Mast Cell Disorders

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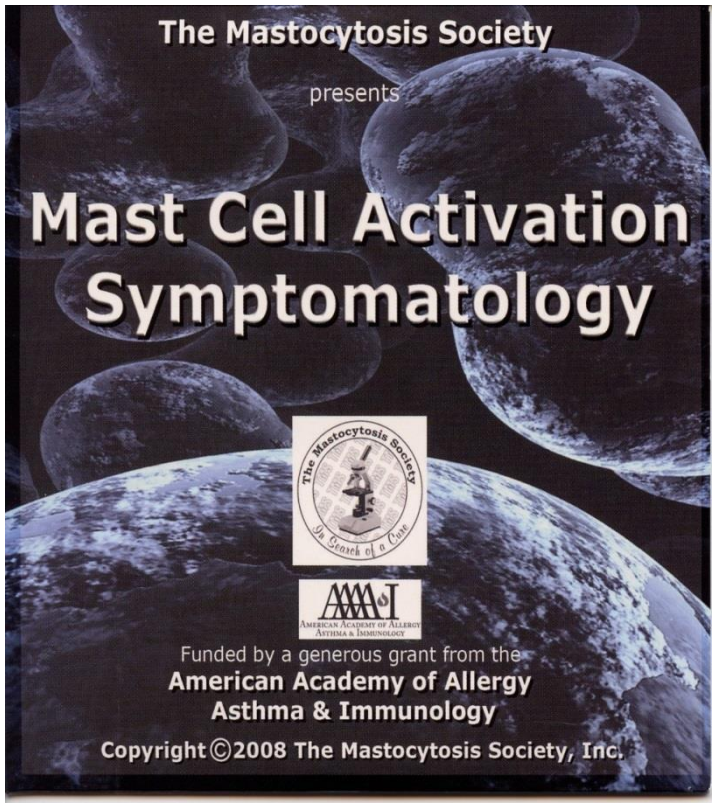
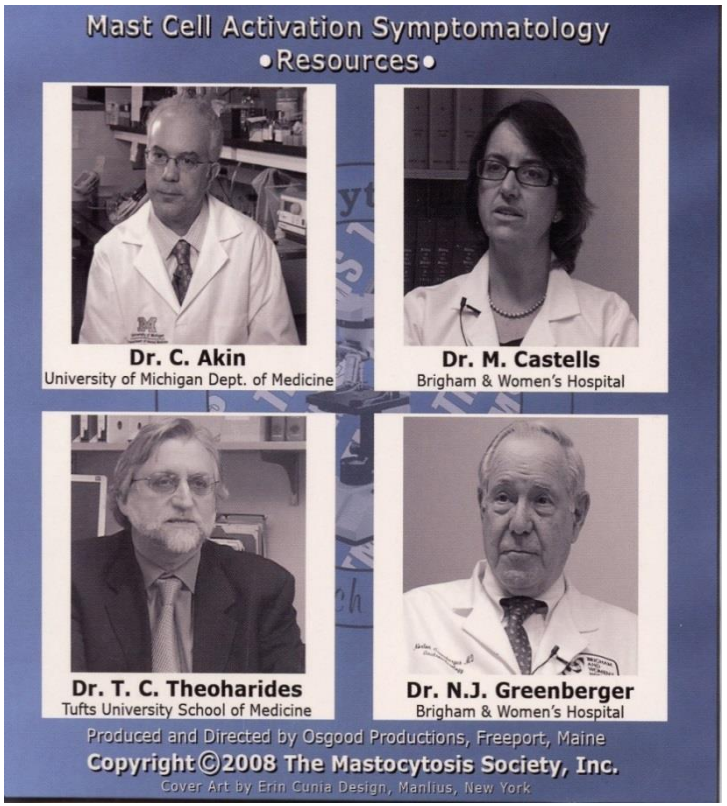
www.mastcellmaster.com

www.autismfreebrain.org

Youtube: My mystery symptoms and mast cells





Youtube

Mast cell activation symptomatology

My mystery symptoms and mast cells

General Principles

- Exclude other diagnoses
- Identify comorbidities
- Prioritize symptoms
- Remove triggers
- Eliminate foods/additives
- Different treatment approaches
- Multiomodal management needed

Allergies

Angioneurotic edema

Asthma

Atopic dermatitis

Food allergy

Food intolerance

Histamine intolerance

Idiopathic urticaria

Mastocytosis

Mast cell activation

Non-IgE food allergy

Rhinitis

Table 1. Conditions That Can Mimic Mast Cell Disorders*

Cardiac
- Coronary Hypersensitivity (Kounis syndrome)*
- Postural Orthostatic Tachycardia syndrome (POTS)

Endocrine
- Fibromyalgia
- Parathyroid tumor
- Pheochromocytoma
- Carcinoid syndrome

Digestive
- Food intolerance*
- Eosinophilic esophagitis*
- Eosinophilic gastroenteritis*
- Gastro Esophageal Reflux disorder (GERD)
- Gluten enteropathy
- Irritable bowel syndrome
- Vasoactive intestinal peptide tumor

Immune
- Auto-inflammatory disorders*
  [e.g. Deficiency of IL-1 receptor antagonist (DIRA)]
- Familial hyper IgE syndrome
- Vasculitis*

Neurologic/Psychiatric
- Anxiety
- Chronic Fatigue syndrome
- Depression
- Headaches
- Mixed Organic Brain syndrome
- Somatization disorder
- Autonomic dysfunction
- Multiple sclerosis

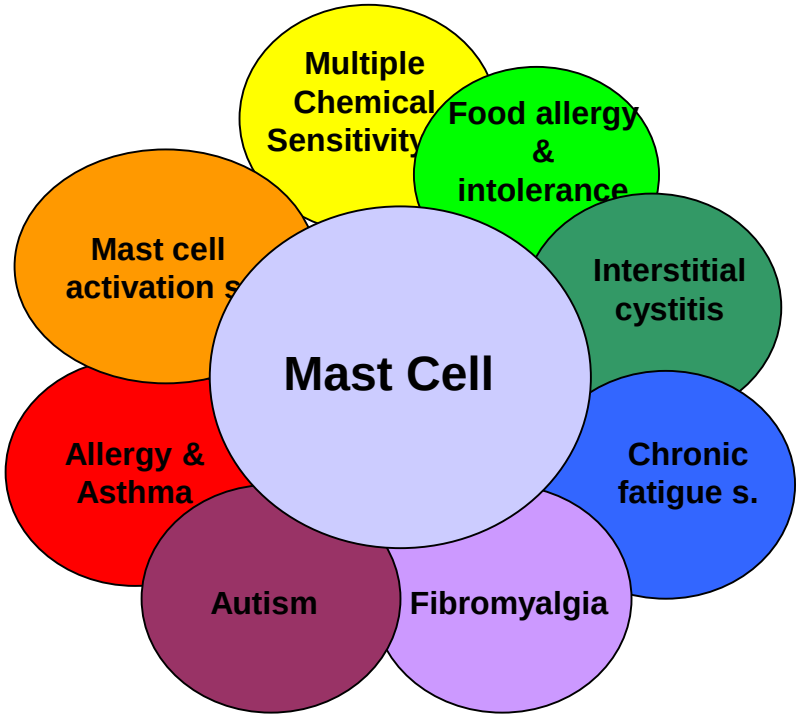
Skin
- Angioedema*
- Atopic dermatitis*
- Chronic urticaria*
- Scleroderma*

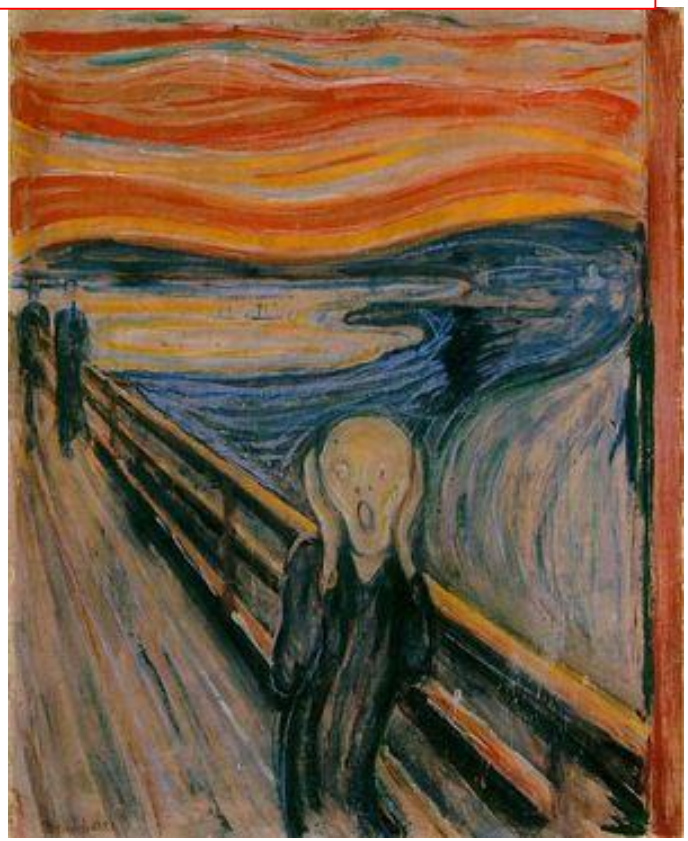
* Mast cell activation may occur

Clinical Therapeutics/Volume 35, Number 5, 2013 · Atopic Clinical Entities Update

Editorial

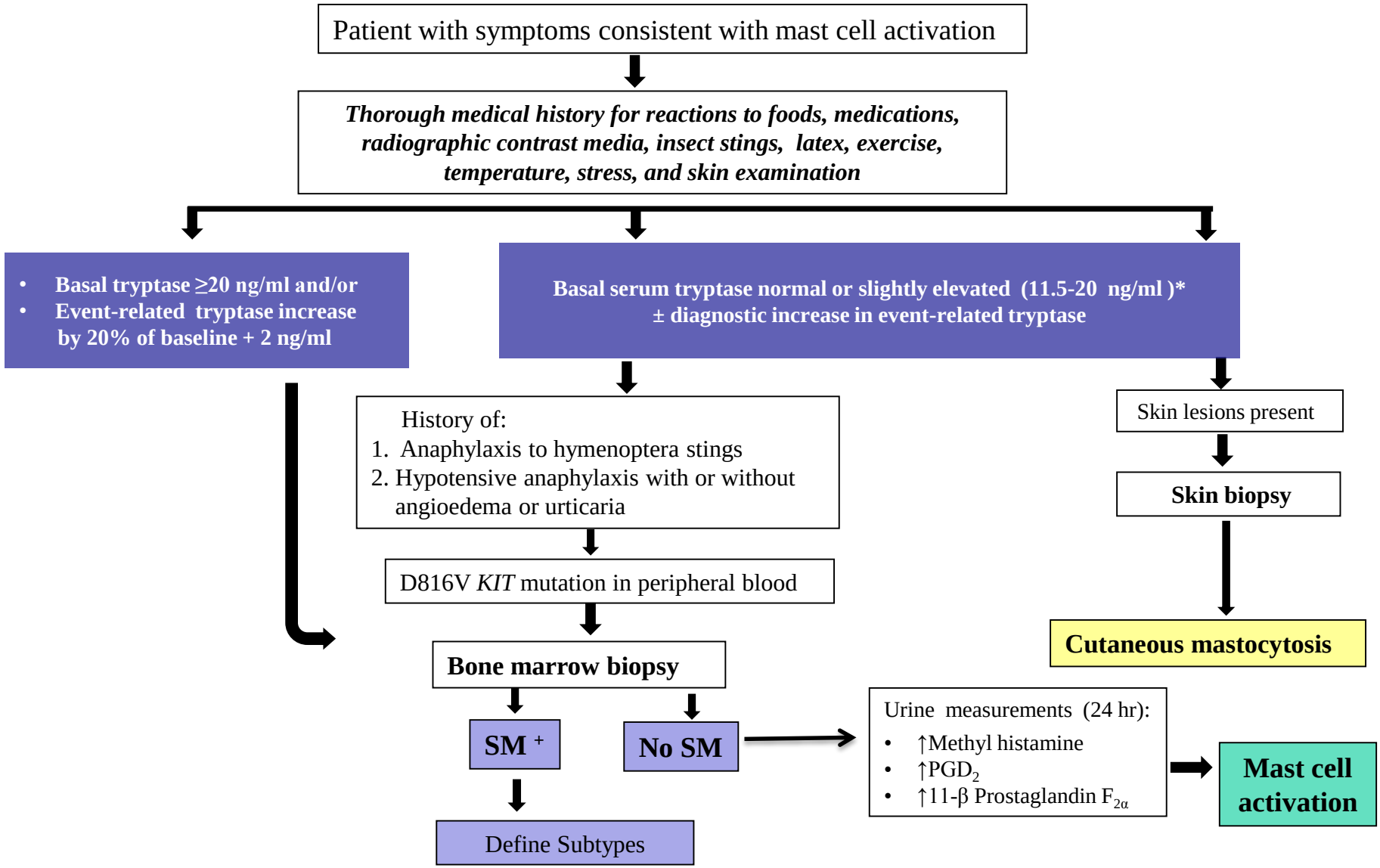
Atopic Conditions in Search of Pathogenesis and Therapy





Edvard Munch, *The Scream* (Skrik, 1893)

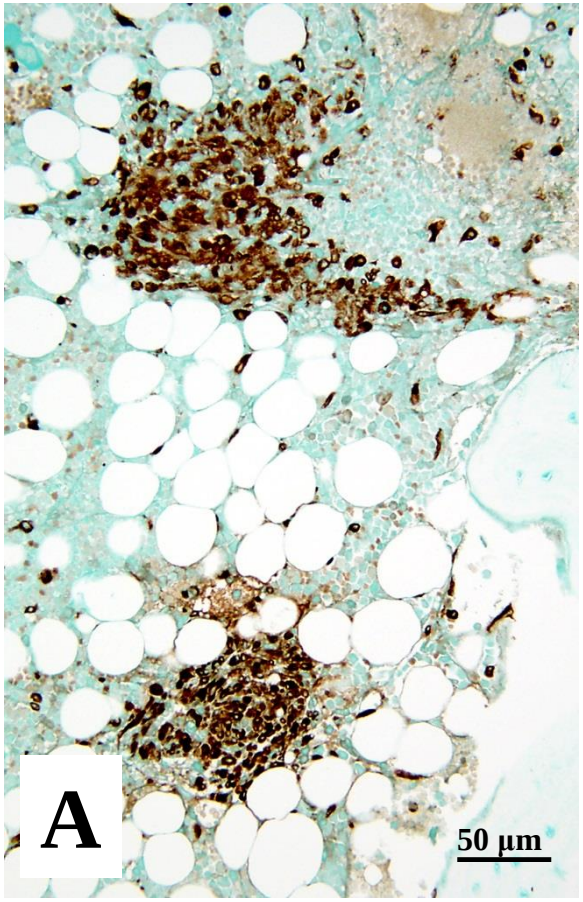
Diagnostic Algorithm for Adult Patients

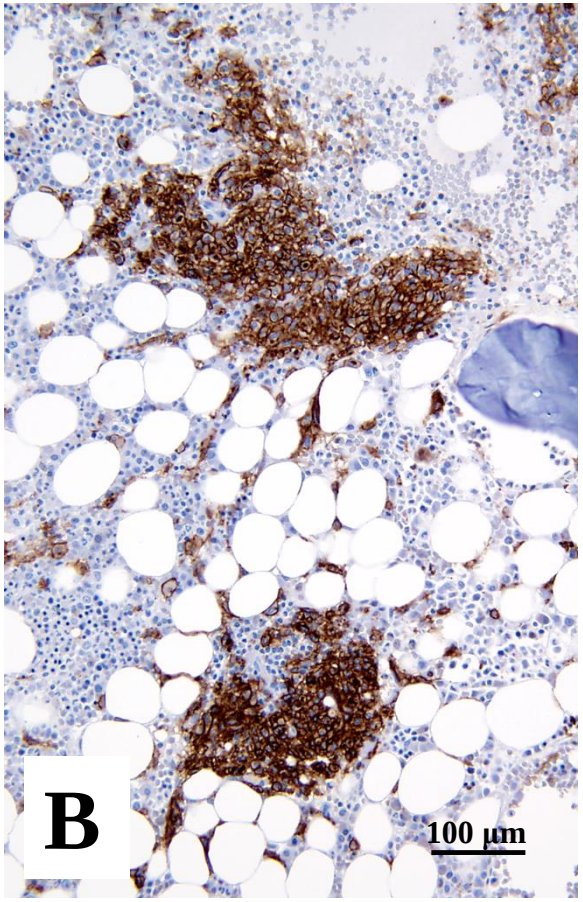


SM= Systemic Mastocytosis
* This range varies among different laboratories and clinical sites

Serum; some experts consider a higher cutoff
+ *KIT* mutations should be investigated

§ A patient with elevated basal tryptase should also have BM biopsy. Most of these patients have SM





Two bone marrow biopsies are needed for >80% chance of finding two mast cell “clusters” for diagnosis

Mast cell activation syndrome: Proposed diagnostic criteria

Cem Akin, MD, PhD,[a]* Peter Valent, MD,[b] and Dean D. Metcalfe, MD[c] *Ann Arbor, Mich, Vienna, Austria, and Bethesda, Md*

The term mast cell activation syndrome (MCAS) is finding increasing use as a diagnosis for subjects who present with signs and symptoms involving the dermis, gastrointestinal track, and cardiovascular system frequently accompanied by neurologic complaints. Such patients often have undergone multiple extensive medical evaluations by different physicians in varied disciplines without a definitive medical diagnosis until the diagnosis of MCAS is applied. However, MCAS as a distinct clinical entity has not been generally accepted, nor do there exist definitive criteria for

Abbreviations used
MCAS: Mast cell activation syndrome
MMAS: Monoclonal mast cell activation syndrome
SCF: Stem cell factor
UP: Urticaria pigmentosa
WHO: World Health Organization

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Clinical Neurology and Neurosurgery 113 (2011) 570–574

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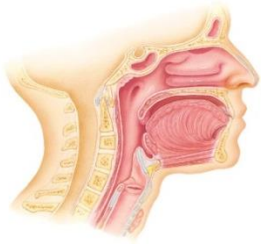
Neurologic symptoms and diagnosis in adults with mast cell disease

Jonathan H. Smith[a], Joseph H. Butterfield[b], Animesh Pardanani[c], Gabriele C. DeLuca[a], F. Michael Cutrer[a,*]



Respiratory

Nasal congestion
Nasal pruritus
Shortness of breath
Throat swelling
Wheezing

Neurologic
Anxiety
Depression
Decreased concentration and memory (Brain Fog)
Insomnia
Migraines

Histamine, IL-6, LCT_4, PAF, PGD_2

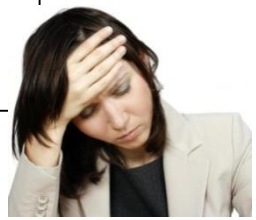
CRH, histamine, IL-6, NT, PAF, PGD_2, TNF

Cardiovascular

Hypotension
Syncope or near syncope
Lightheadedness
Tachycardia

Allergens
Bacteria, fungi, viruses
Drugs
Peptides
Toxins
Cytokines

Systemic
Fatigue
Generalized malaise
Weight loss



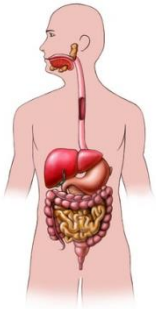
CRH, chymase, histamine,IL-6, PAF, renin, TNF, tryptase

CRH, histamine, IL-6, TNF

CRH, histamine, IL-6, NT, PAF, PGD_2, serotonin, TNF, tryptase, VIP

IL-6, PGD_2, RANKL, TNF, tryptase

CRH, histamine, IL-6, IL-8, IL-33, PAF, PGD_2, TNF, tryptase



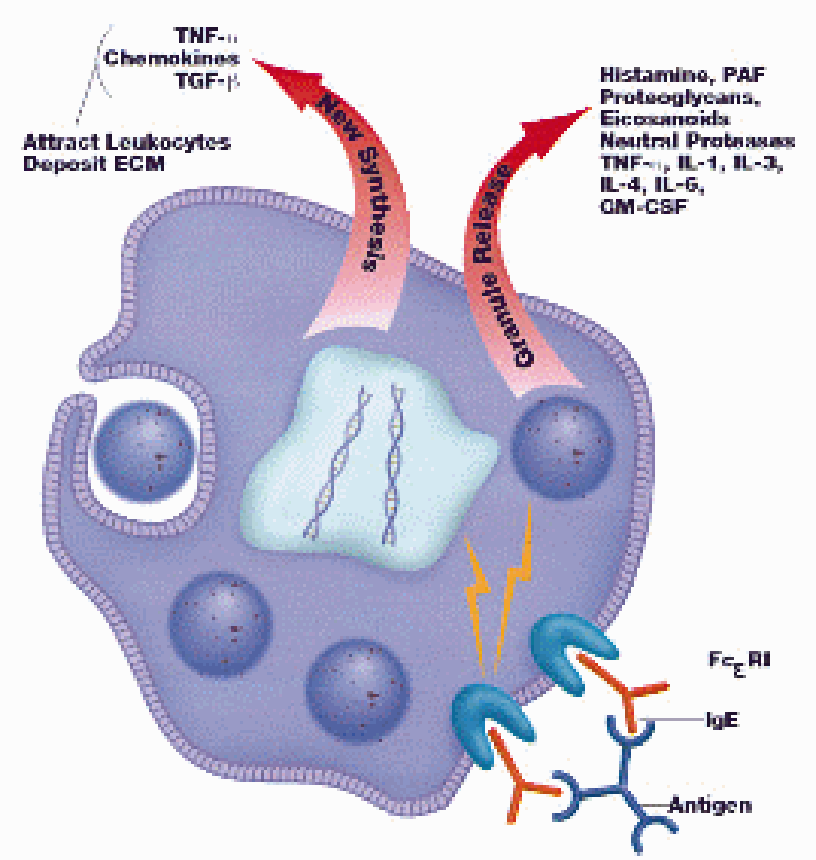
Digestive
Abdominal cramps
Diarrhea
Esophageal reflux
Nausea and vomiting

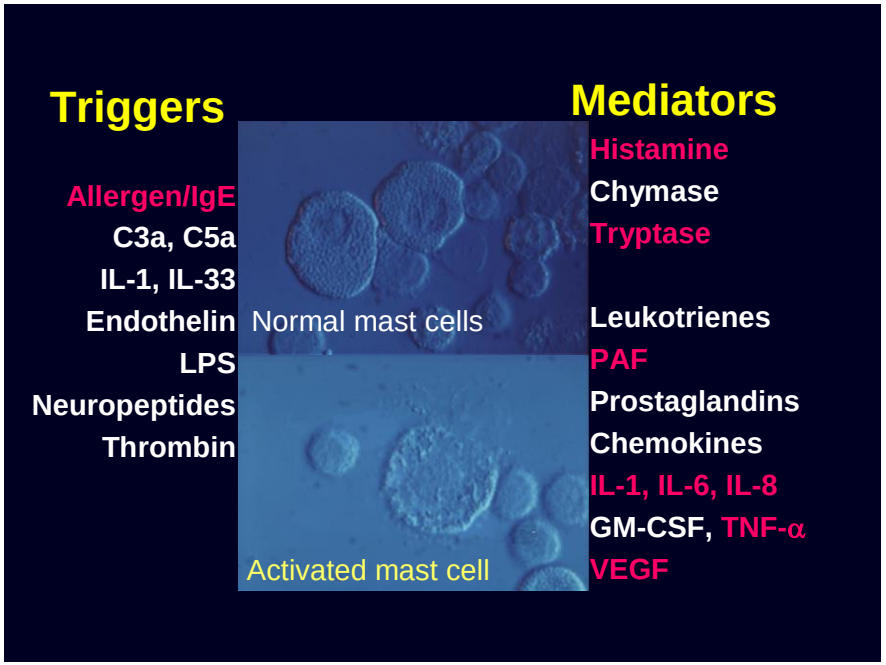
Musculoskeletal
Aches
Bone pain
Osteopenia/Osteoporosis

Cutaneous
Flushing
Pruritus
Urticaria
Angioedema

Mast Cell Activation

Nomarski Optics

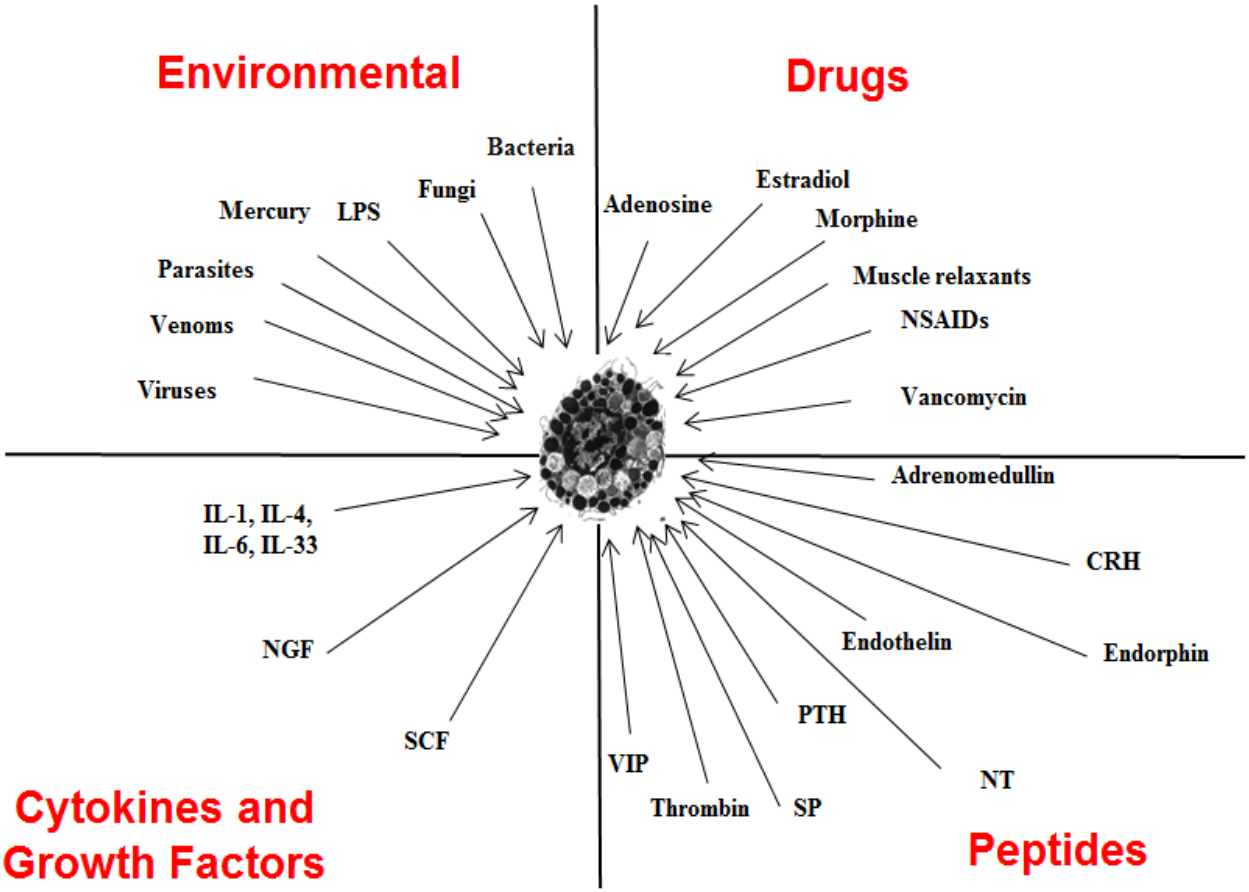




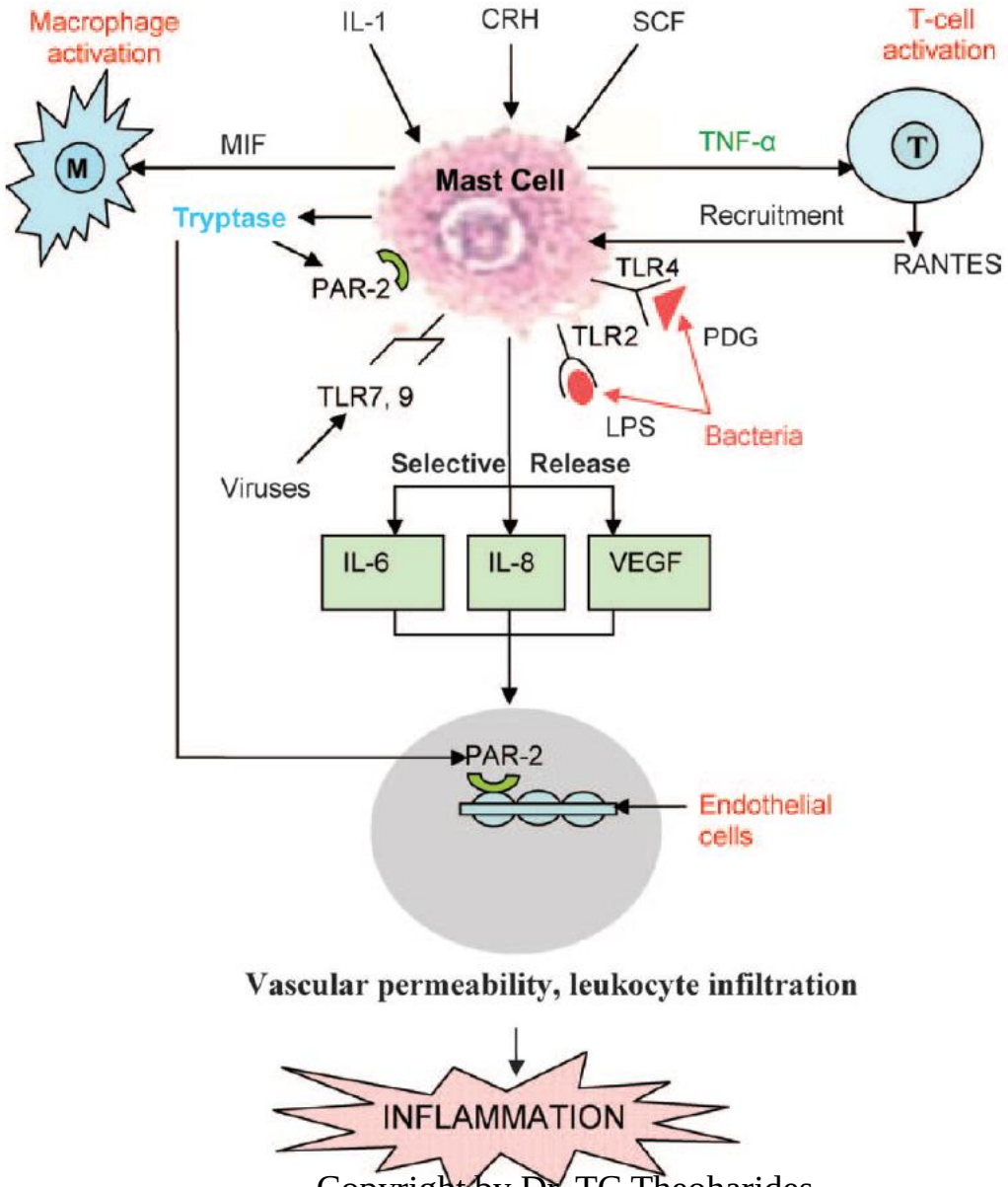
Mast cell degranulation leads to the release of mediators with potent

vasodilatory, **nociceptive**, and **inflammatory** properties

Figure S1


Environmental
Drugs
Bacteria
Fungi
Mercury
LPS
Parasites
Venoms
Viruses
Adenosine
Estradiol
Morphine
Muscle relaxants
NSAIDs
Vancomycin
Adrenomedullin
CRH
Endorphin
Endothelin
PTH
NT
SP
Thrombin
VIP
SCF
NGF
IL-1, IL-4,
IL-6, IL-33
Cytokines and
Growth Factors
Peptides

Mast Cells Communicate with Many Pathogens and Other Immune Cells



Typical Skin Mast Cell Degranulation Observed by Metachromasia as First Noted by Paul Ehrlich in 1887

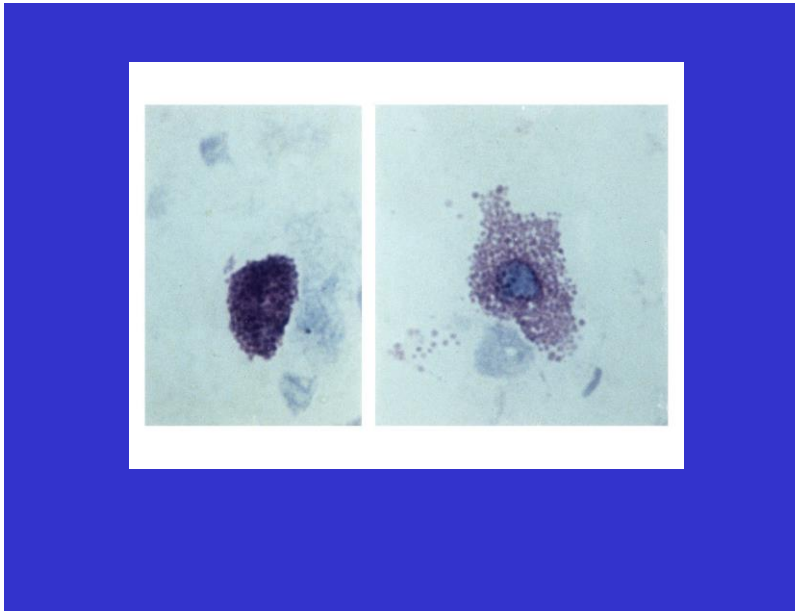
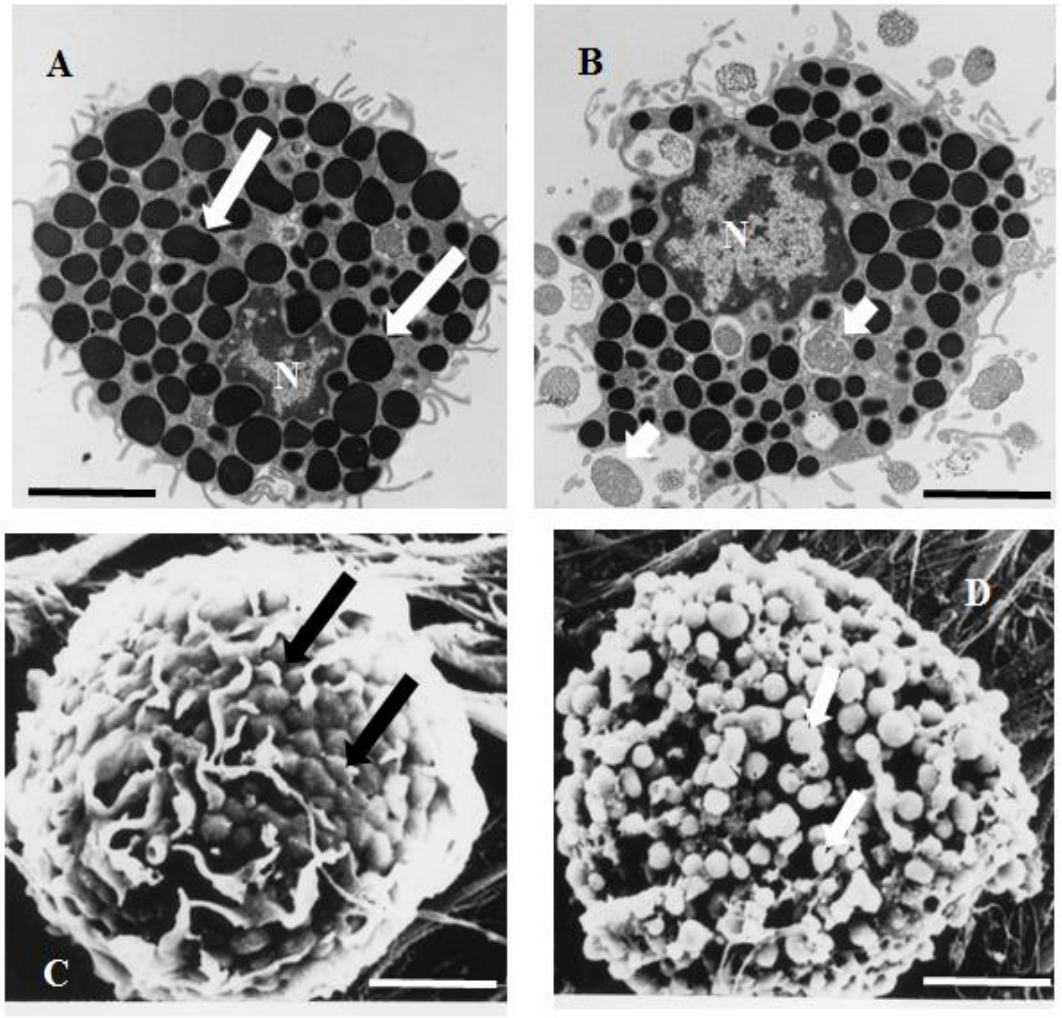


Figure S2



Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

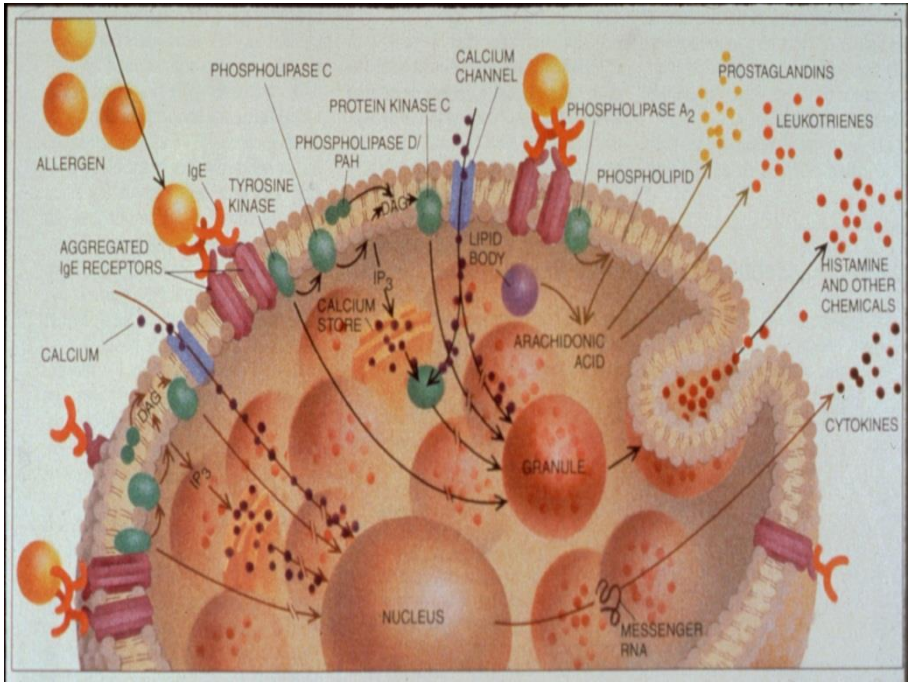
journal homepage: www.elsevier.com/locate/bbadis

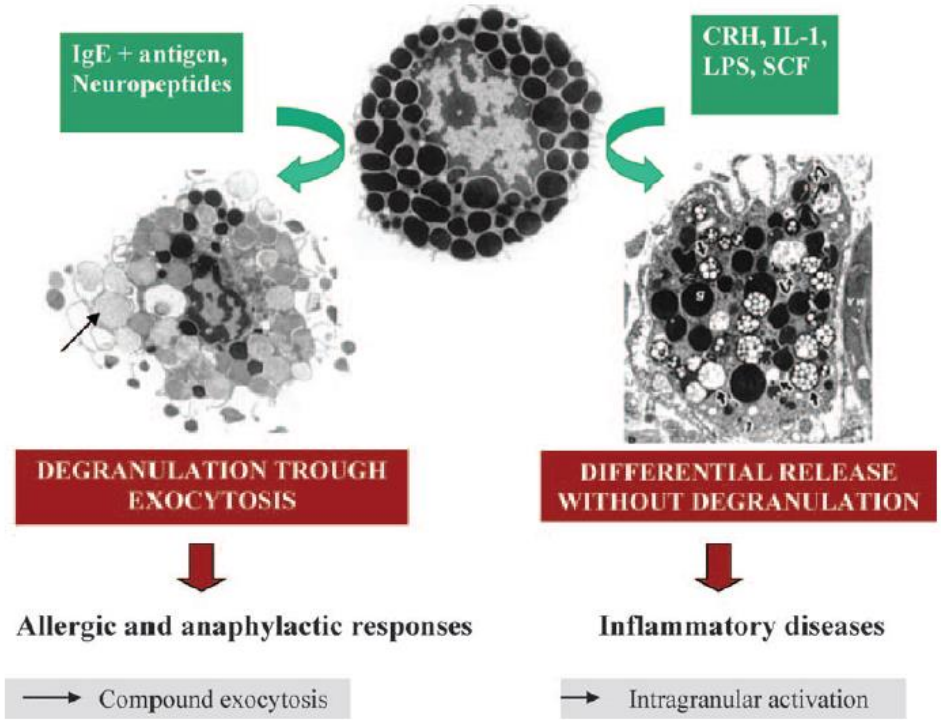
Review

Mast cells and inflammation ☆

Theoharis C. Theoharides [a,b,c,d,*], Konstantinos-Dionysios Alysandratos [a,d], Asimenia Angelidou [a,d], Danae-Anastasia Delivanis [a], Nikolaos Sismanopoulos [a], Bodi Zhang [a,b], Shahrzad Asadi [a], Magdalini Vasiadi [a,d], Zuyi Weng [a], Alexandra Miniati [a,d], Dimitrios Kalogeromitros [d]

[a] Laboratory of Molecular Immunopharmacology and Drug Discovery, Department of Molecular Physiology and Pharmacology, Tufts University School of Medicine, Boston, MA, USA
[b] Department of Biochemistry, Tufts University School of Medicine, Boston, MA, USA
[c] Department of Internal Medicine, Tufts University School of Medicine and Tufts Medical Center, Boston, MA, USA
[d] Allergy Clinical Research Center, Allergy Section, Attikon General Hospital, Athens Medical School, Athens, Greece





Mast cell activation syndrome: Proposed diagnostic criteria

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Neurologic symptoms and diagnosis in adults with mast cell disease

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Original Article

J ALLERGY CLIN IMMUNOL PRACT
JANUARY/FEBRUARY 2014

The Mastocytosis Society Survey on Mast Cell Disorders: Patient Experiences and Perceptions☆

Susan Jennings, PhD*, Nancy Russell, DrPH*, Blair Jennings, BS*, Valerie Silva, RN, BSN*, Lisa Sterling, BS*, Mariana Castells, MD, PhD, FAAAAI†, Peter Valent, MD‡, and Cem Akin, MD, PhD, FAAAAI† *Hastings, Nebr; Boston, Mass; and Vienna, Austria*

TABLE II. Severity and frequency of pain and other symptoms among 420 respondents

	Severity			
	Any*		Moderate or extreme	
Symptom	Total responses, no. (%)	Daily or occasionally, no. (%)†	Total responses, no. (%)	Daily or occasionally, no. (%)†
Pain				
Stomach	306 (72.9)	275 (89.9)	253 (60.2)	244 (96.4)
Lower abdomen	237 (56.4)	202 (85.2)	194 (46.2)	179 (92.3)
Joint	258 (61.4)	228 (88.4)	193 (46.0)	188 (97.4)
Bone	237 (56.4)	197 (83.1)	190 (45.2)	166 (87.4)
Muscle, nerve, connective tissue	210 (50.0)	185 (88.1)	166 (39.5)	158 (95.2)
Upper abdomen	195 (46.4)	159 (81.5)	151 (36.0)	138 (91.4)
Chest	154 (36.7)	96 (62.3)	96 (22.9)	73 (76.0)
Other				
Fatigue	320 (76.2)	296 (92.5)	262 (62.4)	255 (97.3)
Headache	267 (63.6)	202 (75.7)	216 (51.4)	182 (84.3)
Brain fog and/or cognitive difficulties	281 (66.9)	242 (86.1)	193 (46.0)	184 (95.3)
Lightheadedness/syncope	257 (61.2)	182 (70.8)	185 (44.0)	146 (78.9)
Weakness	225 (53.6)	173 (76.9)	171 (40.7)	149 (87.1)
Anaphylactic shock	175 (41.7)	82 (46.9)	158 (37.6)	80 (50.6)
Anxiety	255 (60.7)	190 (74.5)	156 (37.1)	146 (93.6)
Depression	207 (49.3)	148 (71.5)	121 (28.8)	111 (91.7)
Wheezing or asthma	186 (44.3)	125 (67.2)	111 (26.4)	92 (82.9)
Angioedema	146 (34.8)	83 (56.8)	107 (25.5)	66 (61.7)
High blood pressure episodes	123 (29.3)	93 (75.6)	89 (21.2)	72 (80.9)
Cardiac	120 (28.6)	83 (69.2)	82 (19.5)	66 (80.5)

Brain Fog

Reduced

- **Attention span**
- **Cognition**
- **Memory**
- **Multitasking**
- **Processing**
- **Word finding**

Original Article
Allergy Asthma Immunol Res. 2013 September;5(5):315-321.
http://dx.doi.org/10.4168/aair.2013.5.5.315
pISSN 2092-7355 • eISSN 2092-7363

AAIR
Allergy, Asthma & Immunology Research

Allergic Diseases in Preschoolers Are Associated With Psychological and Behavioural Problems

Hyoung Yoon Chang,[1†] Ju-Hee Seo,[3†] Hyung Young Kim,[2] Ji-Won Kwon,[4] Byoung-Ju Kim,[5] Hyo Bin Kim,[6] So-Yeon Lee,[7] Gwang Cheon Jang,[8] Dae Jin Song,[9] Woo Kyung Kim,[10] Jung Yeon Shim,[11] Ha-Jung Kim,[12] Jung-Won Park,[13] Sang-Heon Cho,[14] Joo-Shil Lee,[15] Yee-Jin Shin,[1*] Soo-Jong Hong,[3*]

ORIGINAL ARTICLE **Skin and eye disease**

Infant atopic eczema and subsequent attention-deficit/ hyperactivity disorder – A prospective birth cohort study

Jon Genuneit[1], Stefanie Braig[1], Stephanie Brandt[2], Martin Wabitsch[2], Ines Florath[3], Hermann Brenner[3] & Dietrich Rothenbacher[1]

[1]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany; [2]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm, Ulm, Germany; [3]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany

Pediatric Allergy and Immunology **25** (2014)

Neuropsychological Features of Adult Mastocytosis

Daniela S. Moura, PhD[a,b,c,d,e],
Sophie Georgin-Lavialle, MD, PhD[a,b,c,d,e,f],
Raphaël Gaillard, MD, PhD[g,h], Olivier Hermine, MD, PhD[a,b,c,d,e,*]

Immunol Allergy Clin N Am 34 (2014) 407–422

OPEN ACCESS Freely available online

PLoS one

Evidence for Cognitive Impairment in Mastocytosis: Prevalence, Features and Correlations to Depression

Daniela Silva Moura[1,2]*, Serge Sultan[7,8], Sophie Georgin-Lavialle[1,3,4], Stéphane Barete[1,3,5], Olivier Lortholary[1,6], Raphael Gaillard[9,10], Olivier Hermine[1,3,11,12]*

Mast Cell May Serve as the Canary in the Mine of the Body

Many substances originating in the environment, intestine or brain can trigger mast cell secretion of mood-altering molecules.

- Environmental substances such as:

Aluminum

Antibiotics

Bacterial and viral antigens

Drugs

Estrogens

Mercury

Mold

PBC

Mol. Nutr. Food Res. 2011, *55*, S7–S14 DOI 10.1002/mnfr.201000408

REVIEW

A systematic review of salicylates in foods: Estimated daily intake of a Scottish population

Adrian Wood[1], Gwen Baxter[2], Frank Thies[1], Janet Kyle[1] and Garry Duthie[3]

Table 1. Total salicylate content of foods purchased from local Scottish retailers as determined by HPLC with electrochemical detection

Food item	Salicylates (mg/kg)	Food item	Salicylates (mg/kg)
Fruits		*Vegetables*	
Banana	0.34	Asparagus	1.29
Blackberries	0.81	Aubergine	0.0
Blueberries	0.57	Broccoli	0.0
Gala melon	0.62	Cabbage green	0.0
Grapefruit	0.44	Carrots	0.16
Green apple	0.55	Cauliflower	0.01
Kiwi fruit	0.31	Celery	0.04
Lime	0.0	Courgette	0.0
Mango	0.03	Cucumber	0.02
Nectarine	3.29	Green bean	0.07
Orange	0.11	Green pepper	0.01
Peach	0.12	Lettuce (iceberg)	0.05
Pear	0.23	Mange tout	0.20
Plum	0.01	Mushroom (button)	0.13
Raspberry	0.09	Onion (white)	0.80
Red grape	0.02	Potato	0.02
Strawberry	0.61	Red pepper	0.09
White grape	0.02	Swede	0.07
Yellow melon	0.11	Tomato	0.13
		Yellow pepper	0.09
Juices		*Spices*	
Apple	0.83	Black cumin	25.05
Cranberry	0.99	Cumin	29.76
Grapefruit	0.10	Chat masala	5.74
Orange	0.68	Cinnamon	0.78
Pineapple	4.06	Garam masala	12.85
Tomato	1.32	Paprika	28.25
		Turmeric	20.88

Annals of Epidemiology 23 (2013) 185–188

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Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Association between atopic diseases and attention-deficit/hyperactivity disorder in childhood: a population-based case-control study

Jeng-Dau Tsai MD[a,b], Shih-Ni Chang MS[c,d], Chih-Hsin Mou MS[c,d], Fung-Chang Sung PhD, MPH[c,d,**], Ko-Huang Lue MD, PhD[a,b,*]

Physiology & Behavior 104 (2011) 989–995

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Cognitive function of 6-year old children exposed to mold-contaminated homes in early postnatal period. Prospective birth cohort study in Poland

Wieslaw Jedrychowski [a,*], Umberto Maugeri [b,f], Frederica Perera [c], Laura Stigter [c], Jeffrey Jankowski [d], Maria Butscher [e], Elzbieta Mroz [a], Elzbieta Flak [a], Anita Skarupa [a], Agata Sowa [a]

Review article

Neurologic and neuropsychiatric syndrome features of mold and mycotoxin exposure

LD Empting

Toxicology and Industrial Health
25(9-10) 577–581

DOI: 10.1177/0748233709348393
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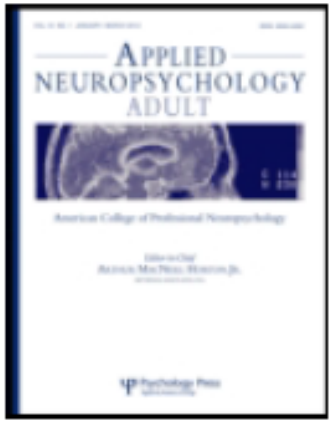


Applied Neuropsychology
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/hapn20

Cognitive Impairment Associated With Toxigenic Fungal Exposure: A Replication and Extension of Previous Findings

Wayne A. Gordon , Joshua B. Cantor , Eckardt Johanning , Heather J. Charatz , Teresa A. Ashman , Janis L. Breeze , Lisa Haddad & Steven Abramowitz
Published online: 07 Jun 2010.

Life Sciences, Vol. 46, pp. 607-617, 1990
Printed in the U.S.A.
Pergamon Press

MINIREVIEW

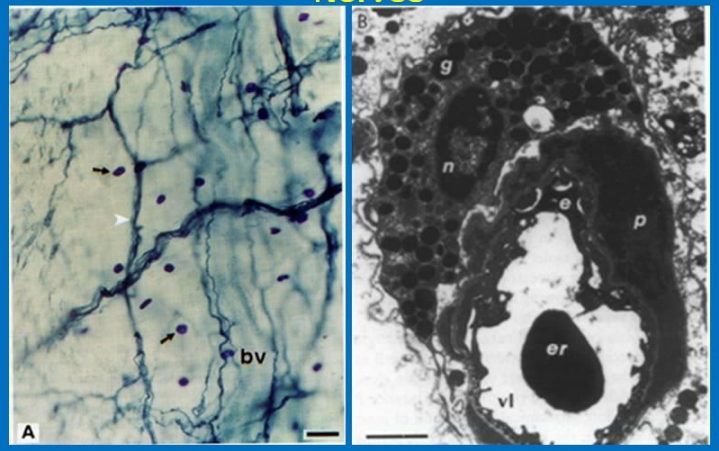
MAST CELLS: THE IMMUNE GATE TO THE BRAIN

T.C. Theoharides, Ph.D., M.D.

Department of Pharmacology, Tufts University School of Medicine
136 Harrison Avenue, Boston, MA 02111

(Received in final form January 4, 1990)

Mast cells are Located Close to Blood Vessels and Nerves



Rozniecki, Dimitriadou, et al. (1999) Brain Res 849: 1. Lambracht-Hall

Bv=blood vessel; white arrowhead=nerve endings; dark arrow=mast cells; g=granule; e=endothelial Cell; er=erythrocyte; n=nucleus; p=pericyte; vl=blood vessel lumen

Available online at www.sciencedirect.com

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Brain Research Reviews 49 (2005) 65–76

BRAIN RESEARCH REVIEWS

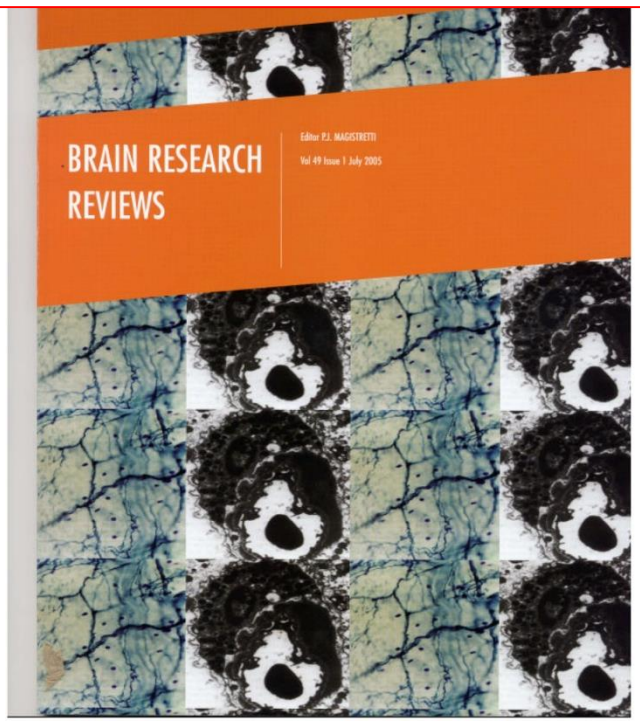
www.elsevier.com/locate/brainresrev

Review

The role of mast cells in migraine pathophysiology

Theoharis C. Theoharides*, Jill Donelan,
Kristiana Kandere-Grzybowska[1], Aphrodite Konstantinidou[2]

Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine and Tufts-New England Medical Center, 136 Harrison Avenue, Boston, MA 02111, USA



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THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
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Sensitization and Activation of Intracranial Meningeal Nociceptors by Mast Cell Mediators

Xi-Chun Zhang, Andrew M. Strassman, Rami Burstein, and Dan Levy

Department of Anesthesia, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center (X.-C.Z., A.M.S., R.B., D.L.); and Harvard Medical School, Boston, Massachusetts (A.M.S., R.B., D.L.)

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Review

Mast cells: Versatile gatekeepers of pain☆

Devavani Chatterjea*, Tijana Martinov

Department of Biology, Macalester College, St. Paul, MN, USA

ARTICLE IN PRESS
JNI-475800; No of Pages 7
Journal of Neuroimmunology xxx (2013) xxx–xxx
Contents lists available at ScienceDirect
Journal of Neuroimmunology
journal homepage: www.elsevier.com/locate/jneuroim

Review article

A focus on mast cells and pain

Anne Héron[a,*], David Dubayle[b]

[a] Physiology Department, Faculty of Pharmaceutical and Biological Sciences, Paris Descartes University, 4 avenue de l'Observatoire, F-75270 Paris Cedex 06, France
[b] Laboratory of Neurophysics and Physiology, CNRS UMR 8119, Paris Descartes University, 45 rue des Saints Pères, F-75270 Paris Cedex 06, France

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Mast cells

ABSTRACT

Mast cells (MCs) are immunocytes with secretory functions that act locally in peripheral tissues to modulate local hemodynamics, nociceptor activation and pain. They are also able to infiltrate the central nervous system (CNS), especially the spinal cord and the thalamus, but their cerebral function remains an enigma. A role in regulating the opening of the blood–brain barrier has been proposed. Paracrine-like action of MCs on synaptic transmission might also signal a modulation of the nervous system by the immune system. In this review, we examine the link between MCs and nociceptive process, at the periphery as well as in the CNS.

ELSEVIER

Brain Research 849 1999) 1–15

BRAIN RESEARCH

www.elsevier.com/locate/bres

Research report

Morphological and functional demonstration of rat dura mater mast cell–neuron interactions in vitro and in vivo

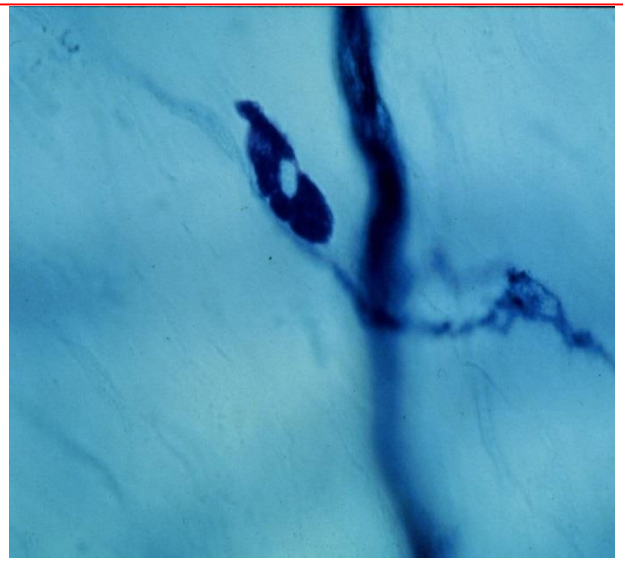
Jacek J. Rozniecki [1], Violetta Dimitriadou [2], Mona Lambracht-Hall [3], Xinzhu Pang [4], Theoharis C. Theoharides [*]

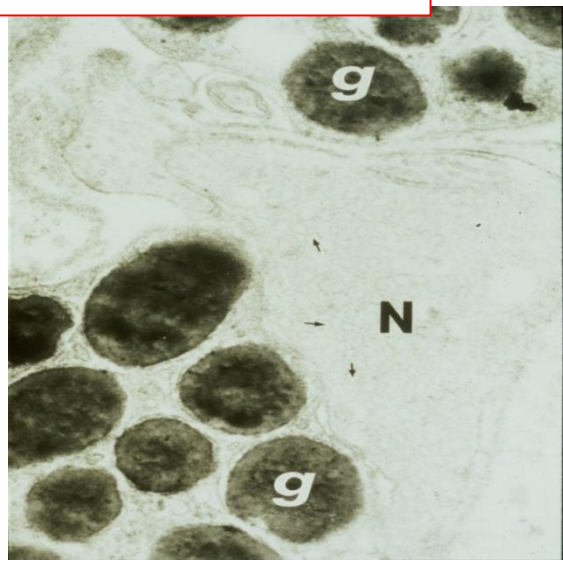
Department of Pharmacology, and Experimental Therapeutics, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA

Accepted 13 July 1999

Number of Mast Cells in Rat Brain During Ontogenic Development

Postnatal Age (Days)	Number of Mast Cells	
	Cells/Brain	Cells/g, Tissue
1	6500 ± 519	22,429 ± 1790
3	10,332 ± 664	23,661 ± 1521
6	12,640 ± 721	20,334 ± 1159
10	11,000 ± 808	11,058 ± 807
14	9300 ± 730	6991 ± 548
24	3152 ± 320	2083 ± 211
60	2295 ± 231	1200 ± 121





Review

Cell PRESS

Mast cells on the mind: new insights and opportunities

Rae Silver[1,2,3] and James P. Curley[2]

[1] Department of Psychology, Barnard College, 3009 Broadway, New York, NY 10027, USA
[2] Department of Psychology, Columbia University, 1190 Amsterdam Avenue, New York, NY 10027, USA
[3] Department of Pathology and Cell Biology, Columbia University Medical Center, 630 West 168th Street, New York, NY 10032, USA

Mast cells (MCs) are both sensors and effectors in communication among nervous, vascular, and immune systems. In the brain, they reside on the brain side of the blood–brain barrier (BBB), and interact with neurons, glia, blood vessels, and other hematopoietic cells via their neuroactive prestored and newly synthesized chemicals. They are first responders, acting as catalysts and recruiters to initiate, amplify, and prolong other immune and nervous responses upon activation. MCs both promote deleterious outcomes in brain function and contribute to normative behavioral functioning, particularly cognition and emotionality. New experimental tools enabling isolation of brain MCs, manipulation of MCs or their products, and measurement of MC products in very small brain volumes present unprecedented opportunities for examining these enigmatic cells.

Trends Neurosci. 2013 Sep;36(9):513-21

Mast cells in the brain: evidence and functional significance

Rae Silver, Ann-Judith Silverman, Ljubiša Vitković and Israel I. Lederhendler

For the past two decades the brain has been considered to be an immune-privileged site that excludes circulating cells from the parenchyma. New evidence indicates that some hematocytes reside in the brain, while others traffic through it. Mast cells belong to both of these functional types. Moreover, the appearance of mast cells in the CNS can be triggered behaviorally. After a brief period of courtship, for example, there is a marked increase in mast cells in the medial habenula of sexually active doves compared with controls. Exposure to gonadal steroids that occur endogenously or that are administered exogenously increases both the number of mast cells and their state of activation in the brain. These results show that hematopoietic cells can provide targeted delivery of neuromodulators to specific regions of the brain, thereby influencing neural–endocrine interactions.

Trends Neurosci. (1996) 19, 25–31

Inflamm Res. 1999 Jun;48(6):296-300.

Biogenic amines in foods: histamine and food processing.

Bodmer S[1], Imark C, Kneubühl M.

Author information

Critical Reviews in Food Science and Nutrition, 48:697–714 (2008)

ISSN: 1040-8398
DOI: 10.1080/10408390701639041

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Updated Molecular Knowledge about Histamine Biosynthesis by Bacteria

JOSÉ MARÍA LANDETE, BLANCA DE LAS RIVAS, ANGELA MARCOBAL, and ROSARIO MUÑOZ

The American Journal of Clinical Nutrition

Histamine and histamine intolerance[1–3]

Am J Clin Nutr 2007;85:1185–96. Printed in USA.

Laura Maintz and Natalija Novak

Histamine and histamine intolerance[1–3]

Laura Maintz and Natalija Novak

Am J Clin Nutr 2007;85:1185–96.

TABLE 3
Foods rich in histamine[1]

Food categories	Histamine		Recommended upper limit for histamine		Tyramine	
	mg/kg	*mg/L*	*mg/kg*	*mg/L*	*mg/kg*	*mg/L*
Fish (frozen/smoked or salted/canned)			200		ND	
Mackerel	1–20/1–1788/ND–210					
Herring	1–4/5–121/1–479					
Sardine	ND/14–150/3–2000					
Tuna	ND/ND/1–402					
Cheese			No recommendation			
Gouda	10–900				10–900	
Camembert	0–1000				0–4000	
Cheddar	0–2100				0–1500	
Emmental	5–2500				0–700	
Swiss	4–2500				0–700	
Parmesan	10–581				0–840	
Meat			No recommendation			
Fermented sausage	ND–650				ND–1237	
Salami	1–654				-	
Fermented ham	38–271				123–618	
Vegetables						
Sauerkraut	0–229		10		2–951	
Spinach	30–60					
Eggplant	26					
Tomato ketchup	22					
Red wine vinegar	4					
Alcohol						
White wine		ND–10		2		1–8
Red wine		ND–30		2		ND–25
Top-fermented beer		ND–14				1.1–36.4
Bottom-fermented beer		ND–17				0.5–46.8
Champagne		670				

[1] ND, not detected. Data taken from references 13, 73, 75, 78, and 86.

Table 1. Effect of Histamine on Brain Function

Histamine	Source	Mechanism	Cognition-Learning-Attention, Motivation	Brain Fog Anxiety
Low		Activation of H3 autoinhibitory receptors shuts down histamine synthesis and release	++	N/A
Normal			+++	N/A
High	Mast cell secretion, histamine containing foods, gut bacterial histamine production Excessive use of H1 receptor antagonists		+	+++

frontiers in
SYSTEMS NEUROSCIENCE

REVIEW ARTICLE
published: 04 July 2012
doi: 10.3389/fnsys.2012.00051

Histamine and motivation

Fernando Torrealba[1,2]*, *Maria E. Riveros*[1,2], *Marco Contreras*[1,2] and *Jose L. Valdes*[3]

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[2] Millenium Nucleus in stress and addiction, Pontificia Universidad Católica de Chile, Santiago, Chile
[3] Facultad de Medicina, Departamento de Fisiología y Biofísica, Instituto de Ciencias Biomédicas, Universidad de Chile, Santiago, Chile

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Ritchie E. Brown, VA Boston Healthcare System, USA
Saara Nuutinen, University of Helsinki, Finland
José-Antonio Arias-Montaño, Centro de Investigación y de Estudios Avanzados, Mexico

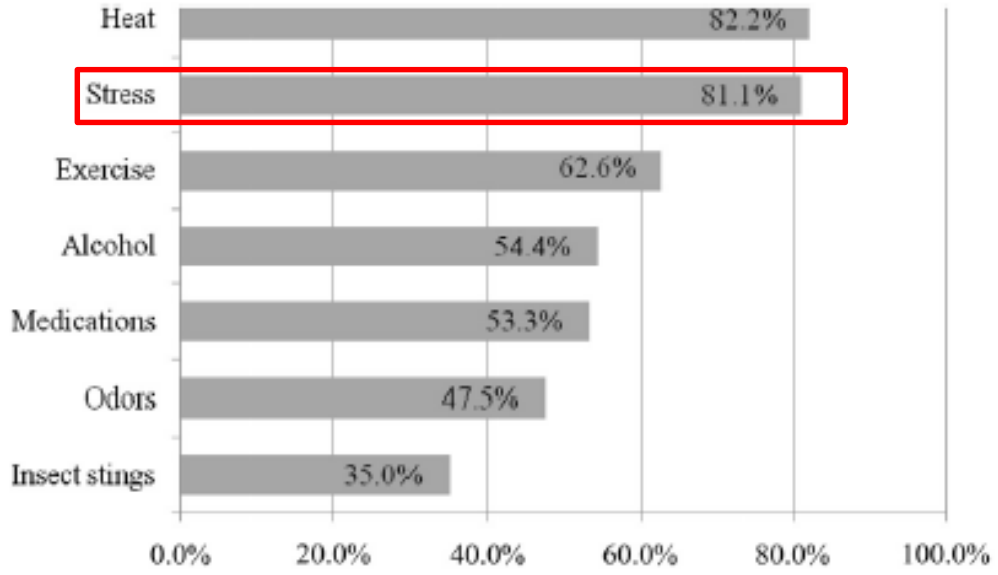
Brain histamine may affect a variety of different behavioral and physiological functions; however, its role in promoting wakefulness has overshadowed its other important functions. Here, we review evidence indicating that brain histamine plays a central role in motivation and emphasize its differential involvement in the appetitive and consummatory phases of motivated behaviors. We discuss the inputs that control histaminergic neurons of the tuberomamillary nucleus (TMN) of the hypothalamus, which determine the distinct role of these neurons in appetitive behavior, sleep/wake cycles, and food anticipatory responses. Moreover, we review evidence supporting the dysfunction of histaminergic neurons and the cortical input of histamine in regulating specific forms of decreased motivation (apathy). In addition, we discuss the relationship between the histamine system and drug addiction in the context of motivation.

Original Article

J ALLERGY CLIN IMMUNOL PRACT
JANUARY/FEBRUARY 2014

The Mastocytosis Society Survey on Mast Cell Disorders: Patient Experiences and Perceptions☆

Susan Jennings, PhD*, Nancy Russell, DrPH*, Blair Jennings, BS*, Valerie Shea, RN, BSN*, Lisa Sterling, BS*, Mariana Castells, MD, PhD, FAAAAI†, Peter Valent, MD‡, and Cem Akin, MD, PhD, FAAAAI§ *Hastings, Neb; Boston, Mass; and Vienna, Austria*



Brain mast cells link the immune system to anxiety-like behavior

Katherine M. Nautiyal[a], Ana C. Ribeiro[b], Donald W. Pfaff[b,1], and Rae Silver[a,c,d,2]

[a]Department of Psychology, Columbia University, 1190 Amsterdam Avenue, New York, NY 10027; [b]Laboratory of Neurobiology and Behavior, The Rockefeller University, 1230 York Avenue, New York, NY 10021; [c]Department of Psychology, Barnard College, 3009 Broadway, New York, NY 10027; and [d]Department of Pathology and Cell Biology, Columbia University, 630 West 168th Street, New York, NY 10032

Contributed by Donald W. Pfaff, S

PNAS | November 18, 2008 | vol. 105 | no. 46 | 18053–18057

0271-0749/02/2202-0103/0
Journal of Clinical Psychopharmacology

Vol. 22, No. 2
Printed in U.S.A.

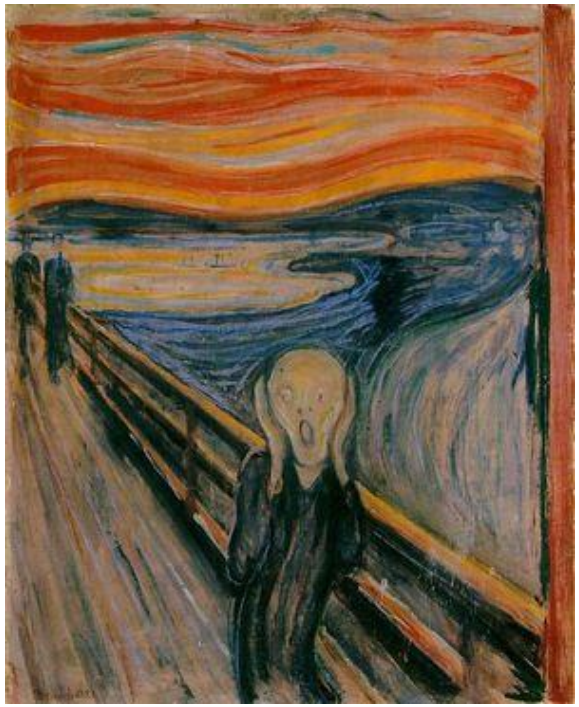
GUEST EDITORIAL

Mast Cells and Stress—A Psychoneuroimmunological Perspective

THEOHARIS C. THEOHARIDES, PHD, MD

Tufts University School of Medicine, Boston, Massachusetts

- **Allergies/Atopic dermatitis**
- **Autism**
- **Bipolar disorder**
- **Chronic fatigue syndrome**
- **Fibromyalgia**
- **Interstitial cystitis**
- **Irritable bowel syndrome**
- **Mastocytosis**
- **Migraines**
- **Multiple sclerosis**
- **Psoriasis**



Edvard Munch, *The Scream* (Skrik, 1893)

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

Prenatal negative life events increases cord blood IgE: interactions with dust mite allergen and maternal atopy

J. L. Peters[1], S. Cohen[2], J. Staudenmayer[3], J. Hosen[4,5], T. A. E. Platts-Mills[4] & R. J. Wright[6,7]

[1]Department of Environmental Health, Boston University School of Public Health, Boston, MA, USA; [2]Department of Psychology, Carnegie Mellon University, Pittsburgh, PA, USA; [3]Department of Mathematics and Statistics, University of Massachusetts, Amherst, MA, USA; [4]Division of Allergy and Clinical Immunology, University of Virginia, Charlottesville, VA, USA; [5]Department of Entomology, University of Maryland, College Park, MD, USA; [6]Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA; [7]The Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Neurogastroenterology

Long-term alterations of colonic nerve–mast cell interactions induced by neonatal maternal deprivation in rats

F Barreau, C Salvador-Cartier, E Houdeau, L Bueno, J Fioramonti

Gut 2008:**57**:582–590.

0022-3565/02/3033-1061–1066$7.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
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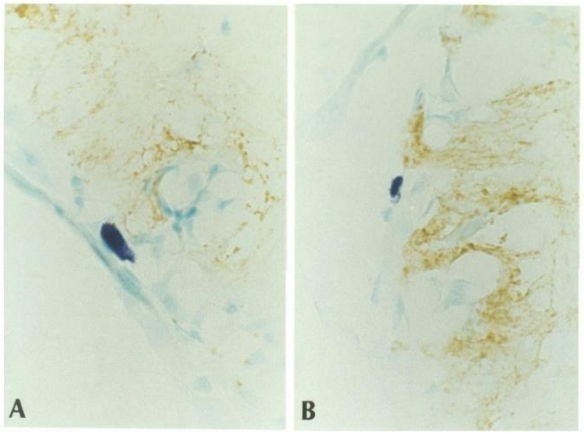
JPET 303:1061–1066, 2002

Vol. 303, No. 3
38497/1026539
Printed in U.S.A.

Corticotropin-Releasing Hormone and Brain Mast Cells Regulate Blood-Brain-Barrier Permeability Induced by Acute Stress

PAMELA ESPOSITO, NATHAN CHANDLER, KRISTIANA KANDERE, SUBIMAL BASU, STANLEY JACOBSON, RAYMOND CONNOLLY, DAVID TUTOR, and THEOHARIS C. THEOHARIDES



OPEN ACCESS Freely available online

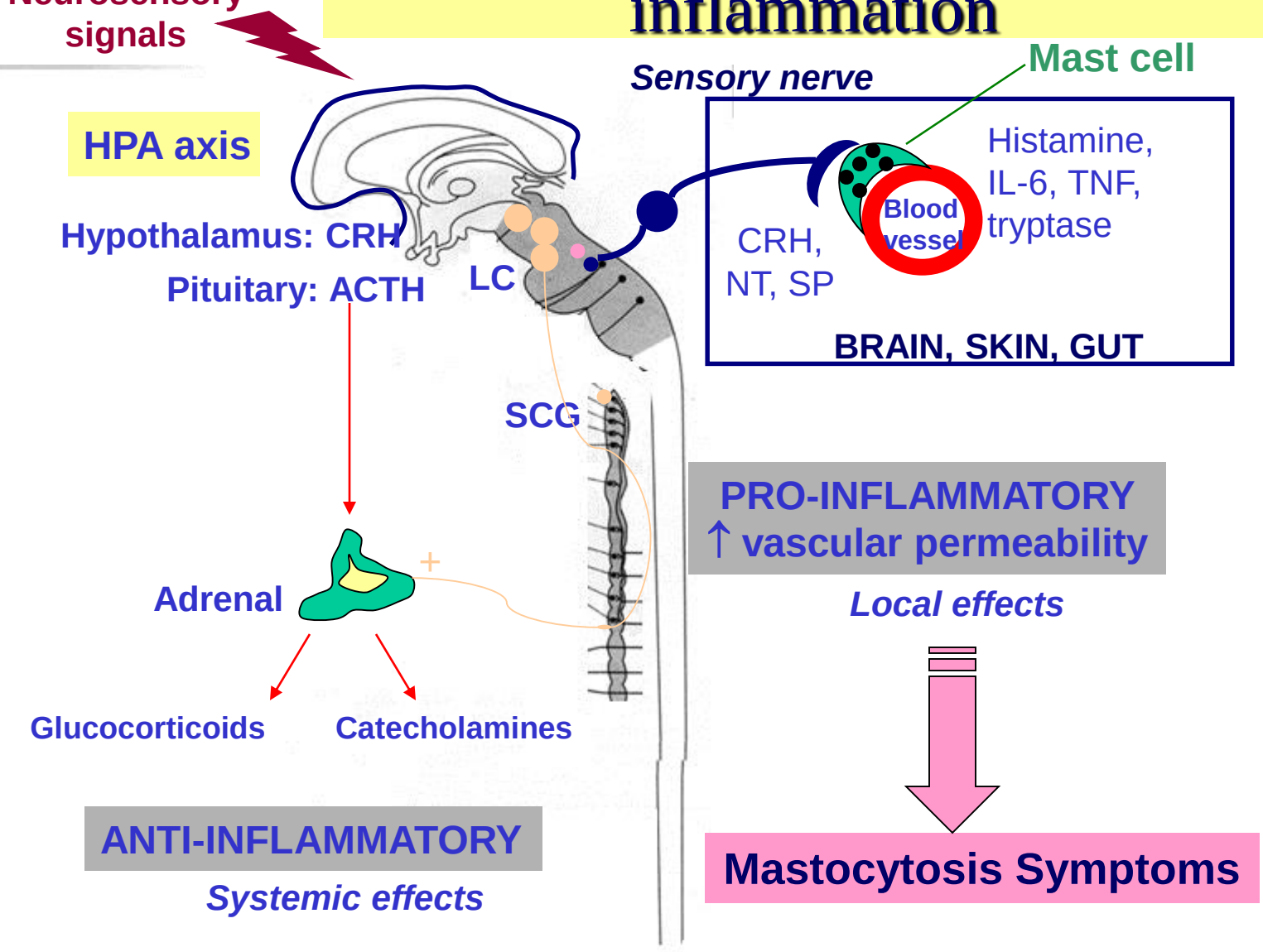
PLoS one

CRF Induces Intestinal Epithelial Barrier Injury via the Release of Mast Cell Proteases and TNF-α

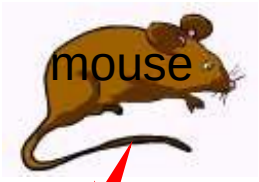
Elizabeth L. Overman[1], Jean E. Rivier[2], Adam J. Moeser[1]*

1 College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina, United States of America, **2** The Salk Institute, La Jolla, California, United States of America

Mast cells in neurogenic inflammation



Stress-induced brain vascular permeability is dependent on cells

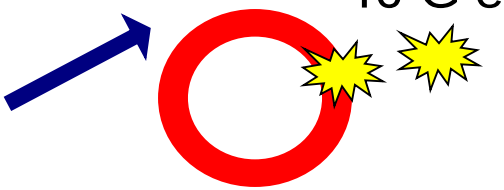


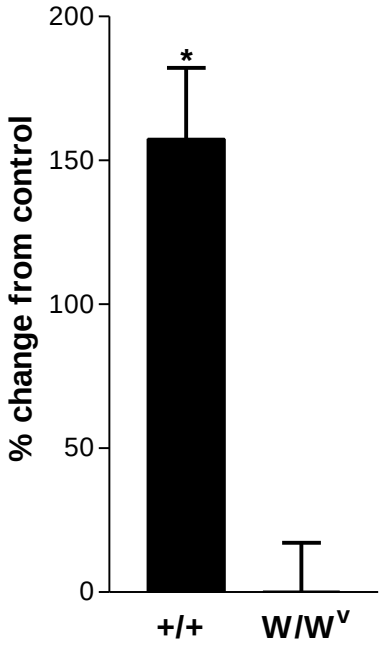
tv ^{99}Tc-G

30 minutes restraint stress

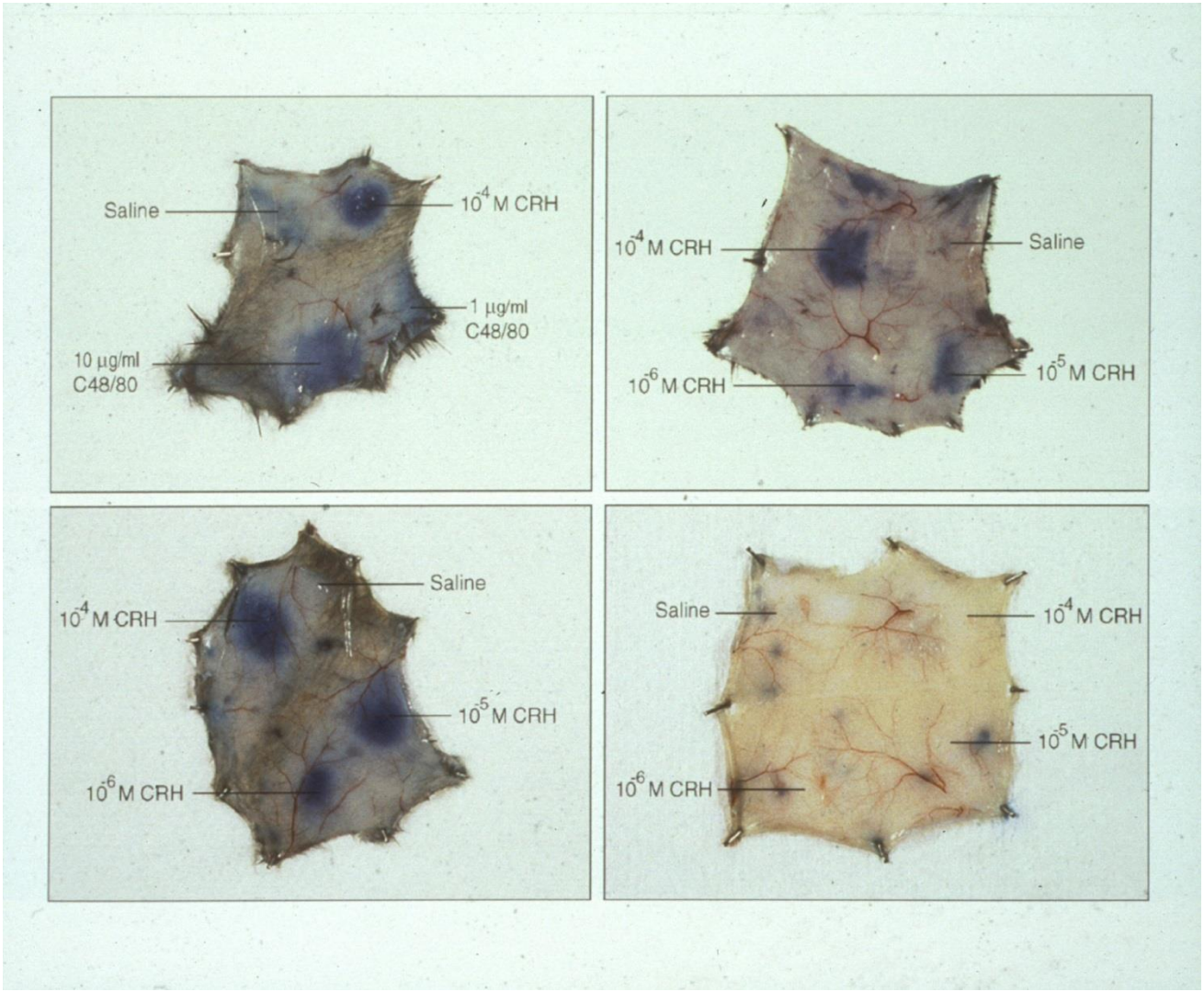
C57BL +/+ normal
W/Wv mast cell-deficient

Plasma leak
-^{99}Tc-G extravasation





Intradermal CRH Injection Induces Skin Vascular Permeability, but not in W/W^v Mast Cell Deficient Mice



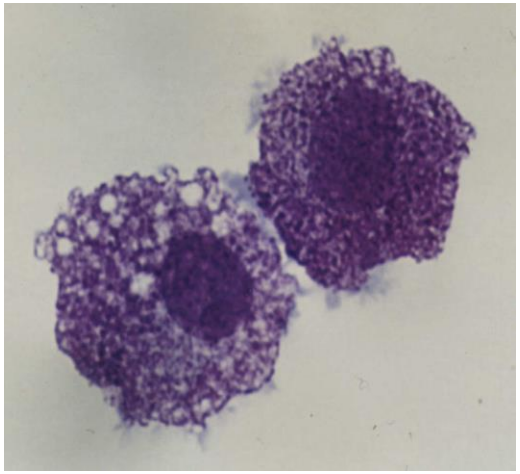
Culture of human umbilical cord blood-derived mast cells (hCBMCs)

CD34+ cells

MNCs

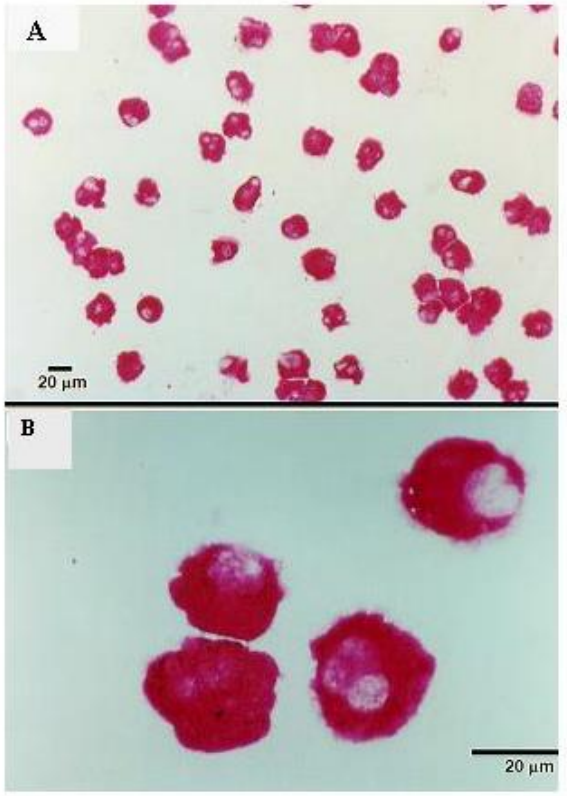
AC133 mAb

RBCs



MACs

Culture with SCF (100 ng/ml) and IL-6 (50 ng/ml) for 8-16 wk yields 100% tryptase-positive mast cells



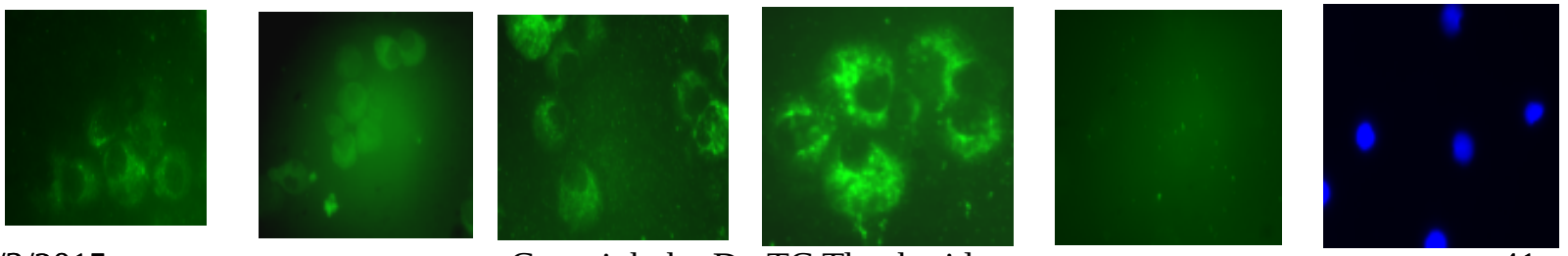
Kempuraj D., Saito H. et al. Blood 93: 3338-3346, 1999.

Human Mast Cells Express Corticotropin-Releasing Hormone (CRH) Receptors and CRH Leads to Selective Secretion of Vascular Endothelial Growth Factor[1]

Jing Cao,*† Nikoletta Papadopoulou,† Duraisamy Kempuraj,† William S. Boucher,† Koreaki Sugimoto,[2]† Curtis L. Cetrulo,‡ and Theoharis C. Theoharides[3]*†§

Mast cells are critical for allergic reactions, but also for innate or acquired immunity and inflammatory conditions that worsen by stress. Corticotropin-releasing hormone (CRH), which activates the hypothalamic-pituitary-adrenal axis under stress, also has proinflammatory peripheral effects possibly through mast cells. We investigated the expression of CRH receptors and the effects of CRH in the human leukemic mast cell (HMC-1) line and human umbilical cord blood-derived mast cells. We detected mRNA for CRH-R1α, 1β, 1c, 1e, 1f isoforms, as well as CRH-R1 protein in both cell types. CRH-R2α (but not R2β or R2γ) mRNA and protein were present only in human cord blood-derived mast cells. CRH increased cAMP and induced secretion of vascular endothelial growth factor (VEGF) without tryptase, histamine, IL-6, IL-8, or TNF-α release. The effects were blocked by the CRH-R1 antagonist antalarmin, but not the CRH-R2 antagonist astressin 2B. CRH-stimulated VEGF production was mediated through activation of adenylate cyclase and increased cAMP, as evidenced by the fact that the effect of CRH was mimicked by the direct adenylate cyclase activator forskolin and the cell-permeable cAMP analog 8-bromo-cAMP, whereas it was abolished by the adenylate cyclase inhibitor SQ22536. This is the first evidence that mast cells express functional CRH receptors and that CRH can induce VEGF secretion selectively. CRH-induced mast cell-derived VEGF could, therefore, be involved in chronic inflammatory conditions associated with increased VEGF, such as arthritis or psoriasis, both of which worsen by stress. *The Journal of Immunology*, 2005, 174: 7665–7675.

R1 no IL-4 **R1 + IL-4** **R2 no IL-4** **R2 + IL-4** **No R1 primary** **DAPI**



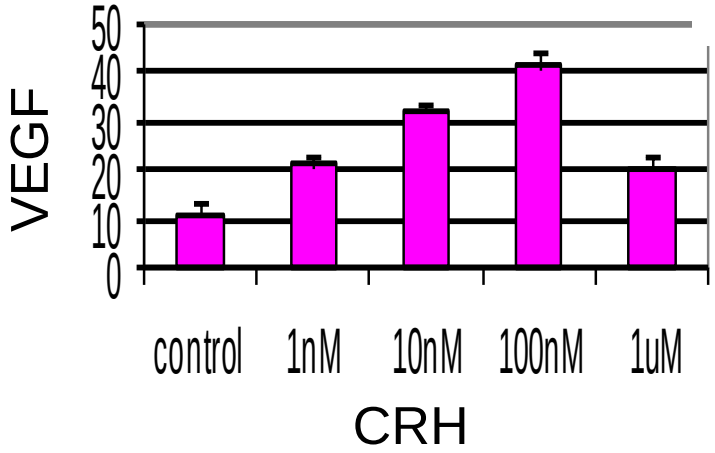
PNAS

Corticotropin-releasing hormone induces skin vascular permeability through a neurotensin-dependent process

Jill Donelan*, William Boucher*, Nikoletta Papadopoulou*, Michael Lytinas*, Dean Papalliodis*, Paul Dobner†, and Theoharis C. Theoharides*‡§¶

Departments of *Pharmacology and Experimental Therapeutics, ‡Biochemistry, and §Internal Medicine, Tufts University School of Medicine, Tufts–New England Medical Center, 136 Harrison Avenue, Boston, MA 02111; and †Department of Molecular Genetics and Microbiology, University of Massachusetts Medical School, Worcester, MA 01655

PNAS | May 16, 2006 | vol. 103 | no. 20 | 7759–7764



Opinion TRENDS in Pharmacological Sciences Vol.25 No.11 November 2004

ELSEVIER

Mast cells as targets of corticotropin-releasing factor and related peptides

Theoharis C. Theoharides[1,2,3], Jill M. Donelan[1], Nikoletta Papadopoulou[1], Jing Cao[3], Duraisamy Kempuraj[1] and Pio Conti[4]

Substance P (SP) Induces Expression of Functional Corticotropin-Releasing Hormone Receptor-1 (CRHR-1) in Human Mast Cells

Shahrzad Asadi[1,2], Konstantinos-Dionysios Alysandratos[1,3,7], Asimenia Angelidou[1,3,8], Alexandra Miniati[1], Nikolaos Sismanopoulos[1,3], Magdalini Vasiadi[1,3,4], Bodi Zhang[1,4,5], Dimitrios Kalogeromitros[3,9] and Theoharis C. Theoharides[1,3,4,5,6]

Corticotropin-releasing hormone (CRH) is secreted under stress and regulates the hypothalamic–pituitary–adrenal axis. However, CRH is also secreted outside the brain where it exerts proinflammatory effects through activation of mast cells, which are increasingly implicated in immunity and inflammation. Substance P (SP) is also involved in inflammatory diseases. Human LAD2 leukemic mast cells express only CRHR-1 mRNA weakly. Treatment of LAD2 cells with SP (0.5–2 μM) for 6 hours significantly increases corticotropin-releasing hormone receptor-1 (CRHR-1) mRNA and protein expression. Addition of CRH (1 μM) to LAD2 cells, which are "primed" with SP for 48 hours and then washed, induces synthesis and release of IL-8, tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF) 24 hours later. These effects are blocked by pretreatment with an NK-1 receptor antagonist. Treatment of LAD2 cells with CRH (1 μM) for 6 hours induces gene expression of NK-1 as compared with controls. However, repeated stimulation of mast cells with CRH (1 μM) leads to downregulation of CRHR-1 and upregulation in NK-1 gene expression. These results indicate that SP can stimulate mast cells and also increase expression of functional CRHR-1, whereas CRH induces NK-1 gene expression. These results may explain CRHR-1 and NK-1 expression in lesional skin of psoriatic patients.

Journal of Investigative Dermatology advance online publication, 17 November 2011; doi:10.1038/jid.2011.334

ORIGINAL ARTICLE EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Neuropeptide blood levels correlate with mast cell load in patients with mastocytosis

Allergy 2011; **66**: 862–869.

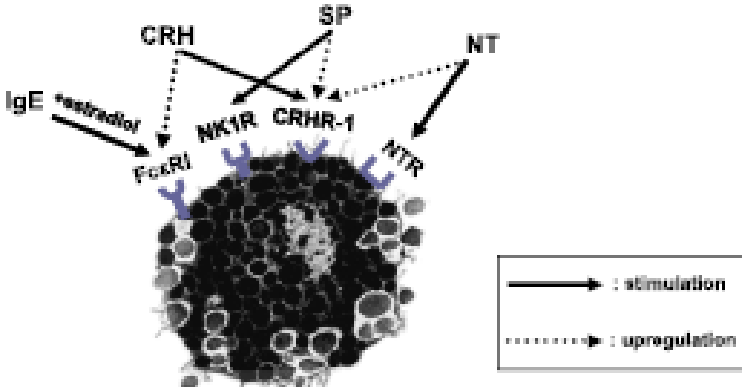
L. Maintz[1], E. Wardelmann[2], K. Walgenbach[3], R. Fimmers[4], T. Bieber[1], U. Raap[5] & N. Novak[1]

[1]Department of Dermatology and Allergy; [2]Department of Pathology; [3]Department of Plastic Surgery; [4]Department of Medical Biometry, Informatics and Epidemiology, University of Bonn, Bonn; Germany; [5]Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany

LETTERS TO THE EDITORS

J Clin Psychopharmacol. 2002 Apr;22(2):221-4.

Acute Stress-Induced Seizures and Loss of Consciousness in a Ten-Year-Old Boy With Cutaneous Mastocytosis



Michail Alevizos, MD*
Anna Karagkouni, MD*
Kalliopi Kontou-Fili, MD, PhD†,‡
Theoharis C. Theoharides, MS, PhD, MD*,§,||

Ann Allergy Asthma Immunol 112 (2014) 383–394

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ELSEVIER

Letters

A probable case report of stress-induced anaphylaxis

Clinical dermatology • **Concise report**

Clinical and Experimental Dermatology

Urticaria pigmentosa associated with acute stress and lesional skin mast-cell expression of CRF-R1

T. C. Theoharides,* D. Kempuraj,* J. Marchand,† L. Tzianoumis,‡ M. Vasiadi,* A. Katsarou-Katsari,¶ M. Makris§ and D. Kalogeromitros§

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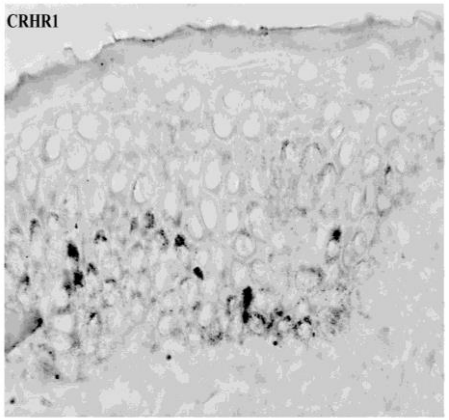
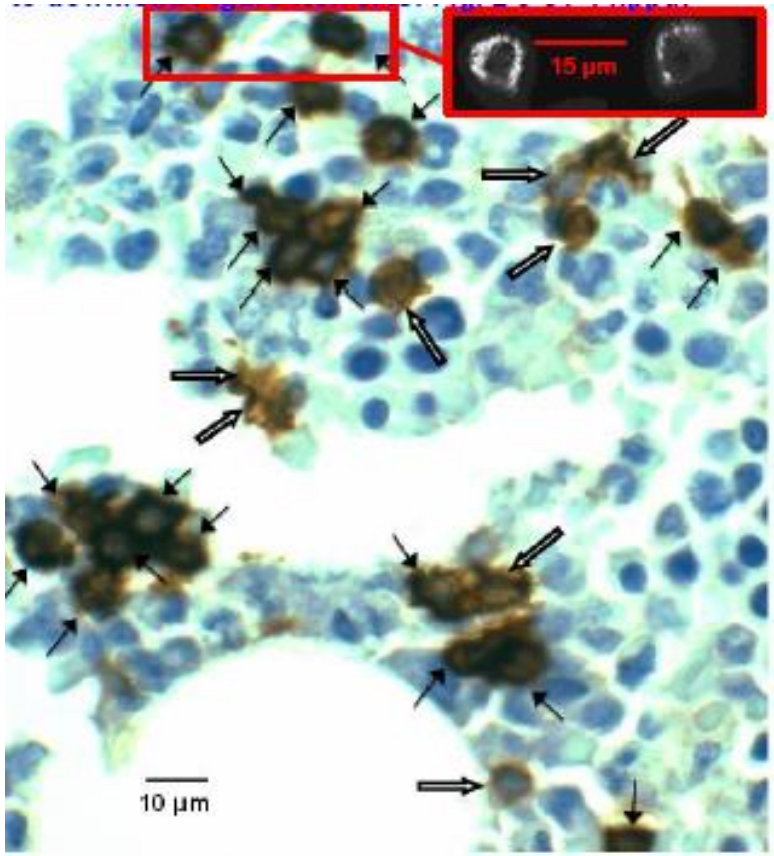
doi:10.1111/j.1365-2230.2008.03043.x



High serum CRH and bone marrow mast cell CRH receptor expression in a mastocytosis patient

Theoharis C. Theoharides, MS, PhD, MD[1,2], Anastasia I. Petra, MD[1], Julia M. Stewart, RN[1], Irene Tsilioni, PhD[1], Cem Akin, MD, PhD[3]

J Allergy Clin Immunol. 2014 Jun 27.



Review TRENDS in Immunology Vol.27 No.1 January 2006

Neuroimmunoendocrine circuitry of the 'brain-skin connection'

Ralf Paus[1], Theoharis C. Theoharides[2] and Petra Clara Arck[3]

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[2]Departments of Pharmacology & Experimental Therapeutics, Biochemistry and Internal Medicine, Tufts University School of Medicine, Boston, MA 02111, USA
[3]Biomedical Research Center, Charité – University Medicine Berlin, D-13353 Berlin, Germany

Endocrine Reviews. First published ahead of print August 12, 2013 as doi:10.1210/er.2012-1092

1

Key Role of CRF in the Skin Stress Response System

Andrzej T Slominski, MD, PhD[1,2], Michal A Zmijewski, PhD[3], Blazej Zbytek, MD, PhD[1], Desmond J Tobin, PhD[4], Theoharis C Theoharides, MS, PhD, MD[5], and Jean Rivier[6*], PhD

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Key terms: CRF, urocortins, HPA, skin, stress, POMC, immune cells

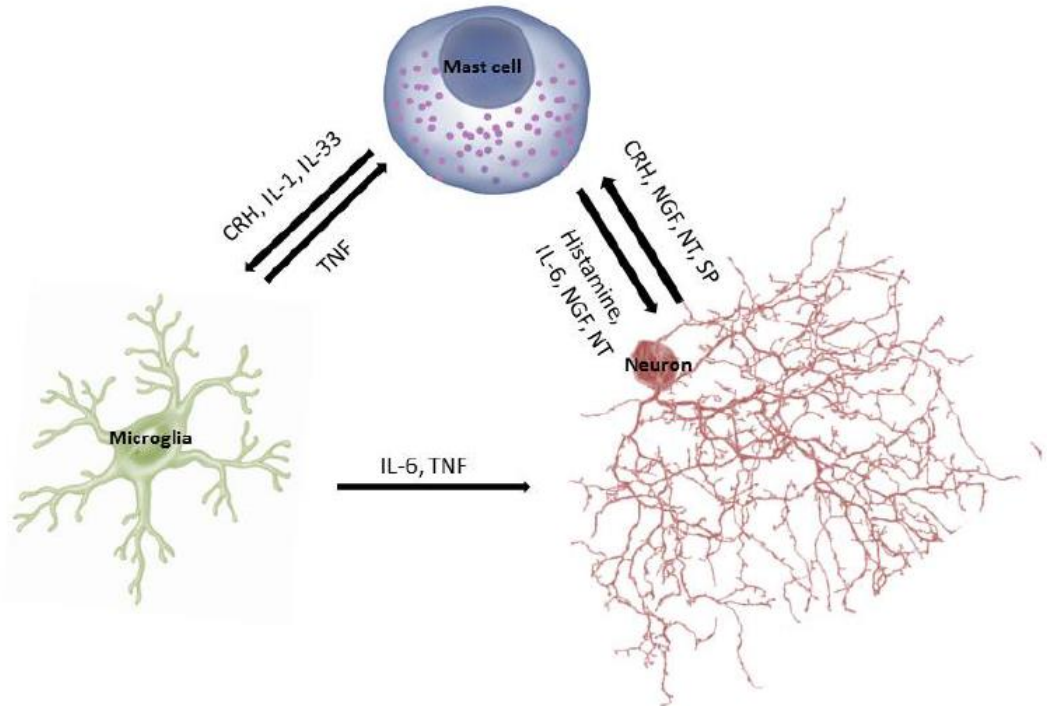
frontiers in
NEUROSCIENCE

IMPACT FACTOR July 2015

Neuropharmacology

Brain "fog," inflammation and obesity : key aspects of neuropsychiatric disorders improved by luteolin

Theoharis Constantin Theoharides, Julia M Stewart and Erifili Hatziagelaki



The FASEB Journal article fj.11-197194. Published online April 19, 2012.

The FASEB Journal • Review

Microglia and mast cells: two tracks on the road to neuroinflammation

Stephen D. Skaper,[1] Pietro Giusti, and Laura Facci

Dipartimento di Scienze del Farmaco, Largo Egidio Meneghetti 2, University of Padova, Padua, Italy

BRAIN RESEARCH 1456 (2012) 72–81

Available online at www.sciencedirect.com

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BRAIN RESEARCH

Research Report

Abnormal microglial–neuronal spatial organization in the dorsolateral prefrontal cortex in autism

John T. Morgan[a,], Gursharan Chana[b], Ian Abramson[c], Katerina Semendeferi[d], Eric Courchesne[a,1], Ian P. Everall[b,1]*

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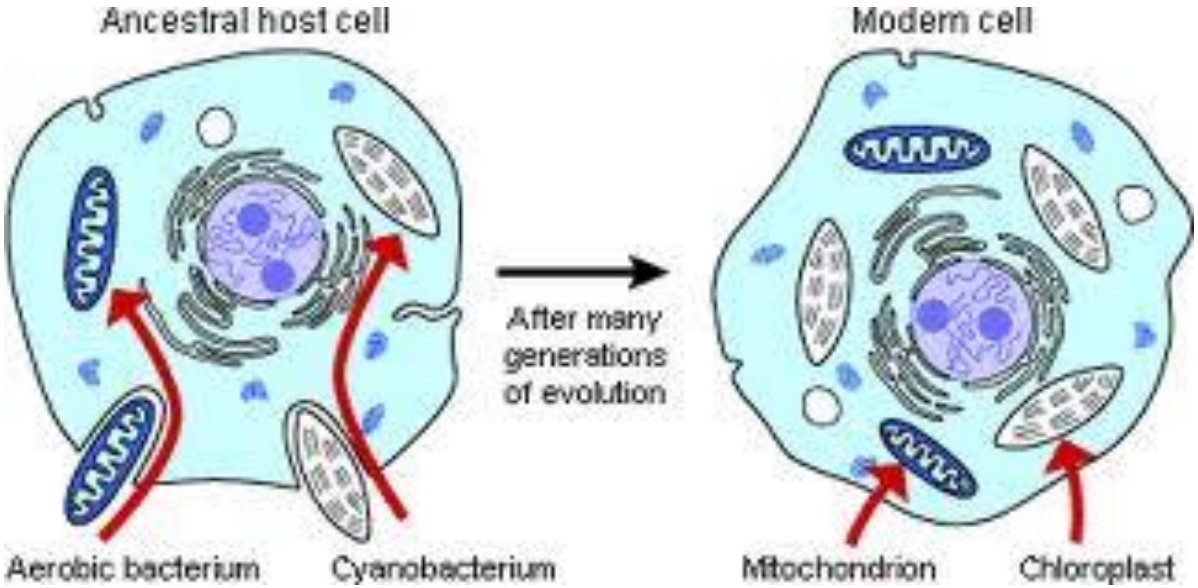
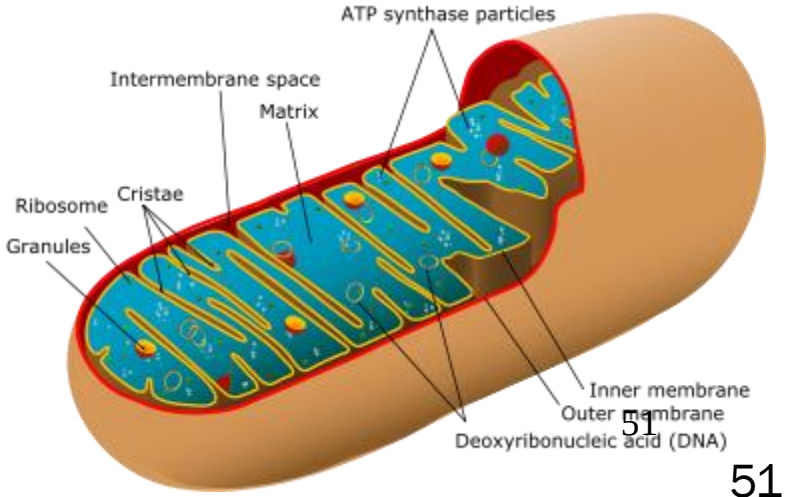
Allergy AND Clinical
Immunology
STAT3 /ON
PIAS3 /OFF
Mitochondrial STAT3
plays a major role in
IgE-Ag mediated mast
cell exocytosis.

Margulis L. Symbiotic theory of the origin of eukaryotic organelles; criteria for proof.
Symp Soc Exp Biol. 1975;(29):21-38.

Lynn Margulis (1938 –2011)



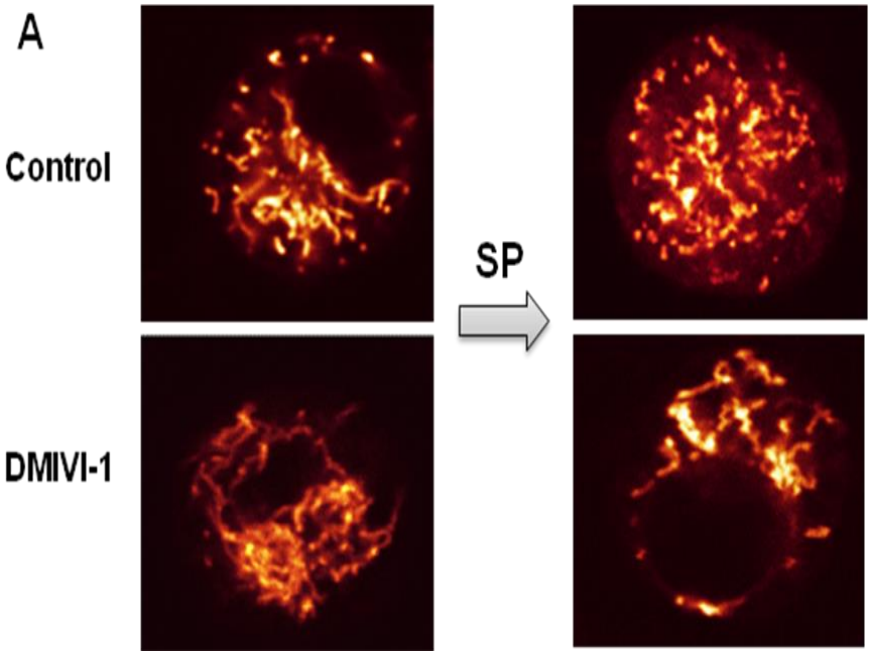


Human mast cell degranulation and preformed TNF secretion require mitochondrial translocation to exocytosis sites: Relevance to atopic dermatitis

Bodi Zhang, MD, MPH, PhD,[a,b] Konstantinos-Dionysios Alysandratos, MD,[a,e] Asimenia Angelidou, MD,[a,e] Shahrzad Asadi, PharmD,[a] Nikolaos Sismanopoulos, MD,[a] Danae-Anastasia Delivanis, MD,[a] Zuyi Weng, MS,[a] Alexandra Miniati, MD,[a,e] Magdalini Vasiadi, BS,[a,e] Alexandra Katsarou-Katsari, MD, PhD,[f] Benchun Miao, PhD,[c] Susan E. Leeman, PhD,[g] Dimitrios Kalogeromitros, MD, PhD,[e] and Theoharis C. Theoharides, MS, PhD, MD[a,b,d,e]

Boston, Mass, and Athens, Greece

J Allergy Clin Immunol 2011;127:1522-31



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PLOS | ONE

Stimulated Human Mast Cells Secrete Mitochondrial Components That Have Autocrine and Paracrine Inflammatory Actions

Bodi Zhang[1,2,3], Shahrzad Asadi[1,4], Zuyi Weng[1,3], Nikolaos Sismanopoulos[1¤], Theoharis C. Theoharides[1,2,3,4,5*]

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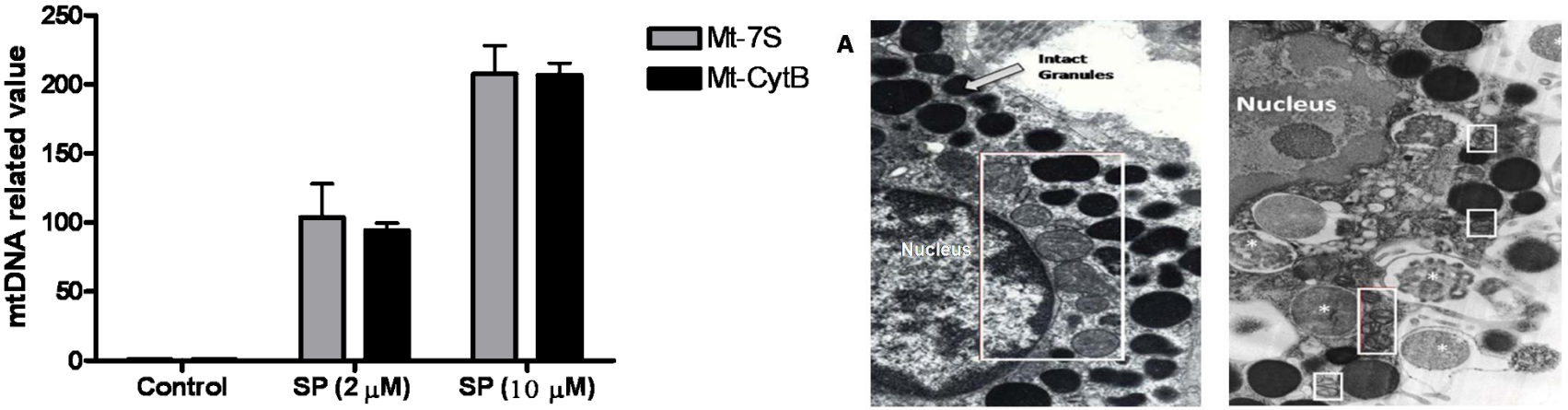
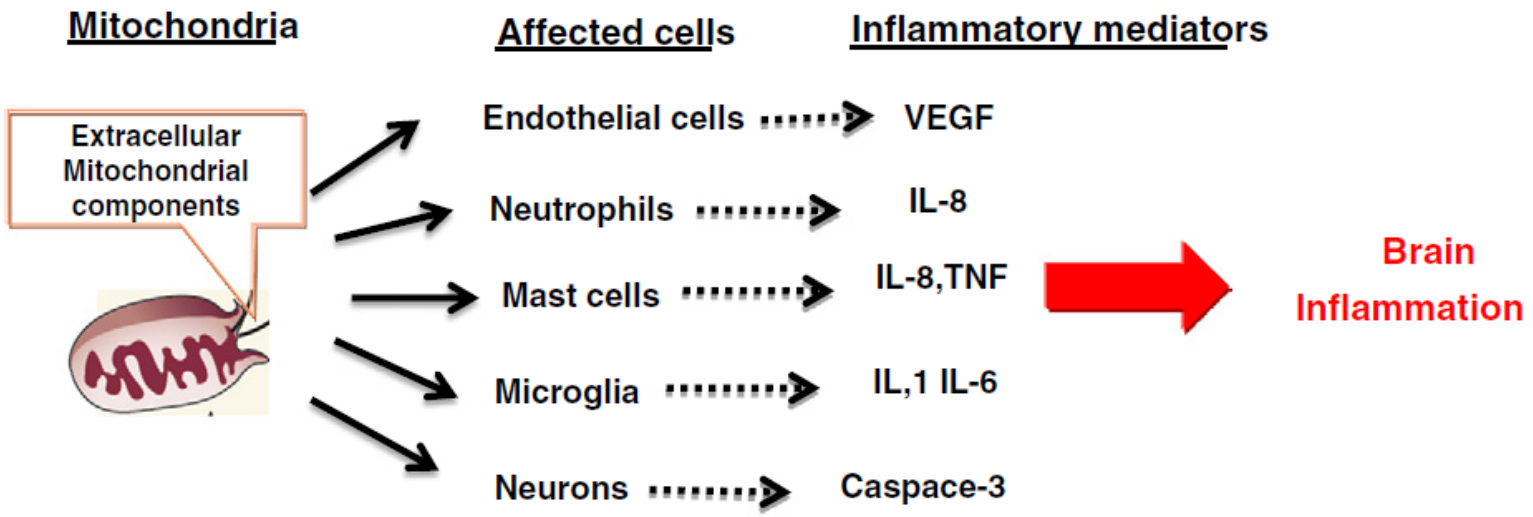


Mast cell-derived mitochondrial components stimulate other cell types



MOLECULAR AND CELLULAR BIOLOGY, Mar. 2010, p. 1357–1367 Vol. 30, No. 6
0270-7306/10/$12.00 doi:10.1128/MCB.01149-09

Mitochondrial DNA Toxicity in Forebrain Neurons Causes Apoptosis, Neurodegeneration, and Impaired Behavior▽

Knut H. Lauritzen,[1] Olve Moldestad,[2] Lars Eide,[3] Harald Carlsen,[4] Gaute Nesse,[1] Johan F. Storm,[2] Isabelle M. Mansuy,[5] Linda H. Bergersen,[6]* and Arne Klungland[1,7]*

Centre for Molecular Biology and Neuroscience, Institute of Medical Microbiology, Oslo University Hospital and University of Oslo, NO-0027 Oslo, Norway[1]; Department of Physiology, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Domus Medica, Sognsvannsveien 9, PB1103 Blindern, 0317 Oslo, Norway[2]; Institute of Clinical Biochemistry, Oslo University Hospital and University of Oslo, Oslo, Norway[3]; Department of Nutrition Research, Institute of Basic Medical Sciences, University of Oslo, Sognsvannsveien 9, 0372 Oslo, Norway[4]; Brain Research Institute, Medical Faculty of the University of Zurich and Department of Biology, Swiss Federal Institute of Technology, Winterthurerstrasse 190, 8057 Zurich, Switzerland[5]; Brain and Muscle Energy Group; Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway[6]; and Institute of Basic Medical Sciences, University of Oslo, P.O. Box 1018 Blindern, NO-0315 Oslo, Norway[7]

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/bbadis

Review

Mast cells and inflammation ☆

Theoharis C. Theoharides [a,b,c,d,*], Konstantinos-Dionysios Alysandratos [a,d], Asimenia Angelidou [a,d], Danae-Anastasia Delivanis [a], Nikolaos Sismanopoulos [a], Bodi Zhang [a,b], Shahrzad Asadi [a], Magdalini Vasiadi [a,d], Zuyi Weng [a], Alexandra Miniati [a,d], Dimitrios Kalogeromitros [d]

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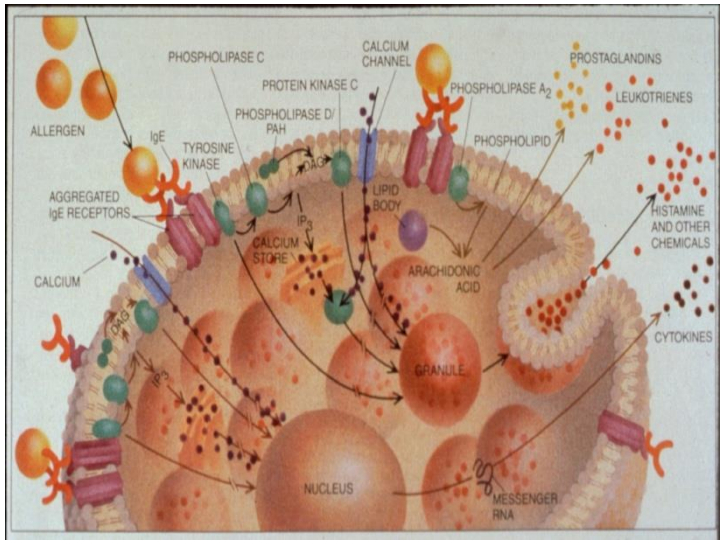
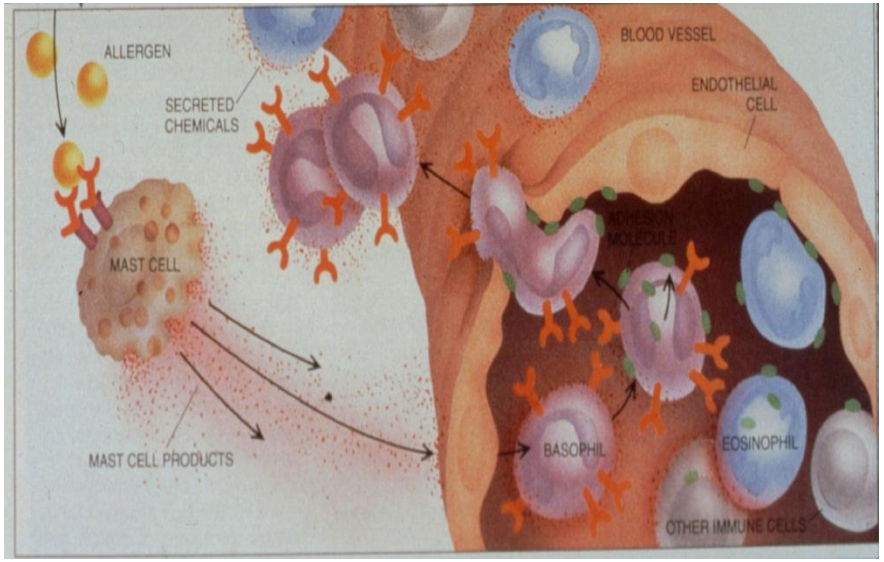
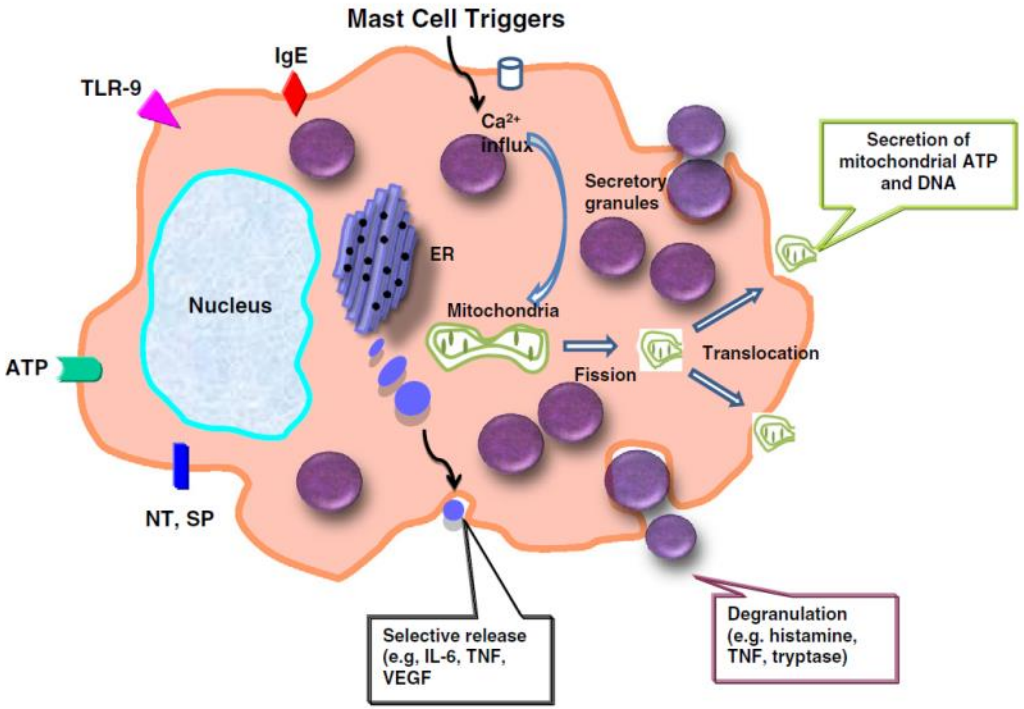
[b] Department of Biochemistry, Tufts University School of Medicine, Boston, MA, USA
[c] Department of Internal Medicine, Tufts University School of Medicine and Tufts Medical Center, Boston, MA, USA
[d] Allergy Clinical Research Center, Allergy Section, Attikon General Hospital, Athens Medical School, Athens, Greece





Investigation of Why Some Human Mast Cells Do Not Degranulate



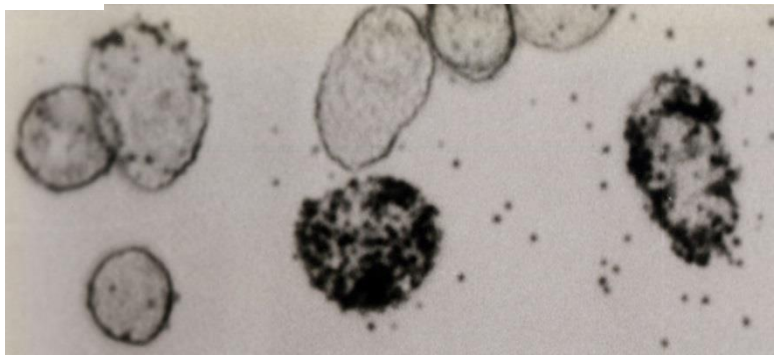


Table 4. Frequently Used Medications for Mild to Moderate Symptoms

Agent	Usual Dose
Acetylsalicylic acid	80-325 mg qD
Cromolyn sodium, oral	200 mg TID
Cyproheptadine	1-2 mg qD
Diphenhydramine	25-50 2-3 times qD prn
Doxepine	25-75 mg qHS
Hydroxyzine	10-50 mg qHS
Ketotifen	1-4 mg qD
Lorazepam	1-2 mg qD
Montelukast	10 mg BID
Ranitidne	200-1,200 qD
Rupatadine	10-20 mg qD
Pain Control	
Tiagabine	2 mg TID
Gabapentin	400 mg TID
Tramadol	50 mg TID
Supplement	
Luteolin/quercetin/olive kernel extract	2 capsules TID

Sleep

- Amitriptyline (Elavil)
- Lorazepam (Ativan)
- Diphenhydramine (Benadryl)
- Hydroxyzine (Atarax)
- Melatonin

Pain

- Amitriptyline (Elavil)
- Codeine
- Fentanyl transdermal (Duragesic)
- Gabapentin (Neurontin)
- Hydroxyzine (Atarax)
- Pregabalin (Lyrica)
- Tiagabine (Gabitril)
- Tramadol (Ultram)

Varied Effects of Antihistamines

Histamine-1 receptor antagonists	Characteristics
• Cetirizine (Zyrtec)	Nonsedating
• Cyproheptadine (Periactin)	Antiserotonin
• Diphenhydramine (Benadryl)	Sedating
• Hydroxyzine (Atarax)	Anxiolytic
• Ketotifen (Zaditen)	Antieosinophilic
• Loratadine (Allegra)	Nonsedating
• Rupatadine (Rupafin)	Antieosniophilic
Tricyclic Antidepressants	
• Amitriptyline (Elavil)	Weight gain
• Doxepin (Sinequan)	Nightmares
Phenothiazines	
• Promethazine (Phenergan)	Cloudy brain
• Prochlorperazine (Compazine)	Antiemetic

International Archives of Allergy and Immunology

Original Paper

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Published online: August 6, 2009

Rupatadine Inhibits Proinflammatory Mediator Secretion from Human Mast Cells Triggered by Different Stimuli

Magdalini Vasiadi[a, e] Dimitris Kalogeromitros[e] Duraisamy Kempuraj[a]
Anthony Clemons[a] Bodi Zhang[a] Caterina Chliva[e] Michael Makris[e]
Adam Wolfberg[b] Michael House[b] Theoharis C. Theoharides[a, c–e]

Ann Allergy Asthma Immunol 111 (2013) 542–547

Contents lists available at ScienceDirect

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Rupatadine inhibits inflammatory mediator release from human laboratory of allergic diseases 2 cultured mast cells stimulated by platelet-activating factor

Michail Alevizos, MD [*,¶]; Anna Karagkouni, MD [*,#]; Magdalini Vasiadi, DSc [*,†,‡];
Nikolaos Sismanopoulos, MD [*,†,**]; Michael Makris, MD, DSc [†]; Dimitrios Kalogeromitros, MD, DSc [†,††];
and Theoharis C. Theoharides, MS, PhD, MD [*,†,‡,§,‖]

Full Text Online Wiley Online Library

Allergy. 2013 Jul;68(7):949-52. doi: 10.1111/all.12159. Epub 2013 Jun 4.

Rupatadine improves quality of life in mastocytosis: a randomized, double-blind, placebo-controlled trial.

Siebenhaar F[1], Förtsch A, Krause K, Weller K, Metz M, Magerl M, Martus P, Church MK, Maurer M.

Amitriptyline and Prochlorperazine Inhibit Proinflammatory Mediator Release From Human Mast Cells

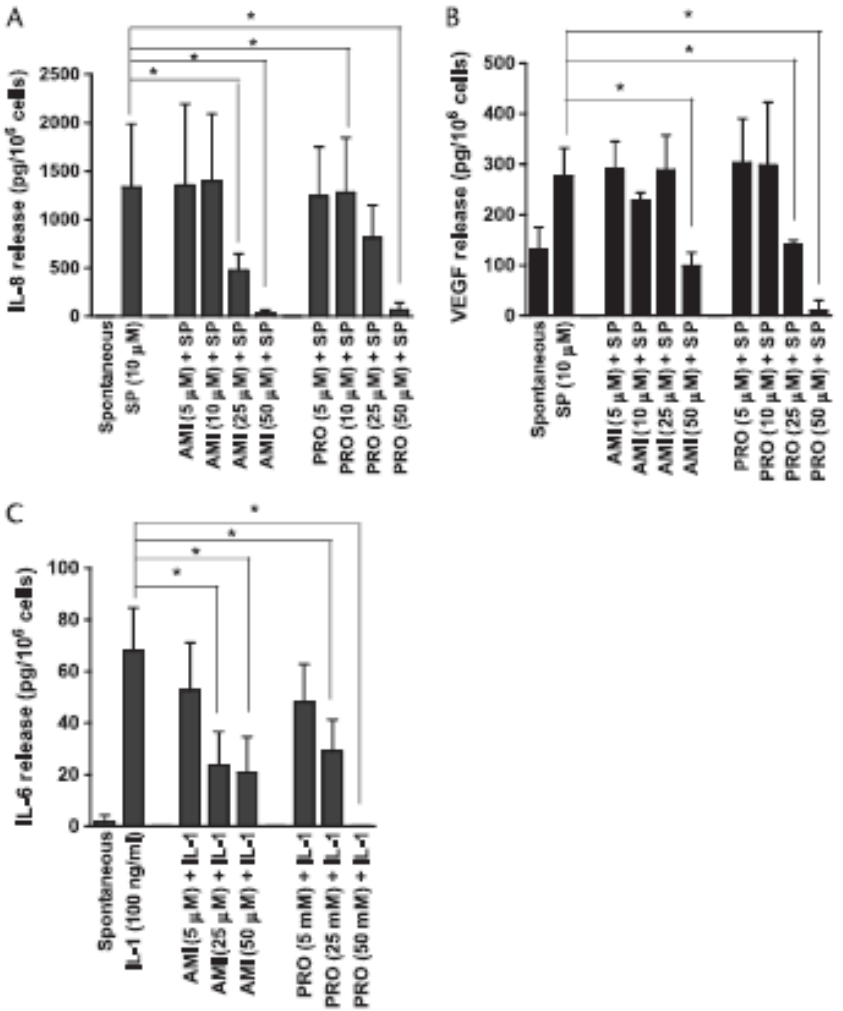
Possible Relevance to Chronic Fatigue Syndrome

To the Editors:

Chronic fatigue syndrome (CFS), a complex disorder characterized by unexplained severe fatigue for more than 6 months with a broad range of additional symptoms involving the nervous, endocrine, and immune systems and an estimated prevalence of 1%.[1] Tricyclic antidepressants (TCAs) are prescribed off label for a number of painful diseases that often are comorbid, such as CFS, fibromyalgia, interstitial cystitis, and irritable bowel syndrome, the symptoms of which are worsened by stress.[2] However, there is no known mechanism to explain the apparent beneficial action of TCAs.[3]

Mast cells and their mediators have been implicated in inflammatory diseases,[4] including CFS.[5] Mast cells are located perivascularly in proximity to neurons in the thalamus and hypothalamus, especially the median eminence,[6] where they are juxtaposed to corticotropin-releasing hormone-positive nerve processes.[7] Corticotropin-releasing hormone activates mast cells to release vascular endothelial growth factor (VEGF),[8] which could participate in neurogenic inflammation and contribute to the pathogenesis of CFS. Such mediators may be released locally in the brain or may cross the blood-brain barrier, which can be disrupted by

Amitriptyline (25 and 50 μM) inhibited (Fig. 1A) interleukin (IL) 8 release by 64.2% (from 1334 ± 267 to 478 ± 69 pg/μL) and 98.1% (from 1334 ± 267 to 25 ± 16 pg/μL; n = 3 and n = 6, $P < 0.05$), respectively. Prochlorperazine (50 μM)



Other Mediators

Leukotrienes
- Montelukast (Singulair)

Prostaglandins
- Ibuprofen
- Asetylsalicylic acid (Aspirin)

Platelet Activating Factor (PAF)
- Rupatadine (Rupafin)

Cytokines (IL-6, TNF)
- Luteolin, Quercetin

Mast cell “blockers”

- Anti-IgE (Xolair)
- Cromolyn sodium (Gastrocrom)
- Flavonoids (luteolin, quercetin)
- Ketotifen (Zaditen)
- Prochlorperazine (Compazine)
- Rupatadine (Rupafin)

Omalizumab (Xolair)

The Journal of Allergy and Clinical Immunology: In Practice

Volume 3, Issue 2, March–April 2015, Pages 162–166

Review and Feature Article

The Use of Anti-IgE Therapy Beyond Allergic Asthma

Jeffrey R. Stokes, MD[a], , Thomas B. Casale, MD[b]

Potential Mechanisms

- Neutralizes circulating IgE
- Downregulates IgE receptors
- Inhibits c-kit activation
- Interferes with other triggers

The Effectiveness of Cromolyn Varies

Evidence questioning cromolyn's effectiveness and selectivity as a 'mast cell stabilizer' in mice

Tatsuya Oka, Janet Kalesnikoff, Philipp Starkl, Mindy Tsai and Stephen J Galli

Cromolyn, widely characterized as a 'mast cell stabilizer', has been used in mice to investigate the biological roles of mast cells *in vivo*. However, it is not clear to what extent cromolyn can either limit the function of mouse mast cells or influence biological processes in mice independently of effects on mast cells. We confirmed that cromolyn (at 10 mg/kg *in vivo* or 10–100 μM *in vitro*) can inhibit IgE-dependent mast cell activation in rats *in vivo* (measuring Evans blue extravasation in passive cutaneous anaphylaxis (PCA) and increases in plasma histamine in passive systemic anaphylaxis (PSA)) and *in vitro* (measuring peritoneal mast cell (PMC) β-hexosaminidase release and prostaglandin D_2 synthesis). However, under the conditions tested, cromolyn did not inhibit those mast cell-dependent responses in mice. In mice.

Laboratory Investigation (2012) 92, 1472–1482

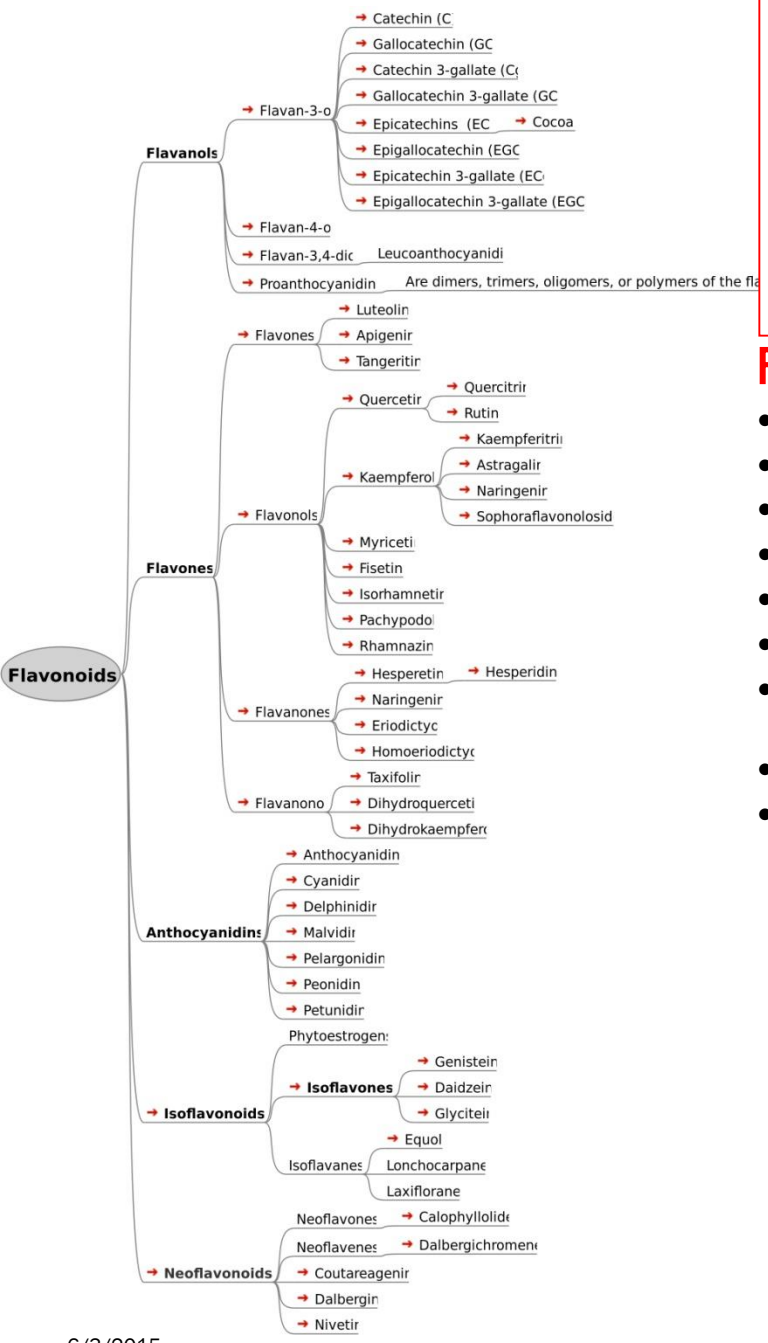
CONCISE COMMUNICATION

BJD
British Journal of Dermatology

Topical sodium cromoglicate relieves allergen- and histamine-induced dermal pruritus

R. Vieira dos Santos, M. Magerl, P. Martus,* T. Zuberbier, M.K. Church, L. Escribano† and M. Maurer

Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, 10117 Berlin, Germany
**Institute for Biostatistics and Clinical Epidemiology, Charité – Universitätsmedizin Berlin, Berlin, Germany*
†Centro de Estudios de Mastocitosis de Castilla La Mancha, Hospital Virgen del Valle, Toledo, Spain



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PHARMACOLOGICAL REVIEWS
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47/867401
Printed in U.S.A
Pharmacol Rev 52:673–751, 2000

The Effects of Plant Flavonoids on Mammalian Cells: Implications for Inflammation, Heart Disease, and Cancer

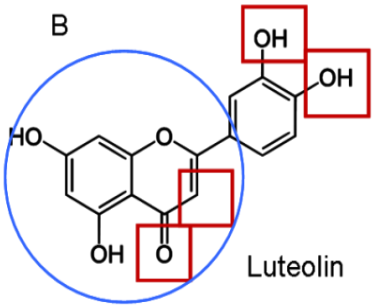
ELLIOTT MIDDLETON, JR.,† CHITHAN KANDASWAMI, AND THEOHARIS C. THEOHARIDES‡

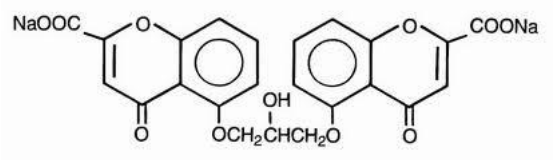
Chebeague Island Institute of Natural Product Research, Chebeague Island, Maryland (E.M., C.K.); and Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, Massachusetts (T.C.T.)

This paper is available online at http://www.pharmrev.org

Flavonoids are potent:

- Anti-oxidant
- Anti-inflammatory
- Mast cell inhibitors
- Metal chelators
- Neuroprotective
- Are lipophilic
- Less than 15% are absorbed orally
- Are metabolized in the liver
- Need to be formulated in liposomes





Cromolyn

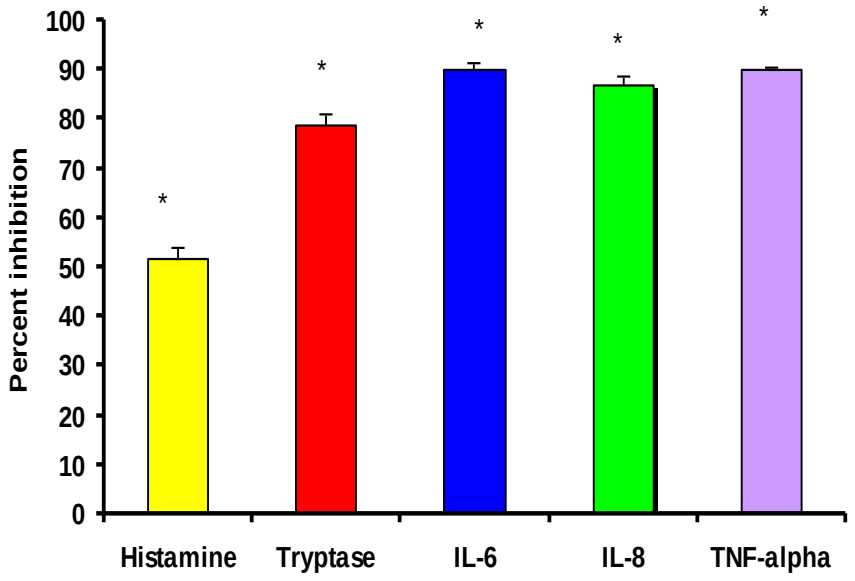
British Journal of Pharmacology (2005) 145, 934–944
www.nature.com/bjp

Flavonols inhibit proinflammatory mediator release, intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells

[1]Duraisamy Kempuraj, [1]Bhuvaneshwari Madhappan, [1]Spyridon Christodoulou, [1]William Boucher, [1,2]Jing Cao, [1]Nikoletta Papadopoulou, [3]Curtis L. Cetrulo & *,[1,2,4]Theoharis C. Theoharides

Allergic stimulation of human mast cells results in secretion of histamine, the proteolytic enzyme tryptase, and the pro-inflammatory cytokines IL-6, IL-8 and TNF-α, all of which are inhibited by luteolin.

Effect of luteolin on neurotensin-induced human mast cell secretion



British Journal of Pharmacology (2008) 153, 1383–1387

www.brjpharmacol.org

RESEARCH PAPER

The flavonoid luteolin inhibits niacin-induced flush

D Papaliodis[1], W Boucher[1], D Kempuraj[1] and TC Theoharides[1,2,3]

OPEN ACCESS Freely available online

PLOS ONE

Luteolin Inhibits Human Keratinocyte Activation and Decreases NF-κB Induction That Is Increased in Psoriatic Skin

Zuyi Weng[1,2], Arti B. Patel[1,3], Magdalini Vasiadi[1,2], Anastasia Therianou[4], Theoharis C. Theoharides[1,2,3,5]*

February 2014 | Volume 9 | Issue 2 | e90739

blood

2011 118: 5466-5475
Prepublished online September 16, 2011;
doi:10.1182/blood-2010-09-309955

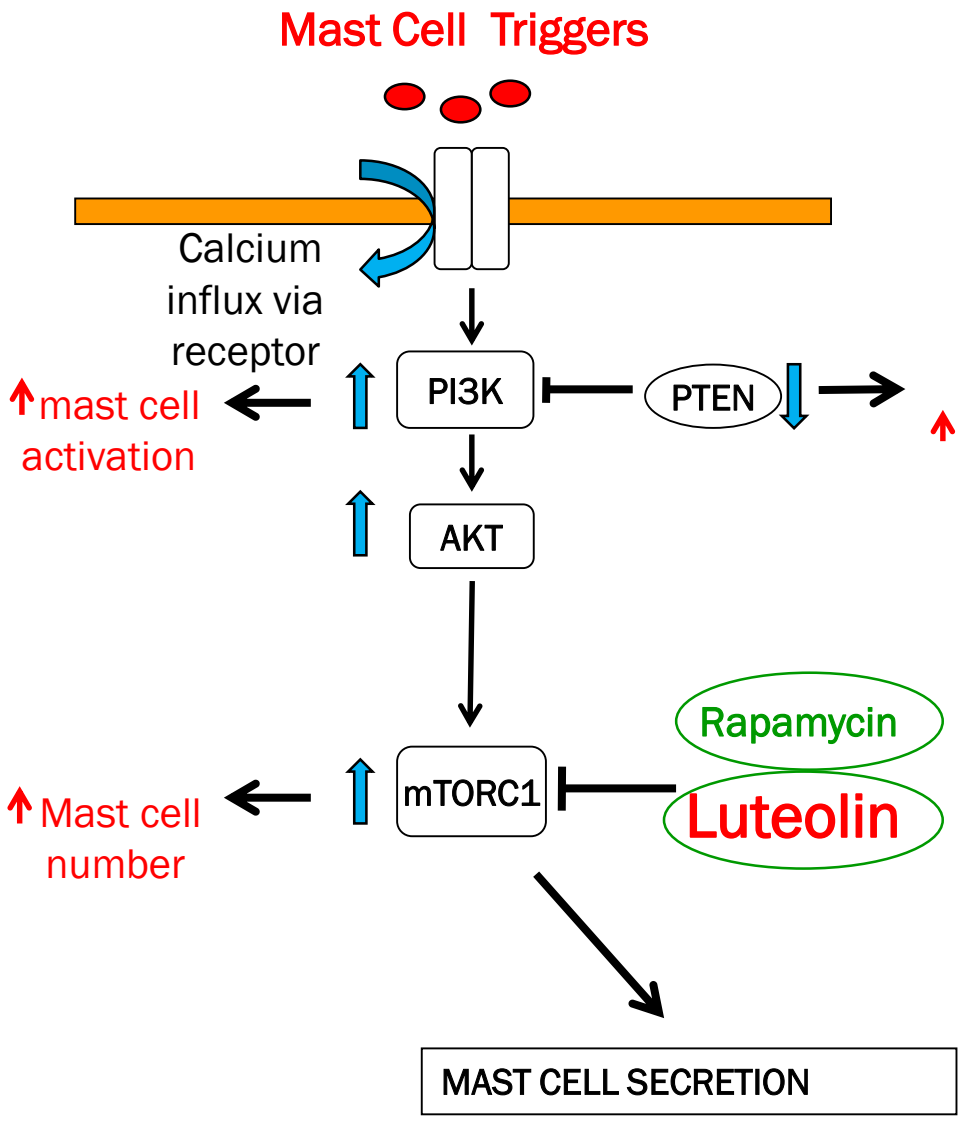
PTEN deficiency in mast cells causes a mastocytosis-like proliferative disease that heightens allergic responses and vascular permeability

Yasuko Furumoto, Nicolas Charles, Ana Olivera, Wai Hang Leung, Sandra Dillahunt, Jennifer L. Sargent, Kevin Tinsley, Sandra Odom, Eric Scott, Todd M. Wilson, Kamran Ghoreschi, Manfred Kneilling, Mei Chen, David M. Lee, Silvia Bolland and Juan Rivera

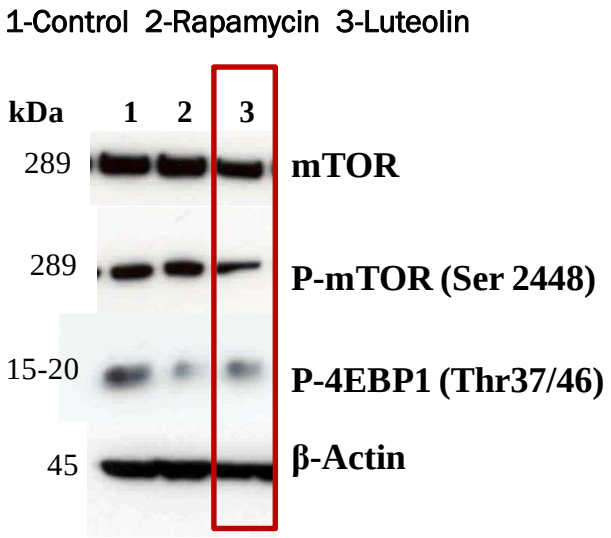
Published in final edited form as:
J Immunol. 2008 April 1; 180(7): 4586–4595.

Activation and function of the mTORC1 pathway in mast cells

Mi-Sun Kim, **Hye Sun Kuehn**, **Dean D. Metcalfe**, and **Alasdair M. Gilfillan**[2]
Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10 Center Drive MSC 1881, Bethesda, MD 20892-1881, USA.



Luteolin inhibits mTOR activation better than rapamycin



Children with Autism Spectrum Disorders Have Allergic and Food Intolerance Problems

J Autism Dev Disord (2011) 41:1579–1585
DOI 10.1007/s10803-010-1171-z

BRIEF REPORT

Brief Report: "Allergic Symptoms" in Children with Autism Spectrum Disorders. More than Meets the Eye?

Asimenia Angelidou · Konstantinos-Dionysios Alysandratos · Shahrzad Asadi · Bodi Zhang · Konstantinos Francis · Magdalini Vasiadi · Dimitrios Kalogeromitros · Theoharis C. Theoharides

Original Article
Allergy Asthma Immunol Res. 2013 September;5(5):315-321.
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AAIR
Allergy, Asthma & Immunology Research

Allergic Diseases in Preschoolers Are Associated With Psychological and Behavioural Problems

Hyoung Yoon Chang,[1†] Ju-Hee Seo,[3†] Hyung Young Kim,[2] Ji-Won Kwon,[4] Byoung-Ju Kim,[5] Hyo Bin Kim,[6] So-Yeon Lee,[7] Gwang Cheon Jang,[8] Dae Jin Song,[9] Woo Kyung Kim,[10] Jung Yeon Shim,[11] Ha-Jung Kim,[12] Jung-Won Park,[13] Sang-Heon Cho,[14] Joo-Shil Lee,[15] Yee-Jin Shin,[1*] Soo-Jong Hong,[3*]

Annals of Epidemiology 23 (2013) 185–188

Contents lists available at SciVerse ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Association between atopic diseases and attention-deficit/hyperactivity disorder in childhood: a population-based case-control study

Jeng-Dau Tsai MD[a,b], Shih-Ni Chang MS[c,d], Chih-Hsin Mou MS[c,d], Fung-Chang Sung PhD, MPH[c,d,**], Ko-Huang Lue MD, PhD[a,b,*]

Articles

Comorbidity of Allergic and Autoimmune Diseases Among Patients With ADHD: A Nationwide Population-Based Study

Journal of Attention Disorders
XX(X) 1–9

DOI: 10.1177/1087054712474686
http://jad.sagepub.com

SAGE

Mu-Hong Chen[1], Tung-Ping Su[1,2], Ying-Sheue Chen[1], Ju-Wei Hsu[1], Kai-Lin Huang[1,2], Wen-Han Chang[1], Tzeng-Ji Chen[3,4], and Ya-Mei Bai[1,2]

Journal of Neuroimmunology xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Immune allergic response in Asperger syndrome

Elizabeth S. Magalhães [a], Fernanda Pinto-Mariz [b], Sandra Bastos-Pinto [c], Adailton T. Pontes [a], Evandro A. Prado [b], Leonardo C. deAzevedo [a,*]

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Journal of Neuroimmunology 261 (2013) 77–81

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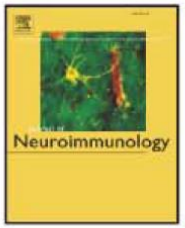
Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim



The possible relationship between allergic manifestations and elevated serum levels of brain specific auto-antibodies in autistic children ☆,☆☆

Gehan Ahmed Mostafa [a,b,*], Laila Yousef Al-Ayadhi [b]

(12) **United States Patent**
Theoharides

(10) **Patent No.: US 8,268,365 B2**
(45) **Date of Patent: *Sep. 18, 2012**

(54) **ANTI-INFLAMMATORY COMPOSITIONS FOR TREATING BRAIN INFLAMMATION**

(75) Inventor: **Theoharis C. Theoharides**, Brookline, MA (US)

(73) Assignee: **Theta Biomedical Consulting & Development Co., Inc.**, Brookline, MA (US)

5,876,744	A	3/1999	Della Valle et al.
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Clinical Therapeutics/Volume 35, Number 5, 2013 · Atopic Clinical Entities Update

Original Research

An Open-Label Pilot Study of a Formulation Containing the Anti-Inflammatory Flavonoid Luteolin and Its Effects on Behavior in Children With Autism Spectrum Disorders

Anilia Taliou, MD[1]; Elias Zintzaras, MSc, PhD[2]; Lefteris Lykouras, MD, PhD[1]; and Kostantinos Francis, MD, PhD[1]

[1]*Second Department of Psychiatry, Athens University Medical School, "Attikon" General Hospital, Athens, Greece; and* [2]*Department of Mathematics and Bioinformatics, University of Larissa, Larissa, Greece*

Children with ASDs (n=40) completed the protocol. There was significant ($p<0.005$) improvement in adaptive functioning as measured by the VABS age-equivalent scores:

- -8.43 months-communication domain
- -7.17 months daily living skills
- -8.00 months-social domain

There was overall behavior (34.8%) improvement in the Aberrant Behavior Checklist (ABC)

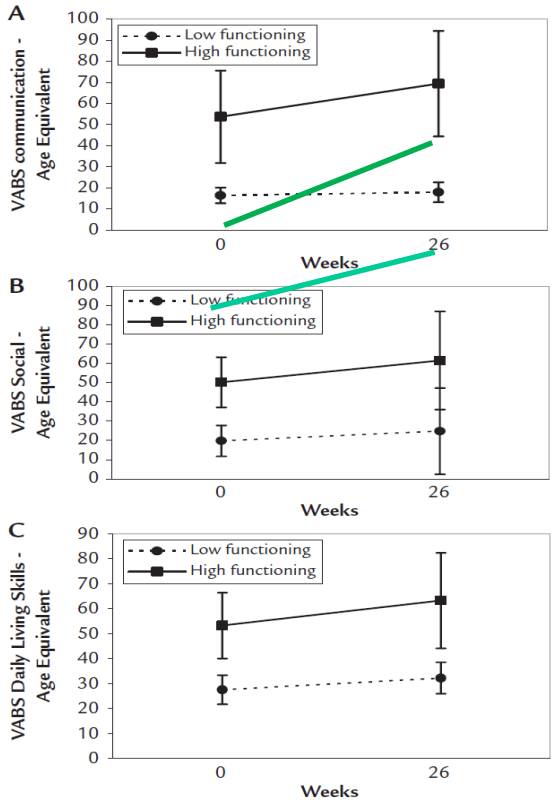


Figure. Effect of baseline functioning on age-equivalent scores from the 3 domains of the Vineland Adaptive Behavior Scales (VABS): (A) communication, (B) social, and (C) daily living skills. Low functioning = baseline score below the median; high functioning = baseline score above the median.

Other Drugs

Cytoreductive agents

- 5-Hydroxyurea
- Interferon-alpha

Tyrosine kinase inhibitors

- Amatinib (Glyvec-useful if no c-kit mutation)
- Dasatinib (Early trials disappointing)
- Midostaurin, staurosporin (ongoing trials)

Flavonoids

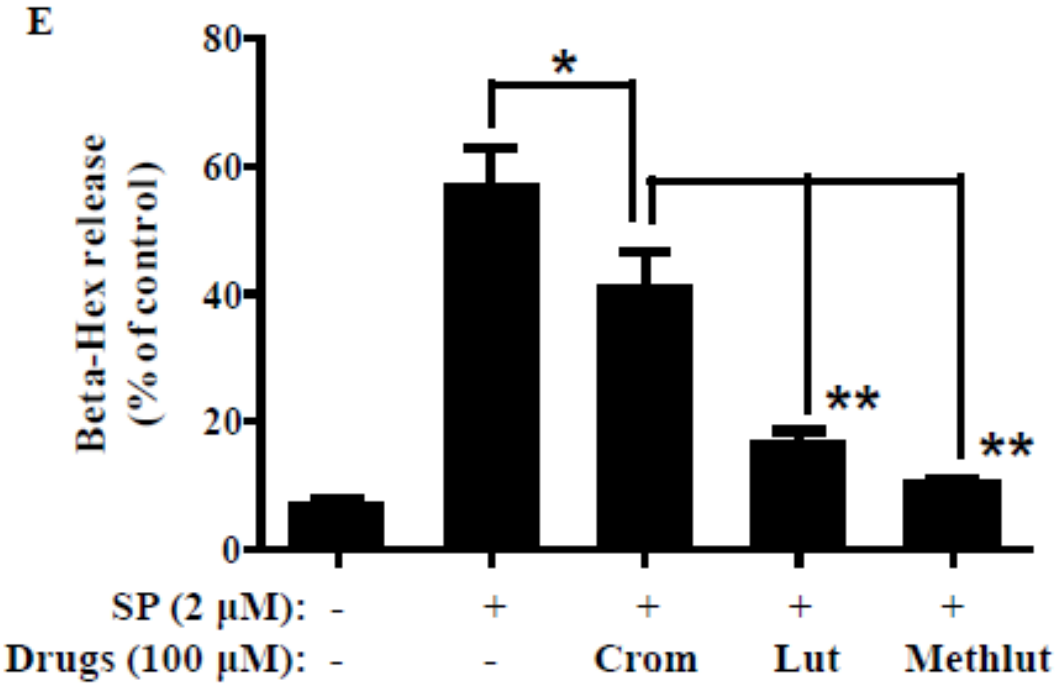
- Methoxyluteolin (experimental)
  (c-kit, IP3K, mTOR inhibitor)

The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells

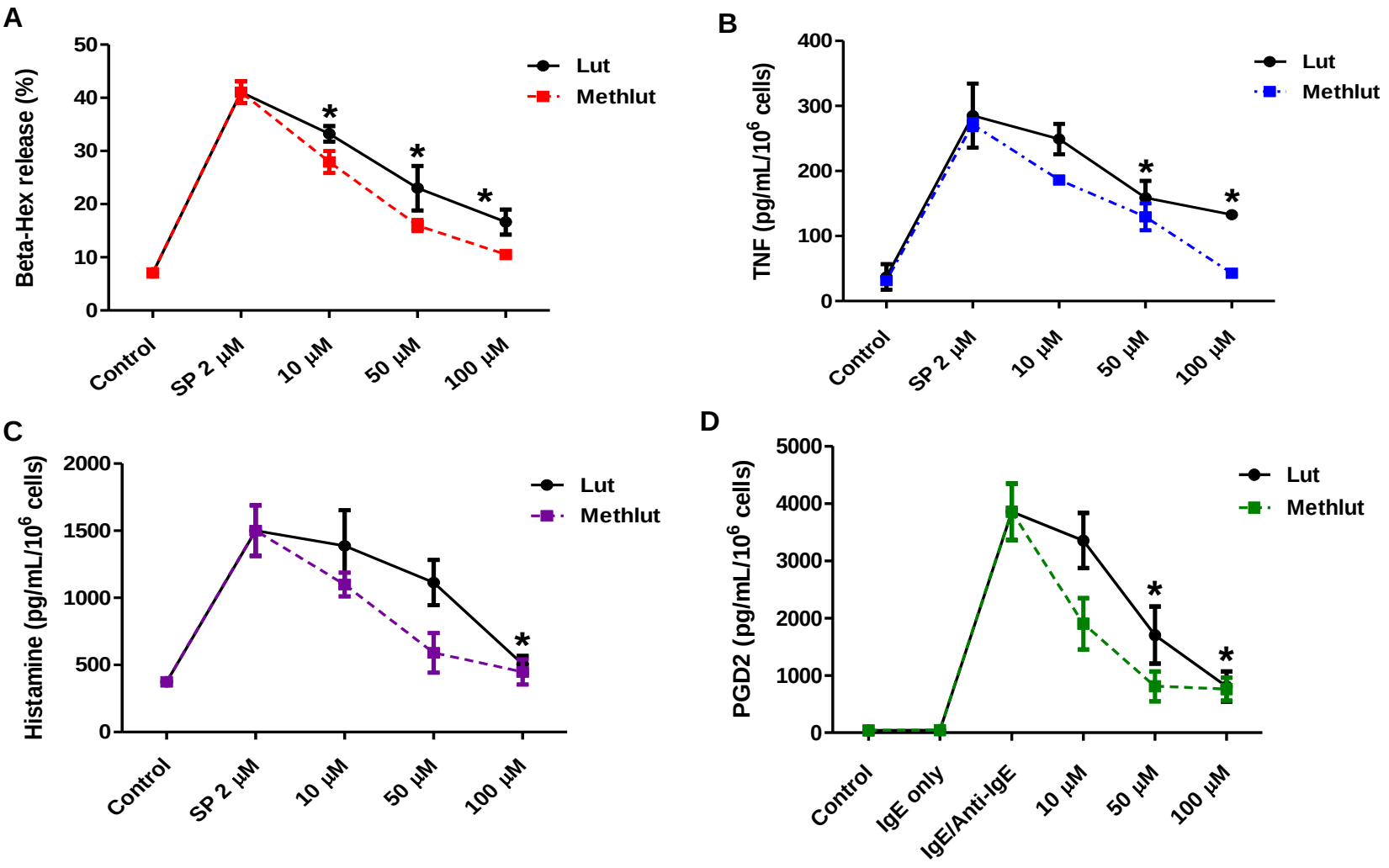
Zuyi Weng, MS, PhD,[a,b] Arti B. Patel, MS,[a,c] Smaro Panagiotidou, MA,[a] and Theoharis C. Theoharides, MS, PhD, MD[a,b,c,d] *Boston, Mass*

Background: Mast cells (MCs) are hematopoietic cells that mature in tissues and are involved in allergy, immunity, and inflammation by secreting multiple mediators. The natural

Conclusion: Methlut is a promising MC inhibitor for the treatment of allergic and inflammatory conditions. (J Allergy Clin Immunol 2014;■■:■■-■■.)



Effect of Luteolin and Methoxyluteolin on MC Secretion



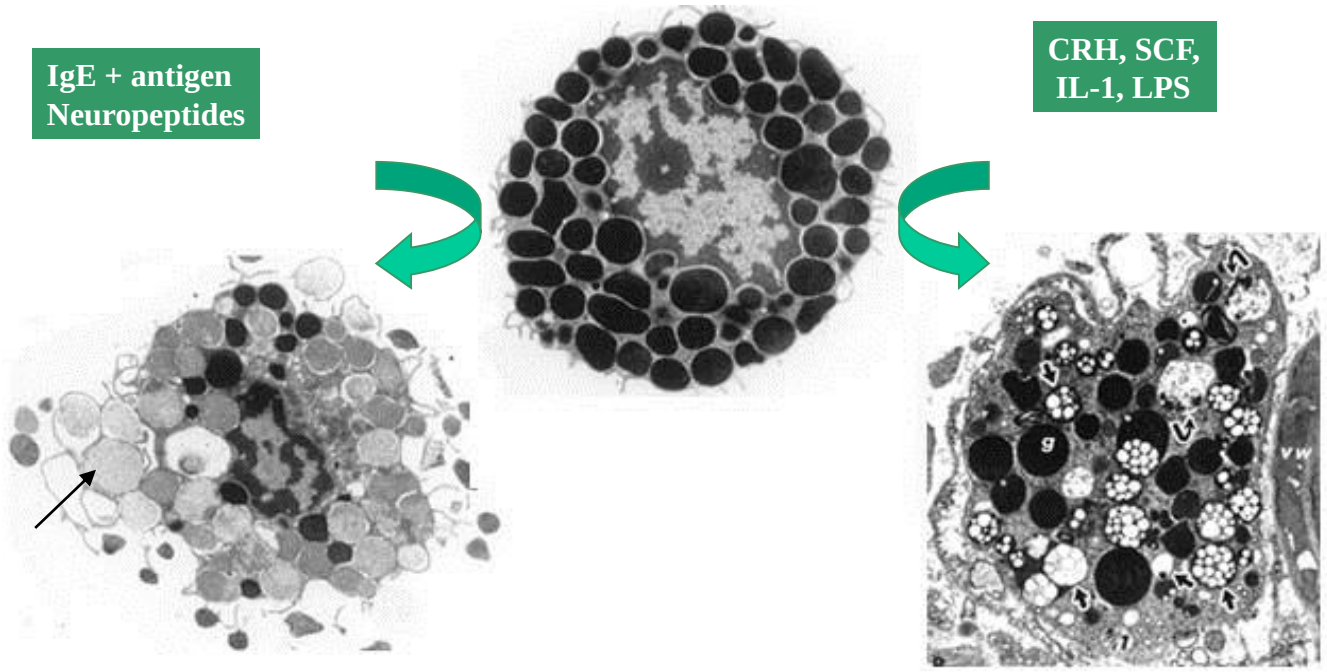
Flavonoids
30 min

Trigger
30 min

Topical

- Hydrocortisone (rarely useful)
- Doxepine (Zonalon)
- Cromolyn (Homemade)
- Methoxyluteolin (GentleDerm)

Divergent Actions of Mast Cells



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- Jane B Johnson Fnd.

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