and -2	1.71 (1.45, 2.01)
Days -1 to -5	1.25 (1.10, 1.42)
Menstrual	
Days 0 to 3	2.50 (2.24, 2.77)
Days 0 to 5	2.19 (2.01, 2.04)

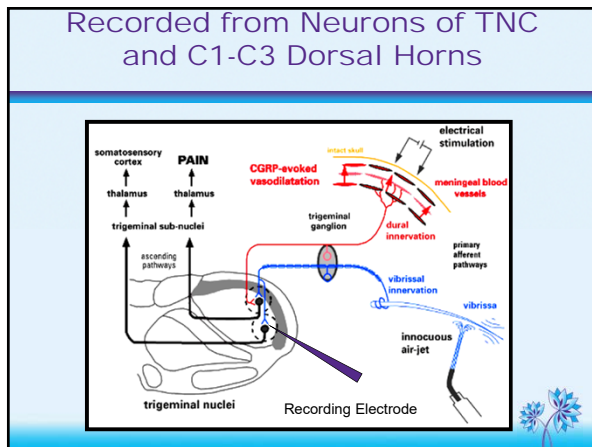
MacGregor A. Neuro 2004; 63: 351-53

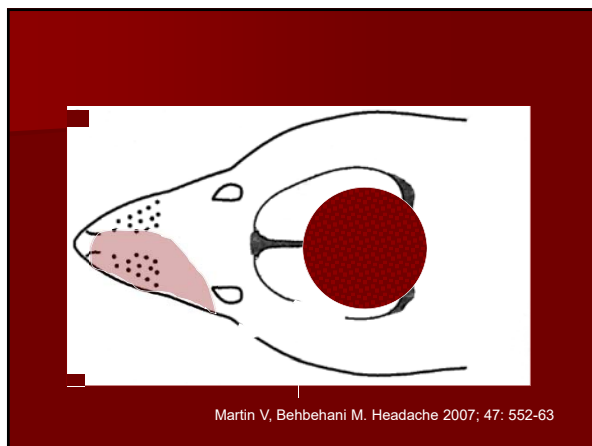
Characteristics of Menstrual Migraine

- Predictable onset
- Usually migraine without aura
- Longer in duration
 - due to a persistent trigger?
- Severity and disability may be slightly higher
- More abortive medication use
- Headache recurrence may be higher

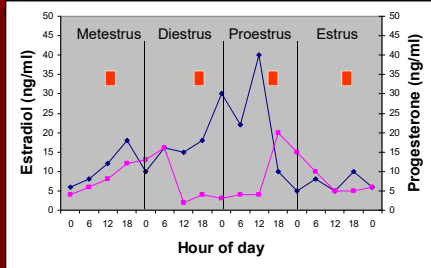
Martin V. Headache 2005; 45: 1190-1201
MacGregor A. Neurology 2004; 63: 351-353
Granello F. Cephalalgia 2004; 24: 707-16





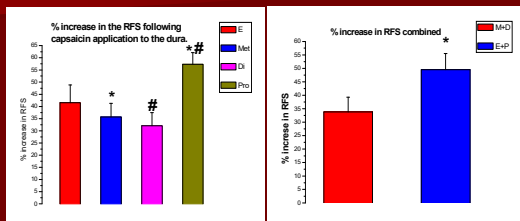


Rat Estrous Cycle



Martin V, Behbehani M. Headache 2007; 47: 552-63

Change in Receptive Field Size



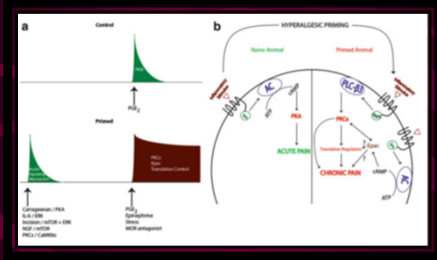
*p<0.05
#p<0.05

Martin V, Behbehani M. Headache 2007; 47: 552-63

Trigger Factors

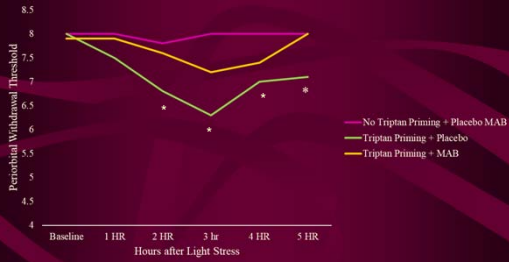
Priming of 1st Order Neurons &
Sensitization of Second Order
Neurons

Hyperalgesic Priming of Afferent Neurons



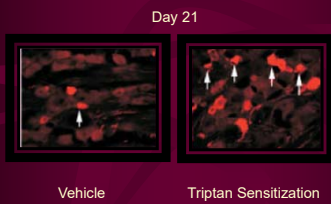
Kandasamy R. Hand Exp Pharmacol 2015; 227: 15-37

Tactile Allodynia after Bright Light Stress in Rats with Triptan Induced Latent Sensitization



Kopruszinski C. Cephalalgia 2017; 560-570

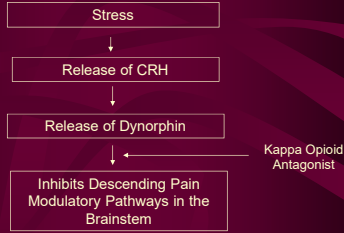
CGRP Containing Neurons after Latent Triptan Sensitization



*Occurred in IB4 (peptide poor) and NF 200 neurons

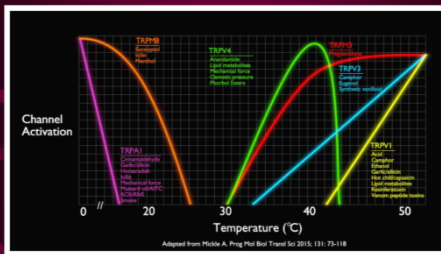
DeFelice M. Ann Neurol 2010; 67: 325-337

Theorized Mechanisms of Stress Induced Allodynia



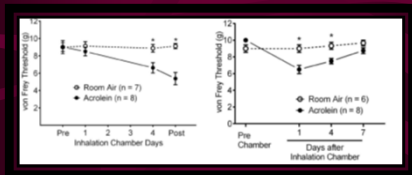
Xie J. Cephalalgia 2017; 790-94; Chen W. Neurosci 2018; 381: 149-158

TRP Receptors



Mickle A. Prog Mol Biol Trans Sci 2015; 131: 74-115

Inhaled TRP Agonists Produce Persistent Periorbital Allodynia



Kunkler P. Pain 2018; 159: 540-549

Conclusion

- Trigger factors have different clinical characteristics
- Some may activate and others may sensitize 1st or second order neurons within trigeminal pain pathways
- It is necessary to understand migraine triggers in order to optimally treat patients with migraine
