The Mast Cell: A Cell for All Seasons

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www.mastcellmaster.com

www.autismfreebrain.org

www.brain-gate.org

What Are Mast Cells and What is Mastocytotsis?

Allergies

Angioneurotic edema

Atopy

Atopic dermatitis

Eczema

Food allergy

Food intolerance

Idiopathic urticaria

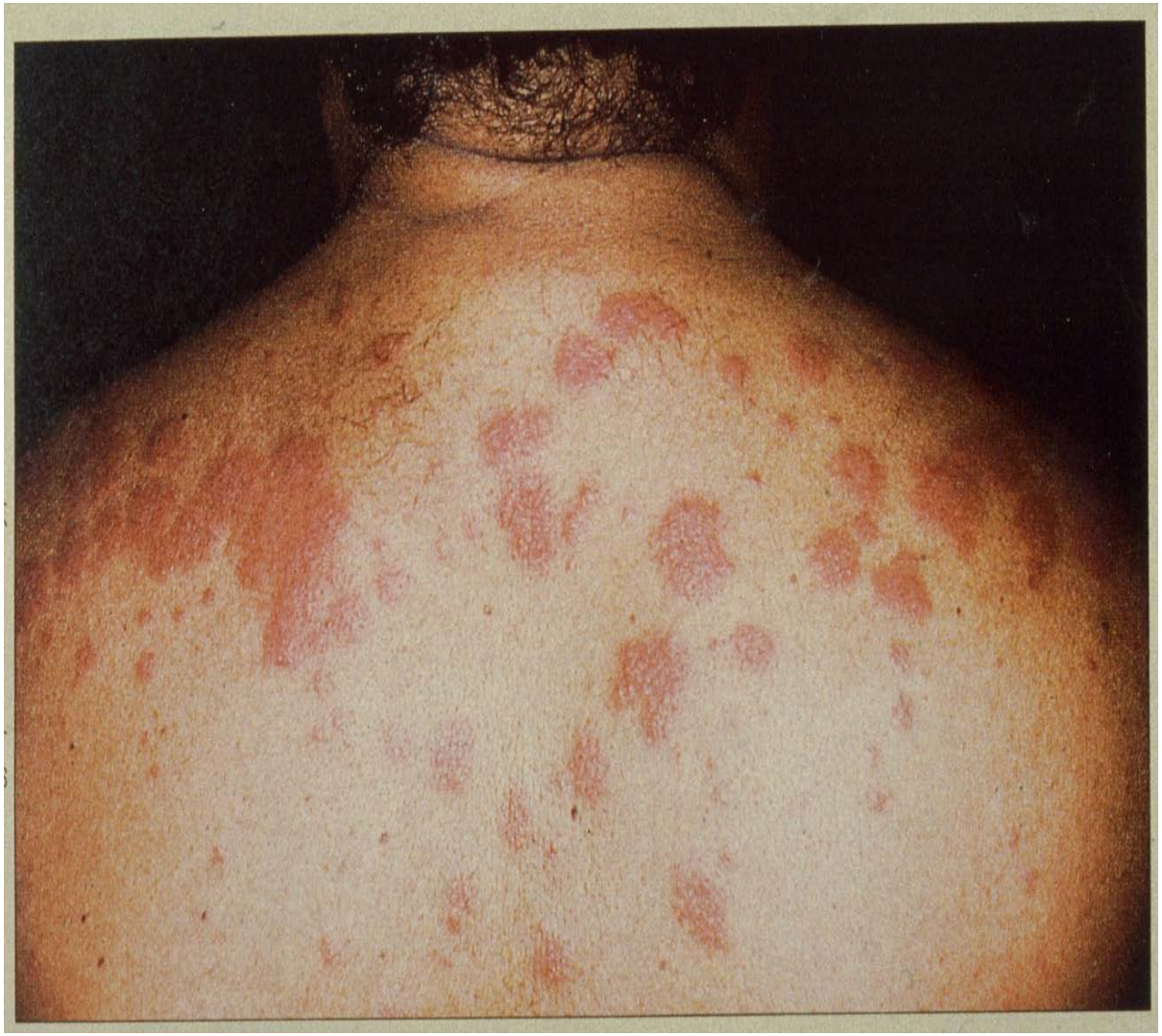
Idiopathic mast activation disorder

Mastocytosis

Mast cell activation syndrome

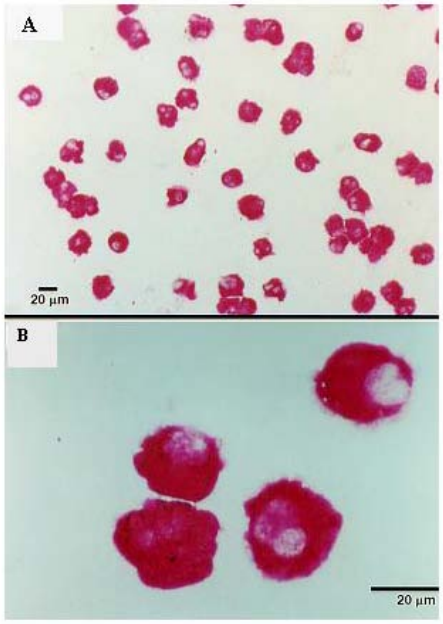
Non-IgE food allergy

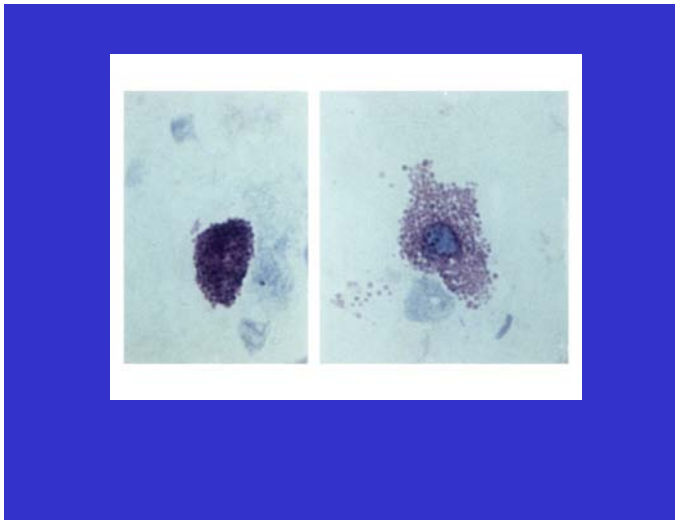
Histamine and kinins are responsible for the cardinal signs of inflammation, the "Triple Response of Lewis": Swelling Heat Pain (wheal owing to local edema, flare due to axon reflexes) as well as itching (pruritus)

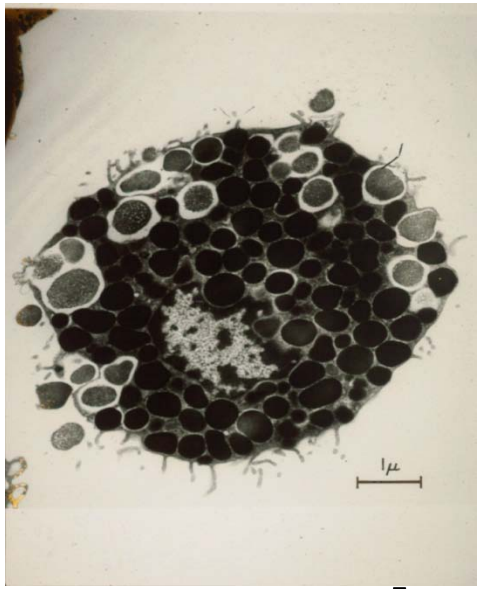


Allergic hives (urticarial wheals)

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

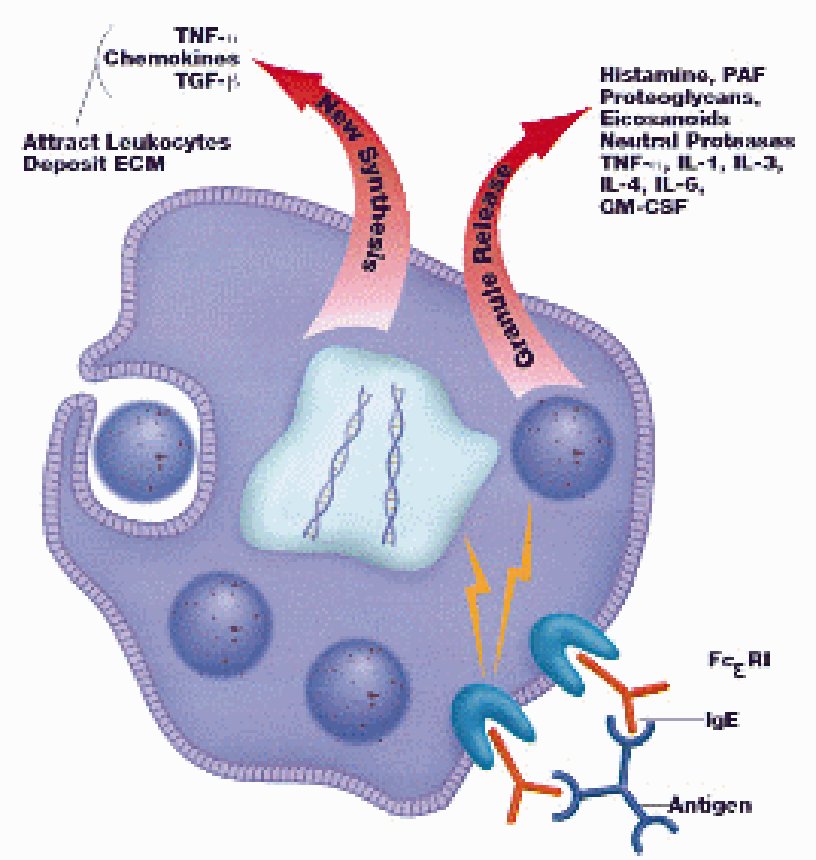


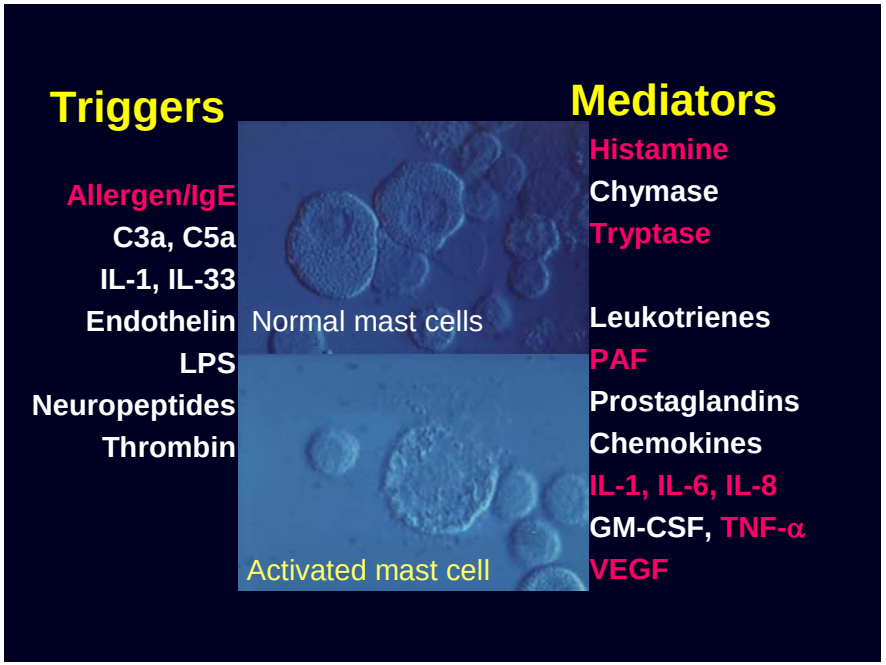




Mast Cell Activation

Nomarski Optics

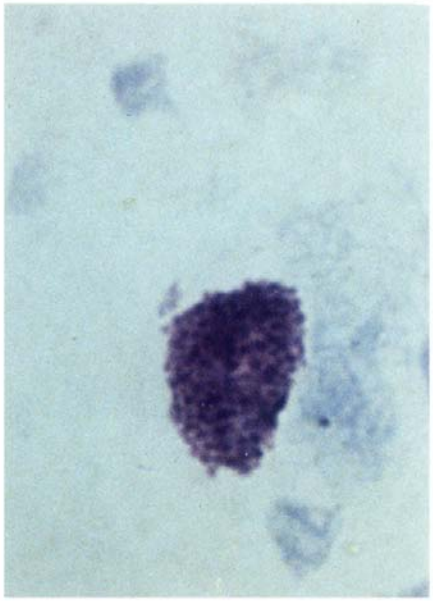


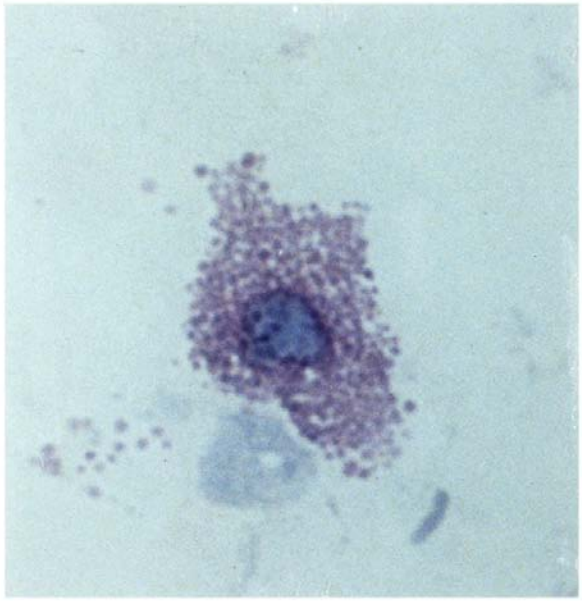


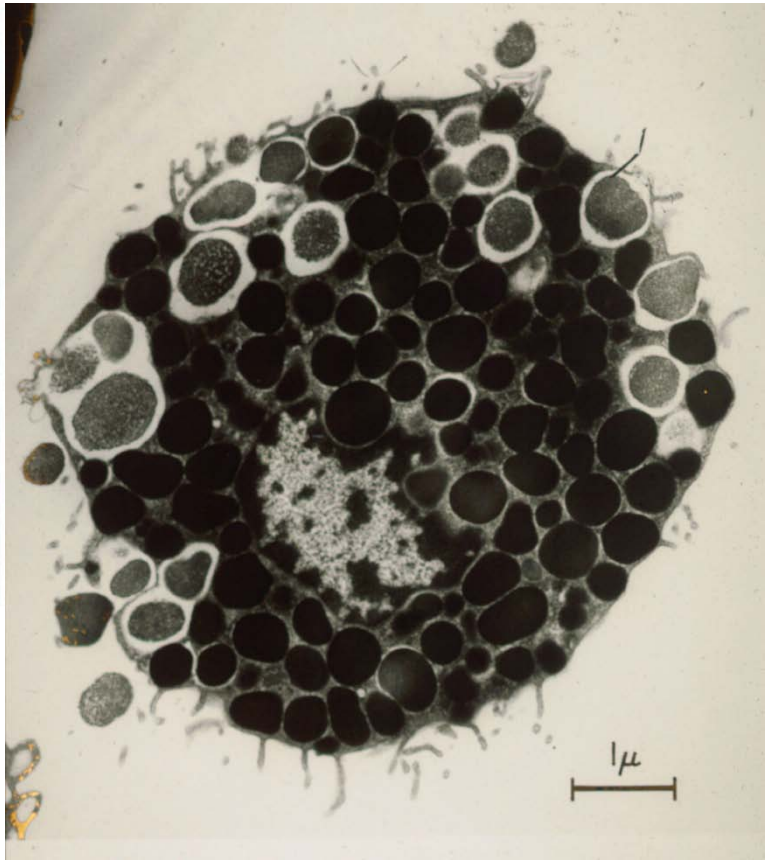
Mast cell degranulation leads to the release of mediators with potent

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

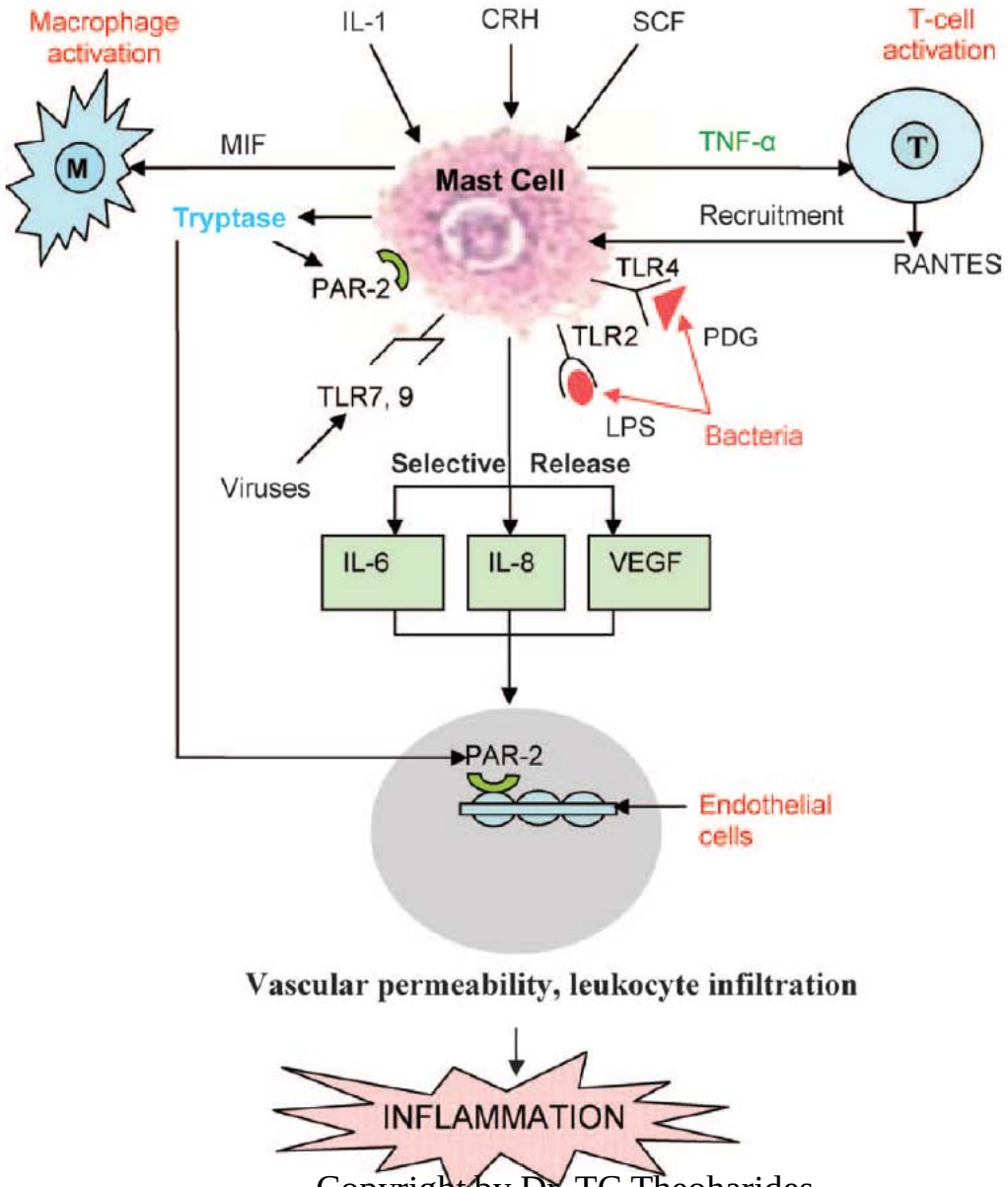
Typical Skin Mast Cell Degranulation







Mast Cells Communicate with Many Pathogens and Other Immune Cells



Contents lists available at ScienceDirect

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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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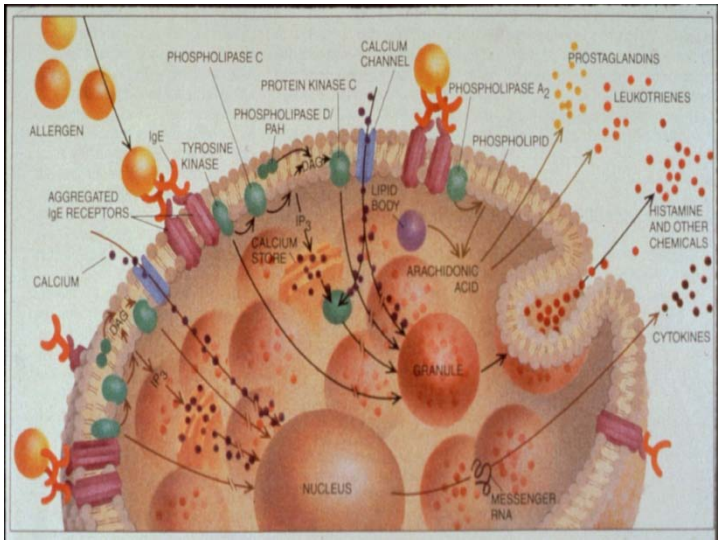
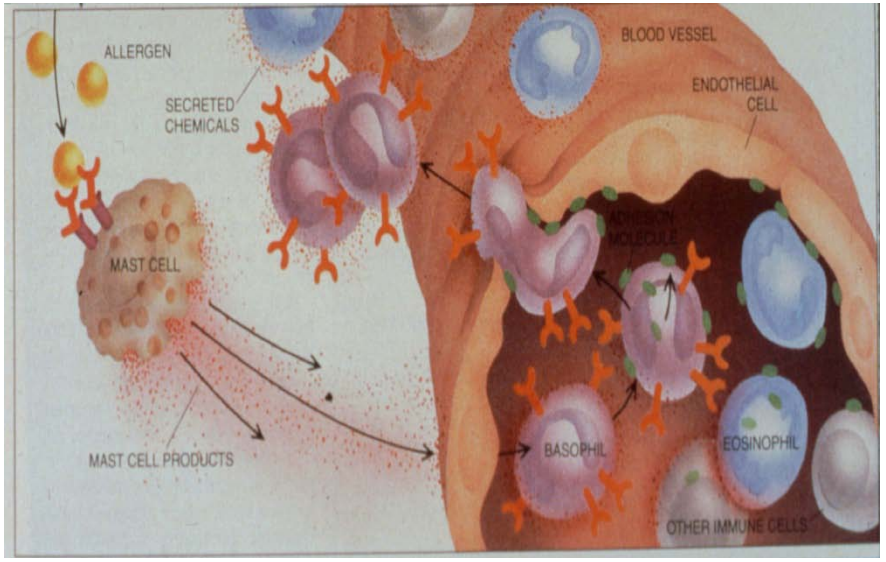




Box 1. Diagnostic criteria for mast cell activation disorders

Clinical signs and symptoms related to recurrent or chronic systemic MC activation (affection of at least two organ systems)

- Dermatologic: flushing, pruritus, urticaria pigmentosa, angioedema, *dermatographism*
- Respiratory: wheezing, sore throat, stridor
- Cardiovascular: chest pain, hypotension, tachycardia
- Gastrointestinal: abdominal pain, nausea, vomiting, diarrhea, bloating, malabsorption, esophagitis
- Naso-ocular: nasal stuffiness, pruritus.
- Neurologic: headache, memory and concentration difficulties/brain fog, paresthesia, peripheral neuropathy
- Musculoskeletal: bone/muscle pain, degenerative disc disease, osteoporosis/osteopenia g
- Systemic: anaphylaxis, fatigue

Box 2. Classification of mast cell activation disorders.

Primary

- Systemic mastocytosis (indolent, aggressive, *AHNMD*)
- Cutaneous mastocytosis (urticaria pigmentosa, diffuse, telangiectasia macularis eruptiva perstans)
- Mast cell leukemia
- Mast cell sarcoma
- Extracutaneous mastocytoma (benign)
- Monoclonal mast cell activation syndrome

Secondary

- IgE-mediated hypersensitivity reactions (e.g., food, insect anaphylaxis)
- Drug induced (e.g., vancomycin, opioids, taxanes, muscle relaxants, adenosine, nonsteroidal anti-inflammatory)
- Mast cell hyperplasia (related with chronic infections, neoplasia, autoimmune conditions due to a possible excess of stem cell factor)

Idiopathic

- Mast cell activation syndrome or nonclonal mast cell activation disorder
- Idiopathic anaphylaxis

AHNMD: Associated with a hematological nonmast cell lineage disease.
Data taken from [33,37].

Table 1. Diagnostic criteria for the establishment of systemic mastocytosis.

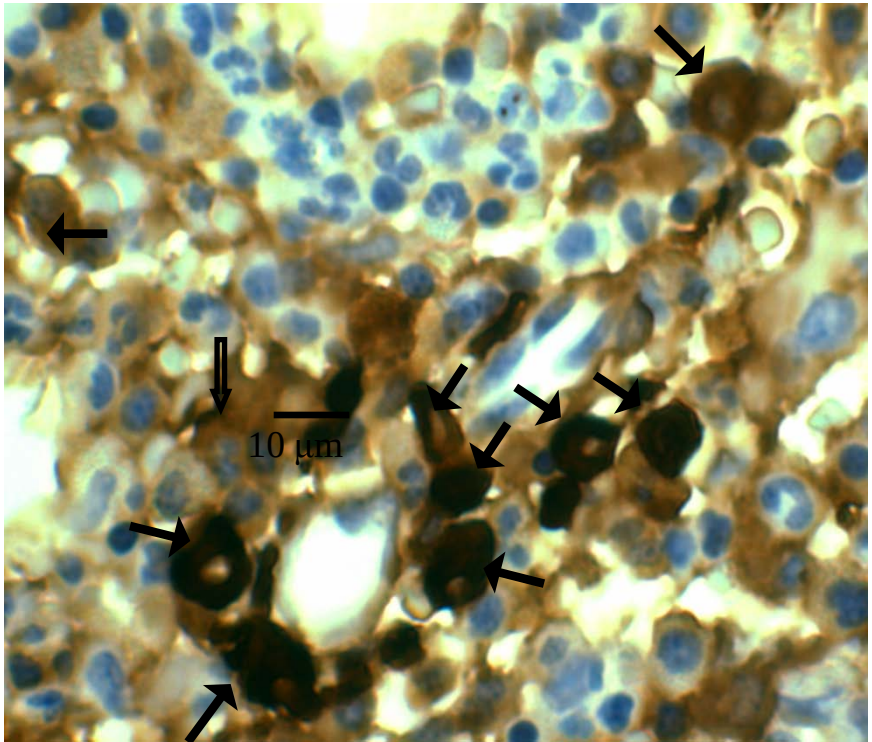
Major criterion	Multifocal, dense infiltrates of mast cells (≥ 15 mast cells in aggregates) detected in intramedullary biopsy sections and/or extramedullary organ(s)
Minor criteria	In intramedullary biopsy sections or other extramedullary ones, >25% of the mast cells in the infiltrate are spindle shaped or have atypical morphology, or of all mast cells in bone marrow aspirate smears, >25% are immature or atypical. Activating point mutation of c-KIT at codon 816 (usually KIT D816V) in bone marrow, blood or other extracutaneous organ. Aberrant immunophenotype of mast cells of CD_2 and/or CD_{25} in bone marrow, blood or other extracutaneous organ, in addition to normal mast cell markers. Persistently elevated baseline serum total tryptase (>20 ng/ml). In the occasion that a clonal myeloid disease exists, this criterion is considered invalid.

MCAD: Mast cell activation disorder.
Data taken from [45].

Table 2. Mast cell activation disorders and related immunohistochemical findings of bone marrow trephine biopsy specimens.

MCADs	Immunohistochemical findings of bone marrow trephine biopsy specimens
SM (mainly indolent/bone marrow mastocytosis, rarer aggressive or leukemic)	Multifocal compact mast cell infiltrates
SM (indolent/bone marrow mastocytosis)	Increase in loosely scattered spindle-shaped mast cells with CD25 expression, KIT D816V mutation and chronically elevated serum tryptase, but without compact tissue infiltrates
MMAS	Increase in loosely scattered spindle-shaped mast cells with KIT D816V mutation, ambiguous presence of CD25 (±) and normal serum tryptase
Secondary (mast cell hyperplasia) and Idiopathic MCAD	Increase in loosely scattered round mast cells without CD25 and KIT D816V

MCAD: Mast cell activation disorder; MMAS: Monoclonal MC activation syndrome; SM: Systemic mastocytosis.
Data taken from [45].



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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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,*]

OPEN ACCESS Freely available online

PLOS ONE

Familial Occurrence of Systemic Mast Cell Activation Disease

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1 Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany, 2 German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany, 3 Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany, 4 Department of Psychiatry, University of Bonn, Bonn, Germany, 5 Institute for Medical Biometry, Informatics and Epidemiology, University Hospital of Bonn, Bonn, Germany

Abstract

Systemic *mast cell activation disease* (MCAD) comprises disorders characterized by an enhanced release of mast cell mediators accompanied by accumulation of dysfunctional mast cells. Demonstration of familial clustering would be an important step towards defining the genetic contribution to the risk of systemic MCAD. The present study aimed to quantify familial aggregation for MCAD and to investigate the variability of clinical and molecular findings (e.g. somatic mutations in KIT) among affected family members in three selected pedigrees. Our data suggest that systemic MCAD pedigrees include more systemic MCAD cases than would be expected by chance, i.e., compared with the prevalence of MCAD in the general population. The prevalence of MCAD suspected by symptom self-report in first-degree relatives of patients with MCAD amounted to approximately 46%, compared to prevalence in the general German population of about 17% ($p<0.0001$). In three families with a high familial loading of MCAD, the subtype of MCAD and the severity of mediator-related symptoms varied between family members. In addition, genetic alterations detected in *KIT* were variable, and included mutations at position 816 of the amino acid sequence. In conclusion, our data provide evidence for common familial occurrence of MCAD. Our findings observed in the three pedigrees together with recent reports in the literature suggest that, in familial cases (i.e., in the majority of MCAD), mutated disease-related operator and/or regulator genes could be responsible for the development of somatic mutations in KIT and other proteins important for the regulation of mast cell activity. Accordingly, the immunohistochemically different subtypes of MCAD (i.e. mast cell activation syndrome and systemic mastocytosis) should be more accurately regarded as varying presentations of a common generic root process of mast cell dysfunction, than as distinct diseases.

EXPERT REVIEWS

Spectrum of mast cell activation disorders

Expert Rev. Clin. Immunol. 10(6), 000–000 (2014)

Anastasia Petra[1], Smaro Panagiotidou[1], Julia Stewart[1,2], Pio Conti[3] and Theoharis C Theoharides*[1,4,5]

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Mast cell activation disorders present with multiple symptoms including flushing, pruritus, hypotension, gastrointestinal complaints, irritability, headaches, concentration/memory loss and neuropsychiatric issues. These disorders are classified as: (1) cutaneous and systemic mastocytosis (SM) with a c-kit mutation, and clonal mast cell activation disorder, (2) allergies, urticarias and inflammatory disorders, and (3) mast cell activation syndrome (MCAS), idiopathic urticaria and angioedema. MC are activated by IgE, but also by cytokines, environmental, food, infectious, drug and stress triggers, leading to secretion of multiple mediators. The symptom profile and comorbidities associated with these disorders, such as chronic fatigue syndrome and fibromyalgia, are confusing. We propose the use of the term "spectrum" and highlight the main symptoms, useful diagnostic tests and treatment approaches.

KEYWORDS: antihistamines • brain • c-kit mutation • IgE • inflammation • mast cell • mastocytosis • mediators • tryptase

Mast Cell Degranulation Video

Can mast cells secrete mediators selectively?

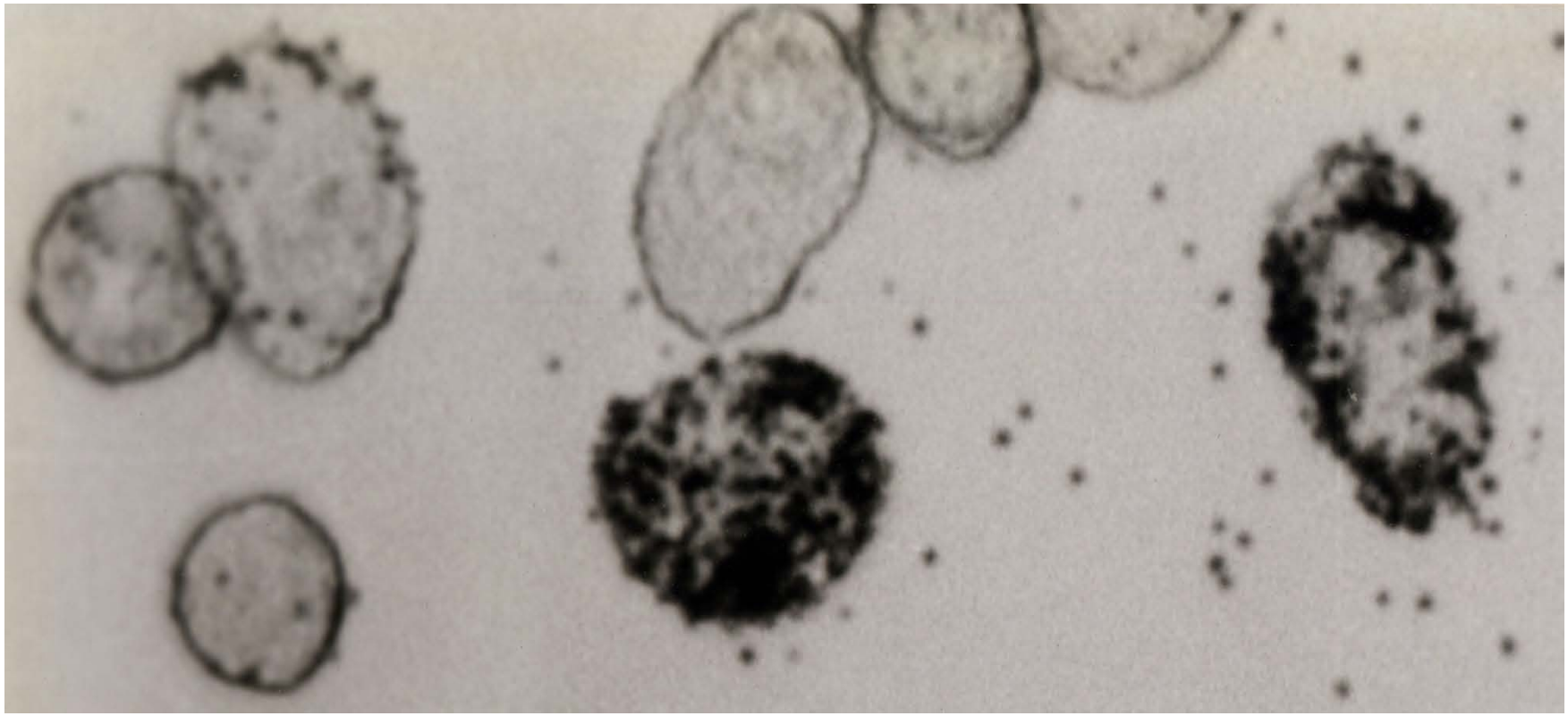
Dig Dis Sci
DOI 10.1007/s10620-013-2988-z

EDITORIAL

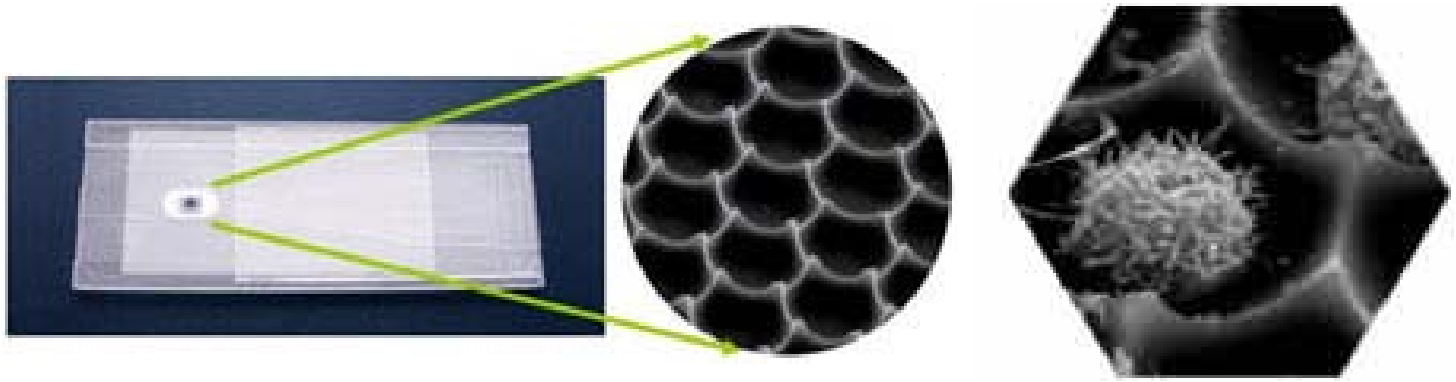
Mast Cells in Irritable Bowel Syndrome and Ulcerative Colitis: Function Not Numbers Is What Makes All the Difference

Theoharis C. Theoharides

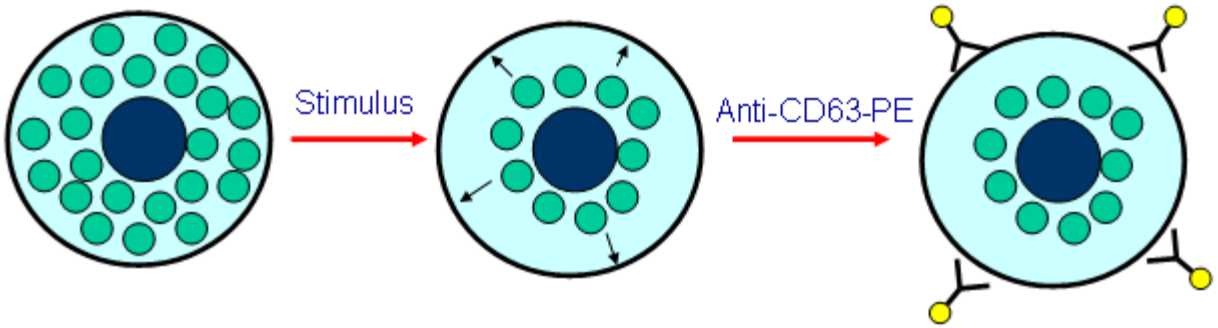
Human mast cells have heterogeneous response to non-maximally activating stimulus



Single cell degranulation assay

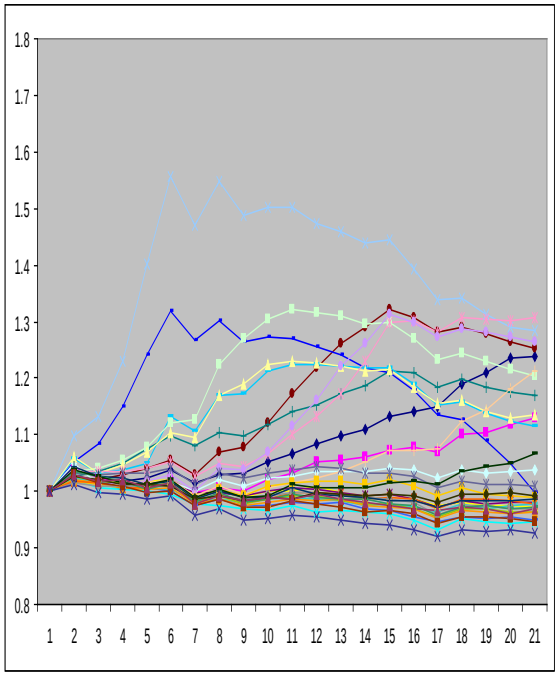


- Utilizes fluorescently-tagged anti-CD63

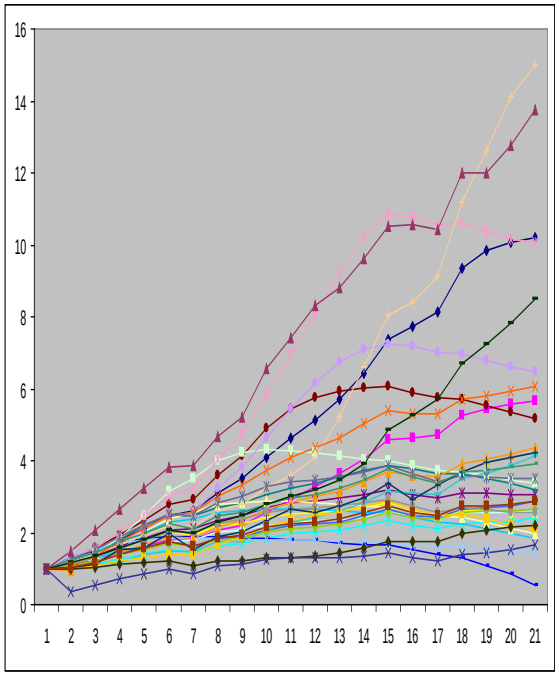


Multiple Measurements in Individual Human Mast Cells Using the Live Cell Array

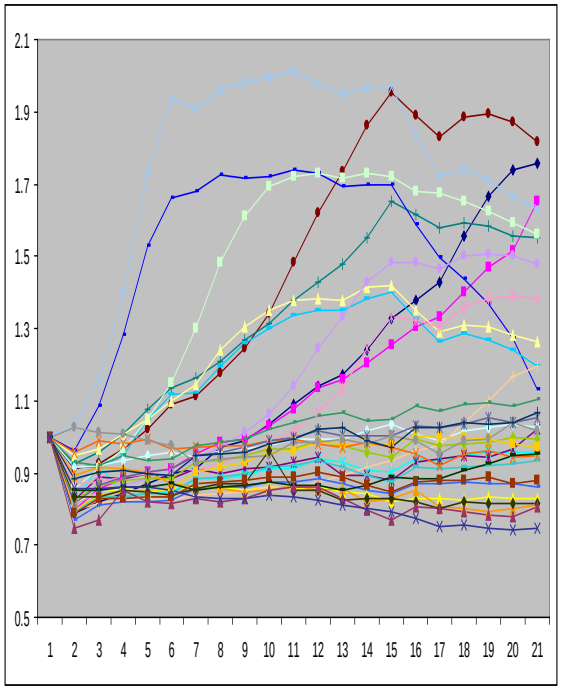
Relative fluorescence



Degranulation



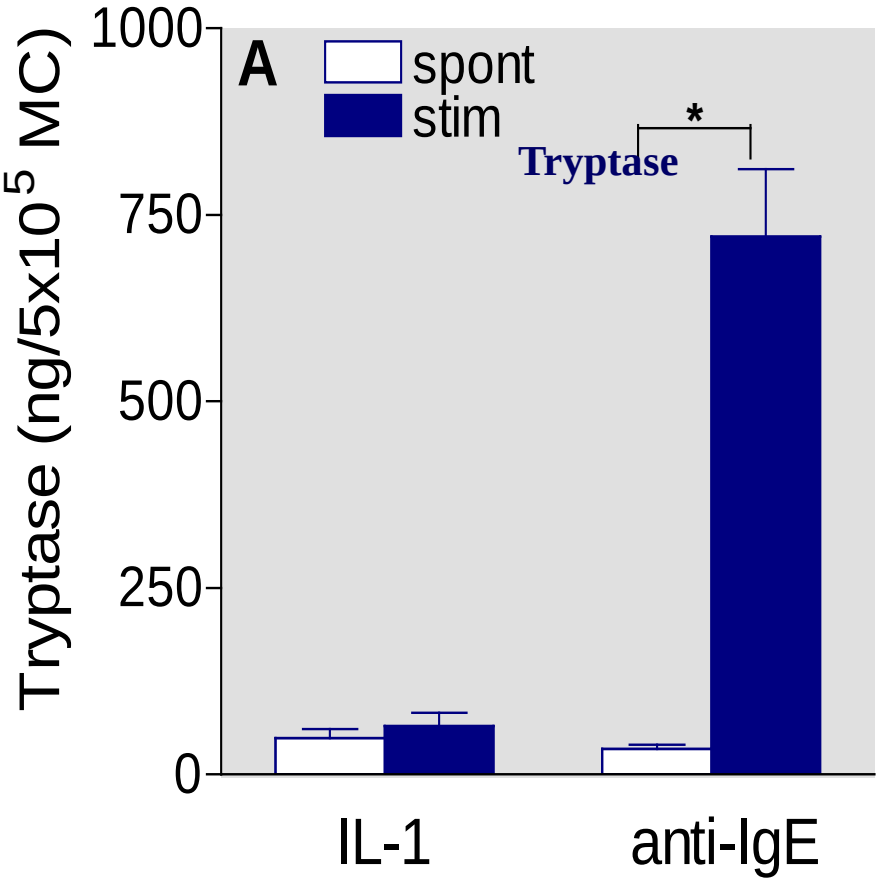
ROS

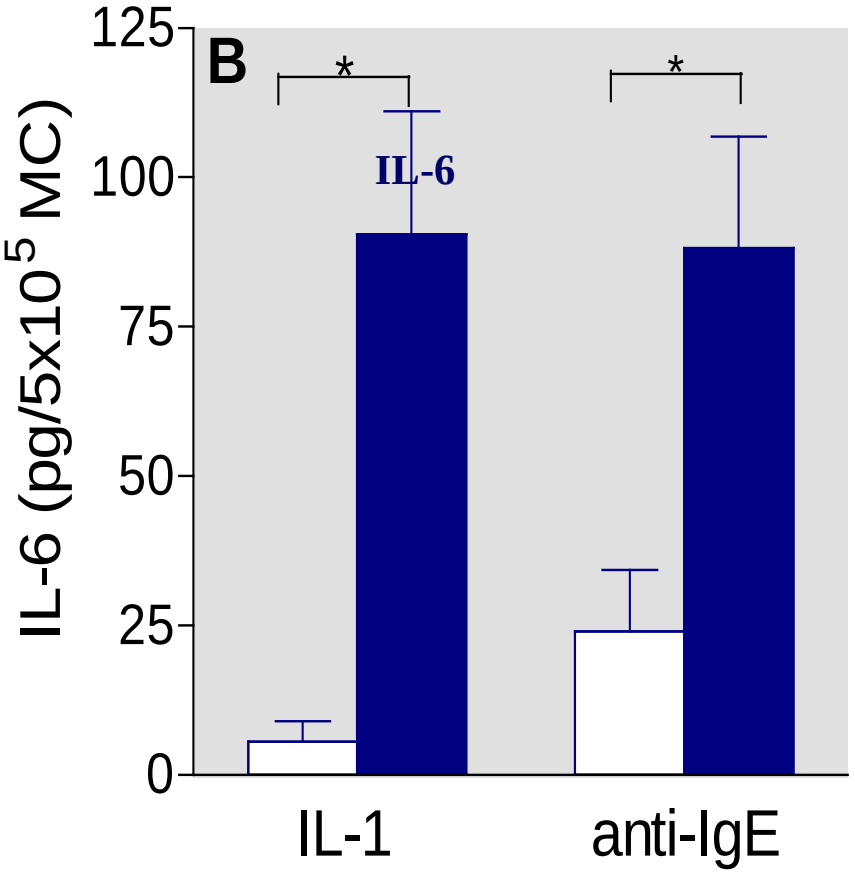


Calcium

IL-1 Stimulates Differential Release of IL-6 Without Degranulation

8-16 wk hCBMCs + IL-1 6 hours → cell free supernatants → assay IL-6 (ELISA) or tryptase (fluoroimmunoenzyme assay).





n=6, *p<0.05 paired t-test

Ultrastructural Cryo-immunocytochemistry of IL-6 Released from a Mast Cell Stimulated with IL-1

The secretory vesicle is 1/10th the diameter of that of secretory granules

140 nm

Theoharis C. Theoharides
Duraisamy Kempuraj
Michael Tagen
Pio Conti
Dimitris Kalogeromitros

Differential release of mast cell mediators and the pathogenesis of inflammation

Immunological Reviews 2007
Vol. 217: 65–78

- **Mast cells can be activated by *bacterial or viral antigens, cytokines, growth factors, neuropeptides and stress hormones*, leading to *selective* release of distinct mediators without degranulation.**
  - **Trigger** | **Mediator** | **Pathpophysiologic Implications**

Trigger	Mediator	Pathpophysiologic Implications
CRH	VEGF	Disrupts BBB
IL-1	IL-6	Th-17 cell maturation
IL-33	IL-6, VEGF	Disrupt BBB
LPS	TNF-a	Th-17 cell maturation
SCF	TGF-beta	Th-17 cell maturation
TLR-9	IL-6	Th-17 cell maturation

Mast Cell Function is Not Static

IL-33 augments substance P–induced VEGF secretion from human mast cells and is increased in psoriatic skin

Theoharis C. Theoharides[a,b,c,d,1], Bodi Zhang[a,b,2], Duraisamy Kempuraj[a,2], Michael Tagen[a,2,3], Magdalini Vasiadi[a,d], Asimenia Angelidou[a], Konstantinos-Dionysios Alysandratos[a], Dimitris Kalogeromitros[d], Shahrzad Asadi[a], Nikolaos Stavrianeas[e], Erika Peterson[f], Susan Leeman[g,1], and Pio Conti[h]

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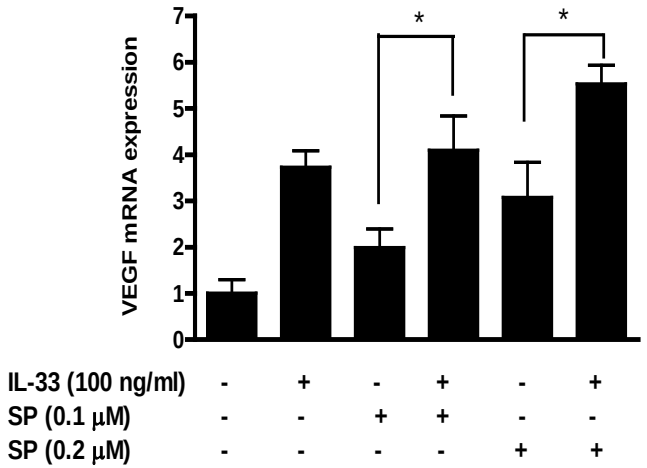
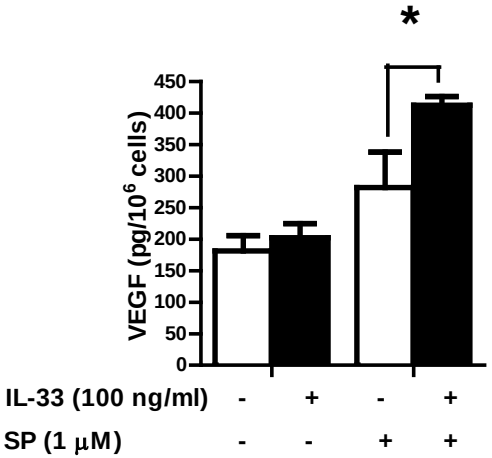
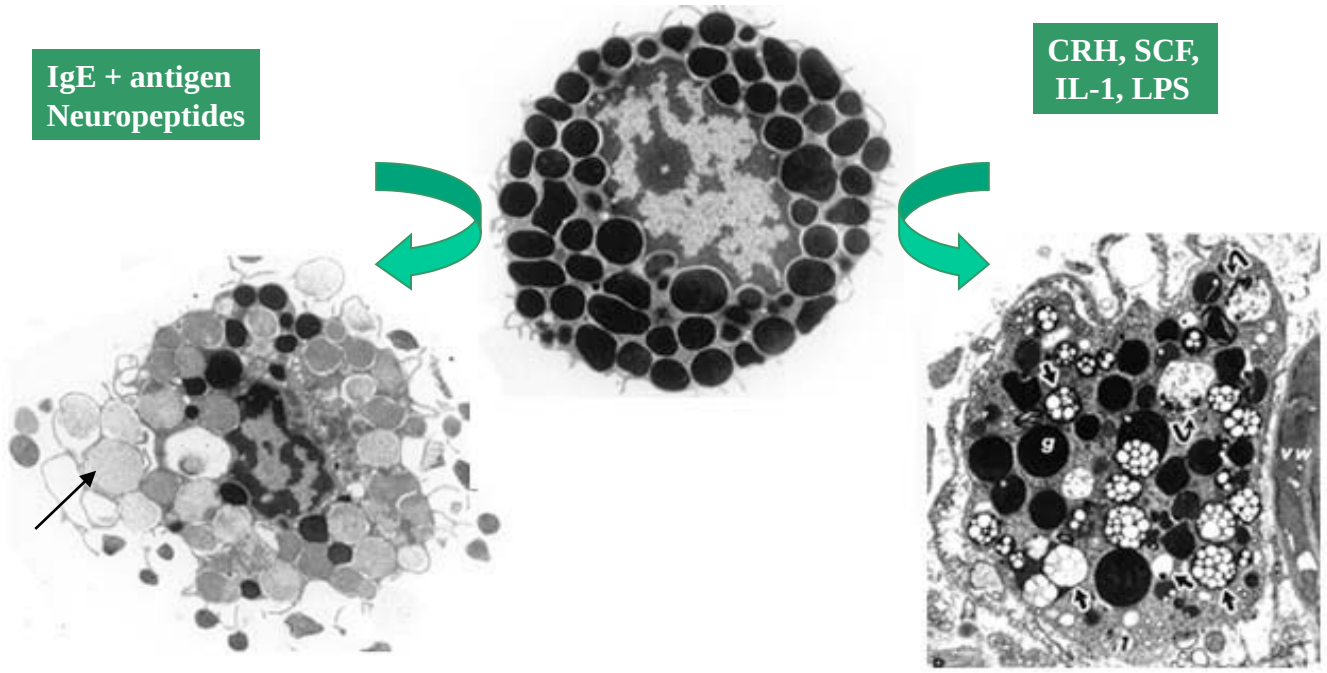
4448–4453 | PNAS | March 2, 2010 | vol. 107 | no. 9





Divergent Actions of Mast Cells



ANAPHYLACTIC DEGRANULATION

DIFFERENTIAL RELEASE WITHOUT DEGRANULATION

Allergic and anaphylactic responses

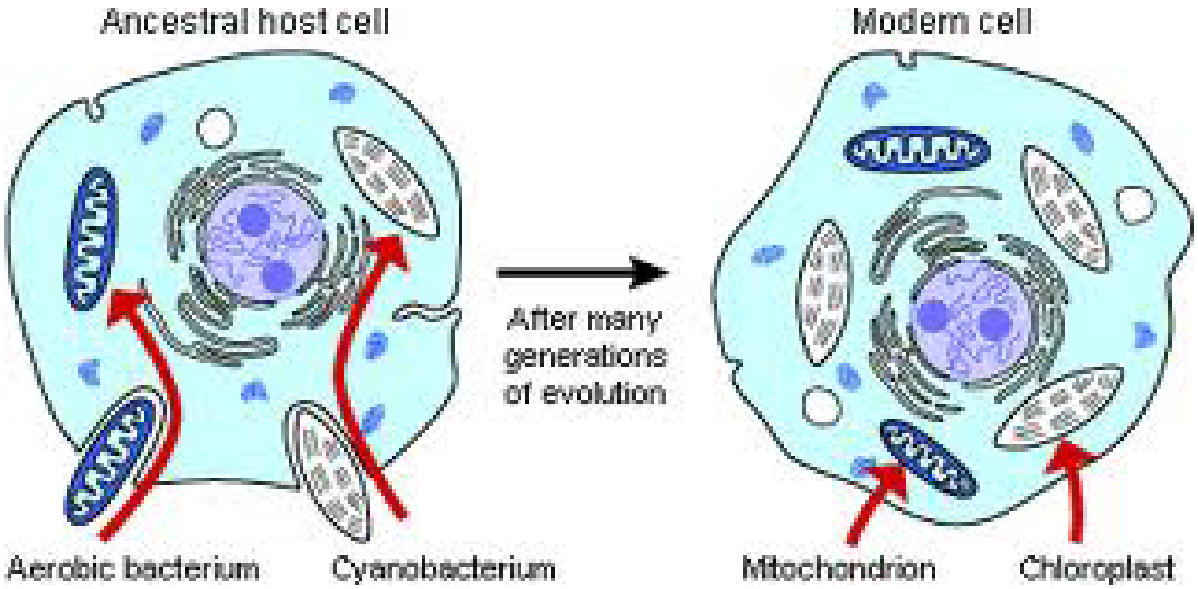
Inflammation

→ Compound exocytosis

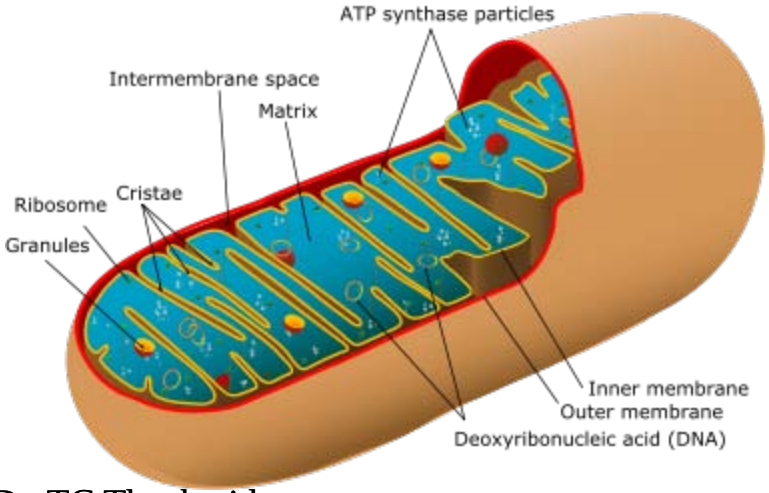
→ Intragranular activation

Do Mast Cells Secrete Autopathogens?

Lynn Margulis (1938 –2011)



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



Atopic dermatitis and skin disease

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

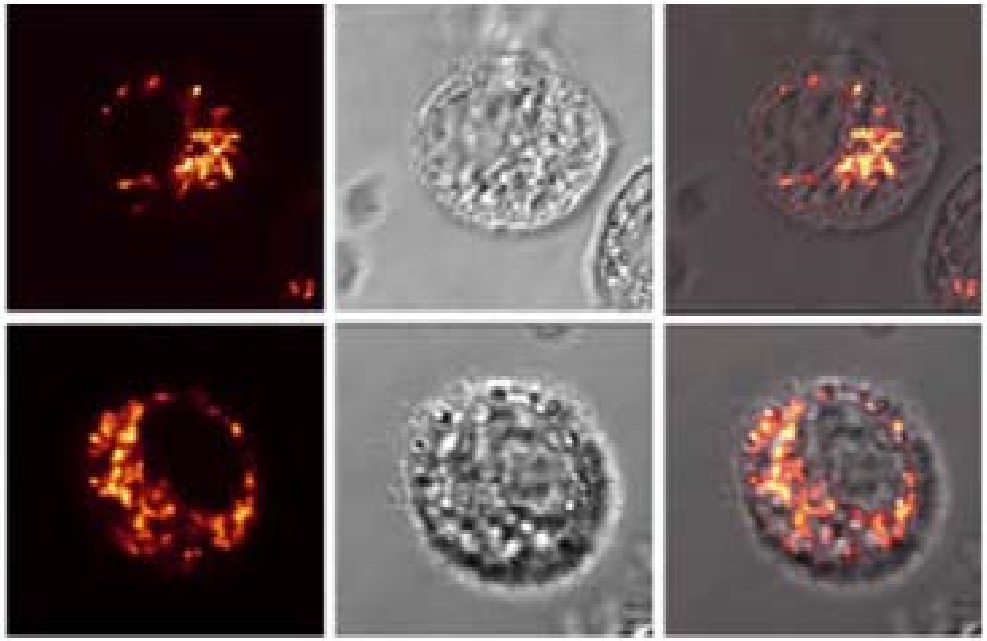
Bodi Zhang, MD, MPH, PhD,[a,b] Konstantinos-Dionysios Alysandratos, MD,[a,e] Asimenia Angelidou, MD,[a,e] Shahrzad Asadi, PharmD,[a] Nikolaos Sismanopoulos, MD,[a] Danae-Anastasia Delivanis, MD,[a] Zuyi Weng, MS,[a] Alexandra Miniati, MD,[a,e] Magdalini Vasiadi, BS,[a,e] Alexandra Katsarou-Katsari, MD, 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

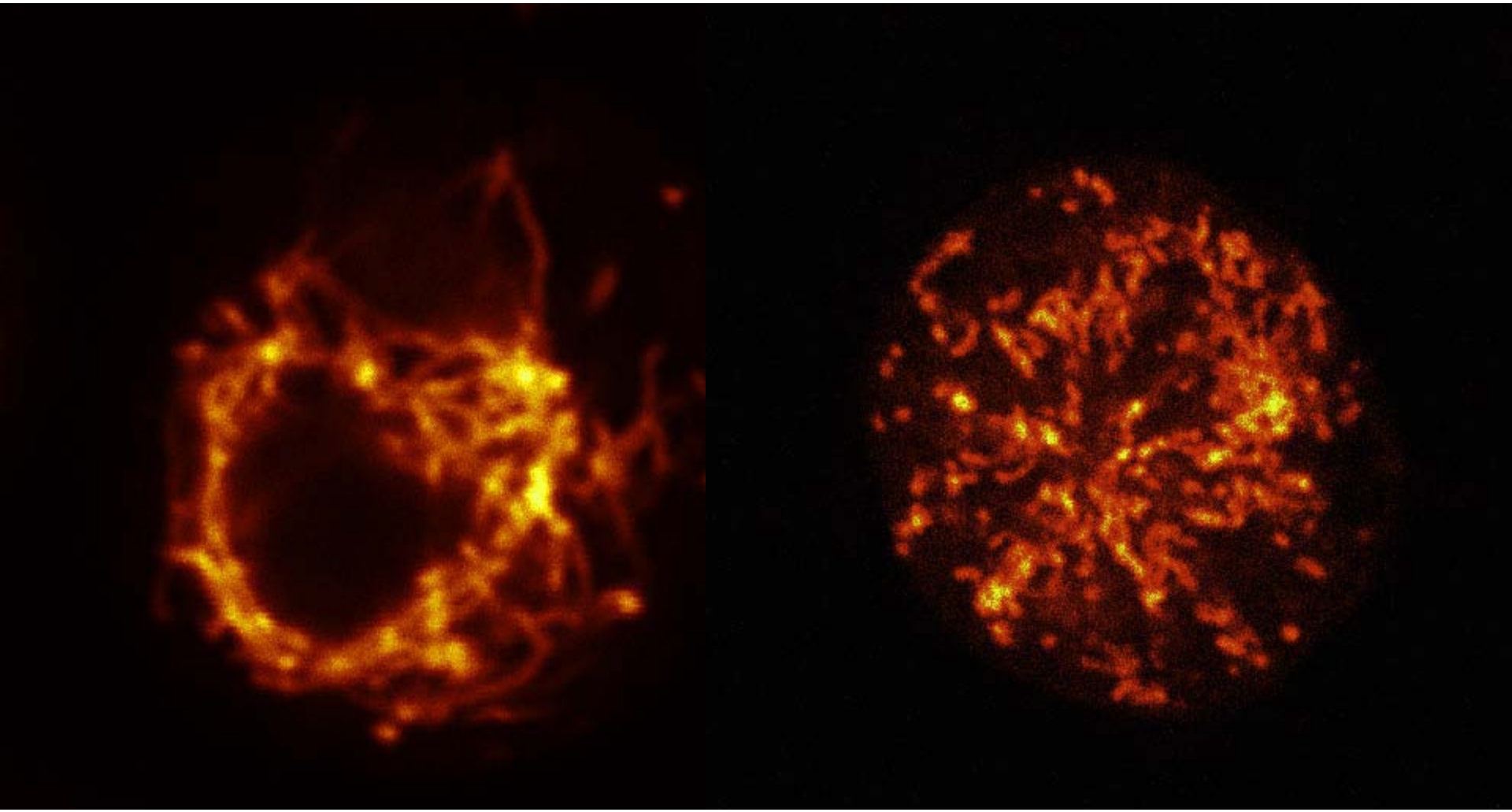
Control

SP (2 μM)

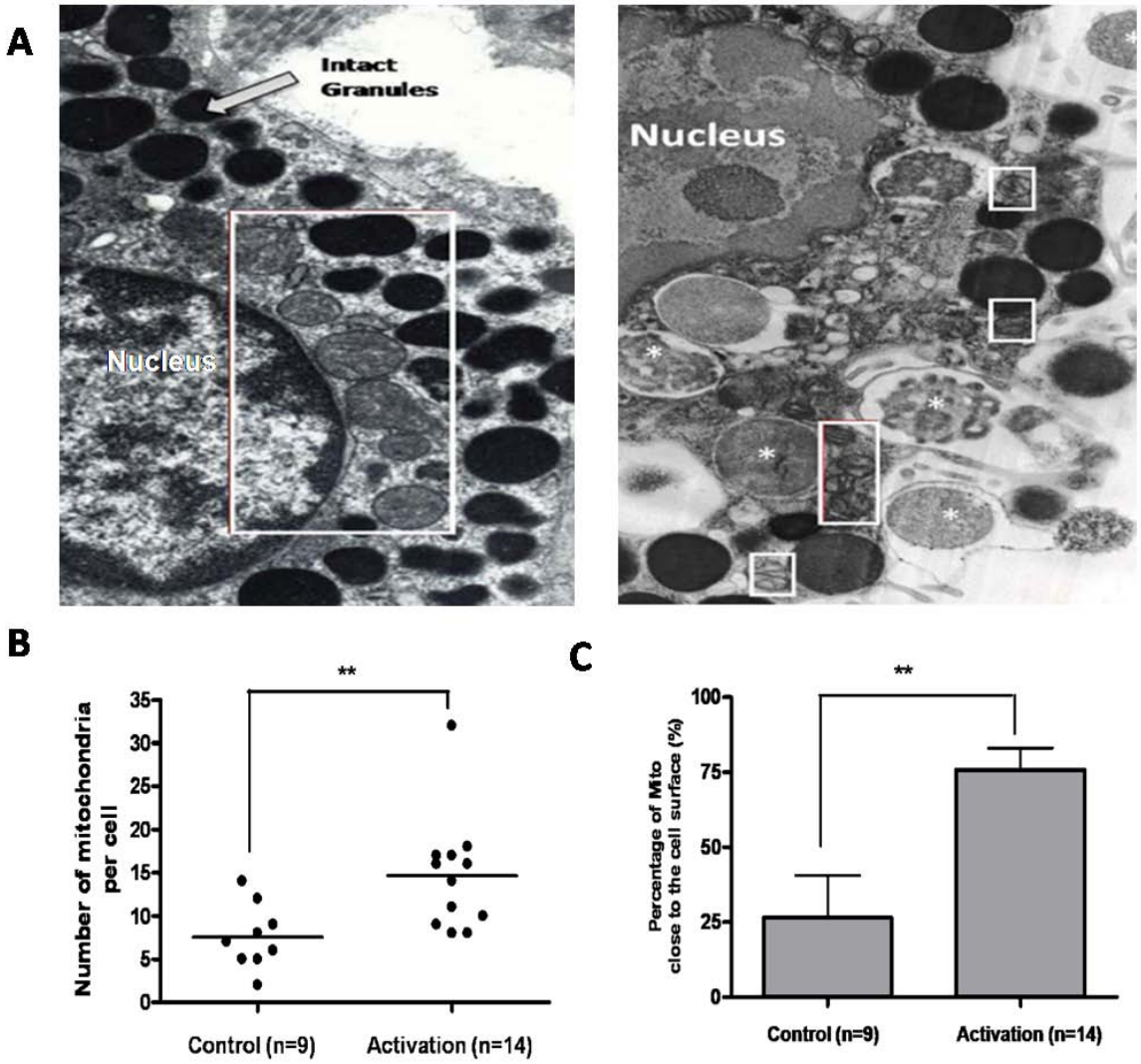


Mitochondrial fluorescence (a) | Light Microscopy (b) | Merged (a+b)

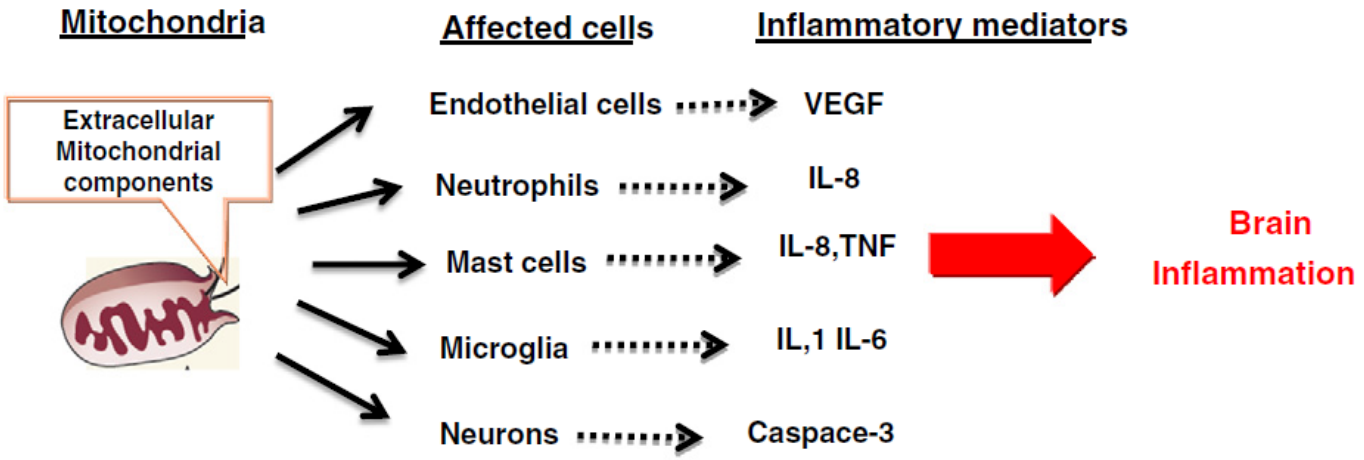
Mitochondrial Fragmentation (fission) During Mast Cell Degranulation



Mitochondria Undergo Fission and Move to the Cell Surface During MC Secretion



Effects of Mitochondrial Components on Different 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]

Autoimmunity Reviews xxx (2013) xxx–xxx

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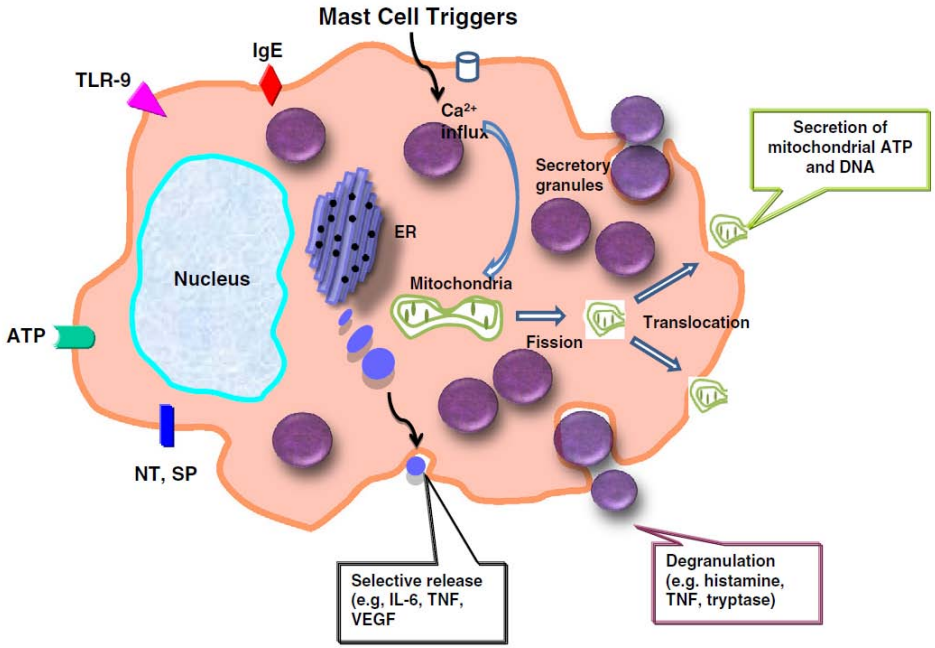
Autoimmunity Reviews

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

Review

The "missing link" in autoimmunity and autism: Extracellular mitochondrial components secreted from activated live mast cells

Theoharis C. Theoharides [a,b,c,d,e,*], Shahrzad Asadi [a,f], Smaro Panagiotidou [a], Zuyi Weng [a,e]



Do Mast Cells Have Any Useful Function?

Wound Healing

The FASEB Journal • FJ Express Full-Length Article

Mast cells are required for normal healing of skin wounds in mice

Karsten Weller,[*,†] Kerstin Foitzik,[‡] Ralf Paus,[§] Wolfgang Syska,[*,‖] and Marcus Maurer[*,‖,1]

*Department of Dermatology and Allergology, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Berlin, Germany; [†]Department of Dermatology, University Hospital Würzburg, Würzburg, Germany; [‡]Department of Dermatology, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [§]Department of Dermatology, University Hospital Lübeck, Lübeck, Germany; and [‖]Department of Dermatology, University Hospital Mainz, Mainz, Germany

The role of mast cells in wound healing

Michael FY Ng

Ng MFY. The role of mast cells in wound healing. Int Wound J 2010; 7:55–61

ABSTRACT

Mast cells are predominantly found in the vicinity of connective tissue vessels of skin and mucosa. The main immunological functions of mast cells are in IgE-mediated reactions and in helminth infestations. Mast cells respond to tissue injury by releasing inflammatory mediators and have been implicated in diseases of excessive fibrosis of the dermis such as scleroderma. Current evidence suggests that mast cells exert its role during inflammation and cellular proliferation. Animal models have shown that by stabilising mast cells at the early stages of wound healing, wound contraction is reduced. Mast cells are an ideal candidate to play a pivotal role in wound healing due to its location, substances released and clinical associations.

Key words: mast cell • wound healing • inflammation • cellular proliferation

Pergamon

Neuroscience Vol. 80, No. 4, pp. 1237–1245, 1997

PII: S0306-4522(97)00052-3
0306–4522/97 $17.00+0.00

MAST CELL NUMBER AND MATURATION IN THE CENTRAL NERVOUS SYSTEM: INFLUENCE OF TISSUE TYPE, LOCATION AND EXPOSURE TO STEROID HORMONES

X. ZHUANG,* A.-J. SILVERMAN† and R. SILVER*‡¶

*Department of Psychology, Columbia University, New York, NY 10027, U.S.A.

†Department of Anatomy and Cell Biology, Columbia University, New York, NY 10032, U.S.A.

‡Department of Psychology, Barnard College of Columbia University, New York, NY 10027, U.S.A.

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 3695–3699, April 1994
Neurobiology

Mast cells with gonadotropin-releasing hormone-like immunoreactivity in the brain of doves

(sexual behavior/habenula/immune–neuroendocrine interactions)

ANN-JUDITH SILVERMAN*, ROBERT P. MILLAR†, JUDY A. KING†, XIAOXI ZHUANG‡, AND RAE SILVER‡

*Department of Anatomy and Cell Biology, Columbia University, New York, NY 10032; †Medical Research Council Regulatory Peptides Research Unit, Department of Chemical Pathology, University of Cape Town Medical School, Cape Town, Republic of South Africa; and ‡Department of Psychology, Barnard College, and Graduate School of Arts and Sciences of Columbia University, New York, NY 10027

Communicated by Fernando Nottebohm, December 6, 1993 (received for review September 8, 1992)

Mast Cells in the Rat Brain Synthesize Gonadotropin-Releasing Hormone

 J Neurobiol 56: 113–124, 2003

Mona H. Khalil,[1] Ann-Judith Silverman,[2] Rae Silver[2,3]

[1] Department of Biochemistry and Molecular Biophysics, Columbia University College of Physicians and Surgeons, New York, New York 10032

[2] Department of Anatomy and Cell Biology, Columbia University College of Physicians and Surgeons, New York, New York 10032

[3] Department of Psychology, Barnard College and Columbia University, New York, New York 10027

frontiers in IMMUNOLOGY

REVIEW ARTICLE
published: 14 February 2013
doi: 10.3389/fimmu.2013.00029

Mast cells as novel mediators of reproductive processes

Katja Woidacki, Federico Jensen and Ana C. Zenclussen*

Department of Experimental Obstetrics and Gynecology, Medical Faculty, Otto-von-Guericke University, Magdeburg, Germany

Edited by:
Ulrich Blank, Inserm U699, Université Paris Diderot-Paris 7, France

Reviewed by:
Ulrich Blank, Inserm U699, Université Paris Diderot-Paris 7, France
Carlo Pucillo, University of Udine, Italy
Nadine Varin-Blank, Institut National de la Santé et de Recherche Médicale, France

The relationship between mast cells (MCs) and pregnancy is a controversially discussed topic. The presence and quantitative distribution of MCs in the reproductive tract was confirmed in different species. A phase-dependent oscillation of MCs during the hormonal regulated estrous cycle was suggested and on this basis, MCs were assumed to play a positive role in implantation because of their ability to secrete histamine. At later pregnancy stages, they were proposed to have rather a negative role, as their exacerbated activation is associated with pre-term delivery. The present review is intended to provide an overview about uterine MCs that bring to light their unexpected relevance for reproductive processes.

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MIMM-4355; No. of Pages 7
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Molecular Immunology xxx (2014) xxx–xxx
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journal homepage: www.elsevier.com/locate/molimm

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]
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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.

Are Mast Cells Associated with Other Diseases?

Atherosclerosis

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Perivascular Mast Cells Promote Atherogenesis and Induce Plaque Destabilization in Apolipoprotein E–Deficient Mice

Ilze Bot, Saskia C.A. de Jager, Alma Zernecke, Ken A. Lindstedt, Theo J.C. van Berkel, Christian Weber and Erik A.L. Biessen

Circulation 2007;115;2516-2525; originally published online Apr 30, 2007;
DOI: 10.1161/CIRCULATIONAHA.106.660472

LETTERS

nature medicine

VOLUME 15 | NUMBER 8 | AUGUST 2009

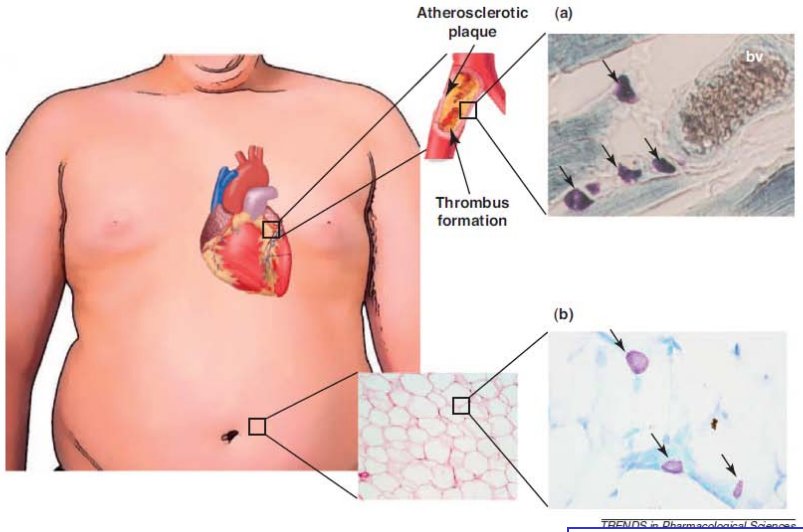
Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice

Jian Liu[1], Adeline Divoux[2], Jiusong Sun[1], Jie Zhang[1], Karine Clément[2–4], Jonathan N Glickman[1], Galina K Sukhova[1], Paul J Wolters[5], Juan Du[1], Cem Z Gorgun[6], Alessandro Doria[7], Peter Libby[1], Richard S Blumberg[1], Barbara B Kahn[8], Gökhan S Hotamisligil[6] & Guo-Ping Shi[1]

Review
Cell
Trends in Pharmacological Sciences, September 2011, Vol. 32, No. 9

Mast cells squeeze the heart and stretch the gird: Their role in atherosclerosis and obesity

Theoharis C. Theoharides[1,2,3,4,5], Nikolaos Sismanopoulos[1,5], Danae-Anastasia Delivanis[1], Bodi Zhang[1,2], Erifili E. Hatziagelaki[4] and Dimitrios Kalogeromitros[5,†]



Allergy
EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY
EAACI
Allergy
2013; 68: 8–15.
REVIEW ARTICLE

Do mast cells link obesity and asthma?

N. Sismanopoulos[1,*], D.-A. Delivanis[1,†], D. Mavrommati[1], E. Hatziagelaki[2], P. Conti[3] & T. C. Theoharides[1,4,5]

Cancer

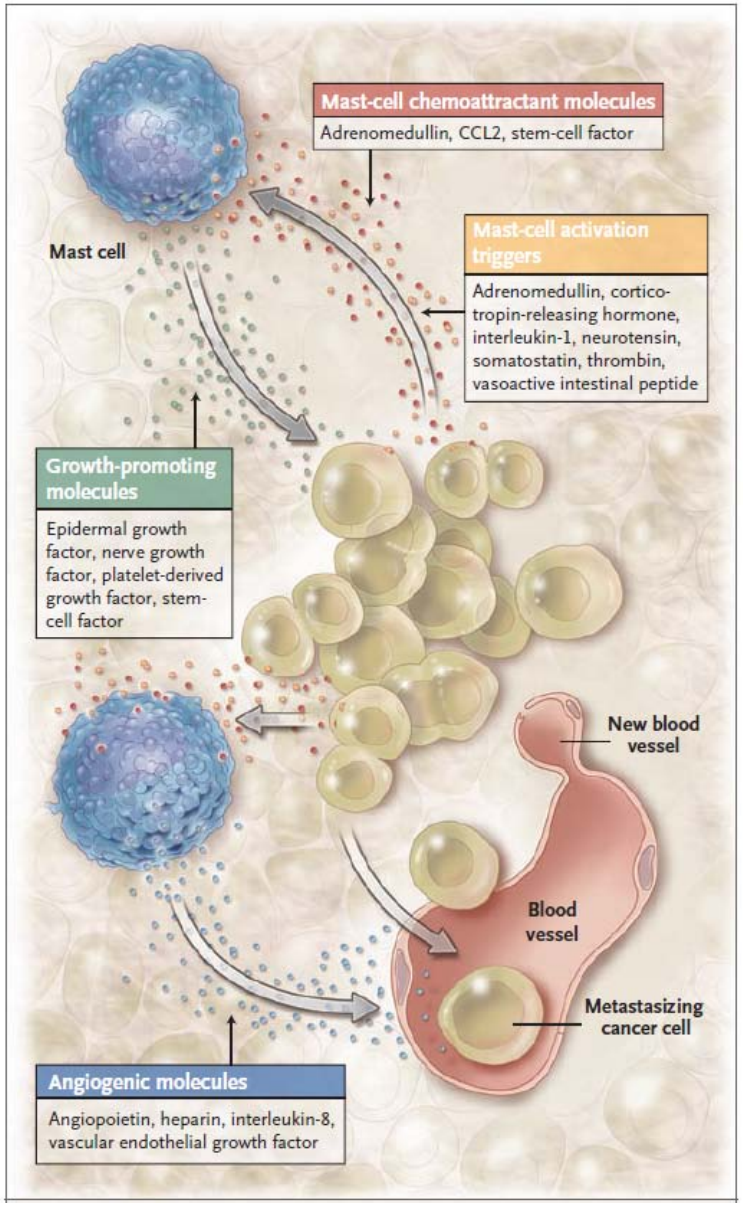
The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

N ENGL J MED 358;17 WWW.NEJM.ORG APRIL 24, 2008

Mast Cells and Pancreatic Cancer

Theoharis C. Theoharides, Ph.D., M.D.



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Brain Research Reviews 49 (2005) 65–76

BRAIN RESEARCH REVIEWS

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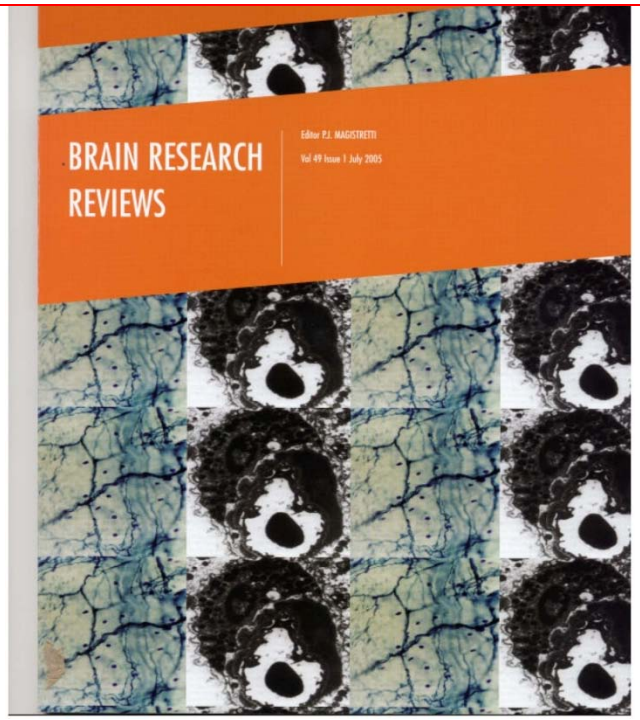
Review

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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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

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Vol. 322, No. 2
123745/3228754
Printed in U.S.A.

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.)

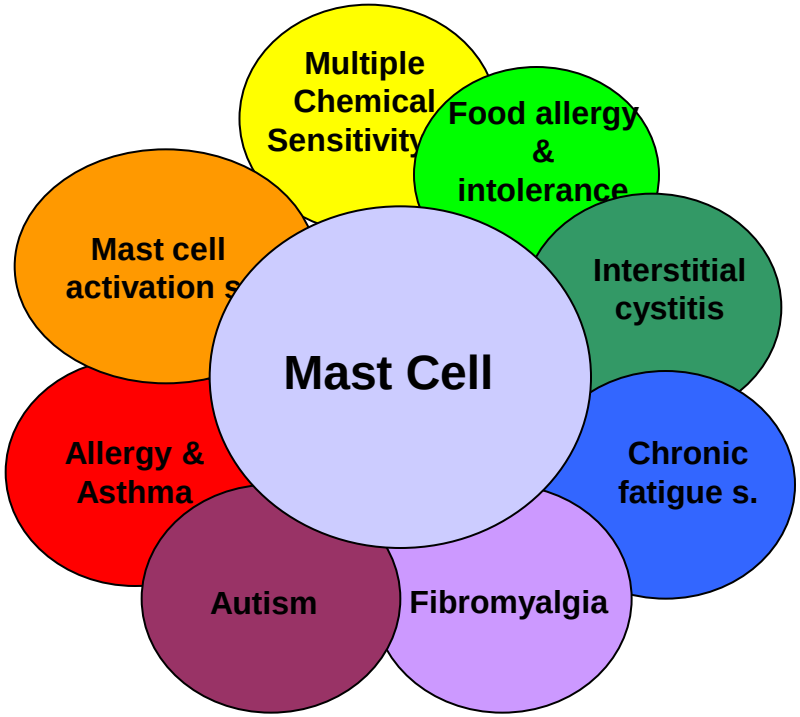
Received March 30, 2007; accepted May 3, 2007

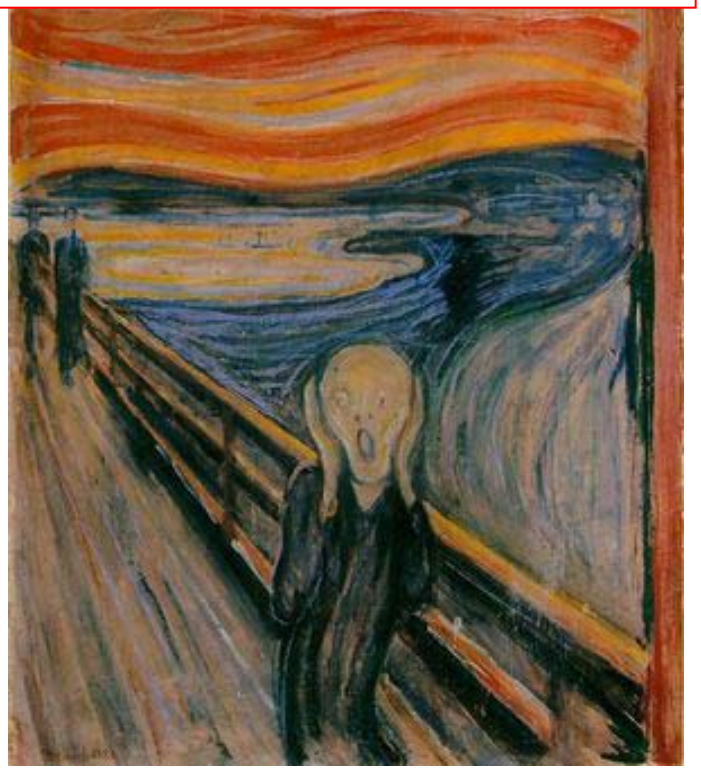
Mast Cells-Related Immune Disorders

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)

Do Mast Cells Exist in the Brain and are Do They Get Stressed Out?

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

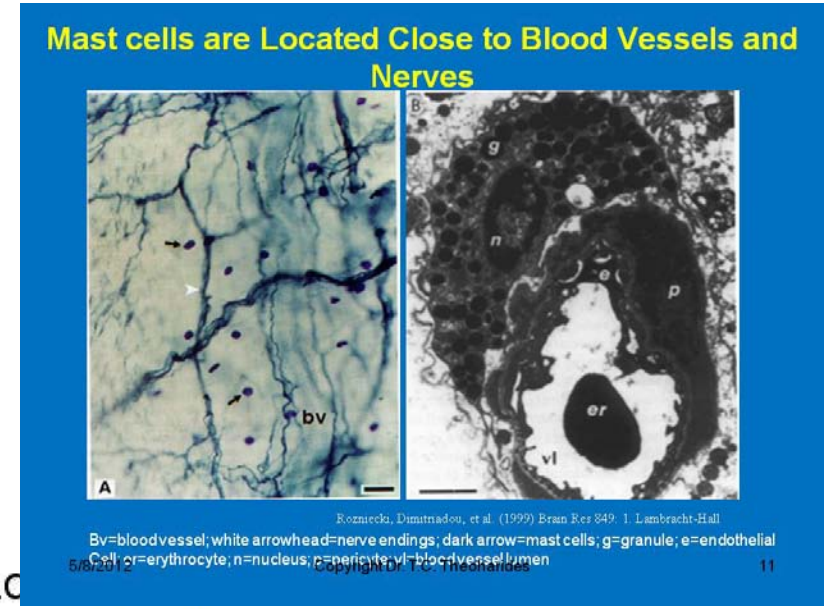
MINIREVIEW

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)



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Brain Research 849 1999) 1–15

BRAIN RESEARCH

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Research report

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

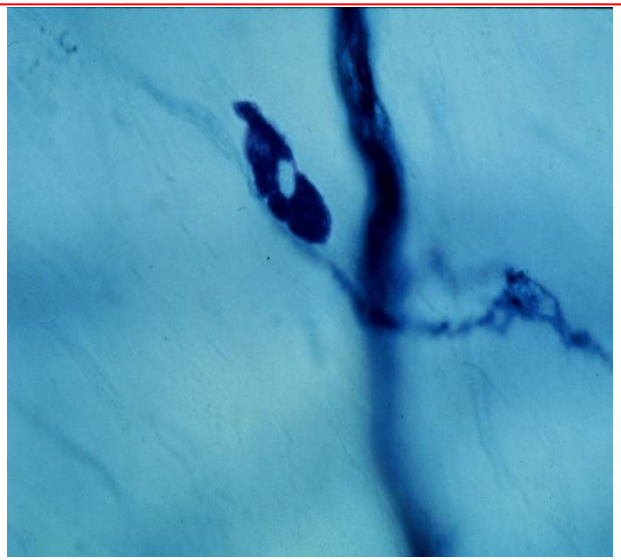
Jacek J. Roznieckí [1], Violetta Dimitriadou [2], Mona Lambracht-Hall [3], Xinzhu Pang [4], Theoharis C. Theoharides *

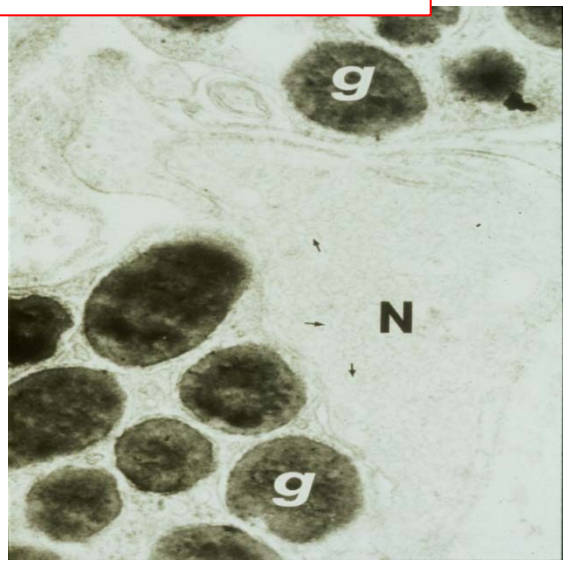
Department of Pharmacology, and Experimental Therapeutics, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA

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





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, September 23, 2008 (sent for review August 5, 2008)

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

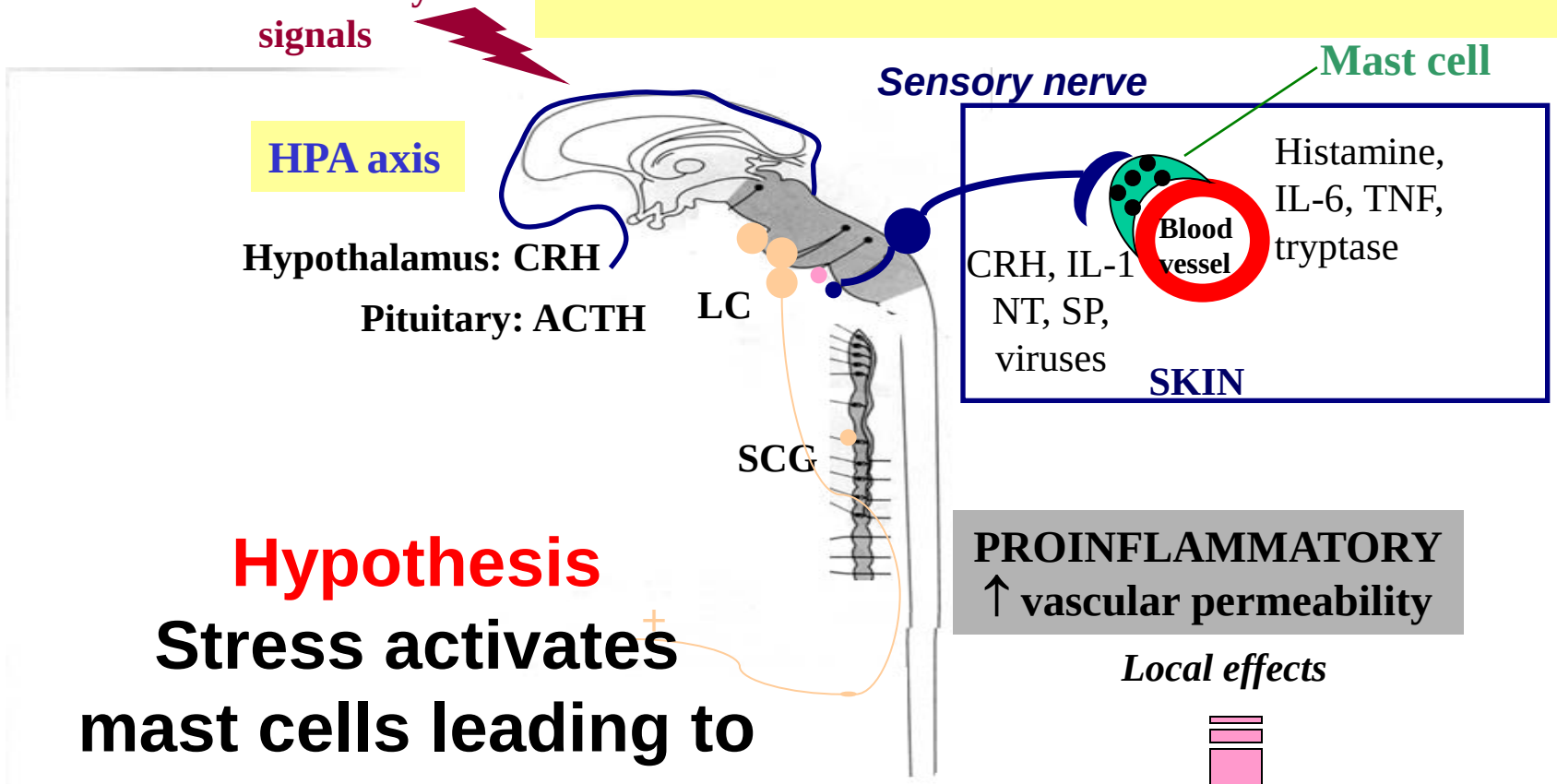
Mast cells in the brain: evidence and functional significance

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

Stress and Skin Mast Cells



Hypothesis

Stress activates mast cells leading to skin inflammation

PROINFLAMMATORY
↑ vascular permeability

Local effects

Triggering or exacerbating
Dermatitis, Flushing

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JPET 303:1061–1066, 2002

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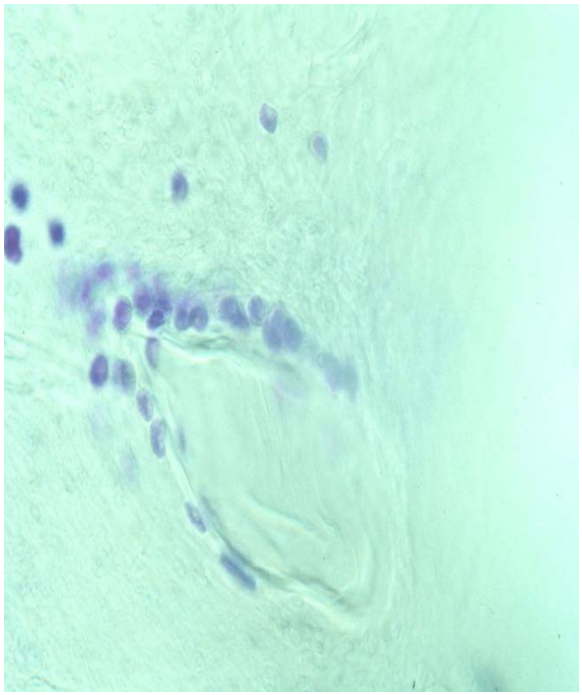
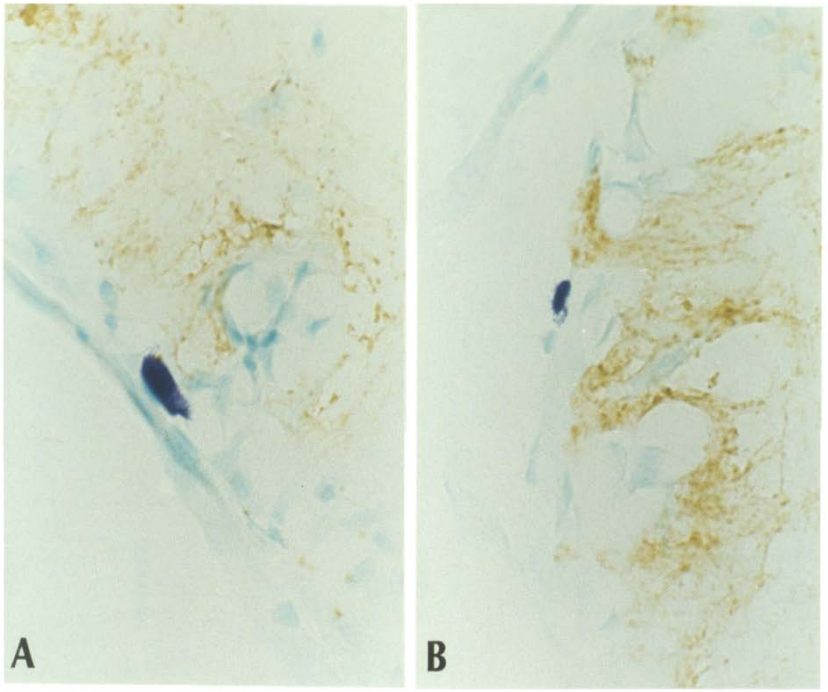
Printed in U.S.A.

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

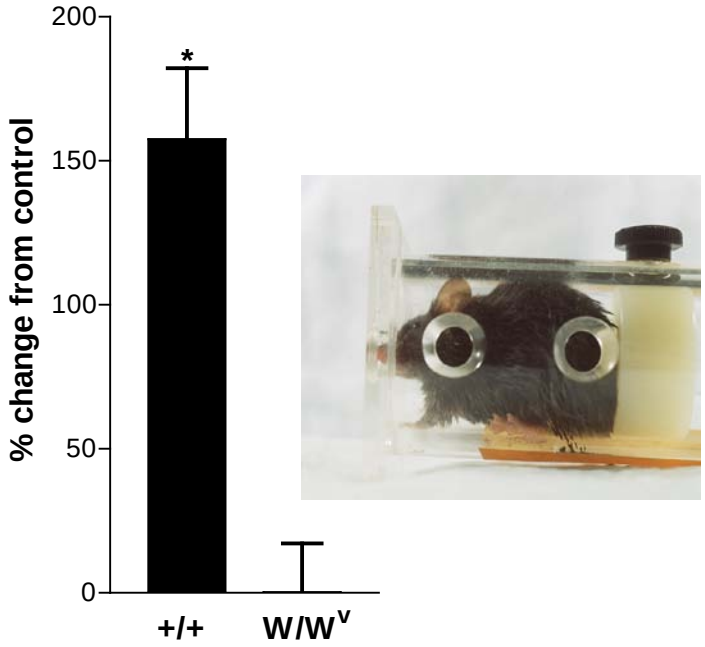
PAMELA ESPOSITO, NATHAN CHANDLER, KRISTIANA KANDERE, SUBIMAL BASU, STANLEY JACOBSON, RAYMOND CONNOLLY, DAVID TUTOR, and THEOHARIS C. THEOHARIDES



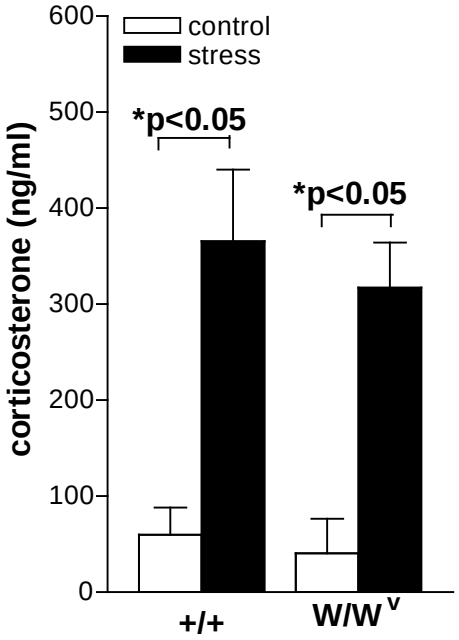


Stress-induced Brain Vascular Permeability is Dependent on Mast Cells

99-Technetium-gluceptate extravasation

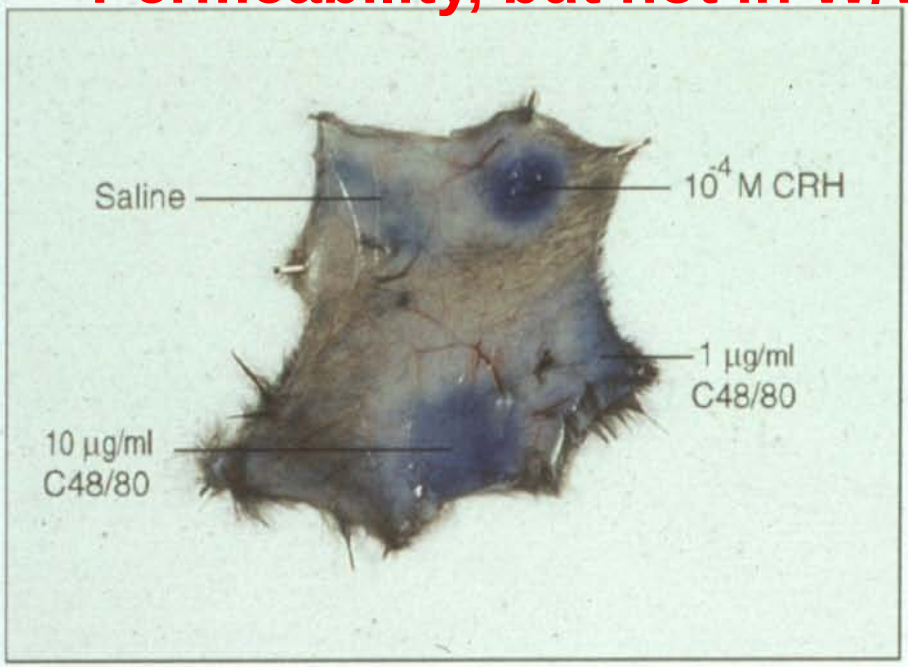


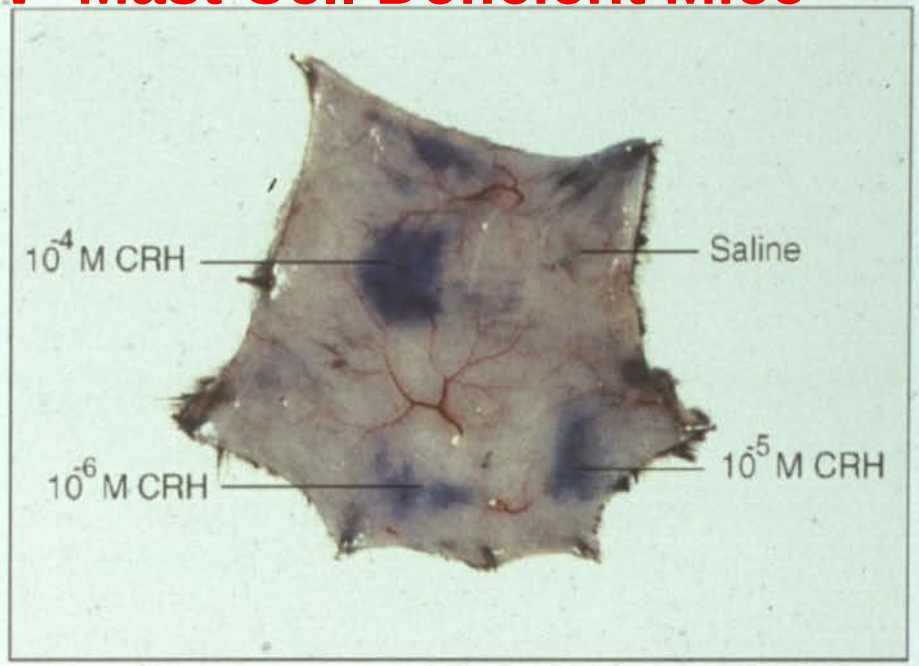
HPA axis activation

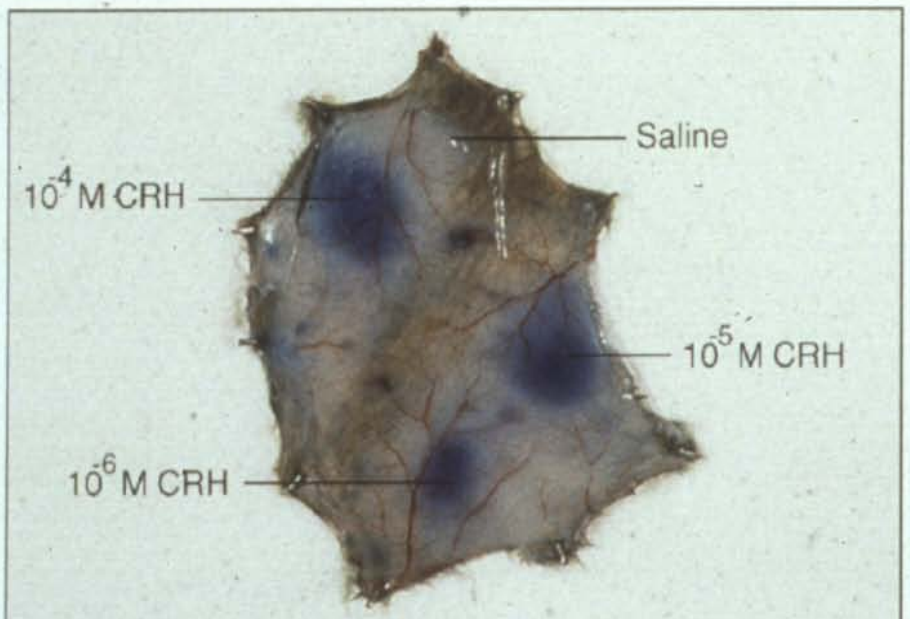


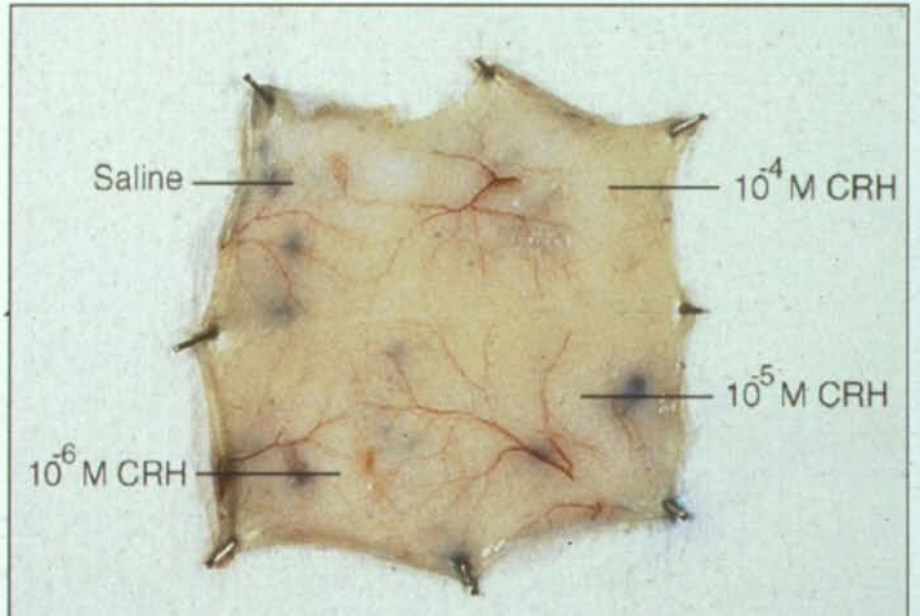
Esposito P, TC. ***J Pharmacol Exp Ther***. 2002 Dec;303(3):1061-6.

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

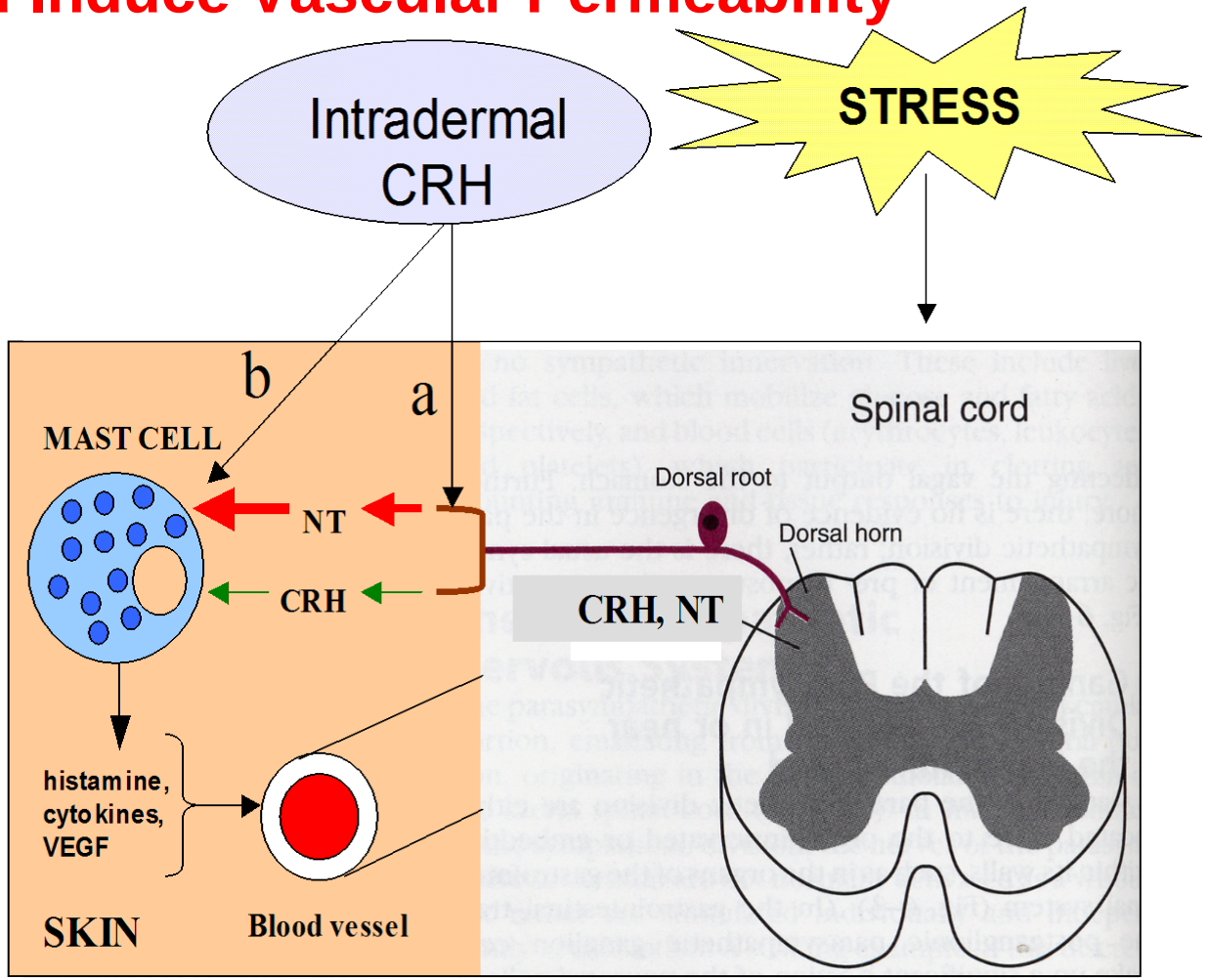






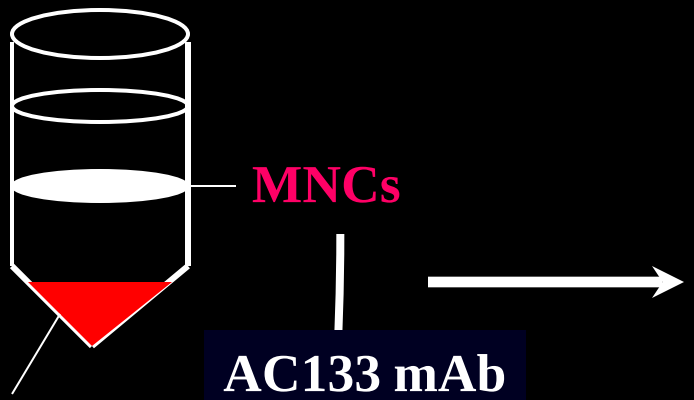


CRH, NT and SP Released from DRG Stimulate Skin Mast Cells and Induce Vascular Permeability



Donelan J et al. ***Proc Natl Acad Sci U S A.*** 2006 May 16;103(20):7759-64.

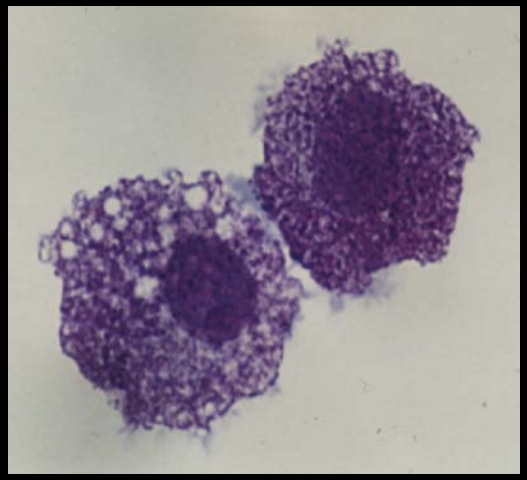
Culture of human umbilical cord blood-derived mast cells (hCBMCs)



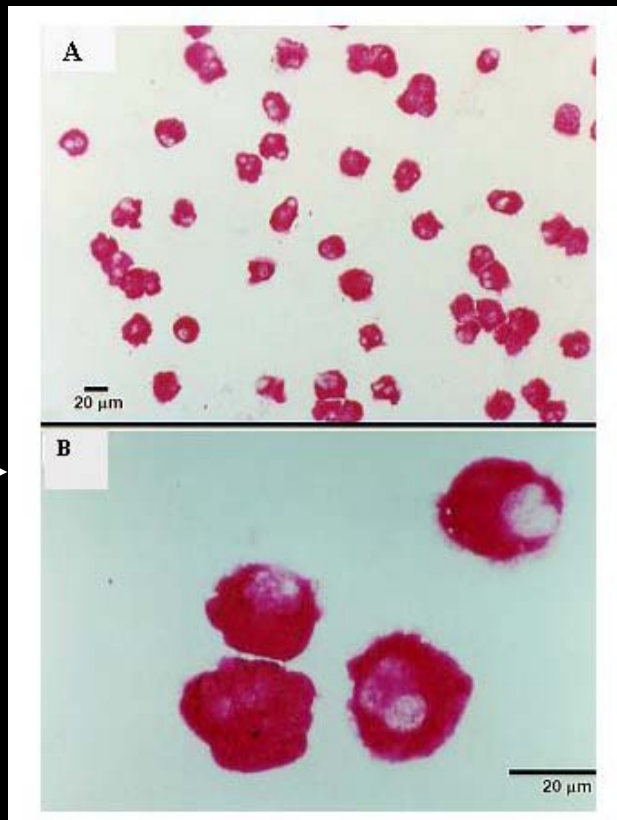
AC133 mAb

MACs

CD34+ cells



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



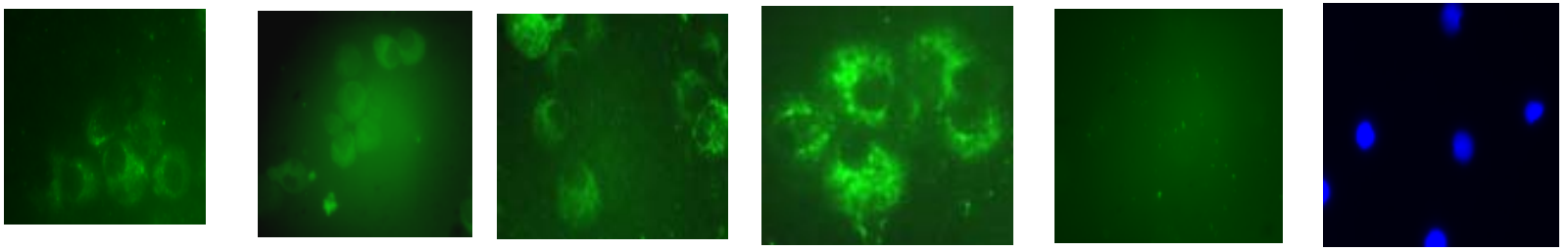
Kempuraj D., Saito H. et al. Blood 93: 3338-3346, 1999.

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**

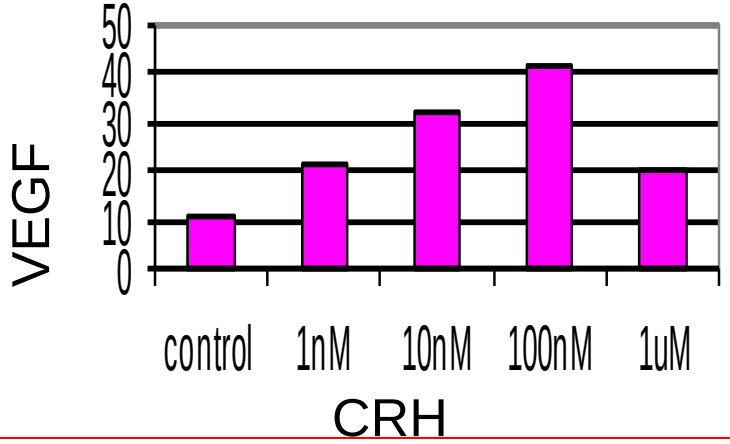


PNAS

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



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

Full text provided by www.sciencedirect.com SCIENCE DIRECT

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

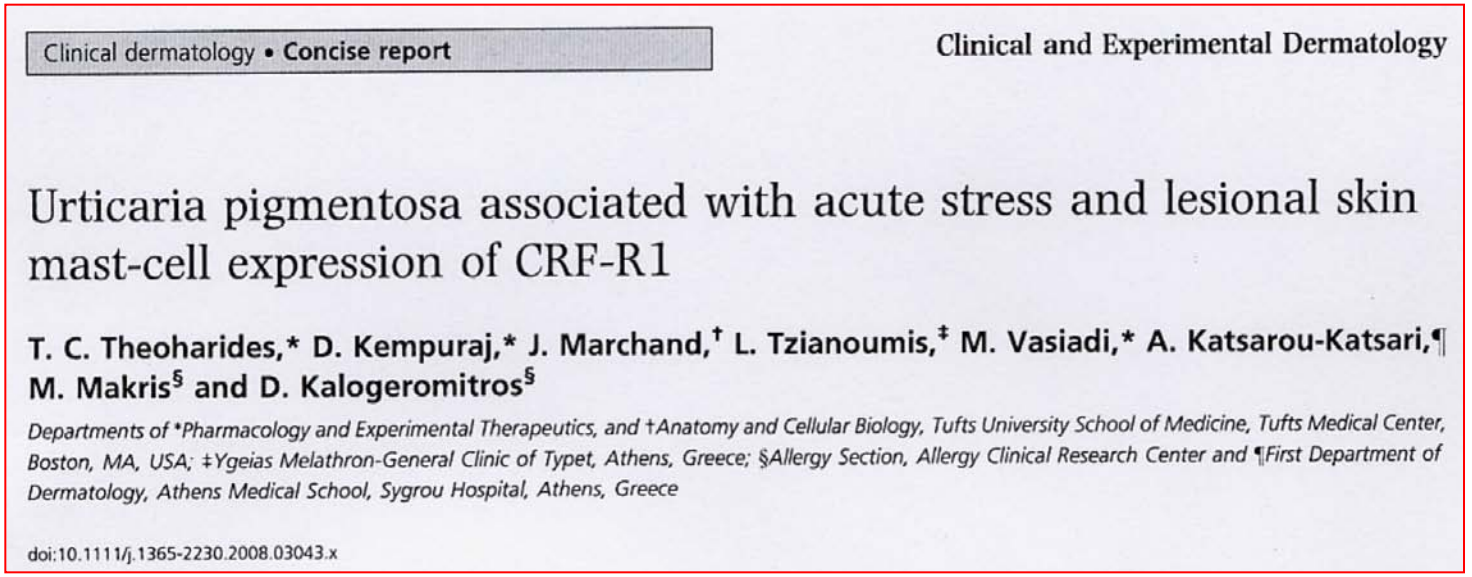
ORIGINAL ARTICLE EXPERIMENTAL ALLERGY AND IMMUNOLOGY

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



Clinical dermatology • **Concise report**

Clinical and Experimental Dermatology

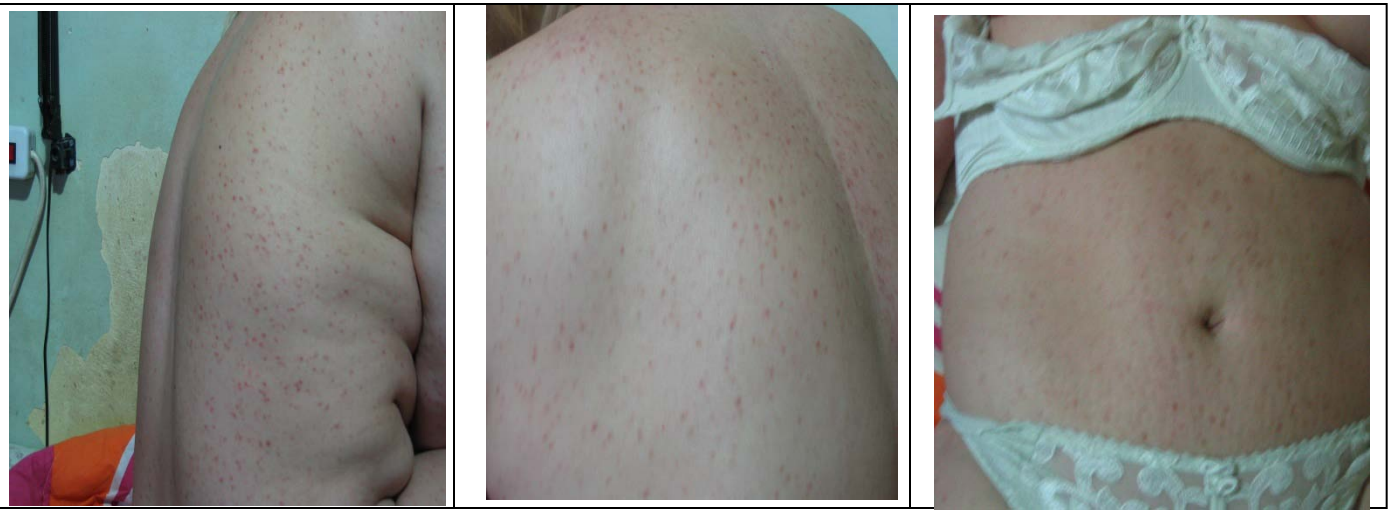
Urticaria pigmentosa associated with acute stress and lesional skin mast-cell expression of CRF-R1

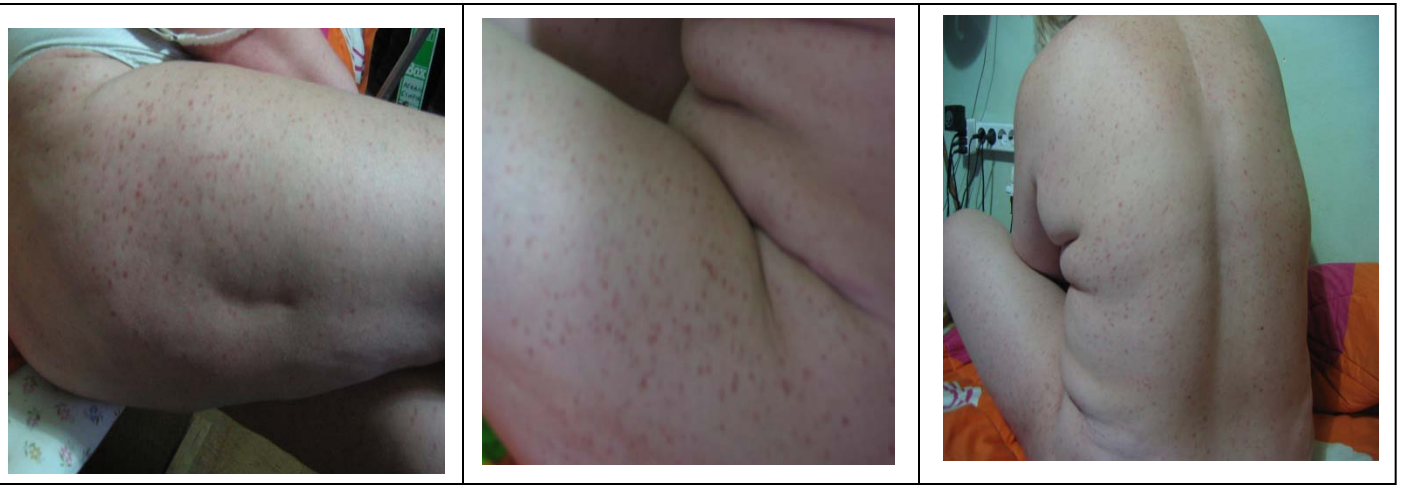
T. C. Theoharides,* D. Kempuraj,* J. Marchand,† L. Tzianoumis,‡ M. Vasiadi,* A. Katsarou-Katsari,¶ M. Makris§ and D. Kalogeromitros§

*Departments of *Pharmacology and Experimental Therapeutics, and †Anatomy and Cellular Biology, Tufts University School of Medicine, Tufts Medical Center, Boston, MA, USA; ‡Ygeias Melathron-General Clinic of Typet, Athens, Greece; §Allergy Section, Allergy Clinical Research Center and ¶First Department of Dermatology, Athens Medical School, Sygrou Hospital, Athens, Greece*

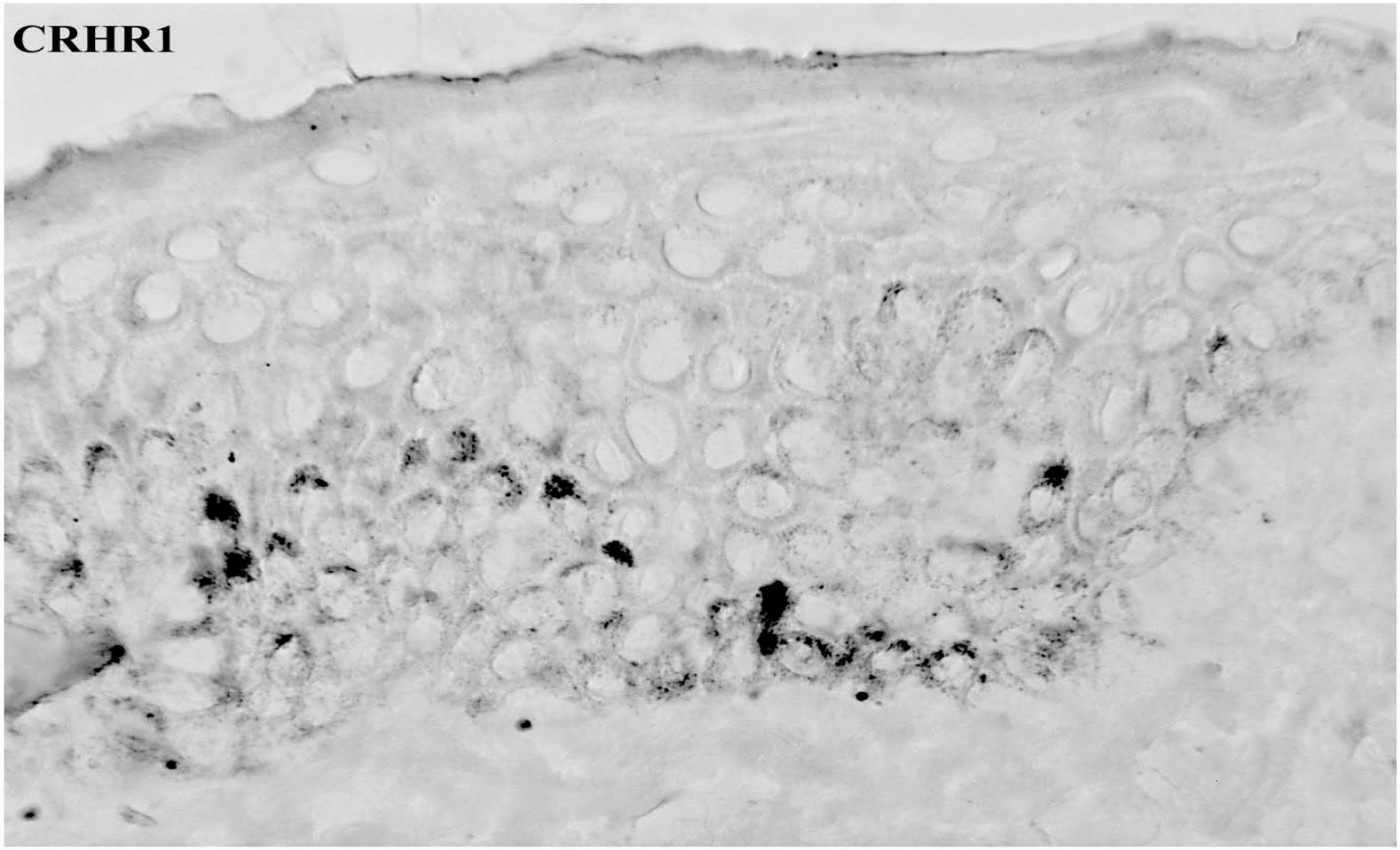
doi:10.1111/j.1365-2230.2008.03043.x

- **A 38-year-old woman presented with a pronounced increase in symptoms and proliferation of urticaria pigmentosa (UP) after acute psychological stress, which was quantified using the Spielberger's State–Trait Anxiety Inventory.**
- **Immunohistochemical examination of a skin biopsy from a new UP lesion showed Mnay CRH-R1-postive cells.**
- **There were many activated mast cells expressing corticotropin-releasing hormone receptor-1 (CRH-R1).**
- **There was high serum CRH.**
- **This is the first documented report to our knowledge of UP worsening associated with acute stress, possibly through activation of skin mast-cell CRH-R1.**





Lesional UP Skin Showing Positive CRH-R1 Immunocytochemistry



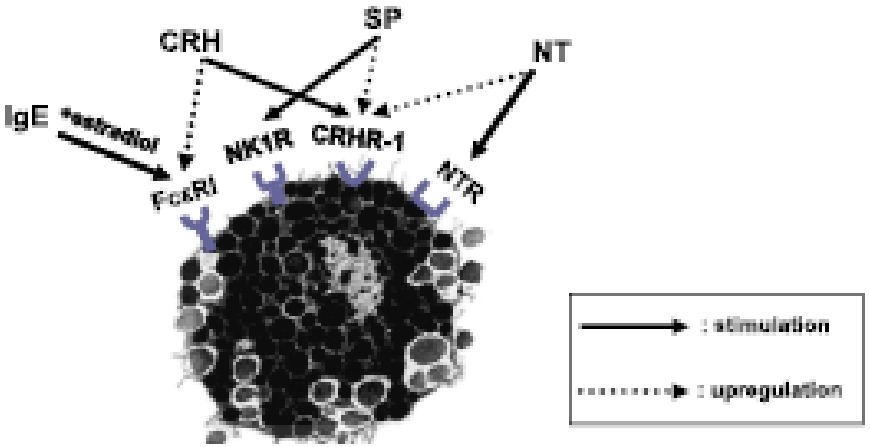
Ann Allergy Asthma Immunol 112 (2014) 383–394

Contents lists available at ScienceDirect

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

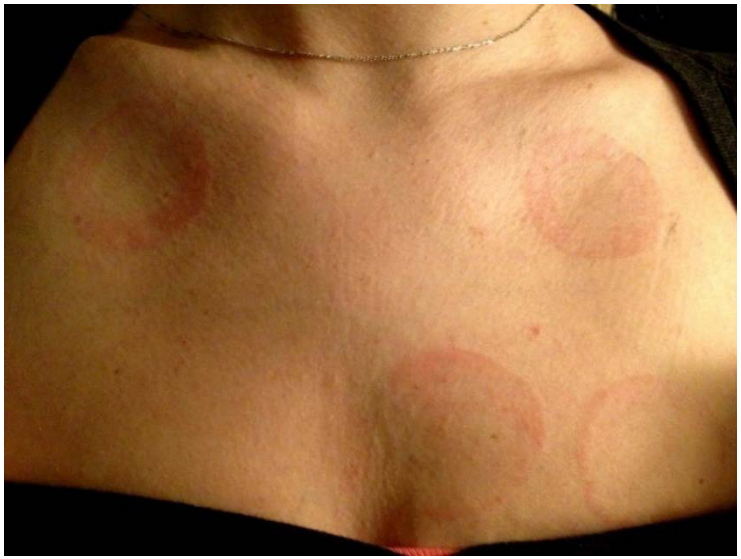
Letters

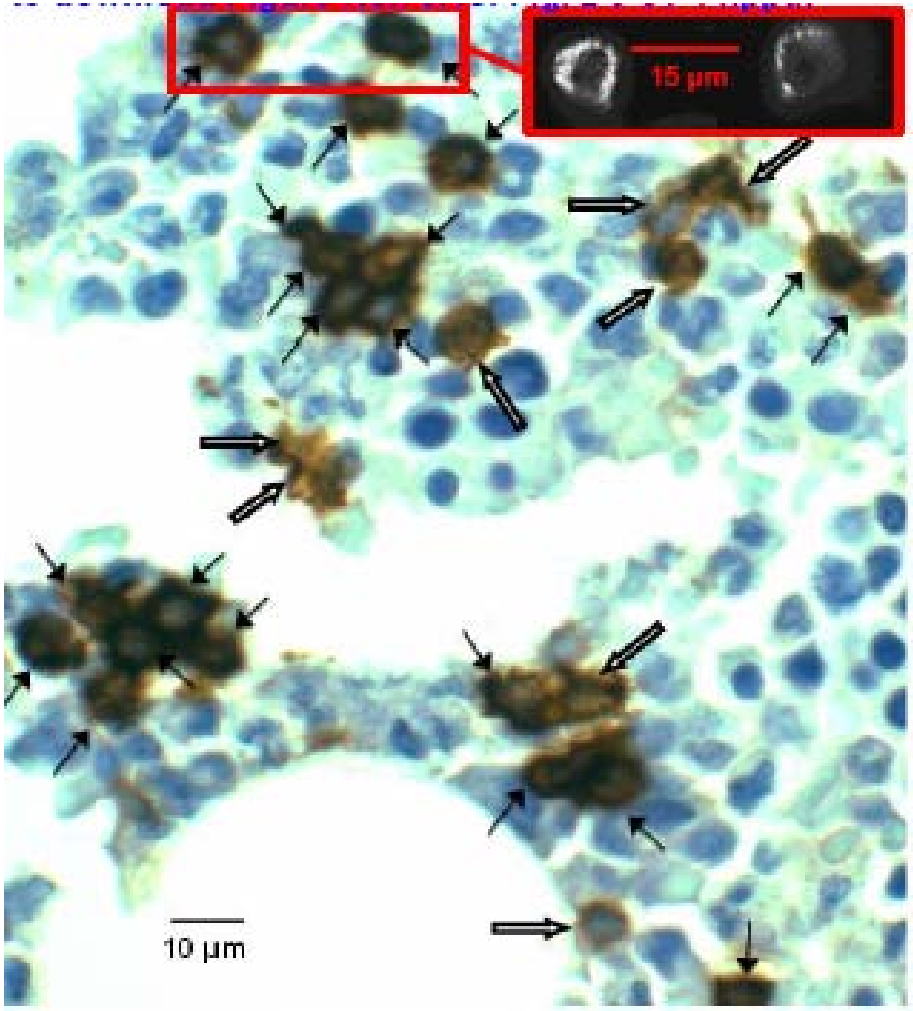
A probable case report of stress-induced anaphylaxis



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]





Do Allergic Symptoms Affect Behavior ?

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)

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.

frontiers in
PSYCHOLOGY

ORIGINAL RESEARCH ARTICLE
published: 19 January 2011
doi: 10.3389/fpsyg.2010.00223

Prenatal maternal stress associated with ADHD and autistic traits in early childhood

Angelica Ronald[1]*, Craig E. Pennell[2] and Andrew J. O. Whitehouse[3]

[1] *Department of Psychological Sciences, Centre for Brain and Cognitive Development, Birkbeck, University of London, London, UK*
[2] *School of Women's and Infants' Health, University of Western Australia, Perth, WA, Australia*
[3] *Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Perth, WA, Australia*

Neuroscience and Biobehavioral Reviews 32 (2008) 1519–1532

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Prenatal stress and risk for autism

Dennis K. Kinney[a,b,*], Kerim M. Munir[b,c], David J. Crowley[a], Andrea M. Miller[a]

[a] *Mailman Research Center, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA*
[b] *Department of Psychiatry, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA*
[c] *Division of Developmental Medicine and Department of Psychiatry, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115, USA*

Original Article

Autism Spectrum Disorders: Concurrent Clinical Disorders

Xue Ming, MD, PhD, Michael Brimacombe, PhD, Janti Chaaban, MD,
Barbie Zimmerman-Bier, MD, and George C. Wagner, PhD

Journal of Child Neurology
Volume 23 Number 1
January 2008 6-13

10.1177/0883073807307102
http://jcn.sagepub.com
hosted at
http://online.sagepub.com

There was significant association with food intolerance (P = 0.001).

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,*]

[a] Laboratory of Neurobiology & Clinical Neurophysiology, Neurology Section, Pediatric Department, Fernandes Figueira Institute, FIOCRUZ, Brazil
[b] Allergy and Immunology Section, Pediatric and Child Care Martagão Gesteira Institute, UFRJ, Brazil
[c] Allergy and Immunology Section, Pediatric Department, Fernandes Figueira Institute, FIOCRUZ, Brazil

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

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Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Mast cell activation and autism ☆

Theoharis C. Theoharides [a,b,c,d,e,*], Asimenia Angelidou [a,e], Konstantinos-Dionysios Alysandratos [a,e], Bodi Zhang [a,b], Shahrzad Asadi [a], Konstantinos Francis [f], Elena Toniato [g], Dimitrios Kalogeromitros [e]

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

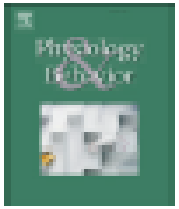
Jeng-Dau Tsai MD[a,b], Shih-Ni Chang MS[c,d], Chih-Hsin Mou MS[c,d], Fung-Chang Sung PhD, MPH[c,d,**], Ko-Huang Lue MD, PhD[a,b,*]

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]

Journal of Neuroimmunology 261 (2013) 77–81

Contents lists available at SciVerse ScienceDirect

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]

[a] Department of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[b] Autism Research and Treatment Center, AL-Amodi Autism Research Chair, Department of Physiology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia

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Keywords:
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Anti-myelin associated glycoprotein antibodies
Anti-myelin basic protein antibodies
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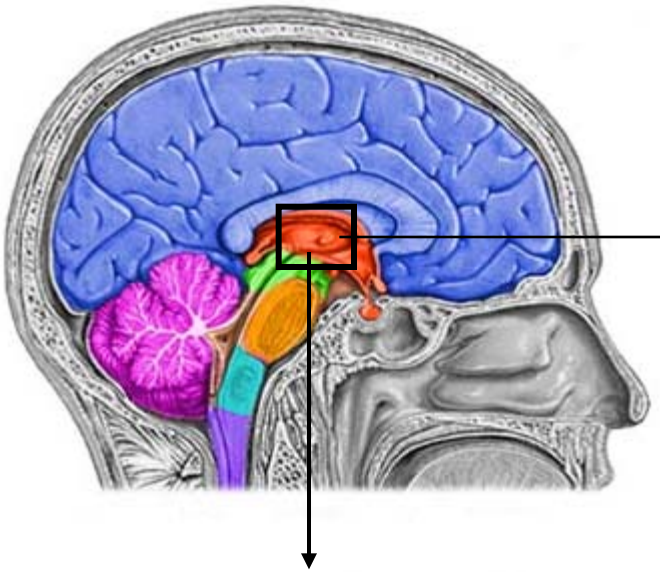
ABSTRACT

Etiology of autism has become an area of a significant controversy. Allergy induced autism is an area of research wherein immune responses to some allergens may play a pathogenic role in autism. Allergy may induce the production of brain specific auto-antibodies in a subgroup of autistic children. We are the first to investigate the possible link between allergic manifestations and serum levels of both anti-myelin basic protein (anti-MBP) and anti-myelin associated glycoprotein (anti-MAG) brain-specific auto-antibodies, which were measured by ELISA method, in 42 autistic children in comparison to 42 healthy-matched children. Allergic manifestations (bronchial asthma, atopic dermatitis and/or allergic rhinitis) were found in 47.6% of autistic patients. Increased serum levels of anti-MBP and anti-MAG auto-antibodies were found in 57.1% and 66.7%, respectively of autistic children. In addition, 78.5% of autistic children had increased serum levels of both anti-MBP and/or anti-MAG auto-antibodies. Autistic patients with allergic manifestations had significantly higher serum levels of anti-MBP and anti-MAG auto-antibodies than those without these manifestations ($P < 0.001$ and $P = 0.001$, respectively). In conclusion, allergy may be a contributing factor to the increased serum levels of anti-MBP and anti-MAG auto-antibodies in some autistic children. Indeed, we need to know more about the links between allergy, immune system and brain in autism for finding new therapeutic modalities in autism.

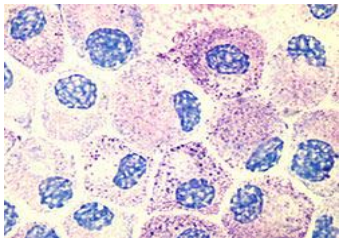
The Genesis of Brain Immunity Storms



Diencephalon

(coordinates sensory input and emotions)

Mast Cell Activation



Affected Behavior

Is there Anything Linking Genes, Environment and Mast cells?

Review

mTOR signaling: At the crossroads of plasticity, memory and disease

Charles A. Hoeffer and Eric Klann

Center for Neural Science, New York University, 4 Washington Place, Room 809, New York, NY 10003, USA

Trends in Neurosciences Vol.33 No.2

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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.

blood

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

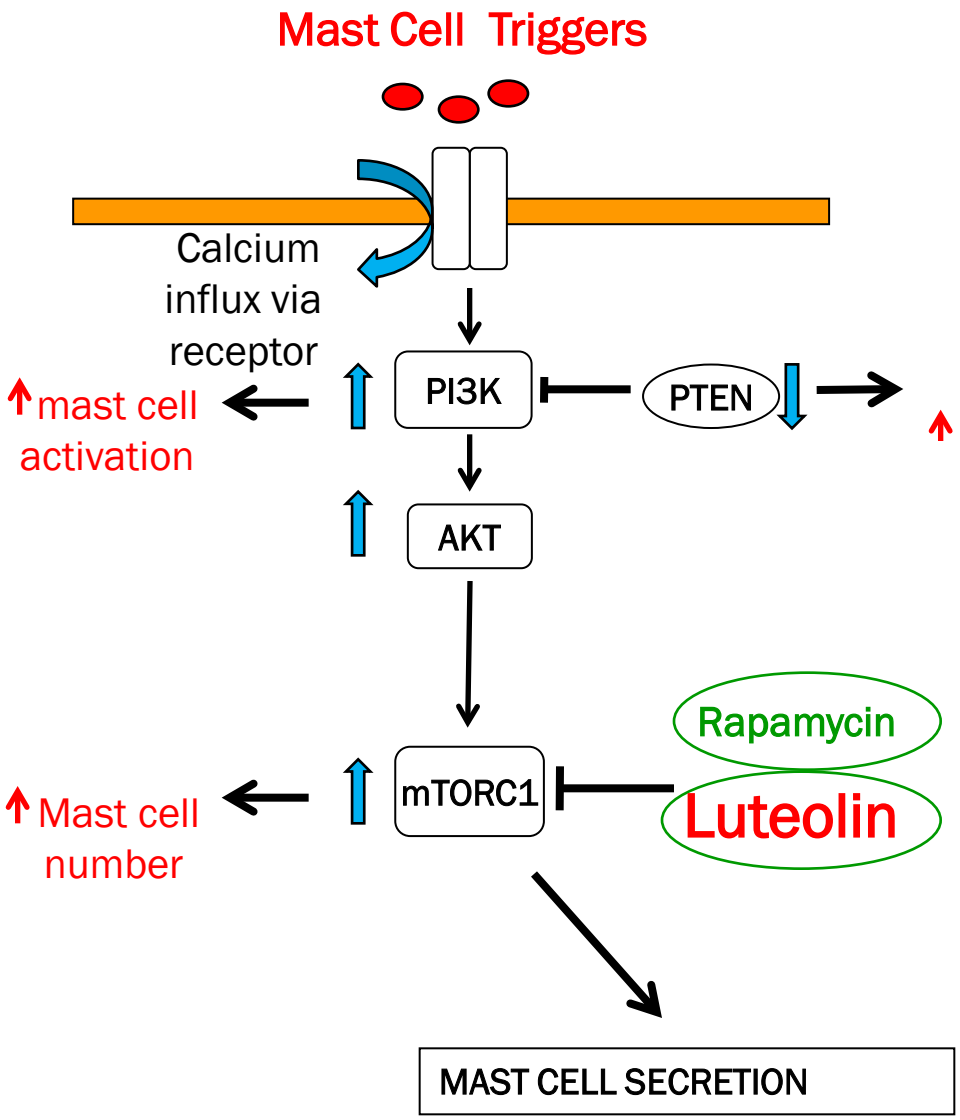
PTEN deficiency in mast cells causes a mastocytosis-like proliferative disease that heightens allergic responses and vascular permeability

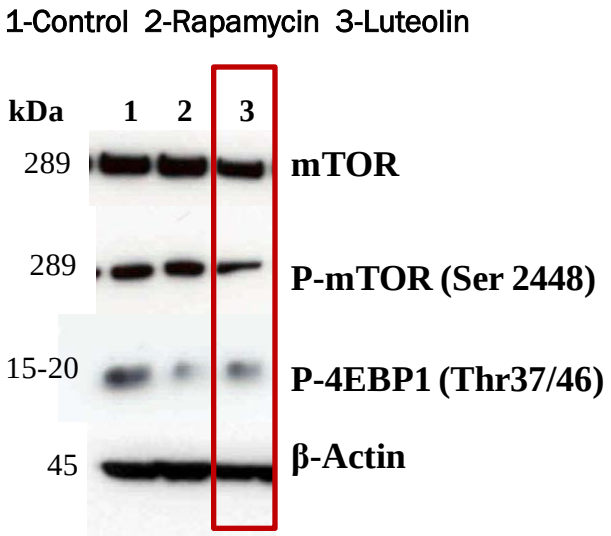
Yasuko Furumoto, Nicolas Charles, Ana Olivera, Wai Hang Leung, Sandra Dillahunt, Jennifer L. Sargent, Kevin Tinsley, Sandra Odom, Eric Scott, Todd M. Wilson, Kamran Ghoreschi, Manfred Kneilling, Mei Chen, David M. Lee, Silvia Bolland and Juan Rivera

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

Are there Any Effective Mast Cell Blockers?

Amitriptyline and Prochlorperazine Inhibit Proinflammatory Mediator Release From Human Mast Cells

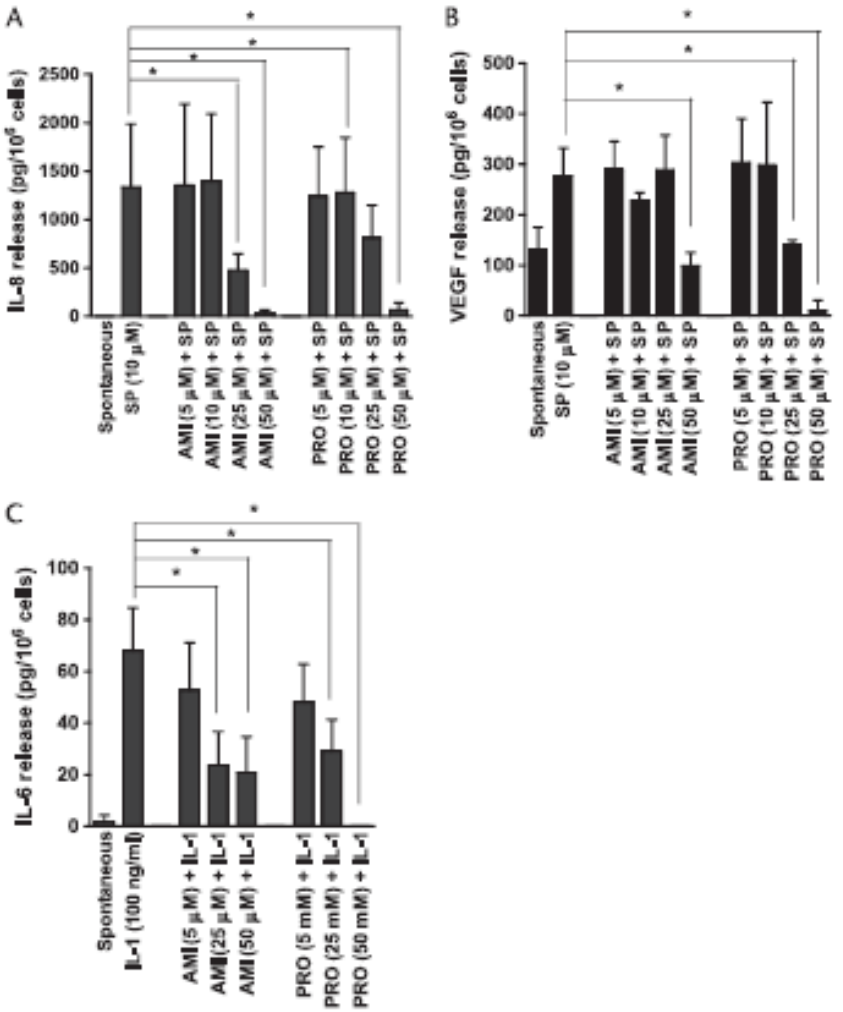
Possible Relevance to Chronic Fatigue Syndrome

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)



International Archives of Allergy and Immunology

Original Paper

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Received: December 20, 2008
Accepted after revision: March 25, 2009
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

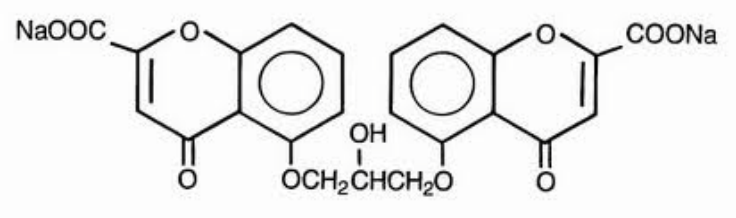
Contents lists available at ScienceDirect

ELSEVIER

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 [*,†,‡,§,‖]

Are there Any Mast Cell Blockers ?



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

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†Centro de Estudios de Mastocitosis de Castilla La Mancha, Hospital Virgen del Valle, Toledo, Spain

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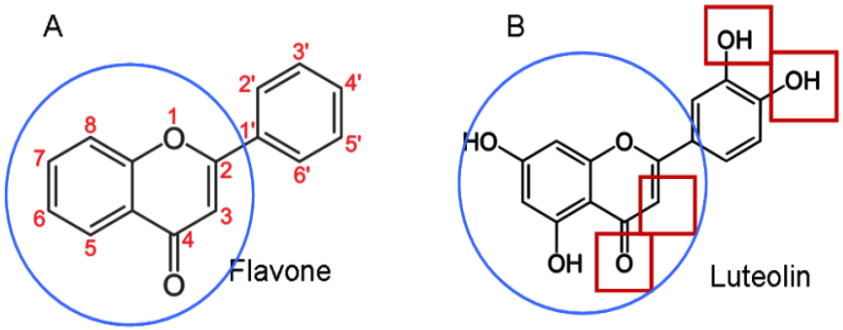
The Effects of Plant Flavonoids on Mammalian Cells: Implications for Inflammation, Heart Disease, and Cancer

ELLIOTT MIDDLETON, JR.,† CHITHAN KANDASWAMI, AND THEOHARIS C. THEOHARIDES[1]

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:

1. **Anti-oxidant**
2. **Anti-inflammatory**
3. **Mast cell inhibitors**
4. **Metal chelators**
5. **Neuroprotective**

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British Journal of Pharmacology (2005) 145, 934–944

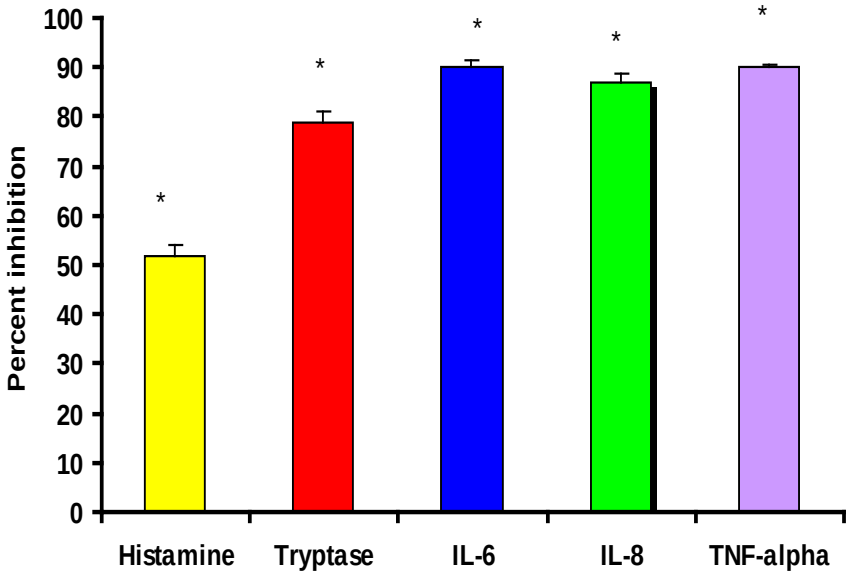
www.nature.com/bjp

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 quercetin.

Inhibition of inflammatory molecules by quercetin from human mast cells



Available online at www.sciencedirect.com
ScienceDirect
Journal of Nutritional Biochemistry xx (2010) xxx–xxx
Journal of Nutritional Biochemistry

Luteolin inhibits cytokine expression in endotoxin/cytokine-stimulated microglia

Tsung-Kuei Kao[a,1], Yen-Chuan Ou[1,b], Shih-Yi Lin[c], Hung-Chuan Pan[d], Pei-Jyuan Song[e], Shue-Ling Raung[f], Ching-Yi Lai[f], Su-Lan Liao[f], Hsi-Chi Lu[e], Chun-Jung Chen[f,g,h,i,*]

PNAS

Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1

Saebyeol Jang*†, Keith W. Kelley*†‡§, and Rodney W. Johnson*†‡¶

*Division of Nutritional Sciences, †Integrative Immunology and Behavior Program, ‡Department of Animal Sciences, and §Department of Pathology, University of Illinois at Urbana–Champaign, 1207 West Gregory Drive, Urbana, IL 61801

Communicated by David H. Baker, University of Illinois at Urbana–Champaign, Urbana, IL, March 25, 2008 (received for review January 31, 2008)

Luteolin, a flavonoid found in high concentrations in celery and green pepper, has been shown to reduce production of proinflam- cytokine production by activated microglia may be useful for preventing neurobehavioral deficits and neurodegeneration.

Treatment of refractory interstitial cystitis/ painful bladder syndrome with CystoProtek – an oral multi-agent natural supplement

T. C. Theoharides, PhD,[1,2,3] D. Kempuraj, PhD,[1] S. Vakali, MD,[1] G. R. Sant, MD[4]

© The Canadian Journal of Urology™; 15(6); December 2008

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

Mast Cell Inhibition Video

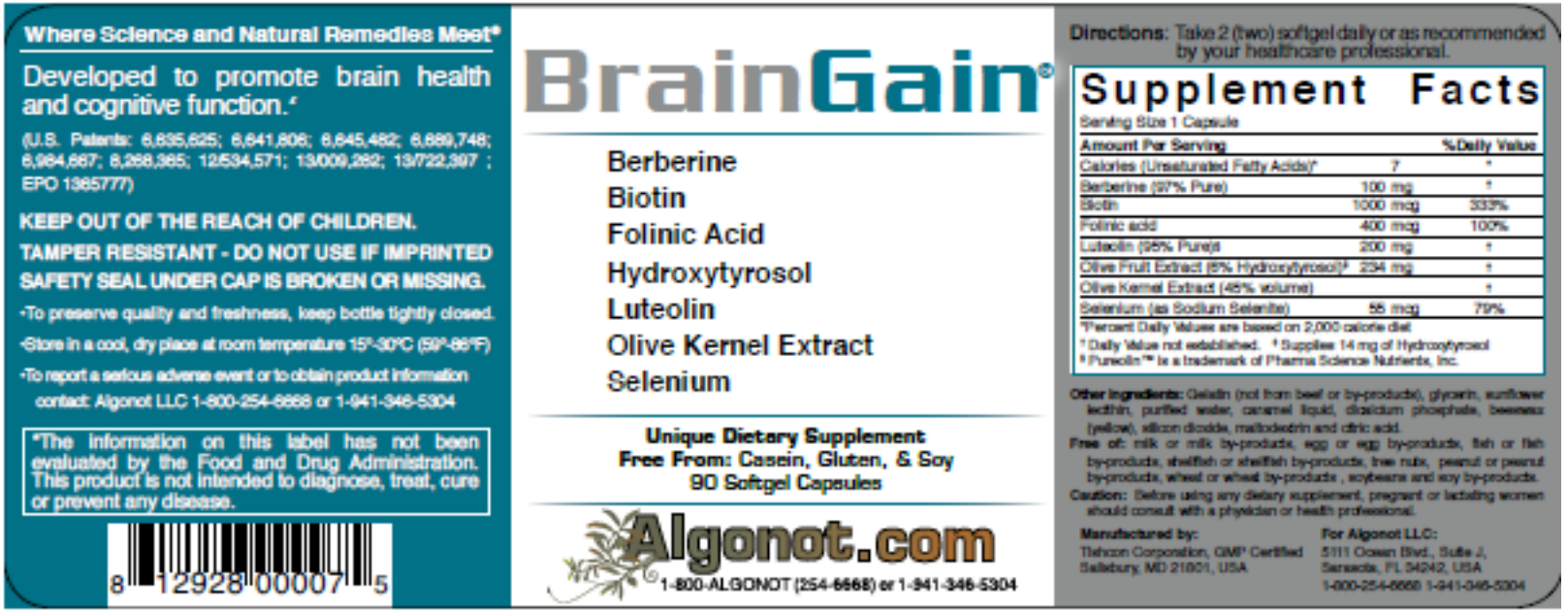
Disclosure

Dr. Theoharides is Medical Director
and holds a major interest in Algonot, LLC

www.algonot.com

NeuroProtek®
US Trademark
3,225,924

Portion of any profits will be donated to autism research. NeuroProtek®



(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)

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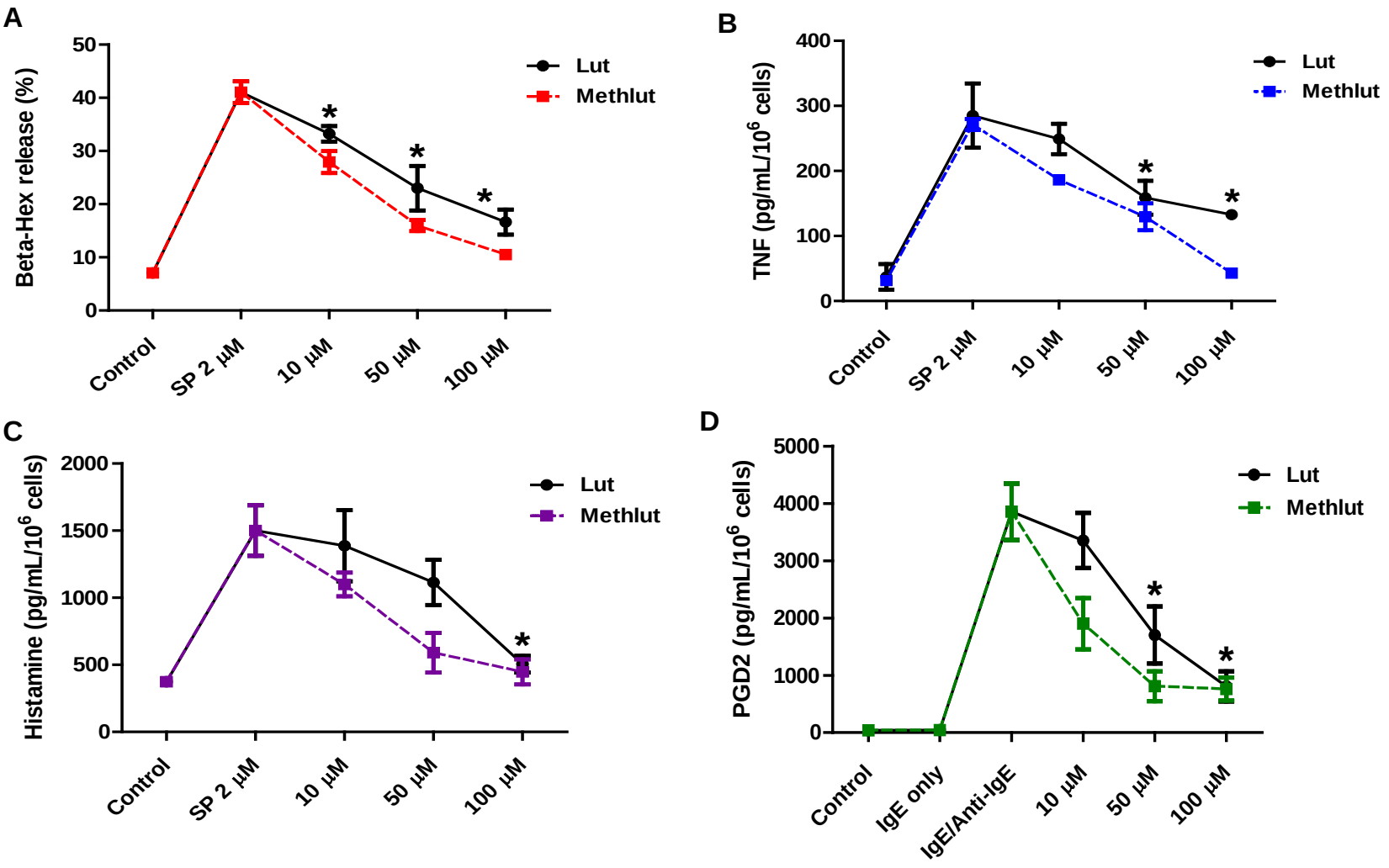
Brain Inflammation, Neuropsychiatric Disorders, and Immunoendocrine Effects of Luteolin

Theoharis C. Theoharides, BA, MS, MPhil, MD, PhD,†‡§ Pio Conti, DSc,‖ and Marina Economu, MD, DSc¶*

Naturally, the question of safety especially in children is an important one. However, any results based on "cell culture models" are fraught with danger of misleading conclusions. Only well-designed studies using in vivo models and clinical trials on appropriate patient populations[57] can provide convincing evidence of tolerability and effectiveness.[58]

In conclusion, flavonoids such as luteolin and quercetin cannot be called *hormonal disruptors*. Luteolin, as other flavonoids, can affect liver metabolism and possibly sex hormone levels, but its anticancer effects are more significant than any effect on hormonal homeostasis.

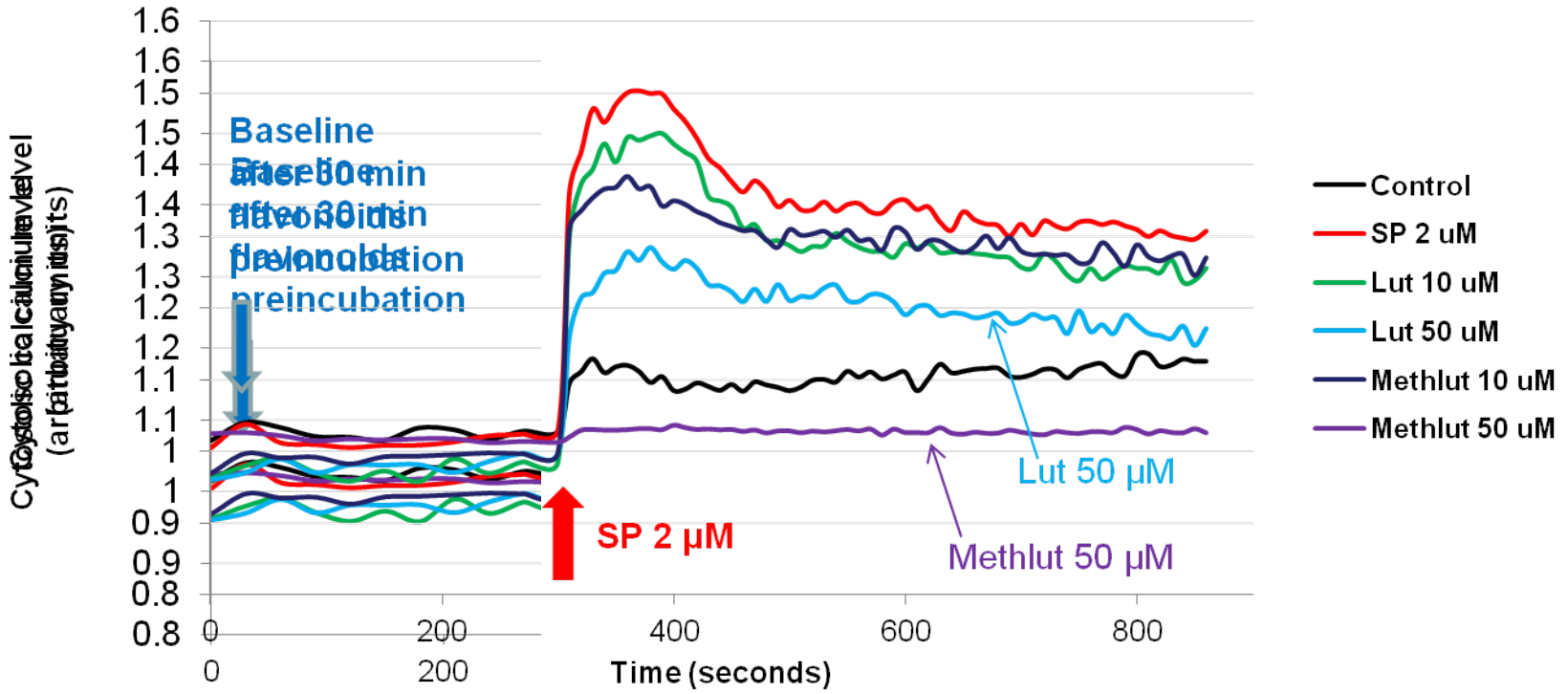
Effect of Luteolin and Methoxyluteolin on MC Secretion



Flavonoids → Trigger

30 min 30 min

Intracellular Calcium Elevation in MC



Cell viability > 95%

Comparative Characteristics of Algonot Dietary Supplements

Formulation	Actions	Mastocytosis "Brain Fog"	Chronic Fatigue Syndrome/ Fibromyalgia	Interstitial Cystitis/Bladder Pain Syndrome	Autism Spectrum Disorders
Algonot-plus®					
Chrondroitin Glusosamine	Tissue Protective	✓		✓	
Quercetin	Anti-inflammatory Mast cell blocker				
OKE*	Antioxidant				
BrainGain®					
Berberine	Anti-bacterial/viral	✓	✓		✓
Folic acid Hydroxytyrosol Selenium	Neuroprotective				
Luteolin	Anti-inflammatory Mast cell blocker				
OKE*	Antioxidant				
CystoProtek®					
Chondroitin Glucosamine Hyaluronate	Tissue Protective			✓	
Quercetin	Anti-inflammatory Mast cell blocker				
OKE*	Antioxidant				
FibroProtek®					
L-Carnitine CoQ12	Energy provider	✓	✓	✓	✓
Luteolin Quercetin	Mast cell blocker				
Willow Extract	Pain reliever				
OKE*	Antioxidant				
NeuroProtek®					
Luteolin Quercetin	Anti-inflammatory Mast cell blocker	✓			
Rutin					
OKE*	Antioxidant				
MethlutForte®	Potent mast cell blocker	✓	✓	✓	✓

*Olive Kernel Extract

Research Funding:

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- AR60951
- NS66205

- Autism Research Collaborative
- National Autism Association
- Safe Minds
- Autism Research Institute
- Jane B Johnson Fnd.

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www.brain-gate.org