The Mast Cell: A Cell for All Seasons

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www.mastcellmaster.com
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www.brain-gate.org
What Are Mast Cells and What is Mastocytosis?
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 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
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
- 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.

<table>
<thead>
<tr>
<th>Major criterion</th>
<th>Multifocal, dense infiltrates of mast cells (≥ 15 mast cells in aggregates) detected in intramedullary biopsy sections and/or extramedullary organ(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor criteria</td>
<td>In intramedullary biopsy sections or other extramedullary ones, &gt;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, &gt;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 CD2 and/or CD25 in bone marrow, blood or other extracutaneous organ, in addition to normal mast cell markers. Persistently elevated baseline serum total tryptase (&gt;20 ng/ml). In the occasion that a clonal myeloid disease exists, this criterion is considered invalid.</td>
</tr>
</tbody>
</table>

MCAD: Mast cell activation disorder.
Data taken from [45].
<table>
<thead>
<tr>
<th>MCADs</th>
<th>Immunohistochemical findings of bone marrow trephine biopsy specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM (mainly indolent/bone marrow mastocytosis, rarer aggressive or leukemic)</td>
<td>Multifocal compact mast cell infiltrates</td>
</tr>
<tr>
<td>SM (indolent/bone marrow mastocytosis)</td>
<td>Increase in loosely scattered spindle-shaped mast cells with CD25 expression, KIT D816V mutation and chronically elevated serum tryptase, but without compact tissue infiltrates</td>
</tr>
<tr>
<td>MMAS</td>
<td>Increase in loosely scattered spindle-shaped mast cells with KIT D816V mutation, ambiguous presence of CD25 (+) and normal serum tryptase</td>
</tr>
<tr>
<td>Secondary (mast cell hyperplasia) and Idiopathic MCAD</td>
<td>Increase in loosely scattered round mast cells without CD25 and KIT D816V</td>
</tr>
</tbody>
</table>

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,*
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.
Spectrum of mast cell activation disorders


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?

**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

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).

A

Tryptase (ng/5x10^5 MC)

IL-1

anti-IgE

B

IL-6 (pg/5x10^5 MC)

IL-1

anti-IgE

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
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.

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Mediator</th>
<th>Pathophysiological Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRH</td>
<td>VEGF</td>
<td>Disrupts BBB</td>
</tr>
<tr>
<td>IL-1</td>
<td>IL-6</td>
<td>Th-17 cell maturation</td>
</tr>
<tr>
<td>IL-33</td>
<td>IL-6, VEGF</td>
<td>Disrupt BBB</td>
</tr>
<tr>
<td>LPS</td>
<td>TNF-a</td>
<td>Th-17 cell maturation</td>
</tr>
<tr>
<td>SCF</td>
<td>TGF-beta</td>
<td>Th-17 cell maturation</td>
</tr>
<tr>
<td>TLR-9</td>
<td>IL-6</td>
<td>Th-17 cell maturation</td>
</tr>
</tbody>
</table>
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, Bodi Zhang, Duraisamy Kempuraj, Michael Tagen, Magdalini Vasiadi, Asimenia Angelidou, Konstantinos-Dionysis Alysandratos, Dimitris Kalogeromitros, Shahrzad Asadi, Nikolaos Stavrianeas, Erika Peterson, Susan Leeman, and Pio Conti

Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Pharmacology and Experimental Therapeutics, Department of

IL-33 (100 ng/ml)     -          +         -        +          -         +
SP (0.1 µM)             -          -          +       +          -         -
SP (0.2 µM)             -          -          -        -          +         +

IL-33 (100 ng/ml)    -        +        -        +
SP (1 µM)                -        -         +       +

VEGF mRNA expression

VEGF (pg/10^6 cells)

*Significant difference
Divergent Actions of Mast Cells

ANAPHYLACTIC DEGRANULATION

IgE + antigen
Neuropeptides

DIFFERENTIAL RELEASE WITHOUT DEGRANULATION

CRH, SCF, IL-1, LPS

Allergic and anaphylactic responses

Inflammation

Compound exocytosis

Intragranular activation
Do Mast Cells Secrete Autopathogens?
Lynn Margulis (1938–2011)

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, Konstantinos-Dionysios Alysandratos, MD, Asimena Angelidou, MD, Shahrzad Asadi, PharmD, Nikolaos Sismanopoulos, MD, Danae-Anastasia Delivanis, MD, Zuyi Weng, MS, Alexandra Miniati, MD, Magdalini Vasiadi, BS, Alexandra Katsarou-Katsari, MD, PhD, Benchun Miao, PhD, Susan E. Leeman, PhD, Dimitrios Kalogeromitros, MD, PhD, and Theoharis C. Theoharides, MS, PhD, MD

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

Mitochondria

Extracellular Mitochondrial components

- Endothelial cells → VEGF
- Neutrophils → IL-8
- Mast cells → IL-8, TNF
- Microglia → IL-1, IL-6
- Neurons → Caspase-3

Brain Inflammation

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

Knut H. Lauritzen,1 Olve Moldestad,2 Lars Eide, Harald Carlsen, Gaute Nesse, Johan F. Storm, Isabelle M. Mansuy, Linda H. Bergersen, and Arne Klungland

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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?
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.

Keywords: mast cell • wound healing • inflammation • cellular proliferation
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.
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Proc. Natl. Acad. Sci. USA
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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

Mona H. Khalil, Ann-Judith Silverman, Rae Silver

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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

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

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.
Review

Mast cells: Versatile gatekeepers of pain

Devavani Chatterjee a, Tijana Martinov
Department of Biology, Macalester College, St. Paul, MN, USA

Review article

A focus on mast cells and pain

Anne Héron a,*, David Dubayle b

* Physiology Department, Faculty of Pharmaceutical and Biological Sciences, Paris Descartes University, 4 avenue de l’Ombilatoire, F-75270 Paris Cedex 06, France
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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?
Perivascular Mast Cells Promote Atherogenesis and Induce Plaque Destabilization in Apolipoprotein E–Deficient Mice
Circulation 2007;115:2516-2525; originally published online Apr 30, 2007; DOI: 10.1161/CIRCULATIONAHA.106.660472

LETTERS

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

Jian Liu¹, Adeline Divoux², Jiusong Sun¹, Jie Zhang¹, Karine Clément²–⁴, Jonathan N Glickman¹, Galina K Sukhova¹, Paul J Wolters⁵, Juan Du¹, Cem Z Gorgun⁶, Alessandro Doria⁷, Peter Libby¹, Richard S Blumberg¹, Barbara B Kahn⁸, Gökhan S Hotamisligil⁶ & Guo-Ping Shi¹
Mast cells squeeze the heart and stretch the gird: Their role in atherosclerosis and obesity

Theoharis C. Theoharides, Nikolaos Sismanopoulos, Danae-Anastasia Delivanis, Bodi Zhang, Efthimiou E. Hatzigeorgiou, and Dimitrios Kalogeromitros

Review Article

Do mast cells link obesity and asthma?

N. Sismanopoulos, D-A. Delivanis, D. Mavrommati, E. Hatzigeorgiou, P. Conti & T. C. Theoharides
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.

[Diagram showing interactions between mast cells and angiogenic molecules]
Review

The role of mast cells in migraine pathophysiology

Theoharis C. Theoharides*, Jill Donelan, Kristiana Kandere-Grzybowska¹, Aphrodite Konstantinidou²

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

Editorial

Atopic Conditions in Search of Pathogenesis and Therapy

Mast Cell

- Multiple Chemical Sensitivity
- Food allergy & intolerance
- Mast cell activation
- Allergy & Asthma
- Interstitial cystitis
- Chronic fatigue s.
- Autism
- Fibromyalgia

Edvard Munch, *The Scream* (Skrik, 1893)
Do Mast Cells Exist in the Brain and are Do They Get Stressed Out?
MINIREVIEW

MAST CELLS: THE IMMUNE GATE TO THE BRAIN

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

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(Received in final form January 4, 1990)
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

<table>
<thead>
<tr>
<th>Postnatal Age (Days)</th>
<th>Number of Mast Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cells/Brain</td>
</tr>
<tr>
<td>1</td>
<td>6,500 ± 519</td>
</tr>
<tr>
<td>3</td>
<td>10,332 ± 864</td>
</tr>
<tr>
<td>5</td>
<td>13,200 ± 790</td>
</tr>
<tr>
<td>6</td>
<td>12,640 ± 721</td>
</tr>
<tr>
<td>10</td>
<td>11,000 ± 866</td>
</tr>
<tr>
<td>14</td>
<td>9,300 ± 730</td>
</tr>
<tr>
<td>21</td>
<td>6,600 ± 770</td>
</tr>
<tr>
<td>24</td>
<td>3,152 ± 320</td>
</tr>
<tr>
<td>60</td>
<td>2,295 ± 231</td>
</tr>
</tbody>
</table>
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.

Stress and Skin Mast Cells

Hypothesis
Stress activates mast cells leading to skin inflammation

HPA axis
Hypothalamus: CRH
Pituitary: ACTH

Limbic & Neurosensory signals

Sensory nerve
Mast cell

Blood vessel
CRH, IL-1, NT, SP, viruses

SKIN
Histamine, IL-6, TNF, tryptase

PROINFLAMMATORY
↑ vascular permeability

Local effects

Triggering or exacerbating Dermatitis, Flushing
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

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

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

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

Jing Cao,*† Nikoletta Papadopoulou,† Duraisamy Kempuraj,† William S. Boucher,† Koreaki Sugimoto,‡ Curtis L. Cetrulo,§ and Theoharis C. Theoharides³*†§

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

4/6/2014  Copyright by Dr. TC Theoharides  57
Corticotropin-releasing hormone induces skin vascular permeability through a neurotensin-dependent process


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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**VEGF**

control 1nM 10nM 100nM 1μM

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

Theoharis C. Theoharides¹,²,³, Jill M. Donelan¹, Nikoletta Papadopoulou¹, Jing Cao³, Duraisamy Kempuraj¹ and Pio Conti⁴
Substance P (SP) Induces Expression of Functional Corticotropin-Releasing Hormone Receptor-1 (CRHR-1) in Human Mast Cells

Shahrzad Asadi, Konstantinos-Dionysios Alysandratos, Asimenia Angelidou, Alexandra Miniati, Nikolaos Sismanopoulos, Magdalini Vasiadi, Bodi Zhang, Dimitrios Kalogeromitros and Theoharis C. Theoharides

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

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

L. Maintz, E. Wardelmann, K. Walgenbach, R. Fimmers, T. Bieber, U. Raap & N. Novak

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

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 many CRH-R1-positive 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
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\textsuperscript{1,2}, Anastasia I. Petra, MD\textsuperscript{1}, Julia M. Stewart, RN\textsuperscript{1}, Irene Tsilioni, PhD\textsuperscript{1}, Cem Akin, MD, PhD\textsuperscript{1}
Do Allergic Symptoms Affect Behavior?
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*
Prenatal negative life events increases cord blood IgE: interactions with dust mite allergen and maternal atopy
J. L. Peters¹, S. Cohen², J. Staudenmayer³, J. Hosen⁴,⁵, T. A. E. Platts-Mills⁴ & R. J. Wright⁶,⁷

¹Department of Environmental Health, Boston University School of Public Health, Boston, MA, USA; ²Department of Psychology, Carnegie Mellon University, Pittsburgh, PA, USA; ³Department of Mathematics and Statistics, University of Massachusetts, Amherst, MA, USA;
⁴Division of Allergy and Clinical Immunology, University of Virginia, Charlottesville, VA, USA; ⁵Department of Entomology, University of Maryland, College Park, MD, USA; ⁶Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA; ⁷The 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

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

Angelica Ronald, Craig E. Pennell and Andrew J. O. Whitehouse

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

Review

Prenatal stress and risk for autism

Dennis K. Kinney, Kerim M. Munir, David J. Crowley, Andrea M. Miller

* Mailman Research Center, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA
* Department of Psychiatry, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA
* Division of Developmental Medicine and Department of Psychiatry, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115, USA
There was significant association with food intolerance (P = 0.001).

Asimena Angelidou · Konstantinos-Dionysios Alysandratos · Shahrzad Asadi · Bodi Zhang · Konstantinos Francis · Magdalini Vasiadi · Dimitrios Kalogeromitros · Theoharis C. Theoharides
Association between atopic diseases and attention-deficit/hyperactivity disorder in childhood: a population-based case-control study

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

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

Wieslaw Jedrychowski \textsuperscript{4,*}, Umberto Maugeri \textsuperscript{b,f}, Frederica Perera \textsuperscript{c}, Laura Stigter \textsuperscript{c}, Jeffrey Jankowski \textsuperscript{d}, Maria Butscher \textsuperscript{e}, Elzbieta Mroz \textsuperscript{d}, Elzbieta Flak \textsuperscript{d}, Anita Skarupa \textsuperscript{d}, Agata Sowa \textsuperscript{d}
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

Abstract

Etiology of autism has become an area of 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?
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

Activation and function of the mTORC1 pathway in mast cells

Mi-Sun Kim, Hye Sun Kuehn, Dean D. Metcalfe, and Alasdair M. Gilfillan
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.
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 Kneillling, Mei Chen, David M. Lee, Silvia Bolland and Juan Rivera

Activation and function of the mTORC1 pathway in mast cells

Mi-Sun Kim, Hye Sun Kuehn, Dean D. Metcalfe, and Alasdair M. Gilfillan

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.
Mast Cell Triggers

Calcium influx via receptor

↑ mast cell activation

PI3K

PTEN

↑ Mast cell number

AKT

mTORC1

Rapamycin

Luteolin

↑ Mast cell number

MAST CELL SECRETION

Luteolin inhibits mTOR activation

1-Control 2-Rapamycin 3-Luteolin

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mTOR

P-mTOR (Ser 2448)

P-4EBP1 (Thr37/46)

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

Magdalini Vasiadi, Dimitris Kalogeromitros, Duraisamy Kempuraj, Anthony Clemons, Bodi Zhang, Caterina Chliva, Michael Makris, Adam Wolfberg, Michael House, Theoharis C. Theoharides

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 D2 synthesis). However, under the conditions tested, cromolyn did not inhibit those mast cell-dependent responses in mice.

Concise Communication

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, Allergic-Centrum-Charité, Charité – Universitätsmedizin Berlin, 10117 Berlin, Germany
*Institute for Biostatistics and Clinical Epidemiology, Charité – Universitätsmedizin Berlin, Berlin, Germany
†Centro de Estudios de Mastocitos de Castilla La Mancha, Hospital Virgen del Valle, Toledo, Spain
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:

1. Anti-oxidant
2. Anti-inflammatory
3. Mast cell inhibitors
4. Metal chelators
5. Neuroprotective
Flavonols inhibit proinflammatory mediator release, intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells

1Duraisamy Kempuraj, 1Bhuvaneshwari Madhappan, 1Spyridon Christodoulou, 1William Boucher, 1,2Jing Cao, 1Nikoletta Papadopoulou, 3Curtis L. Cetrulo & *,1,2,*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.
Luteolin inhibits cytokine expression in endotoxin/cytokine-stimulated microglia

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

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

Saebyeol Jang\textsuperscript{**}, Keith W. Kelley\textsuperscript{**}, and Rodney W. Johnson\textsuperscript{**}

\textsuperscript{*Division of Nutritional Sciences, \textsuperscript{1}Integrative Immunology and Behavior Program, \textsuperscript{4}Department of Animal Sciences, and \textsuperscript{5}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 proinflamm- 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, MD4

© 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, MD1; Elias Zintzaras, MSc, PhD2; Lefteris Lykouras, MD, PhD1; and Kostantinos Francis, MD, PhD1

1Second Department of Psychiatry, Athens University Medical School, “Attikon” General Hospital, Athens, Greece; and 2Department 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

Research by leading physicians is the cornerstone of our work and has produced this special flavonoid based anti-inflammatory compound of natural components that work together to promote normal, healthy tissues and nerves.* These ingredients are combined with unrefined olive kernel oil from Greece to increase absorption. All our products are certified by an independent testing laboratory to ensure accurate amounts and purity of ingredients. U.S. Patents 6,635,625; 6,641,806; 6,645,482; 6,689,748; 6,904,667 & 10/811826; EPO 1365777.

Manufactured by: GMP Certified, Thaicom Corp., Salisbury, MD 21081, USA
Distributed by: Algonot LLC, 5111 Ocean Blvd, Suite J, Sarasota, FL 34242, USA

*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

NeuroProtek®
US Trademark
3,225,924

Portion of any profits will be donated to autism research. NeuroProtek®
**United States Patent**

**Theoharides**

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

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

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

**Publication:**

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- 6,579,544 B1, 6/2003, Rosenberg et al.
- 6,583,123 B2, 6/2003, Henderson et al.
Brain Inflammation, Neuropsychiatric Disorders, and Immunoendocrine Effects of Luteolin

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 can provide convincing evidence of tolerability and effectiveness.

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

**A**

Beta-Hex release (%)

Control

- Lut
- Methlut

**B**

TNF (pg/mL/10^6 cells)

Control

- Lut
- Methlut

**C**

Histamine (pg/mL/10^6 cells)

Control

- Lut
- Methlut

**D**

PGD2 (pg/mL/10^6 cells)

Control

- Lut
- Methlut

Flavonoids and Trigger

30 min

Copyright by Dr. TC Theoharides.
Intracellular Calcium Elevation in MC

Cell viability > 95%
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<td>Quercetin</td>
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*Olive Kernel Extract
Research Funding:

- DK62861
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- NS071361
- NS55681
- AR60951
- NS66205

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

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