TREATMENT OF MIGRAINE AND GENERAL PAIN SYNDROMES

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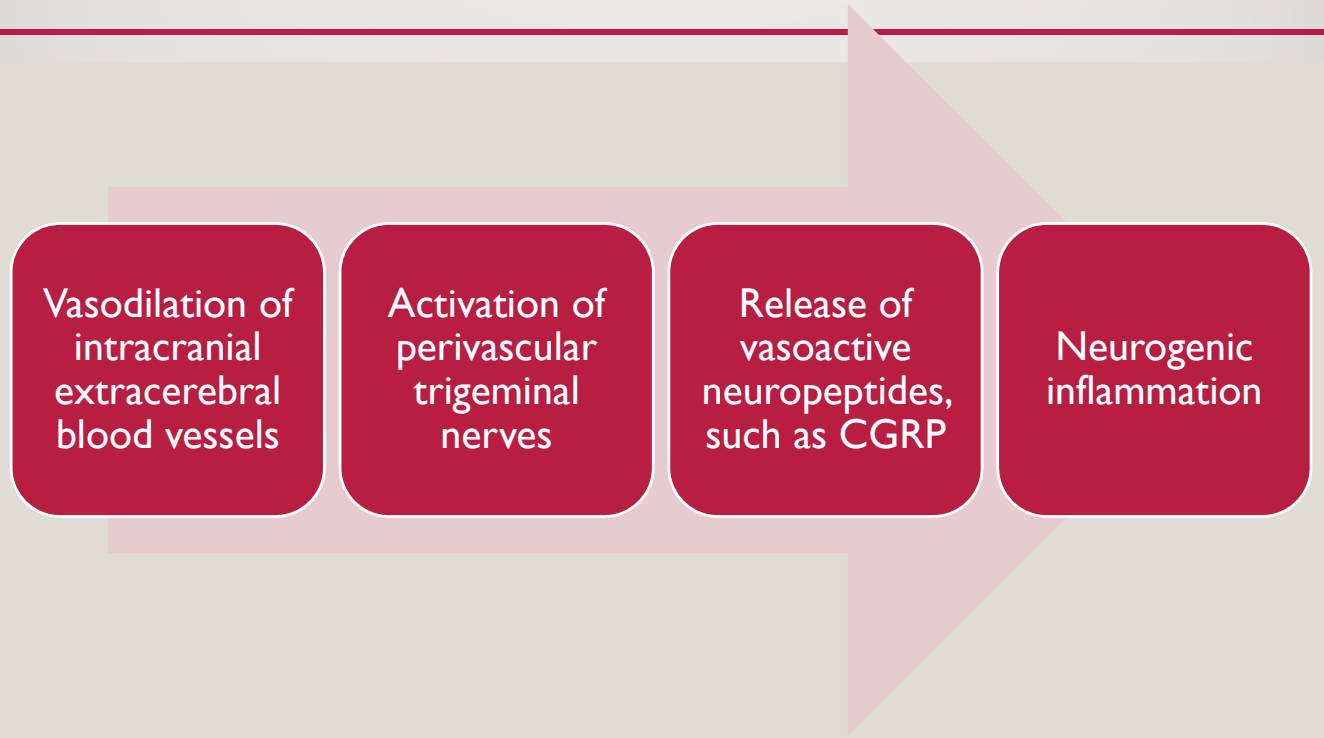
OBJECTIVES

- Identify the nonpharmacological and pharmacological treatment options for Migraines
- Review new studies regarding the new class of CGRP antagonists/monoclonal antibodies
- Review the use of Oxytocin/Ketamine/LDN in pain management

OVERVIEW OF PATHOPHYSIOLOGY OF MIGRAINES



PATHOPHYSIOLOGY OF MIGRAINES

- Cortical spreading depression
  - Self-propagating wave of neuronal and glial depolarization that spreads across the cerebral cortex.
  - Causes migraine aura, activates trigeminal nerve afferents, and alters blood-brain barrier permeability.
  - Causes prolonged activation of trigeminal nociception, which generates the pain of the migraine headache.

- The trigeminovascular pathway conveys nociceptive information from the meninges to the brain.
  - Stimulation of the trigeminal ganglion results in release of vasoactive neuropeptides: substance P, calcitonin gene-related peptide, and neurokinin A

NEUROINFLAMMATION

Neuropeptides interact with:

Endothelial cells, mast cells, immune cells, and vascular smooth muscle

Cascade of inflammatory responses:

Erythema and hyperemia (secondary to local vasodilation), local edema (secondary to plasma-protein extravasation), and hypersensitivity (secondary to alterations in the excitability of certain sensory neurons)

Vasodilation + Increased Vascular Permeability = Neurogenic Inflammation

NEUROINFLAMMATION & SENSITIZATION

- Neurogenic inflammation leads to sensitization
- Sensitization is the process in which neurons become increasingly responsive to nociceptive and non-nociceptive stimulation
  - Response thresholds decrease
  - Response magnitude increases
  - Receptive fields expand
  - Spontaneous neuronal activity develops
- Sensitization is responsible for many symptoms of migraine:
  - Throbbing quality of pain
  - Worsening of pain with coughing, bending, or sudden movements
  - Hyperalgesia
  - Allodynia

DISEASES ASSOCIATED WITH NEUROINFLAMMATION

- Parkinson's
  - Chronic release of pro-inflammatory cytokines by activated astrocytes and microglia leads to the exacerbation of dopamine neuron degeneration
- Alzheimer's
  - Aβ deposits induce an inflammatory response that subsequently leads to Alzheimer's Disease
- Multiple sclerosis
  - Neuroinflammation leads to neurodegeneration and decreases regeneration and remyelination of neurons.
- Depression
  - Obesity and normal aging are associated with an increase in pro-inflammatory markers which correlate with symptoms of depression.

CGRP ANTAGONISTS

PRODUCTS AND INDICATION

CGRP Antagonists are indicated for migraines.

Products discontinued before approval	Products in the pipeline
Telcagepant- concerns for hepatotoxicity	Ubrogepant
Olcegepant- poor bioavailability	Atogepant
	Galcanezumab
	Eptinezumab
	Fremanezumab
	Erenumab

CALCITONIN GENE-RELATED PEPTIDE (CGRP)

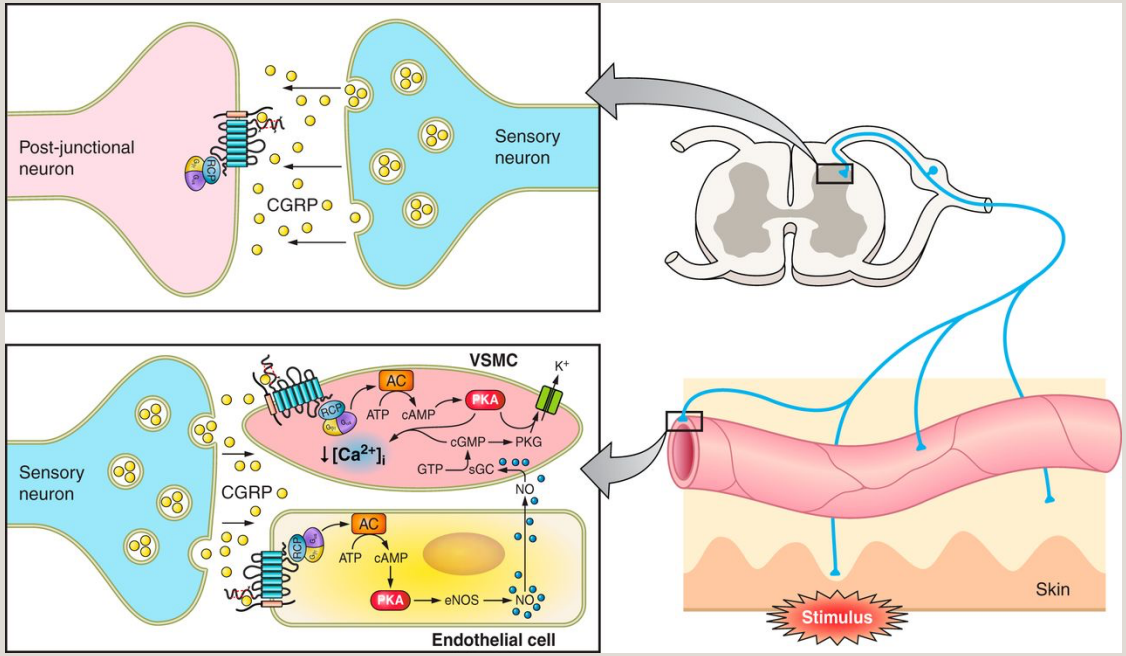
- Calcitonin gene-related peptide (CGRP) is a 37-amino acid peptide located in sensory fibers.
- Has potent vasodilator activity.
- The sensory fibers that contain CGRP are associated with pain processes, such as migraines.

CGRP ANTAGONIST MOA

- Medications in this class include small molecule antagonists and monoclonal antibodies.
- These antagonize the CGRP mechanism by targeting either the peptide or its receptor.

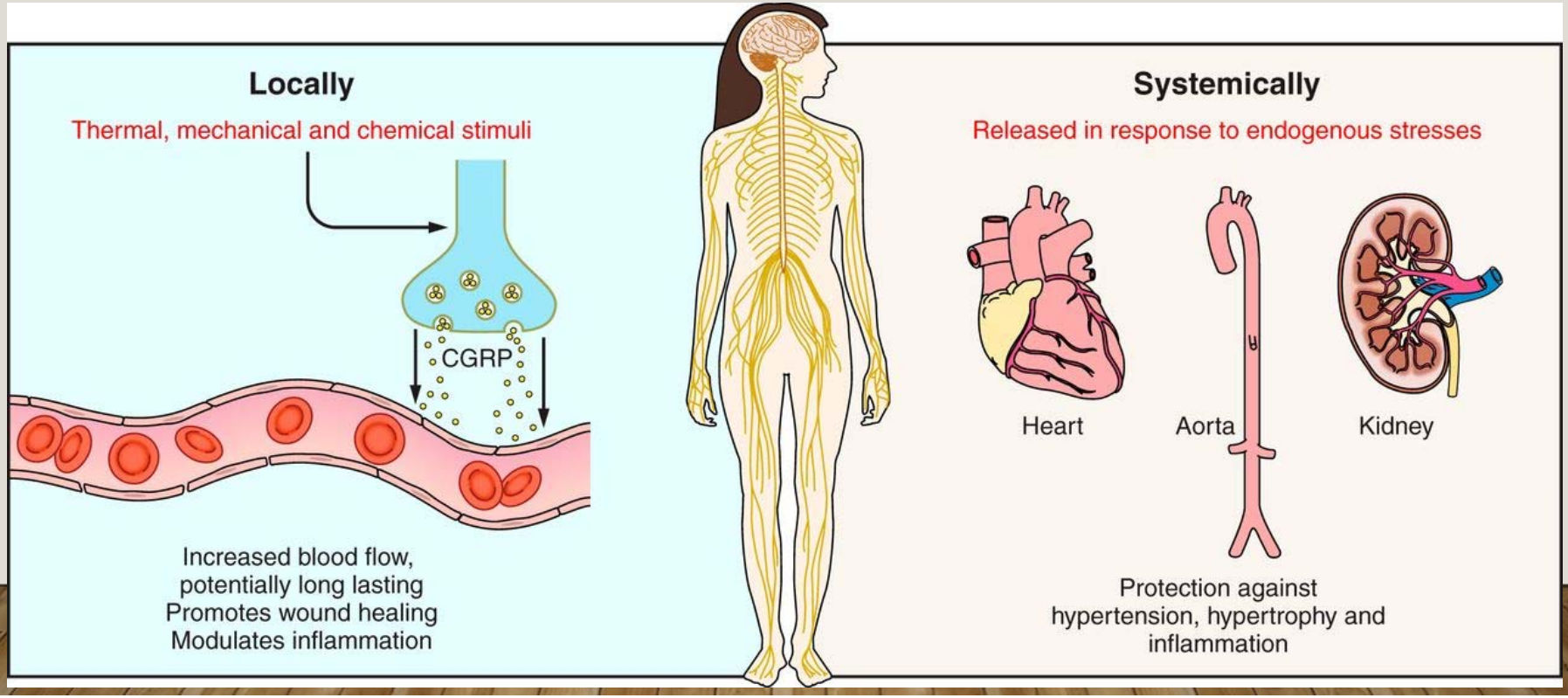
CALCITONIN GENE-RELATED PEPTIDE (CGRP)

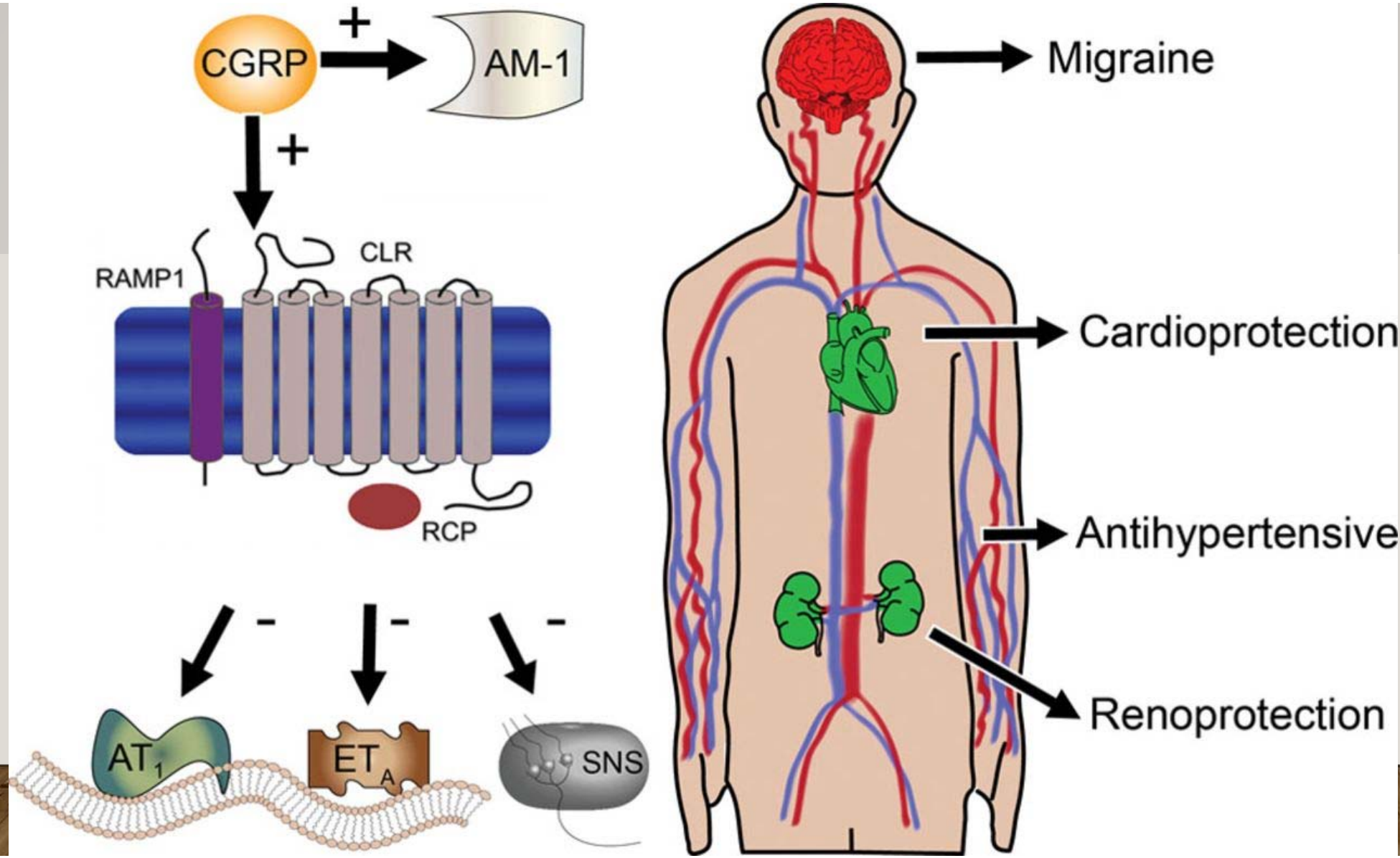
- Found in nerve fibers surrounding cranial nerves
- Provide sensory innervation to the central nervous system
- CGRP levels in cranial circulation as well as in saliva are increased during a migraine attack
- Triptan drugs such as sumatriptan results in the normalization of CGRP levels



American Headache Society. 2013;53:67-80.

CALCITONIN GENE-RELATED PEPTIDE (CGRP): EFFECTS ON THE BODY

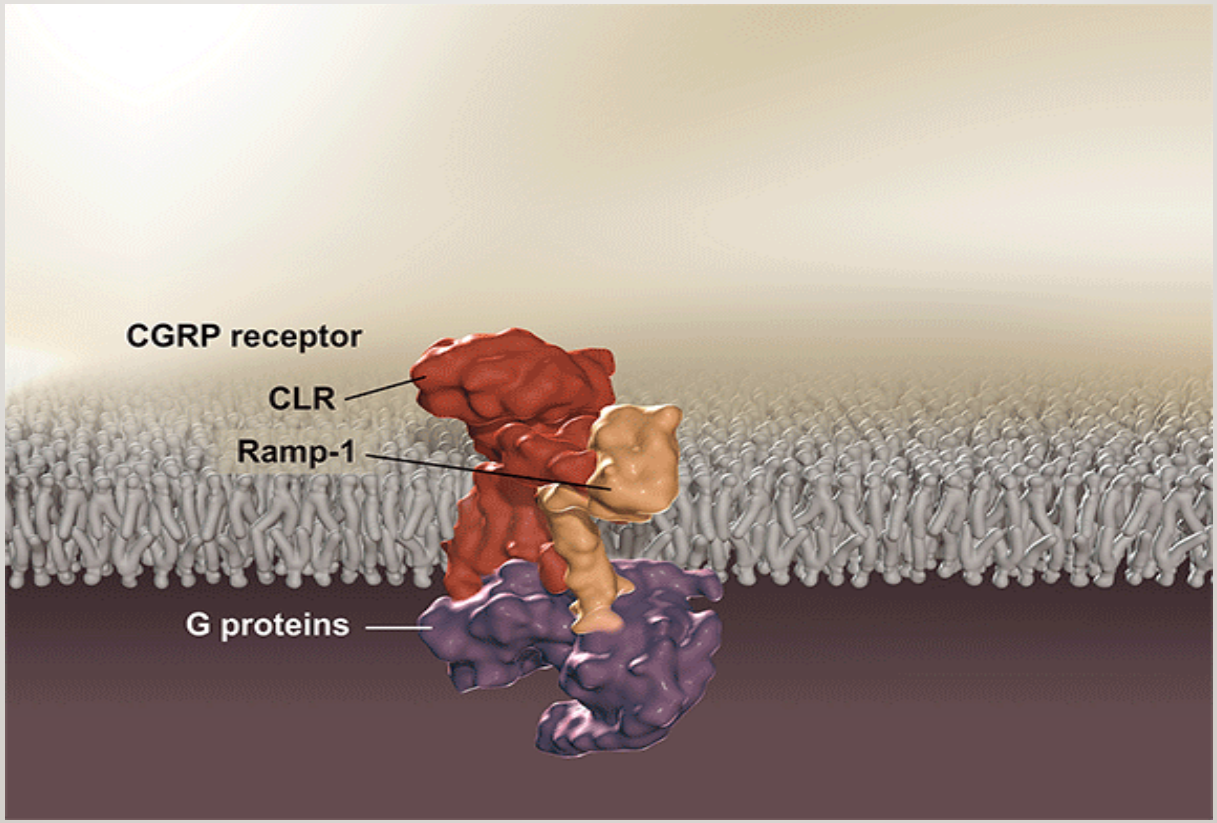



CGRP
+
AM-1
+
RAMP1
CLR
RCP
-
-
-
AT1
ETA
SNS
Migraine
Cardioprotection
Antihypertensive
Renoprotection

CALCITONIN LIKE RECEPTOR (CLR) AND RECEPTOR ACTIVITY MODIFYING PROTEIN (RAMP)

- CLR partners with RAMP1 to form the CGRP receptor
- Co-expression of RAMP is necessary for CLR to reach the cell surface
- RAMPs could modulate pharmacology of the receptor either by:
  - Allosteric modulation of the ligand-binding site on CLR
  - Defining the ligand binding pocket by cell surface RAMP–CLR interaction

British Journal of Pharmacology. 2012;166:66-78.


CGRP receptor
CLR
Ramp-1
G proteins

OLCEGEPANT

- Mallee *et al.*. 2002
  - Olcegepant showed similar potency on a receptor consisting of rat CLR and human RAMP1 as the fully human receptor while its potency on human CLR with rat RAMP1 was similar to the rat receptor
  - Olcegepant is primarily driven by selectivity for RAMP1 rather than CLR

British Journal of Pharmacology. 2012;166:66-78.

UBROGEPANT

- Drug target: CGRP receptor
- Route of administration: Oral
- Phase II clinical trial:
  - Multicenter, randomized, double-blind, placebo-controlled trial
  - Included 834 patients with a ≥1-year history of migraine who experienced 2-8 moderate or severe migraines per month
  - Patients assigned based on self-reported usual triptan response to one of the following groups: 1, 10, 25, 50, and 100 mg of Ubrogepant, or placebo at onset of migraine
  - Ubrogepant 100 mg was significantly superior to placebo for two-hour pain freedom (25.5% vs 8.9%, $p<0.001$)
  - Ubrogepant 50 mg demonstrated a nominally significantly higher two-hour pain-free rate than placebo (21.0% vs 8.9%, $p = 0.020$) as did the 25-mg dose group (21.4% vs 8.9%, $p = 0.013$)

ATOGEPANT

- Drug target: CGRP receptor
- Route of administration: Oral
- Phase II/III clinical trial:
  - Multicenter, randomized, double-blind, placebo controlled
  - Included 834 patients with at least a 1 year history of 4-14 migraine days per month
  - Patients assigned to 10 mg QD, 30 mg QD, 30 mg BID, 60 mg QD, 60 mg BID or placebo
  - Estimated study completion date of April 25, 2018

GALCANNEZUMAB

- Drug target: CGRP molecule
- Route of administration: Subcutaneous
- Phase II clinical trial:
  - Randomized, double-blind, placebo-controlled, multicenter
  - Included 218 patients with episodic migraine (4-14 headache days per month)
  - Patients assigned to two groups: Galcanezumab 150 mg or placebo once every 2 weeks for 12 weeks
  - The mean change in migraine headache days was significantly different in the Galcanezumab group by the third 4-week treatment period: -4.2 days in treatment group vs -3.0 days in placebo group ($p= 0.0030$)

EPTINEZUMAB

- Drug target: CGRP molecule
- Route of administration: IV
- Phase II clinical trial:
  - Randomized, double-blind, placebo-controlled, multicenter
  - Included 174 patients with 5-14 migraine days per 28-day period
  - Patients assigned to two groups: Eptinezumab 1000 mg IV or placebo as a single monthly dose
  - The mean change in migraine days between baseline and weeks 5-8 was -5.6 days in treatment group vs -4.6 days in placebo group ($p= 0.0306$)
  - After 24 of follow up, no safety concerns were noted with treatment

EPTINEZUMAB-

- Alder's PROMISE 1 Phase 3 clinical trial in episodic migraine patients
- Following the third and fourth quarterly infusions (i.e., 12-month data) and improvement in patients' quality of life measures following a single quarterly infusion.

EPTINEZUMAB-

- PROMISE 1 and PROMISE 2 clinical studies
- Supports eptinezumab's differentiated clinical profile and its rapid, effective and sustained migraine prevention benefits,"
- Eptinezumab's consistent and predictable results across both trials support its potential to be a meaningful treatment option for the most severely impacted of these patients
- Eptinezumab is an investigational monoclonal antibody targeting calcitonin gene-related peptide (CGRP) for migraine prevention. Eptinezumab's mAb design, combined with delivery via quarterly infusion, allows for strong and immediate inhibition of CGRP biology.[1] Eptinezumab has been studied in several global, randomized, double-blind, placebo-controlled studies to assess its safety and efficacy in migraine prevention.

EPTINEZUMAB-

- **Platform Presentations**
- Increased Migraine-Free Intervals With Eptinezumab Were Associated With Improved Health-Related Quality-of-Life Outcomes Through Week 12: Results From the Phase 3 PROMISE 1 Trial.
- **Poster Presentations:**

  Eptinezumab Achieved Meaningful Reductions in Migraine Activity Within 24 Hours That Were Sustained Through Week 12: Results From PROMISE 1 (PRevention Of Migraine via Intravenous eptinezumab Safety and Efficacy-1) Phase 3 Trial.

- Repeat Infusions of Eptinezumab Associated With Greater Migraine Reductions and Longer Migraine-Free Intervals: Results From the Phase 3 PROMISE 1 Trial.

- Eptinezumab Reduced Migraine Frequency, Duration, and Pain Intensity Through Week 24: Results From the Phase 3 PROMISE 1 Trial.

- Eptinezumab Achieved Meaningful Reductions in Migraine Activity As Early As Day 1 and Were Sustained Through Week 12: Results From PROMISE 2 (PRevention Of Migraine via Intravenous eptinezumab Safety and Efficacy-2) Phase 3 Trial in Chronic Migraine.

- Eptinezumab Reduced Migraine Frequency and Triptan/Ergotamine Use Over Weeks 1-12, and Improved HIT-6 Scores at Months One and Three: Results From the Phase 3 PROMISE 2 Trial in Chronic Migraine.

FREMANEZUMAB

- Drug target: CGRP molecule
- Route of administration: Subcutaneous
- Randomized, double-blind, placebo-controlled, multicenter phase II clinical trials:

FREMANEZUMAB

High-frequency episodic migraine	Chronic migraine
• Included 297 patients with 8-14 headache days in 4-week baseline period • Patients randomized to either Fremanezumab 225 or 675 mg or placebo every 4 weeks for 12 weeks • The mean change in migraine days: -Placebo: -3.46 days -Fremanezumab 225 mg: -6.27 days -Fremanezumab 675 mg: -6.09 days	• Included 264 patients with chronic migraine (15 or more headache days/month) • Patients randomized to doses given every 4 weeks for a total of 12 weeks of the following: placebo, 675 mg loading dose followed by two doses of 225 mg, or three doses of 900 mg • The mean change in number of headache hours during weeks 9-12: -Placebo: -37.10 h -Fremanezumab 675/225 mg: -59.84 h -Fremanezumab 900 mg: -67.51 h

FREMANEZUMAB

- Phase III HALO clinical trial program
- Fremanezumab, a monoclonal antibody targeting the CGRP (calcitonin gene-related peptide) ligand, currently being investigated as a preventive treatment for migraine.
- These data examined the overall efficacy, safety and tolerability profile of fremanezumab in both chronic and episodic migraine.
- Studies included patients on fremanezumab alone or in combination with other preventive medications.

FREMANEZUMAB

- Efficacy of Two Dose Regimens of Subcutaneous Fremanezumab Versus Placebo for the Preventive Treatment of Chronic Migraine
- The Impact of Fremanezumab on Work Productivity and Activity Impairment in Patients with Chronic Migraine
- The Impact of Headache Free Days on Quality of Life and Costs Among People with Migraine with >4 Headache Days in the Past Month
- Burden of Illness Among Treated Migraine Patients with ≥4 Headache Days in the Past Month
- Efficacy and Safety of 2 Dose Regimens of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine
- The Impact of Fremanezumab on Headache-Related Disability in Patients with Episodic Migraine using the Migraine Disability Assessment
- Efficacy of Fremanezumab in Patients With Chronic Migraine and Comorbid Moderate to Moderately Severe Depression
- Efficacy of Fremanezumab in Patients With Chronic Migraine With or Without Concomitant Use of Preventive Medication
- Impact of Fremanezumab on the Number of Days with Use of Acute Headache Medications in Chronic Migraine
- Onset of Action with Fremanezumab Versus Placebo for the Preventive Treatment of Chronic Migraine

ERENUMAB ARISE TRIAL

- Randomized, double-blind, placebo-controlled, conducted at 69 sites across North America and Europe
- Completed March 2017
- Included 577 patients who experienced 4-14 migraine days each month
- Patients randomized to once monthly Erenumab 70 mg or placebo for 12 weeks with a safety follow-up visit completed 12 weeks after last dose
- Protocol allowed for concomitant use of only one migraine preventive medication if the dose was stable within two months before baseline phase
- Excluded patients with migraine onset older than 50 years of age and patients with medical conditions that might prevent study completion

ERENUMAB ARISE TRIAL

Endpoint	Results
Primary: Change in monthly migraine days	• Placebo: -1.8 days • Erenumab 70 mg: -2.9 days • Difference of -1.0 days (p<0.001)
Secondary: : ≥50% reduction in monthly migraine days (MMD)	• Placebo: 29.5% • Erenumab 70 mg: 39.7% • Odds ratio: 1.59 (p=0.010)
Secondary: change in acute migraine-specific medication treatment days (MSMD)	• Placebo: -0.6 medication days • Erenumab 70 mg: -1.2 medication days • p= 0.002
Secondary: ≥5-point reduction in Physical Impairment and Impact on Everyday Activities domain scores	• Placebo: 33.0% • Erenumab 70 mg: 27.1% • Not statistically significant, p= 0.13

ERENUMAB ARISE TRIAL

- The frequency and severity of adverse events were similar between the Erenumab groups and the placebo group.
- Most common adverse effects:
  - Upper respiratory tract infection
  - Injection site pain
  - Influenza
  - Fatigue
  - Nausea
  - Sinusitis
  - Nasopharyngitis
  - Constipation

- Conclusion: Erenumab treatment resulted in reduction in migraine frequency, use of acute migraine abortive medications, disability, and headache impact.

ERENUMAB STRIVE TRIAL

- Randomized, double-blind, placebo-controlled, at 121 sites across North America, Europe and Turkey
- Completed June 2017
- Included 955 patients who experienced 4-14 migraine days each month
- Excluded patients with migraine onset older than 50 years of age
- Protocol allowed for concomitant use of only one migraine preventive medication if the dose was stable within two months before baseline phase
- Patients randomized to once monthly Erenumab 70 mg, Erenumab 140 mg or placebo for 24 weeks

ERENUMAB STRIVE TRIAL

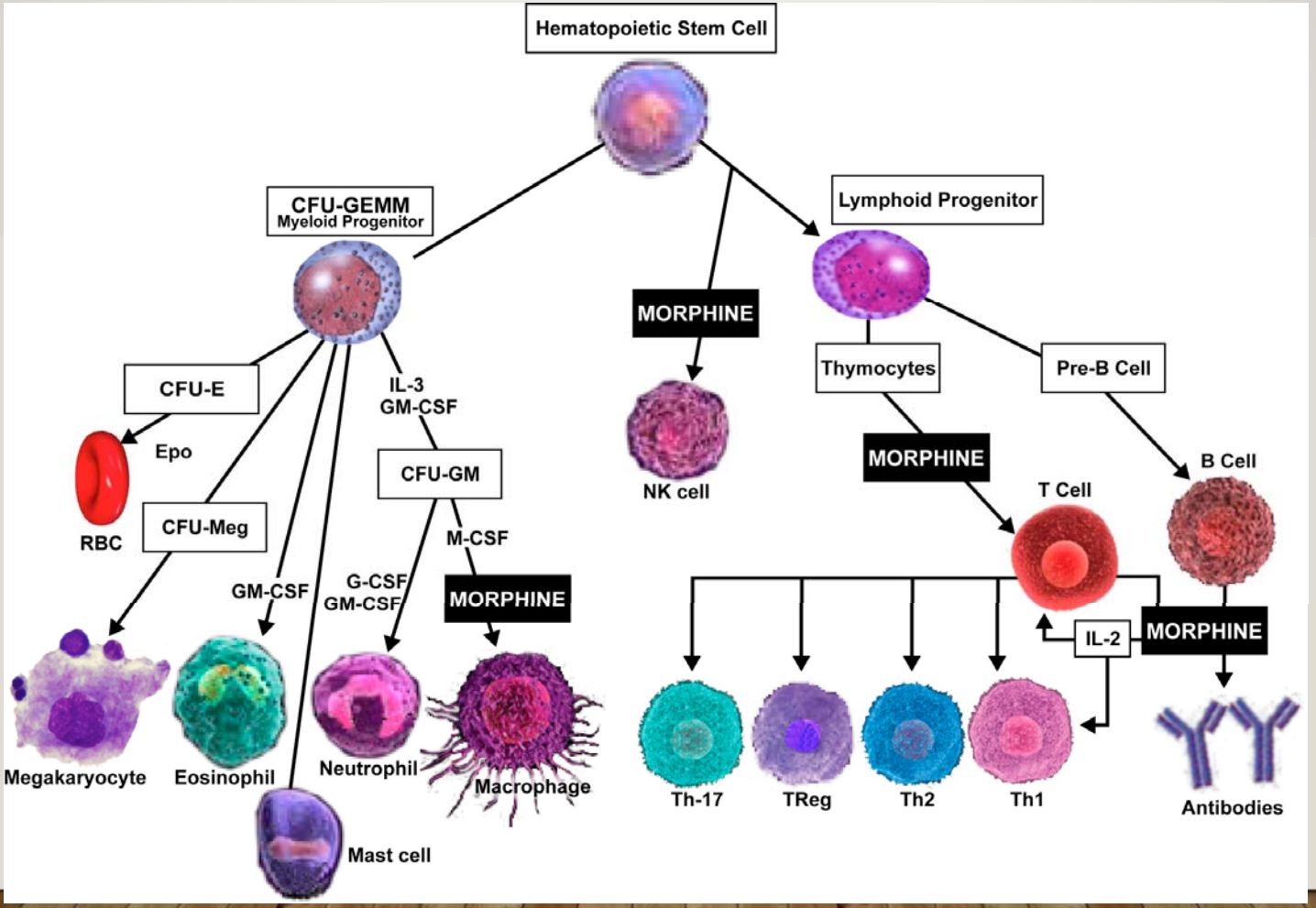
Endpoint	Results
Primary: Change in monthly migraine days	• Placebo: -1.8 days • Erenumab 70 mg: -3.2 days • Erenumab 140 mg: -3.7 days • P < 0.001
Secondary: : ≥50% reduction in monthly migraine days (MMD)	• Placebo: 26.6% • Erenumab 70 mg:: 43.3% • Erenumab 140 mg: 50.0% • P < 0.001
Secondary: change in acute migraine-specific medication treatment days (MSMD)	• Placebo: -0.2 medication days • Erenumab 70 mg: -1.1 medication days • Erenumab 140 mg: -1.6 mediction days • P < 0.001
Secondary: ≥5-point reduction in Physical Impairment and Impact on Everyday Activities domain scores	• Placebo: -3.3 points • Erenumab 70 mg: -5.5 points • Erenumab 140 mg: -5.9 points • P < 0.001

NEW TARGETS FOR MIGRAINES

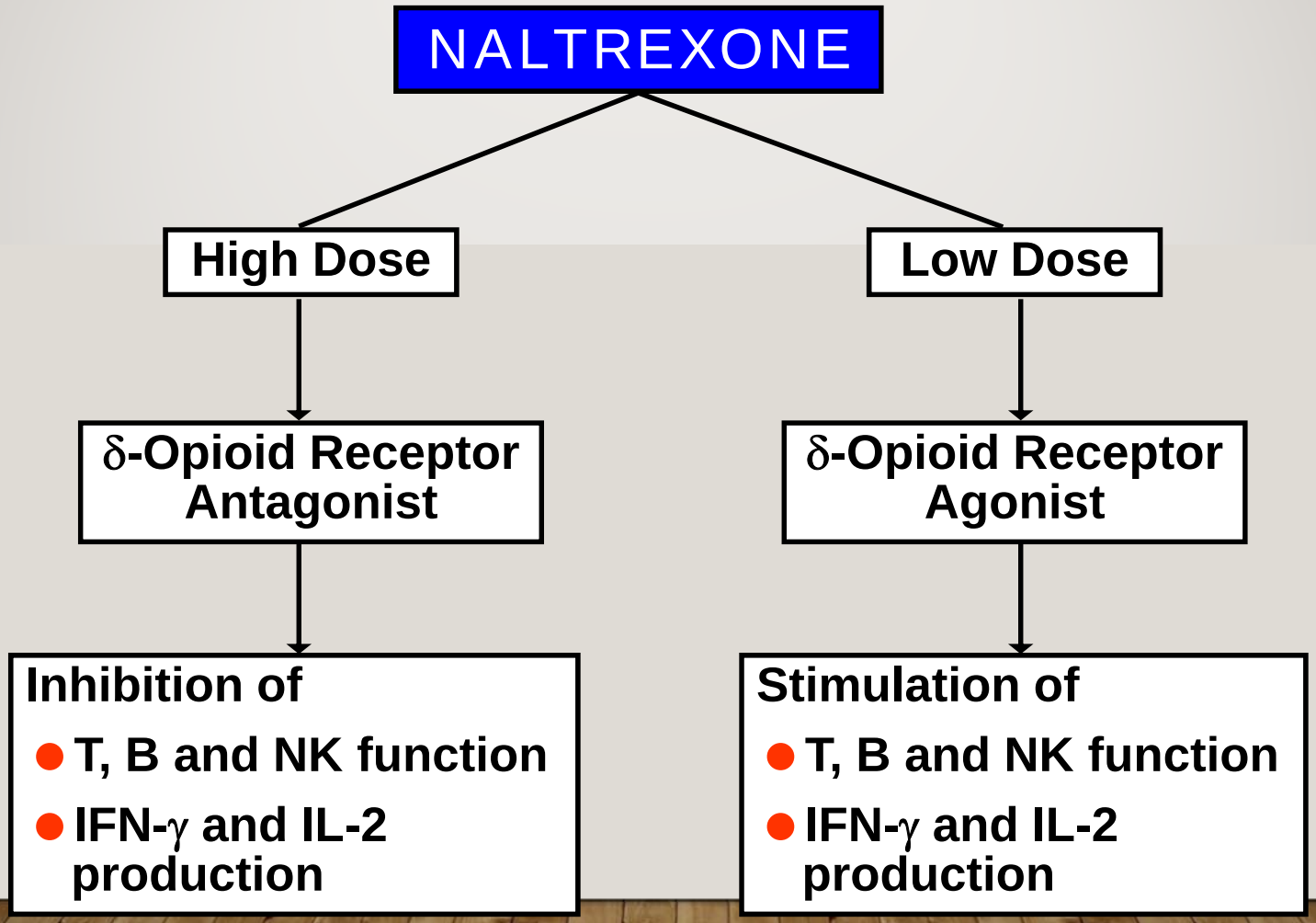
LOW DOSE NALTREXONE

- Naltrexone has been studied for its immune-modulatory and anti-inflammatory effects at low doses.
- Low dose naltrexone (LDN) antagonizes Toll-like receptor 4 (TLR4) on microglia.
  - Antagonism results in downregulation of inflammatory cytokines and immune mediators: Interleukins, interferons, tumor necrosis factors, and granulocyte colony-stimulating factor.
- Low concentrations of naltrexone bind at the opioid receptors intermittently, which sends feedback to the central nervous system to release more endogenous opioids.
- LDN has shown benefit in many neuroinflammatory diseases

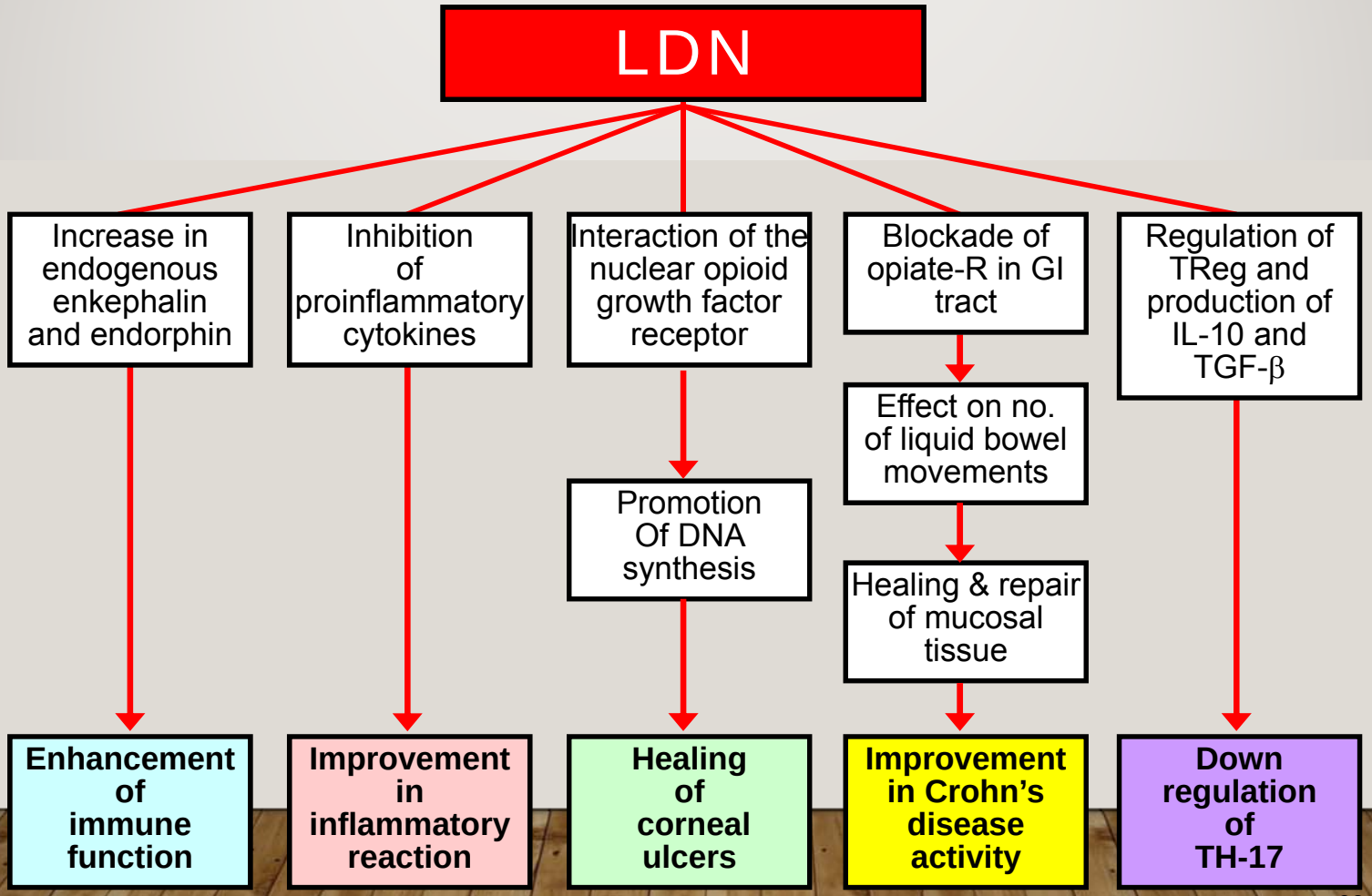
Effects of Opioids on the Immune System



Schematic representation of the hematopoietic system showing the differentiation pathways sensitive to opioids.
from Effects of Opioids on the Immune System – Roy S. and Loh H.H., Neurochemical Research, 21:1375-1386, 1996


NALTREXONE
High Dose
Low Dose
δ-Opioid Receptor Antagonist
δ-Opioid Receptor Agonist
Inhibition of
T, B and NK function
IFN-γ and IL-2 production
Stimulation of
T, B and NK function
IFN-γ and IL-2 production

MECHANISM OF ACTION OF LDN



LOW DOSE NALTREXONE (LDN)

- Dose: 3 to 4.5 mg qhs
- LDN is hypothesized to increase the production of endogenous opioids during short term blockade of opioid receptors.
- LDN has anti-inflammatory effects.
- LDN is a positive effect on the immune system and affects immune modulation.

USES

- Crohn's Disease
- Multiple Sclerosis
- Fibromyalgia
- Complex Regional Pain Syndrome
- Cancer
- Lyme Disease
- Amyotrophic Lateral Sclerosis
- AIDS/HIV
- Itching
- Eczema and Psoriasis
- Irritable Bowel Syndrome
- Weight loss
- Dry Eyes

Bihari B (2013) Bernard Bihari, MD: low-dose naltrexone for normalizing immune system function
Younger, J. Parkitny, L, Mclain, D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment

THE USE OF LDN AS A NOVEL ANTI-INFLAMMATORY TREATMENT FOR CHRONIC PAIN

- Review of evidence that LDN may operate as a novel anti-inflammatory agent in the central nervous system, via action of microglial cells
- Currently used in fibromyalgia, Crohn's disease, multiple sclerosis, and complex regional pain syndrome
- Effects may be unique to LDN and appears to be independent from naltrexone's better known activity on opioid receptors
- LDN is well tolerated
- LDN may represent on of the first glial cell modulators to be used for the management of chronic pain disorders

LDN FOR MIGRAINE

- No large controlled studies for LDN for migraines
- Only anecdotal evidence
- Dose: 1 mg to 4.5 mg
- Can treat chronic pain syndromes such as fibromyalgia, complex regional pain syndrome, migraine headache, and interstitial cystitis
- MOA: reduce pain by blocking the production of inflammatory substances in the human body

J Pain. 2016;17(4):579.

POTENTIAL SHORT-TERM SIDE EFFECTS

- Insomnia—most common
- Vivid dreams
- Fatigue
- Loss of appetite
- Nausea
- Hair thinning
- Mood swings
- Mild disorientation

POTENTIAL LONG-TERM SIDE EFFECTS

- Possible liver and kidney toxicity
- Possible tolerance to the beneficial rebound effect
- Other unknown sequelae
  - There is a long history of use of naltrexone at FDA approved doses (much higher than used in LDN)

TREATMENT OF PAIN
OXYTOCIN

OXYTOCIN

- Released from Posterior Pituitary
  - Similar to Vasopressin
- Prominent in Labor/Delivery/Breast Feeding
- The "CUDDLE HORMONE"
- Engenders Trust/Reduces Anxiety
- Regulates Repetitive Behaviors
  - Treatment for Autism/Schizophrenia

OXYTOCIN BENEFITS

- Releases Endorphins/Reduces Pain
- Fibromyalgia
- Enhances Sexual Desire in Women
- Big Release Following Orgasm

ANALGESIC EFFECTS OF OXYTOCIN

- Analgesic and nociceptive effects thought to be result of interaction with the central endogenous opioid system
- Naloxone can block the analgesic effects of both endogenous and extrinsic oxytocin
- Oxytocin is involved in the modulation of pain experiences
  - One mechanism is thought to be linked to the decreased pain sensitivity by improving mood
- Clinically oxytocin has been used in the treatment of autism, sexual dysfunction, migraine, schizophrenia, drug addiction, and other CNS dysfunctions

Curr Pharm Des. 2015;21(7):906=13.
Neuroscience and Behavioral Reviews. 2015;55:53-67.

ANALGESIA EFFECTS OF OXYTOCIN

- **Somatic nociceptive effects**: Oxytocin indirectly reduces the activity of spinal dorsal horn neurons following application of glutamate
- **Visceral nociceptive effects**: dorsal horn neuronal response to noxious visceral stimulation
- Oxytocin thought the oxytocin receptor appear to be ideal candidates for the treatment of deep tissue pain conditions
- Pain relieving effects of oxytocin, particularly in deep tissue sensation (ischemic pain/muscle pain) or in deep tissue disorders (IBS, migraine)

Curr Pharm Des. 2015;21(7):906=13.

ANALGESIC EFFECTS OF OXYTOCIN

- Exogenously administered oxytocin has been demonstrated to produce minimal toxicity at appropriate doses

- Analgesic effects of exogenous oxytocin through the oxytocin system
  - involves a neuronal mechanism for the transduction of the effects of social support into the neural and physiological changes that modulate the experience of pain

Curr Pharm Des. 2015;21(7):906=13.
Journal of Neuroendocrinology. 2016;28:1-10.

ANALGESIC EFFECTS OF OXYTOCIN

- Has multifunctional actions
  - Anxiety
  - Depression
  - Sexual dysfunction
  - Drug addiction
  - Chronic pain
- More studies need to be done to address long-term analgesic efficacy, long-term safety and toxicity, as well as important assessments related to mechanism of action

Curr Pharm Des. 2015;21(7):906=13.

OXYTOCIN FOR MIGRAINE

- Oxytocin receptors are present on CGRP-expressing trigeminal neurons
  - Administration of oxytocin inhibits the firing of trigeminal ganglia neurons and the release of CGRP
- Intranasal oxytocin may be useful for the treatment of migraine headaches
  - Dose-dependent analgesic effect
  - This has not been shown to occur with IV administration

Headache. 2017;57:64-75.

OXYTOCIN

- Blood Level Peaks at Ovulation
- Levels Decline as We Get Older
- Estrogen and T3 Essential for Oxytocin Production
- 5-10 units SL daily (1mg = 450 units)
- Can lower ACTH production –
  - If Patient feels worse, Could be Cortisol Deficient

KETAMINE

BACKGROUND

- Ketamine first synthesized in 1960s as alternative to phencyclinde
- Initially, used as a dissociative anesthetic
- Limited use in contemporary anesthesia due to side effects, namely psychedelic symptoms (Niesters et al. 2013)
- More commonly used in animal anesthesia (Morgan, Curran 2012)
- At subanesthetic doses, produces analgesia

PHARMACOLOGY

- A non-competitive antagonist of the NMDA receptor – blocks glutamate action
- S(+) isomer has higher affinity for NMDA receptor than R(-) isomer (Morgan, Curran 2012)
- Also interacts with monoaminergic, muscarinic, and opioidergic receptors (Niesters et al. 2013)

PSYCHIATRIC EFFECTS

- Emergence symptoms after IV infusion – hallucinations, delusions, 'out-of-body' experiences
- Induces transient symptoms of schizophrenia in healthy patients but no evidence linking chronic ketamine use to diagnosis of psychiatric disorders
- Frequent users exhibited profound impairment of long and short term memory (Morgan, Curran 2012)

ROLE IN PAIN MANAGEMENT

- Antagonism of NMDA receptor thought to modulate pain
- Potent analgesic at sub-anesthetic doses (0.5-1 mg/kg/hr) that prevents sensitization of spinal neurons to painful stimuli (Morgan, Curran et al. 2012)
- Roles in acute, chronic, and cancer/palliative care pain

INTRANASAL KETAMINE IN DEPRESSION

- 24 patients with major depression; 18 completed 2 days
- DB, PC, Crossover Study
- 50mg intranasal ketamine vs. placebo
- 8/18 in ketamine responded after 24 hours vs 1/18 in placebo
- Effective with minimal adverse effects

Biol Psychiatry. 2014 December 15; 76(12): 970–976. doi:10.1016/j.biopsych.2014.03.026

INTRANASAL KETAMINE IN PAIN

- Cross sectional/observational study/8 years and older
- Moderate to Severe Pain on VAS
- Pain scores and VS recorded Q15min
- Side effects/Sedation level/Patient satisfaction recorded

World J Emerg Med 2015;7(1):19–24

INTRANASAL KETAMINE FOR PAIN

- 34 patients enrolled
- Median age 29.5 years
- VAS 80mm
- 80% showed >20mm decrease in VAS
- No changes in VS/side effects mild and transient

World J Emerg Med 2015;7(1):19–24

INTRANASAL KETAMINE FOR PAIN II

- A single-center, randomized, prospective, parallel clinical trial
- IN ketamine compared to IV and IM morphine in ED
- 90 patients aged 18–70
- Moderate-severe acute traumatic pain (≥80 mm on 100 mm [VAS])
- Randomized to receive either 1.0 mg/kg IN ketamine, 0.1 mg/kg IV MO or 0.15 mg/kg IM MO
- Pain relief and adverse effects recorded for 1 h post-administration

Shimonovich et al. BMC Emergency Medicine (2016) 16:43

INTRANASAL KETAMINE IN PAIN II

- 3 study groups showed a highly significant results
- Similar maximal pain reduction of 56 ± 26 mm for IN Ketamine, and 59 ± 22 and 48 ± 30 for IV MO and IM MO
- IN Ketamine provided clinically-comparable results to those of IV MO with regards to time to onset (14.3 ± 11.2 v. 8.9

CLINICAL PEARLS

- Ketamine 10mg/50mg/100mg/ml each 0.1mL will deliver 1mg/5mg/10mg per spray
- Order with Mucolox 15%-Mucoadhesive, more effective and need lower doses
- Recommend 0.1mL (1mg) into Each Nostril BID to start
- Always Start LOW and GO SLOW
- Some will add a 40% dose increase due to less bioavailability

KETAMINE

- Bioavailability Comparison
- Take a look at the differences in bioavailability of ketamine through these different routes:
- **Intravenous 100%**
- Intramuscular approximately 93%
- Intranasal approximately 45%
- Sublingual approximately 19-50%

Table 1. Route of administration and the starting dose of ketamine.

Route of administration	Starting dose
Intravenous	0.25–1 mg/kg (adults)*
	0.25–2 mg/kg (children)*
	1–2 mg/kg (adults)#
	2–6 $mg \cdot kg^{-1} \cdot min^{-1}$ (children)#
Intraosseous	0.5–1 mg/kg*
	1–2 mg/kg#
Intramuscular	4–5 mg/kg*[17]
	8–10 mg/kg#[17]
By mouth	3–15 mg/kg (children)*[9, 18]
	500 mg maximum (adults)*[9]
Intranasal	0.25–4 mg/kg*[16, 19, 20]
	3–9 mg/kg#[16, 19, 20]

*Analgesa and sedation dose; #Anesthesia dose.

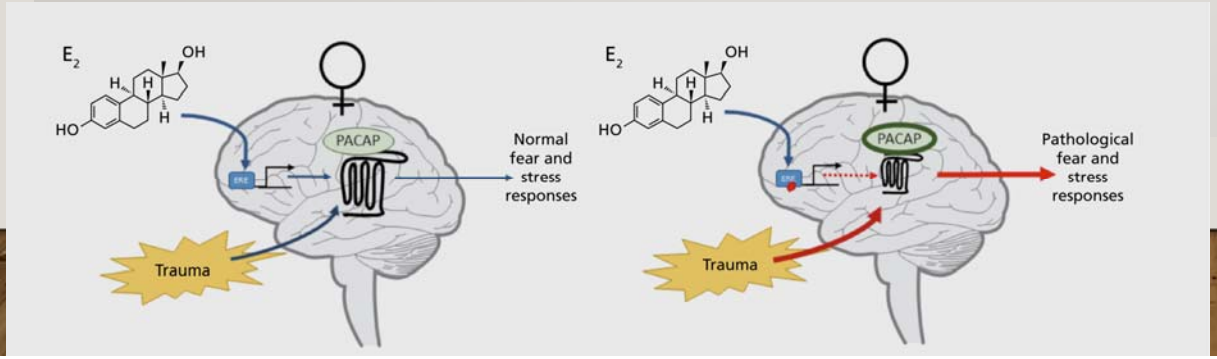
SUMMARY/CONCLUSION

- Ketamine is still undergoing experimental study in regards to its antidepressant effects, not ready for consistent clinical use
- Ketamine has analgesic properties but has limited use in treating various types of pain
- Well-designed, randomized clinical trials required to corroborate case reports of efficacy
- Further investigation into ketamine's mechanisms of action may elucidate how to better utilize ketamine

PACAP

PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE (PCAP)

- The origin of pain during migraine attacks is still not fully elucidated
- PCAP is thought to be involved in migraine pain
- PCAP is a neuropeptide present in perivascular space of cranial nerves
- Belongs to the vasoactive intestinal polypeptide (VIP) secretin growth hormone-releasing hormone-glucagon superfamily
- Present in sensory trigeminal neurons
- May modulate nociception at different levels of the nervous system



Neurotherapeutics. 2010;7(2):191-196.

PERIPHERAL ACTIONS OF PACAP

- Parasympathetic activation is pronociceptive
  - Migraine pain is reduced after anesthetic blocking of the parasympathetic sphenopalatine ganglion
- Parasympathetic and trigeminal fibers are closely related in the perivascular space
  - PACAP could be released from either system and lead to modulation of sensory input in trigeminal neurons

Neurotherapeutics. 2010;7(2):191-196.

PERIPHERAL ACTIONS OF PACAP

- Dilation of cranial vessels might contribute to pain during migraine attacks
  - PACAP-38 dilates cerebral arteries
  - PAC1 receptor antagonism in humans does not change the PACAP induced-dilatation
  - This shows that the activation of the PAC1 receptor does not contribute to extracranial or intracranial vasodilation

Neurotherapeutics. 2010;7(2):191-196.

PERIPHERAL ACTIONS OF PACAP

- Mast cell degranulation causes activation of meningeal nociceptor
  - VPAC2 receptors are expressed on human mast cells
  - VPAC1 are not expressed on human mast cells
- PACAP-38 and VIP degranulate mast cells cause histamine release

Neurotherapeutics. 2010;7(2):191-196.

CENTRAL ACTIONS OF PACAP

- PACAP has immunoreactivity
- PACAP may have a role in central pain transmission
  - PACAP may be released from activated C-fibers in the spinal cord
- Activation of the PAC1 receptor could lead to the modulation of nociceptive input in the second-order neurons to help relieve migraines

Neurotherapeutics. 2010;7(2):191-196.

ISSUE WITH CURRENT TREATMENTS

- Triptans are agonists of the serotonin receptor 5-HT1B/1D
  - Currently the best acute migraine-specific treatment
  - Some patients respond poorly or are unresponsive
- New treatments are needed for people who do not respond well to current therapies or who are at a substantial risk for CV disease

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