Mast Cell Activation Syndrome

Brayden Yellman, MD

University of Utah Health Project ECHO

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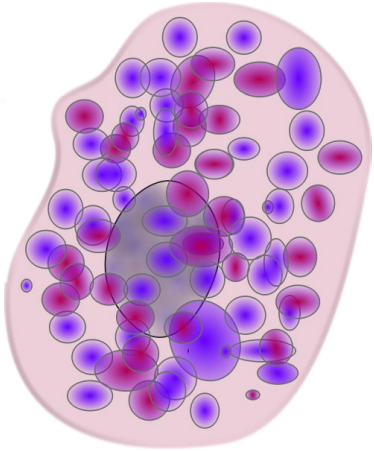
Brief Mast Cell Review

- Mast cells are a type of **white blood cell** found in connective tissues of the body, under the skin, near blood vessels and lymph vessels, in nerves, and in the lungs and intestines.
- Mast cells are prominent **near the boundaries between the outside world and the internal milieu**, such as the skin, mucosa of the lungs, and digestive tract, as well as the mouth, conjunctiva, and nose.



- Although best known for allergy and anaphylaxis, mast cells are involved in wound healing, angiogenesis, immune tolerance, defense against pathogens, and vascular permeability.

Disordered mast cell activation occurs when mast cells are pathologically **overproduced** or if their **activation is out of proportion** to the perceived threat to homeostasis.

Mastocytosis: rare and includes a variety of conditions with TOO MANY mast cells.

- Cutaneous mastocytosis
- Systemic mastocytosis
- Mast cell leukemia
- Mast cell sarcoma
- Others…

MCAS: Mast Cell Activation Syndrome refers to a group of disorders with diverse causes presenting with **episodic** multisystem symptoms as the result of [excess] mast cell mediator release.

Anaphylaxis is an extreme example of inappropriate mast cell activation.

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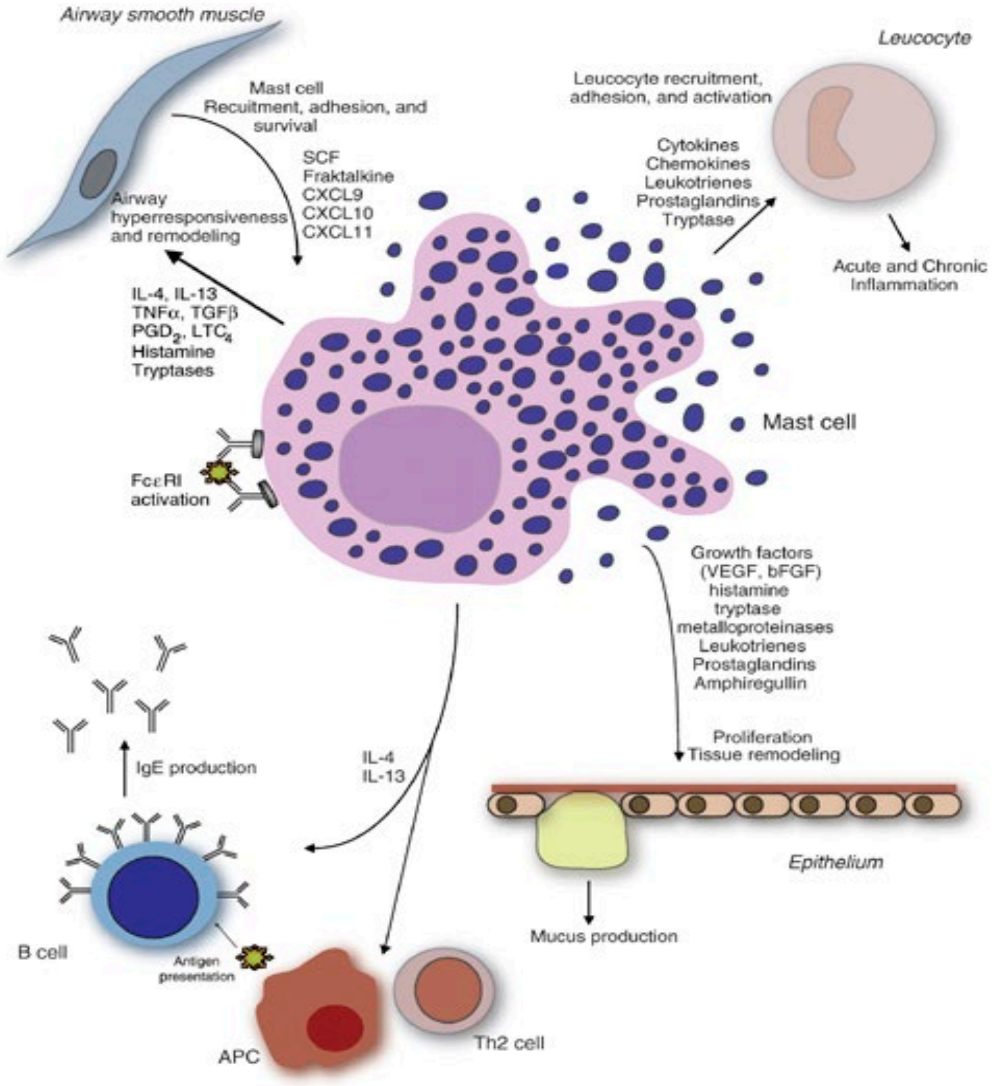
Mast cell activation syndromes. Cem Akin. J Allergy Clin Immunol. 2017 Aug;140(2):349-355. doi: 10.1016/j.jaci.2017.06.007. PMID: 28780942

Mast Cell Activation

- When mast cells are “activated,” inflammatory chemicals or “mediators” are released from granules. **Histamine, leukotrienes, prostaglandins** are familiar examples. **Tryptase** is the most specific for MC (but may be more difficult to detect).

- Locally activated mast cells may also send distress signals, through the nervous system and immune system, often propagating a neuroinflammatory response to other distal areas of the body.



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“Mast Cell Activation Syndrome: AAAAI.” *The American Academy of Allergy, Asthma, &Immunology*, www.aaaai.org/conditions-and-treatments/related conditions/mcas

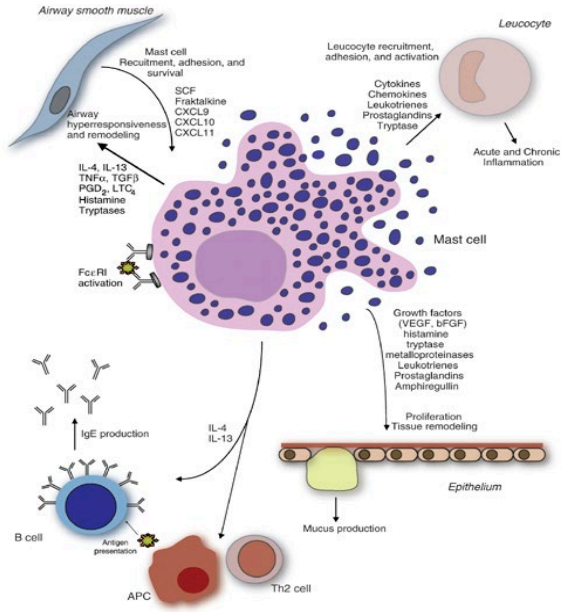
Clinical & Experimental Allergy, Volume: 38, Issue: 1, Pages: 4-18, First published: 21 November 2007, DOI: (10.1111/j.1365-2222.2007.02886.x)

Mast Cell Activation Syndrome: A review. Frieri M., Patel R., Celestin J. Curr Allergy Asthma Rep. 2013 Feb;13(1):27-32. doi: 10.1007/s11882-012-0322-z.

Table 1.

Common Mast Cell Mediators and their Associated Symptoms.

Mast Cell Mediator	Associated Symptoms
Tryptase	Easy bruising and bleeding, fatigue, myalgias, vertigo, flushing, diarrhea, edema
Histamine	urticaria, pruritis, anaphylaxis, diarrhea, angioedema, headache, hypotension
Proteoglycans	Bleeding
Prostaglandin D2	headache, brain fog, abdominal pain, nausea, bronchoconstriction
Platelet activation factor	cardiac arrhythmia, bronchoconstriction, urticaria, abdominal pain
Interleukins	inflammation
Tumor necrosis factor alpha	fatigue
Leukotrienes	bronchoconstriction, mucous production



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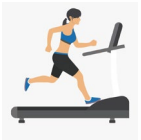
Kurin M, Elangovan A, Alikhan MM, Al Dulaijan B, Silver E, Kaelber DC, Cooper G. Irritable bowel syndrome is strongly associated with the primary and idiopathic mast cell disorders. Neurogastroenterol Motil. 2022 May;34(5):e14265. doi: 10.1111/nmo.14265. Epub 2021 Sep 17. PMID: 34535952; PMCID: PMC9191257.

Mast Cell Activation/Hypersensitivity Triggers

Figure 1. Some *Potential* Mast Cell Triggers[2-5]

- Heat, cold or sudden temperature changes
- Stress: emotional, physical, including *pain*, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)



- Exercise
- Fatigue
- Food or beverages, including alcohol

- Drugs (opioids, NSAIDs, antibiotics and some local anesthetics) and contrast dyes

- Natural odors, chemical odors, perfumes and scents

- Venoms (bee, wasp, mixed vespids, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitos and fleas, etc.)

- Infections (viral, bacterial or fungal)

- Mechanical irritation, friction, vibration

- Sun/sunlight

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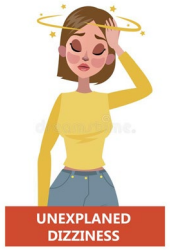
"Symptoms and Triggers of Mast Cell Activation - TMS - The Mastocytosis Society." *The Mastocytosis Society*, 29 July 2019, tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/.

Common Symptoms of MCAS

- **Anaphylaxis**

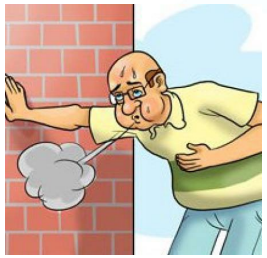
- **Dermatological**

- **Cardiovascular**



- **Gastrointestinal**

- **Respiratory**



MAST CELL MEDIATOR SYMPTOMS
Anaphylaxis
Flushing of the face, neck, and chest
Itching, +/- rash
Hives, skin rashes
Angioedema (swelling)
Nasal itching and congestion
Wheezing and shortness of breath
Throat itching and swelling
Headache and/or brain fog, cognitive dysfunction, anxiety, depression
Diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux disease (GERD)
Bone/muscle pain, osteosclerosis, osteopenia, osteoporosis
Light-headedness, syncope/fainting
Rapid heart rate, chest pain
Low blood pressure, high blood pressure at the start of a reaction, blood pressure instability
Uterine cramps or bleeding

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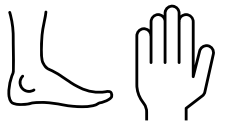
"Symptoms and Triggers of Mast Cell Activation - TMS - The Mastocytosis Society." *The Mastocytosis Society*, 29 July 2019, tmsforacure.org/symptoms /symptoms-and-triggers-of-mast-cell-activation/.

Clinical criteria for mast cell activation syndrome

1) Episodic symptoms consistent with mast cell mediator release affecting **two or more organ systems** evidenced as follows:

- Skin: urticaria (hives), angioedema (sudden swelling), flushing, dermatographia 
- Gastrointestinal: nausea, vomiting, diarrhea, abdominal cramping 
- Cardiovascular: hypotensive syncope (fainting), tachycardia 
- Respiratory: wheezing 
- Naso-ocular: conjunctival injection, pruritus(itching), nasal stuffiness 

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Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. Gerhard J Molderings et al…Afrin. Journal of Hematology & Oncology 20114:10. https://doi.org/10.1186/1756-8722-4-10©. 2011

Clinical criteria for mast cell activation syndrome

2) Improved symptoms after treatment with:

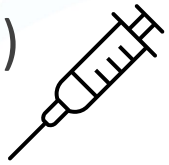
- H1 (antihistamines) and H2 (famotidine) histamine receptor antagonists
- Leukotriene antagonists: montelukast
- Mast cell stabilizers – cromolyn sodium, ketotifen (also an antihistamine)

Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. Gerhard J Molderings et al…Afrin. Journal of Hematology & Oncology 20114:10. https://doi.org/10.1186/1756-8722-4-10©. 2011

CLINICAL CRITERIA FOR MAST CELL ACTIVATION SYNDROME

3) Elevation of a validated urinary or serum marker of mast cell activation:

- Total serum **tryptase** (very specific for mast cells)
- Plasma **prostaglandin D2**, **histamine**



- Biopsy tissue (i.e. GI tissue) with staining positive for increased numbers of mast cells (CD 117 staining)
- 24-hour urine levels of:
  - **N-methylhistamine**
  - **11B -Prostaglandin F2α** (11B-PGF2α)
  - **Leukotriene E4 (LTE4)**

REMEMBER: Empiric trials of therapy when there is a clinical suspicion for MCAS can also be diagnostic!

Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. Gerhard J Molderings et al…Afrin. Journal of Hematology & Oncology 20114:10. https://doi.org/10.1186/1756-8722-4-10©. 2011

Relevance of MCAS to Our Topic?

The acute COVID-19 “cytokine storm” is characterized by rapid proliferation and hyperactivation of T cells, macrophages, and natural killer cells, and the overproduction of >150 inflammatory cytokines and chemical mediators released by immune or nonimmune cells. Mast cells (MCs) are activated by SARS-CoV-2.

- **Dual-histamine receptor blockage with cetirizine-famotidine reduces pulmonary symptoms in COVID-19 patients**. R.B. Hogan 2nd, R.B. Hogan 3rd, T. Cannon, et al. Pulm Pharmacol Ther. Epub 2020 Aug 29. PMID: 32871242 https://pubmed.ncbi.nlm.nih.gov/32871242/

- **Histamine receptors and COVID-19**. M. Ennis, K. Tiligada. Inflamm Res. 2021 Jan. Epub 2020 Nov 18. PMID: 33206207. https://pubmed.ncbi.nlm.nih.gov/33206207/

- **Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome.** Afrin LB, Weinstock LB, Molderings GJ. Int J Infect Dis. 2020 Nov; Epub 2020 Sep 10. PMID: 32920235 https://pubmed.ncbi.nlm.nih.gov/32920235/

Relevance of MCAS to Long COVID or ME/CFS

- **Questionnaires** were given to
  - 136 Long COVID
  - 136 Healthy Controls
  - 80 MCAS patients (5 systems)

- **Mast cell activation symptoms are prevalent in Long-COVID.** Leonard B Weinstock, Jill B Brook, Arthur S Walters, Ashleigh Goris, Lawrence B Afrin, Gerhard J Molderings. Int J Infect Dis. 2021 Nov. Epub 2021 Sep 23. PMID: 34563706. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8459548/

Mean Mast Cell Mediator Release Syndrome scores for each group with whiskers showing 95% confidence intervals

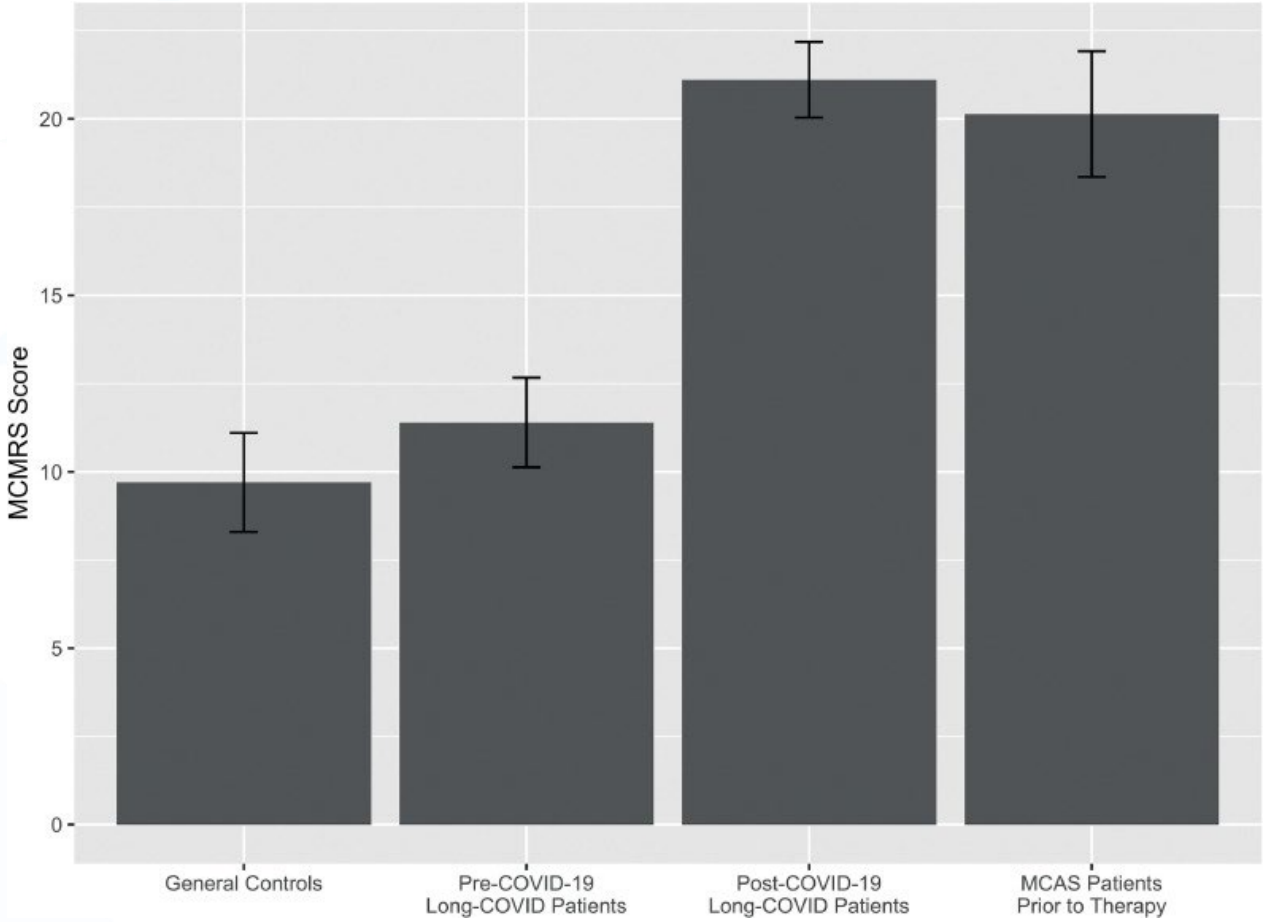


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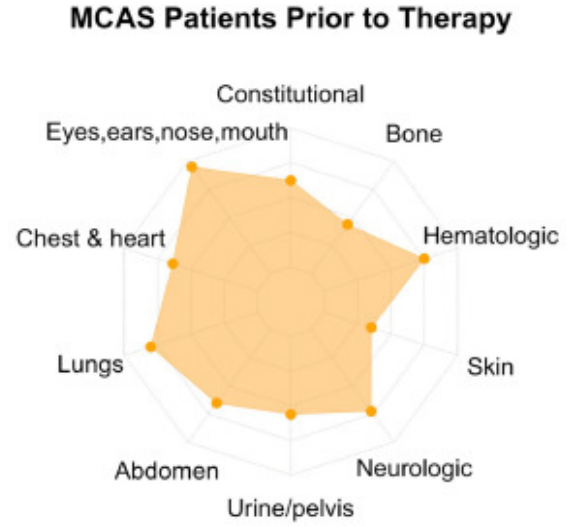
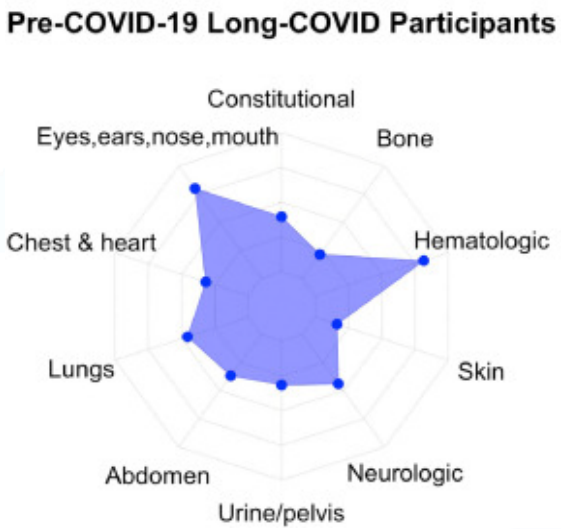
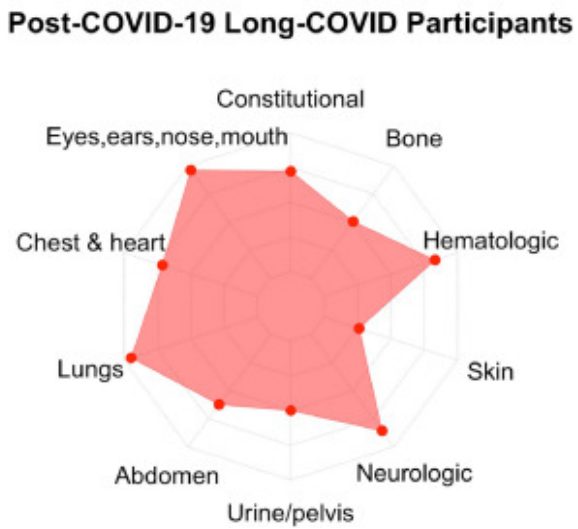
Figure 3

Spider web plots of mean mast cell mediator release syndrome scores.







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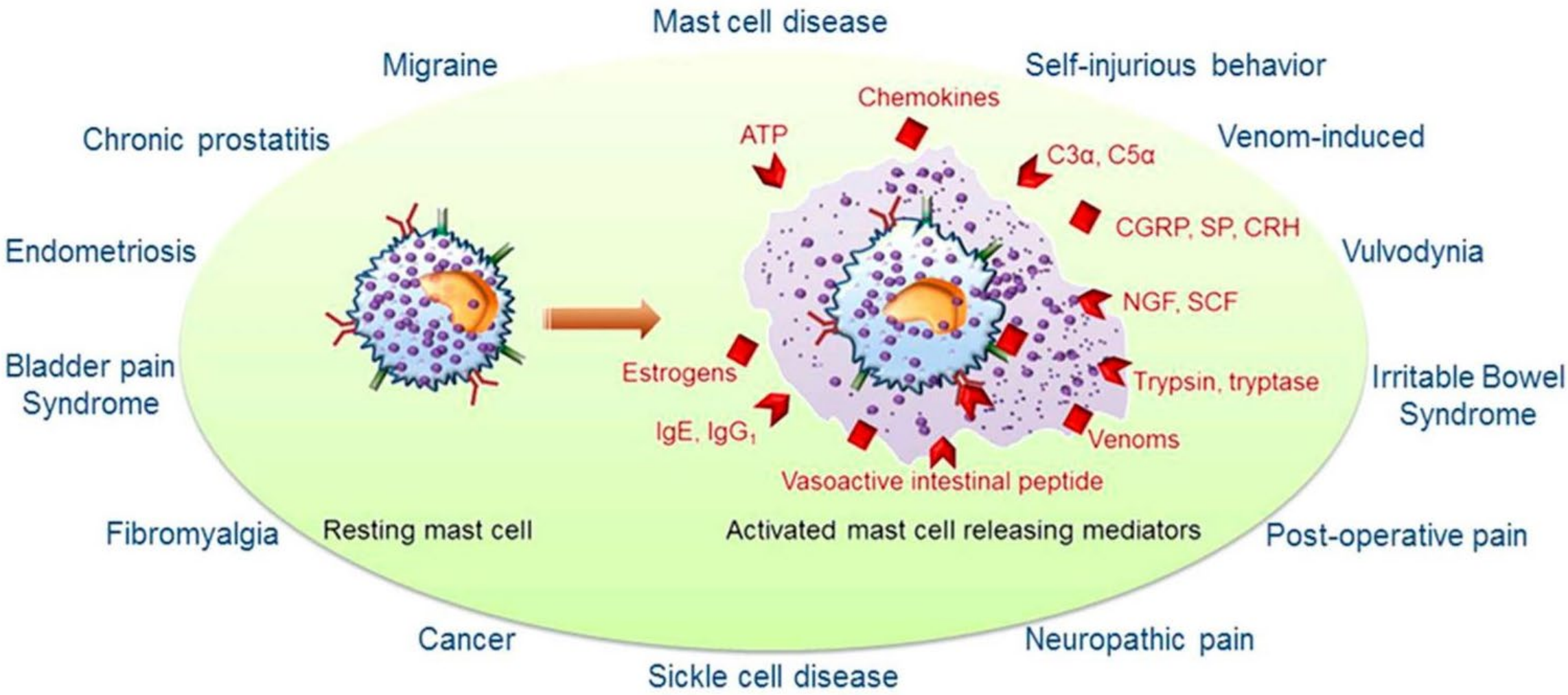
Mast cell activation symptoms are prevalent in Long-COVID. Leonard BW, Jill BB, Arthur SW et al. Int J Infect Dis. 2021 Nov. Epub 2021 Sep 23. PMID: 34563706

Mast cell-associated disease-specific pain syndromes, mast cell activation and its common activators:



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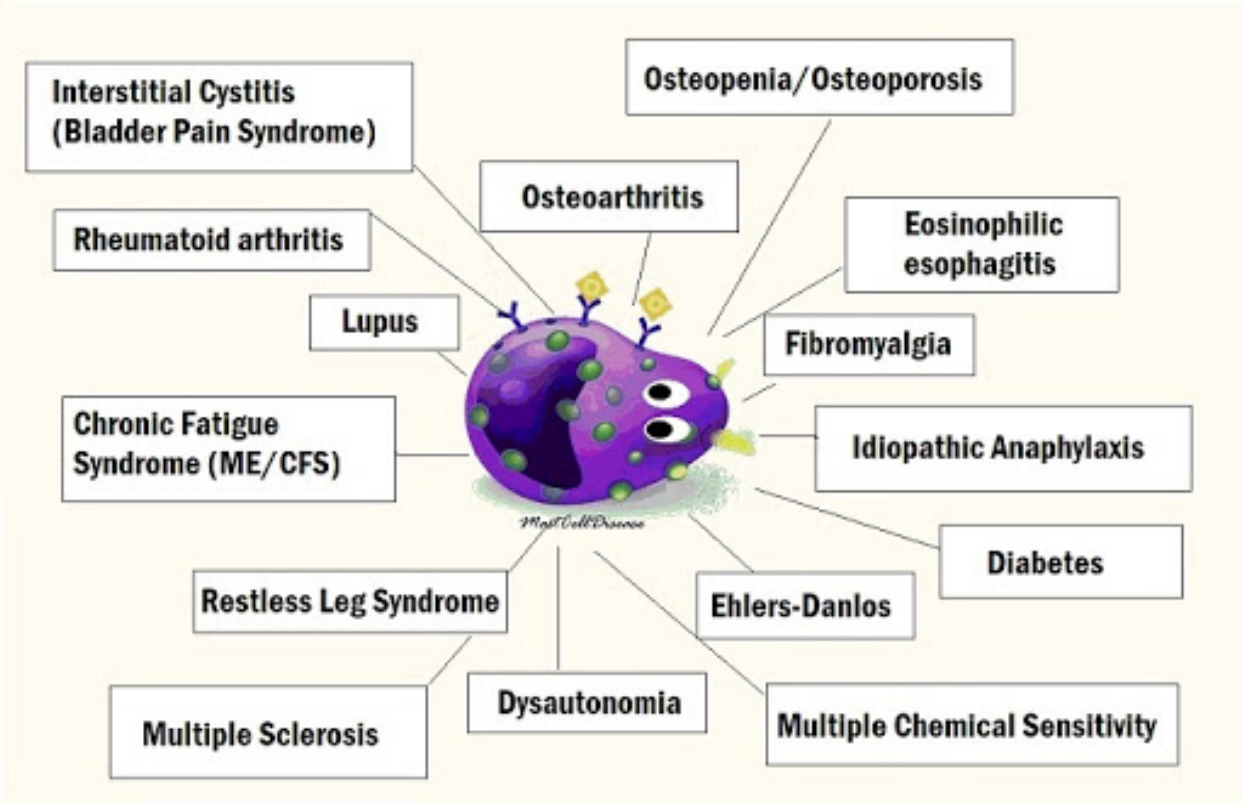
Aich A, Afrin LB, Gupta K. Mast Cell-Mediated Mechanisms of Nociception. Int J Mol Sci. 2015 Dec 4;16(12):29069-92. doi: 10.3390/ijms161226151. PMID: 26690128; PMCID: PMC4691098.

Mast Cell Disease
Coexisting Conditions



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"MCAS." *Clear Health Centers*, 22 Sept. 2019, www.clearhealthcenters.com/mast-cell-activation-syndrome-utah-physician/.

- Abnormal laboratory testing refers to those with POTS whose laboratory workup suggested elevated MCAS-related serum and urine mediators

Table 3

Comparison of Symptoms in 44 Patients Who Underwent Laboratory Testing

	Abnormal Laboratory Tests (n=29)	%	Normal Laboratory Tests (n=15)	%	*P* Value
Age, y, mean±SD	34±9.5		33 ± 12.2		NS
% Female	29/29		13/15		0.111
Palpitation	25/29	86	13/15	87	1.0
Syncope	11/29	38	4/15	27	0.524
Fatigue	21/29	72	8/15	53	0.317
Lightheadedness /dizzy/brain fog	23/29	79	11/15	73	0.714
Migraines	11/29	38	3/15	20	0.314
Depression/anxiety	6/29	21	6/15	40	0.284
Fibromyalgia	4/29	14	1/15	7	0.647
Allergy	13/29	45	2/15	13	0.048
Skin rash	10/29	34	1/15	13	0.067
Gastrointestinal symptoms	18/29	62	3/15	23	0.001

POTS with "Atypical Symptoms"

NS indicates not significant.

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Kohno R, Cannom DS, Olshansky B, Xi SC, Krishnappa D, Adkisson WO, Norby FL, Fedorowski A, Benditt DG. Mast Cell Activation Disorder and Postural Orthostatic Tachycardia Syndrome: A Clinical Association. J Am Heart Assoc. 2021 Sep 7;10(17):e021002. doi: 10.1161/JAHA.121.021002. Epub 2021 Aug 16. PMID: 34398691; PMCID: PMC8649306.

Table 2

Comparison of Symptoms in 44 Patients Who Underwent Laboratory Testing

Abnormal Values	POTS-like With Atypical Symptoms (n=29)	POTS Alone (n=15)	*P* Value
ESR or CRP abnormal	6/28* (21%)	3/14* (21%)	>.99
Tryptase	2/23* (9%)	0/9* (0%	>.99
Prostaglandin	16/28* (57%)	0/15 (0%)	0.0002
Histamine	17/29 (59%)	0/15 (0%)	0.0001
Histamine or methylhistamine abnormal	23/29 (79%)	0/15 (0%)	0.0001

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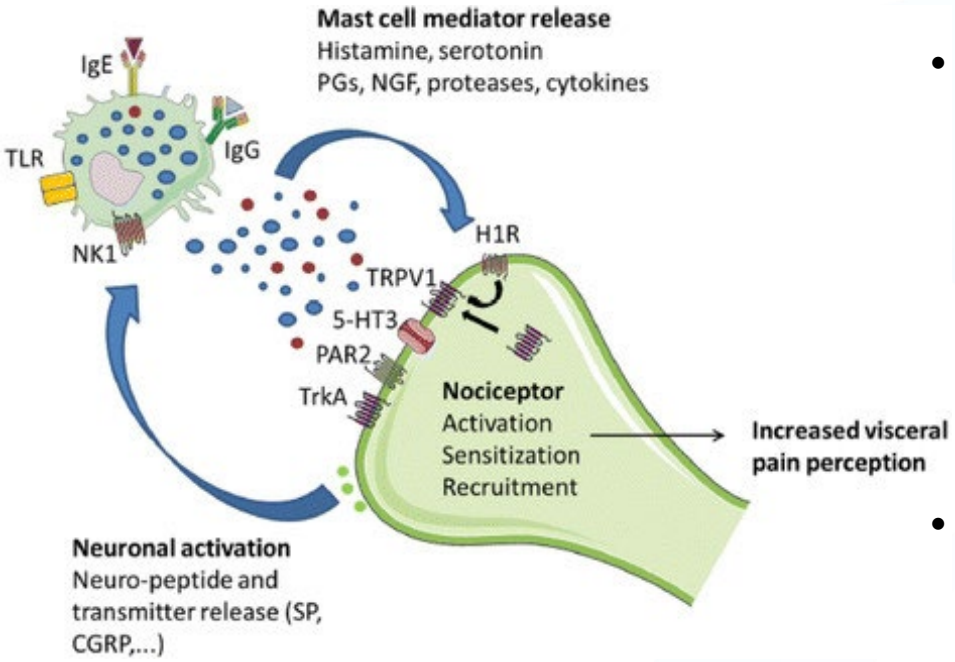
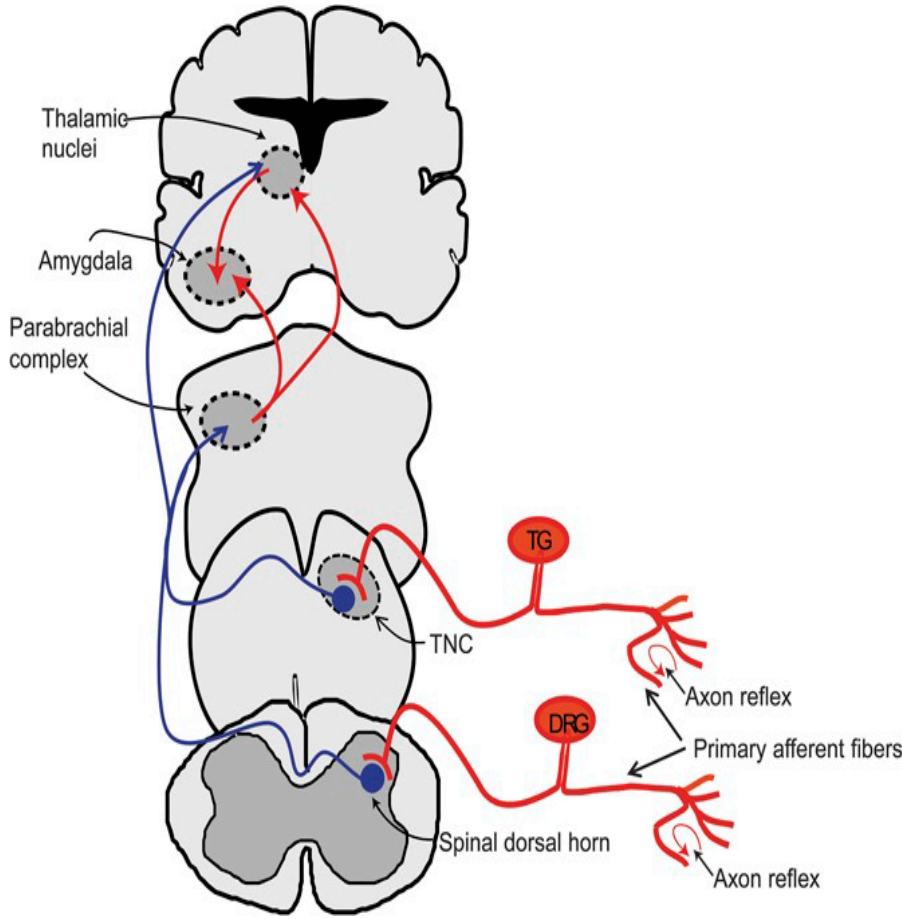
Kohno R, Cannom DS, Olshansky B, Xi SC, Krishnappa D, Adkisson WO, Norby FL, Fedorowski A, Benditt DG. Mast Cell Activation Disorder and Postural Orthostatic Tachycardia Syndrome: A Clinical Association. J Am Heart Assoc. 2021 Sep 7;10(17):e021002. doi: 10.1161/JAHA.121.021002. Epub 2021 Aug 16. PMID: 34398691; PMCID: PMC8649306.



- Nociceptive inputs from these primary afferent fibers signaling peripheral inflammation or other noxious stimuli are relayed through the dorsal root ganglion (DRG) into the spinal dorsal horns
- These signals are then transmitted to second-order neurons in the trigeminal nucleus caudalis (TNC) within the brainstem



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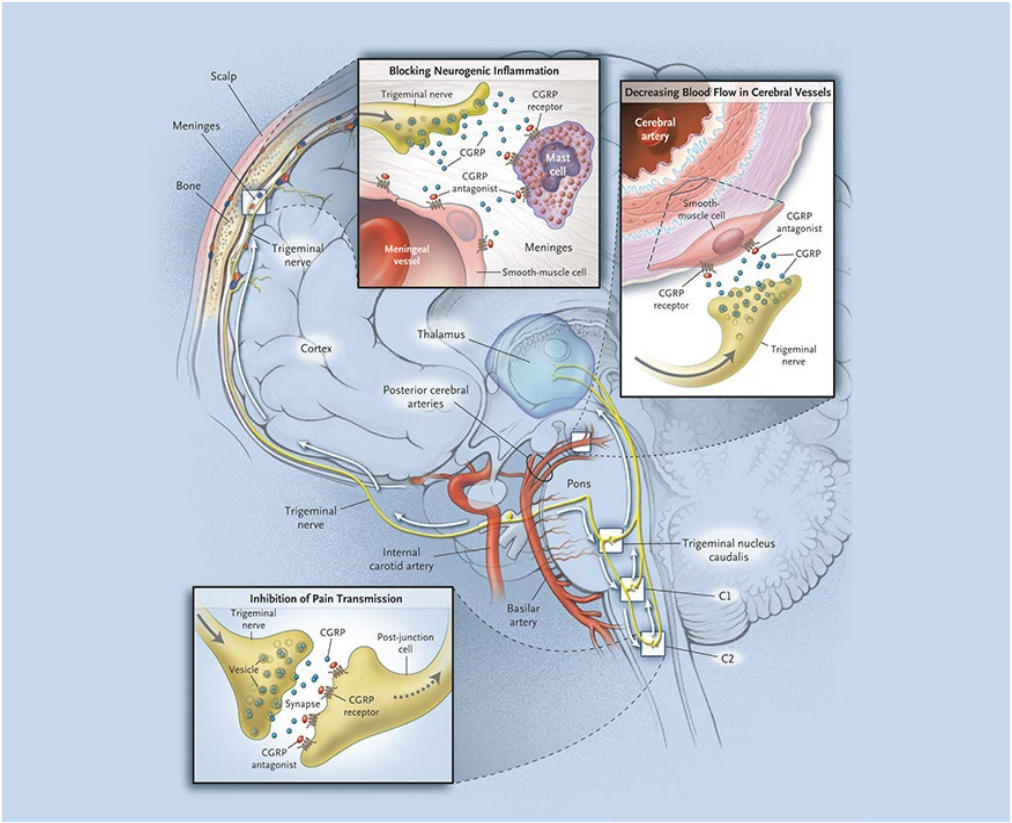
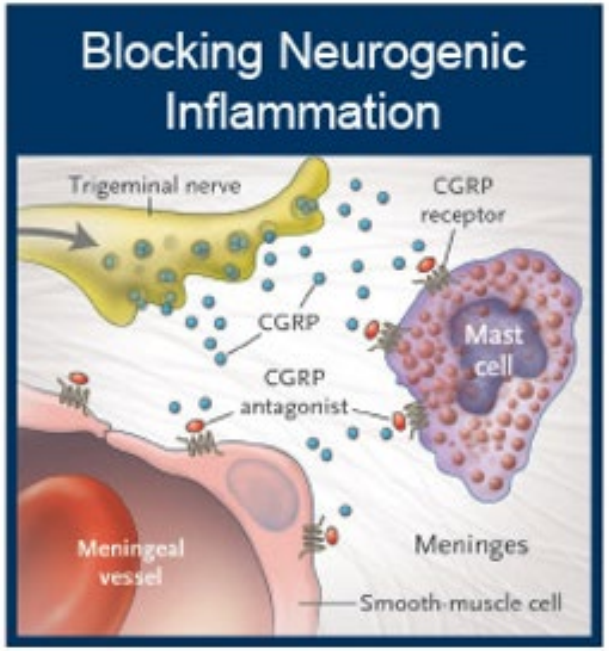
Iyengar S, Ossipov MH, Johnson KW. The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. Pain. 2017;158(4):543–559.

Chumpitazi, Bruno & Shulman, Robert. (2016). Underlying molecular and cellular mechanisms in childhood irritable bowel syndrome. Molecular and cellular pediatrics. 3. 11. 10.1186/s40348-016-0036-8.



- The trigeminal nuclear complex (including the trigeminal nucleus caudalis (TNC) and its related extensions at C1-C2) then send afferent signals to second order neurons
- This signaling is often through trigeminal neuron release of **substance P** and **CGRP** acting upon meningeal vessels of the trigeminovascular system and upon **dural mast cells**
- This activation can lead to triggering or propagation of **migraine** and of **central pain sensitization**



1 Binding of CGRP receptor antagonists (red) to receptors located on mast cells inhibits inflammation caused by trigeminal release of CGRP (blue) onto mast cells within the outer covering of the brain (meninges)

From N Engl J Med, Durham PL, CGRP-Receptor Antagonists — A Fresh Approach to Migraine Therapy? 350:1073-1075, Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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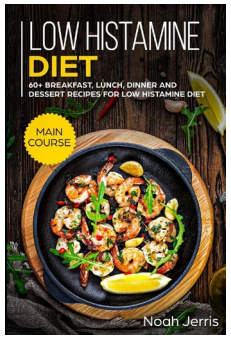
CGRP and the Trigeminal System in Migraine. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. Headache. 2019 May;59(5):659-681.

Mast Cell Activation Treatments



- Low Histamine Diet
- Diamine oxidase (reduce histamine levels in foods)
- H1 Blockade (fexofenadine, loratadine, cetirizine, levocetirizine)
- H2 Blockade (famotidine, ranitidine, cimetidine)
- Benadryl (diphenhydramine)

- Leukotriene Blockade (montelukast)
- Mast Cell Stabilizers
  - Liquid cromolyn/Gastrocrom (1 mL or 20 mg up to 5 ml or 100 mg 15 minutes before meals and medications)
  - Compounded cromolyn sodium (200 mg po tid to qid)
  - Compounded ketotifen (1 mg po bid)
  - OTC Quercetin
- Anti-IgE biologics (omalizumab/Xolair)

REMEMBER: Empiric trials of therapy when a clinical suspicion for MCAS can also be diagnostic!