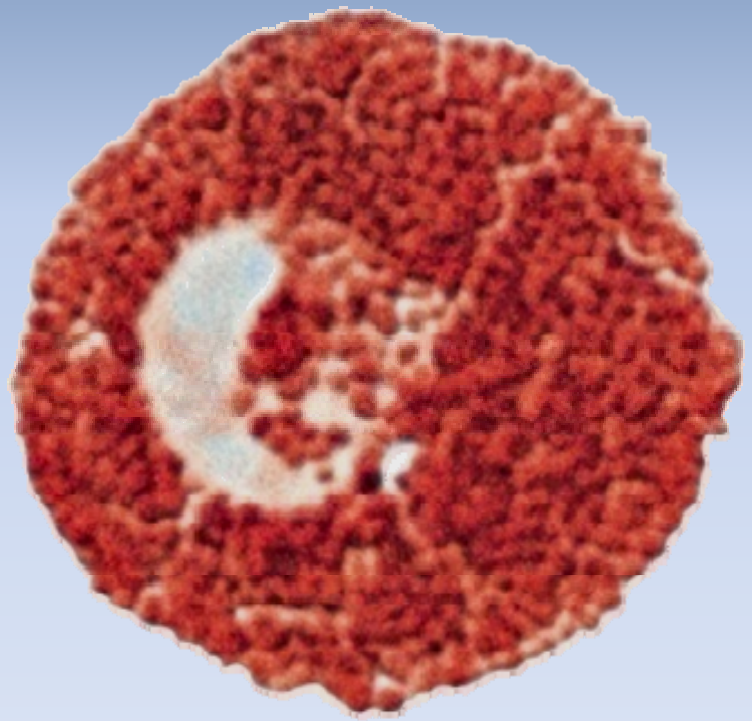
La ricerca come opportunità terapeutica

Roma, 9 febbraio 2011

Dr. Raffaele Migliaccio

Il ruolo fondamentale del mastocita



1879 - Il Mastocita viene individuato e localizzato

Paul Ehrlich (1854 – 1915),
farmacologo tedesco,
Premio Nobel per la Medicina 1908





THE MAST CELLS

BY

JAMES F. RILEY
M.B., Ch.B.(Hons.), M.D., Ph.D., D.M.R.T., F.R.C.S.E.
Consultant Radiotherapist, Royal Infirmary, Dundee. Lecturer in Radiotherapy, University of St. Andrews

FOREWORD BY

SIR HENRY DALE
O.M., G.B.E., F.R.C.P., F.R.S.

HISTAMINE IN TISSUE MAST CELLS: MAST CELLS, HISTAMINE AND HEPARIN IN PATHOLOGICAL CONDITIONS

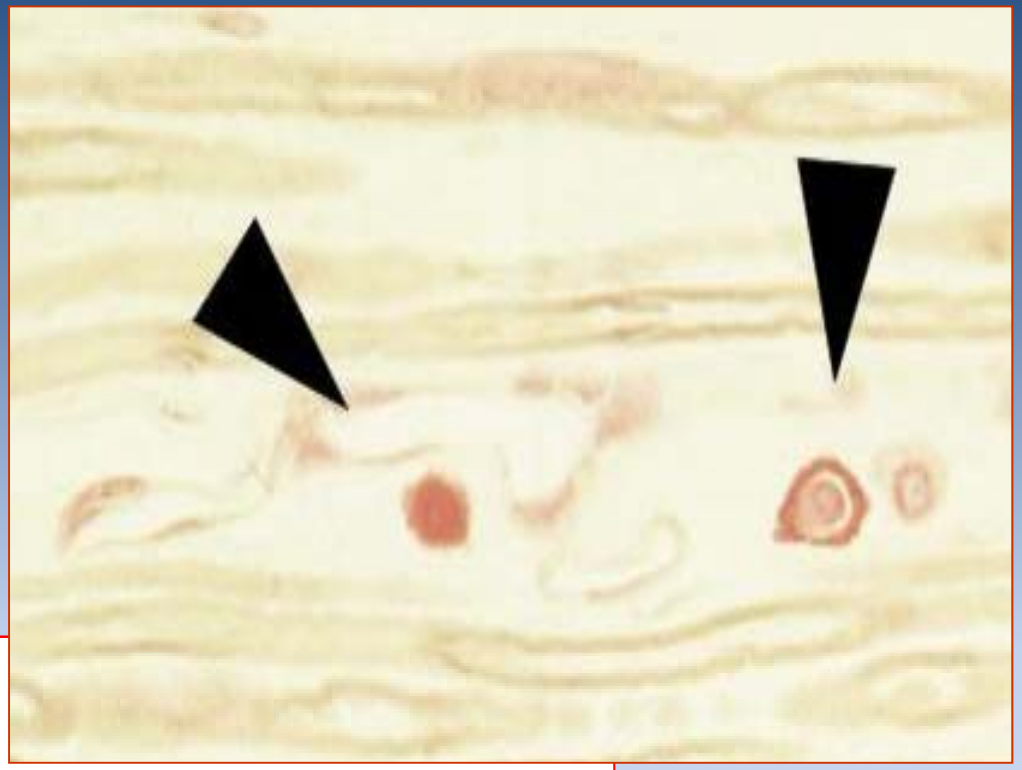
IN view of the apparently close association between the mast cells and histamine in normal tissues, it seemed desirable next to examine certain pathological tissues in which the mast cells are increased in number. Two such conditions are known: urticaria pigmentosa in man, and mast-cell tumours in domestic animals. Both conditions are rare.



E. & S. LIVINGSTONE LTD.
EDINBURGH AND LONDON
1959

1959 -Il Mastocita come liberatore di istamina

1967 -Il Mastocita nel compartimento endoneurale



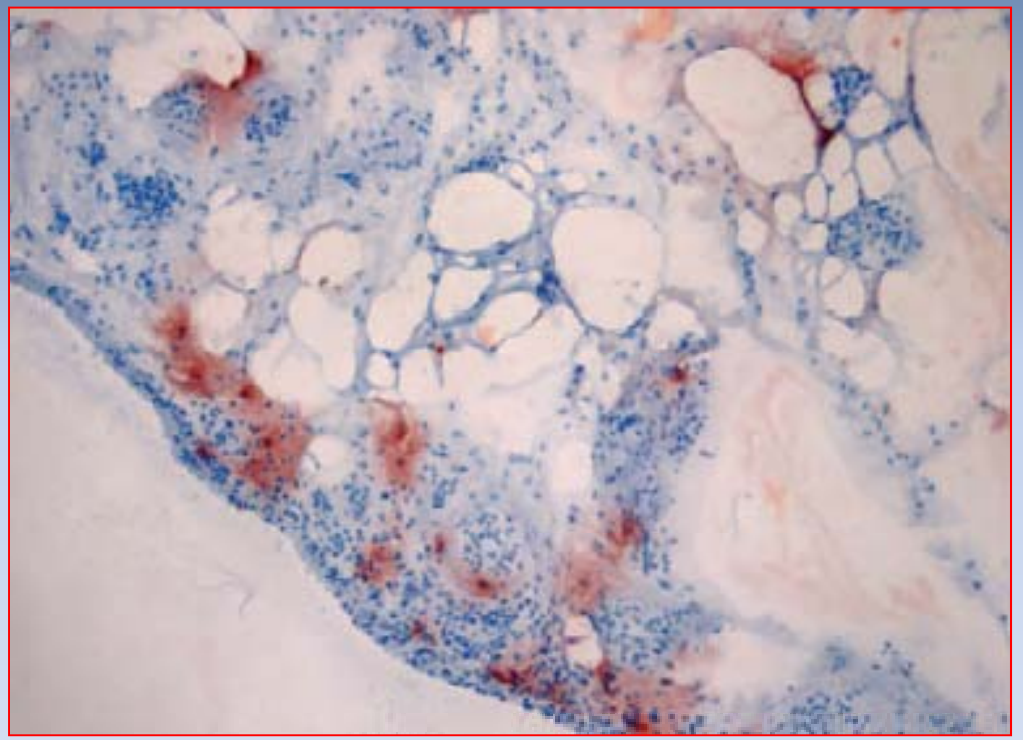
Acta Neurol. Scandinav. 43, 365–374, 1967.

From the Neuropathological Laboratory, Department of Pathology I, University of Göteborg, Sweden.

DEGRANULATION OF MAST CELLS IN PERIPHERAL NERVE INJURIES

YNGVE OLSSON

1986 -Il Mastocita nella capsula articolare



Gruber B et al
Characterization and functional studies of Rheumatoid Synovial Mast Cells – Arthritis Rheum (1986);29:944-955

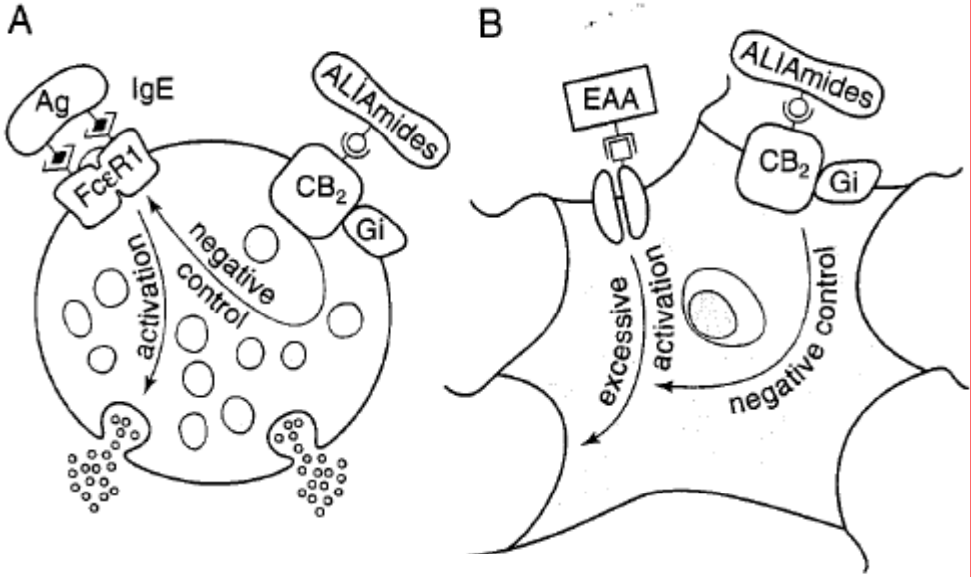
1992 - Il Mastocita è regolato localmente dal meccanismo ALIA; sintetizza, immagazzina e rilascia NGF



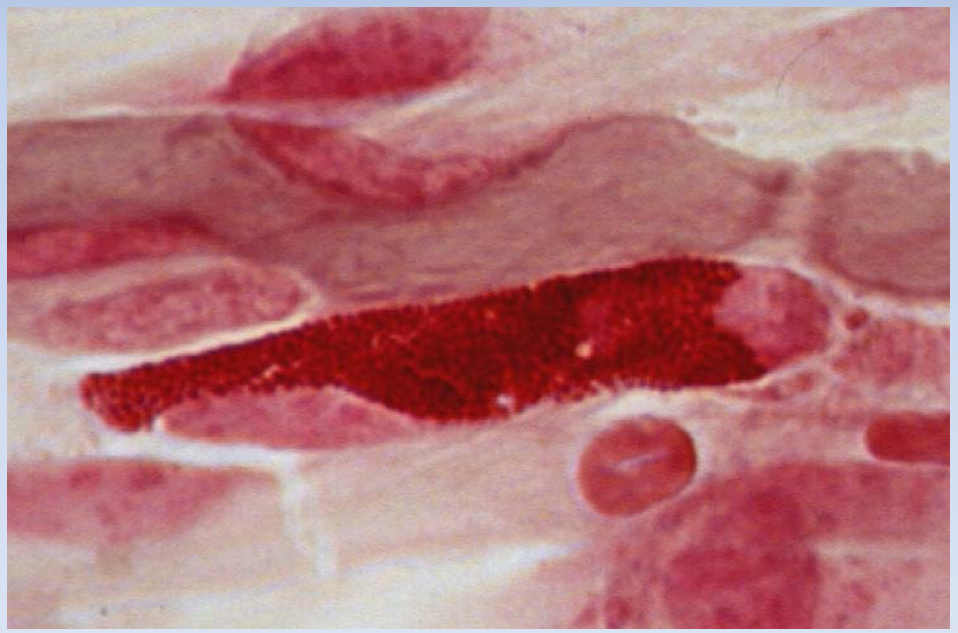
Rita Levi Montalcini
Premio Nobel 1986
per la Medicina

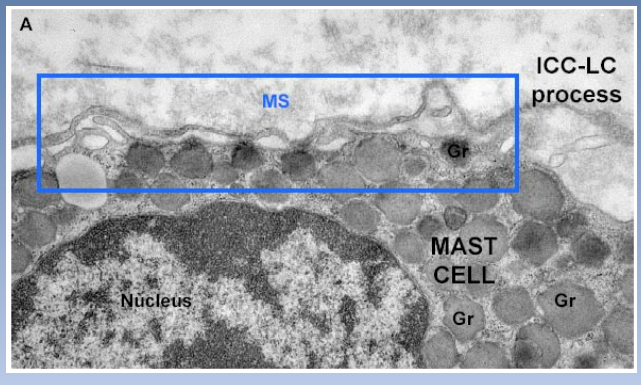
Nerve growth factor: from neurotrophin to neurokine

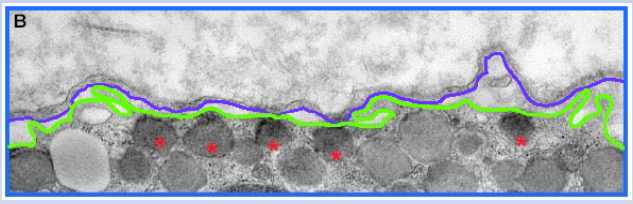
Rita Levi-Montalcini, Stephen D. Skaper, Roberto Dal Toso, Lucia Petrelli and Alberta Leon

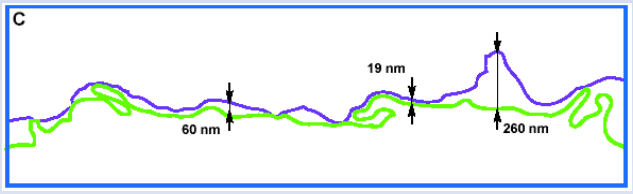


2005 -Il Mastocita crea contatto sinaptico con il nervo





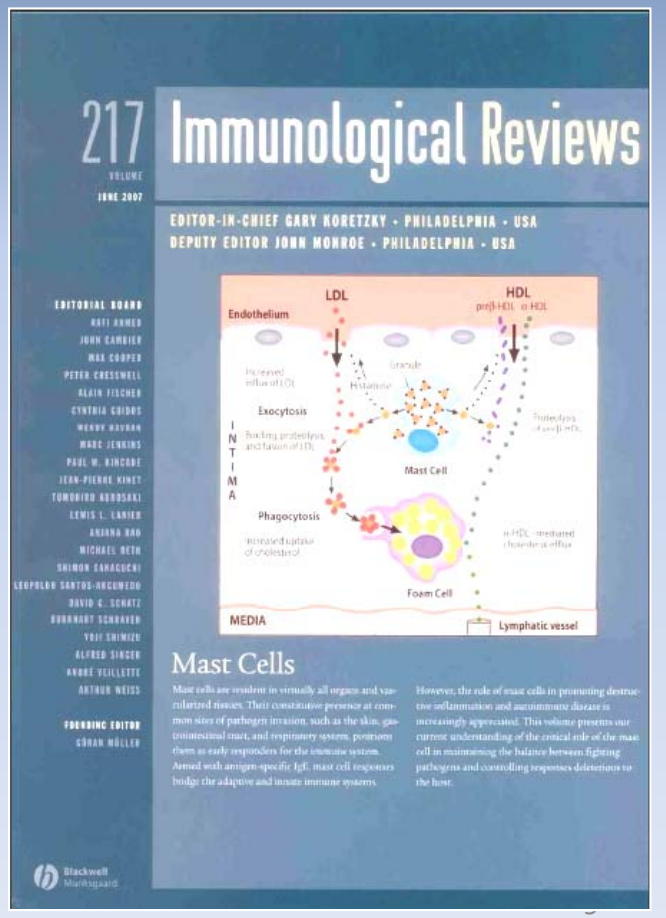




Popescu LM et al, 2005 – J Cell Mol Med 9(3):714-730

2007 -Il Mastocita viene autorevolmente riconosciuto regista dell'infiammazione

"Violins, violas, trumpets, and so on
are necessary to an orchestra,
but only one conductor
directs the music they make.
Following this analogy,
the mast cells are few,
but they are essential
in promoting the
inflammatory response"



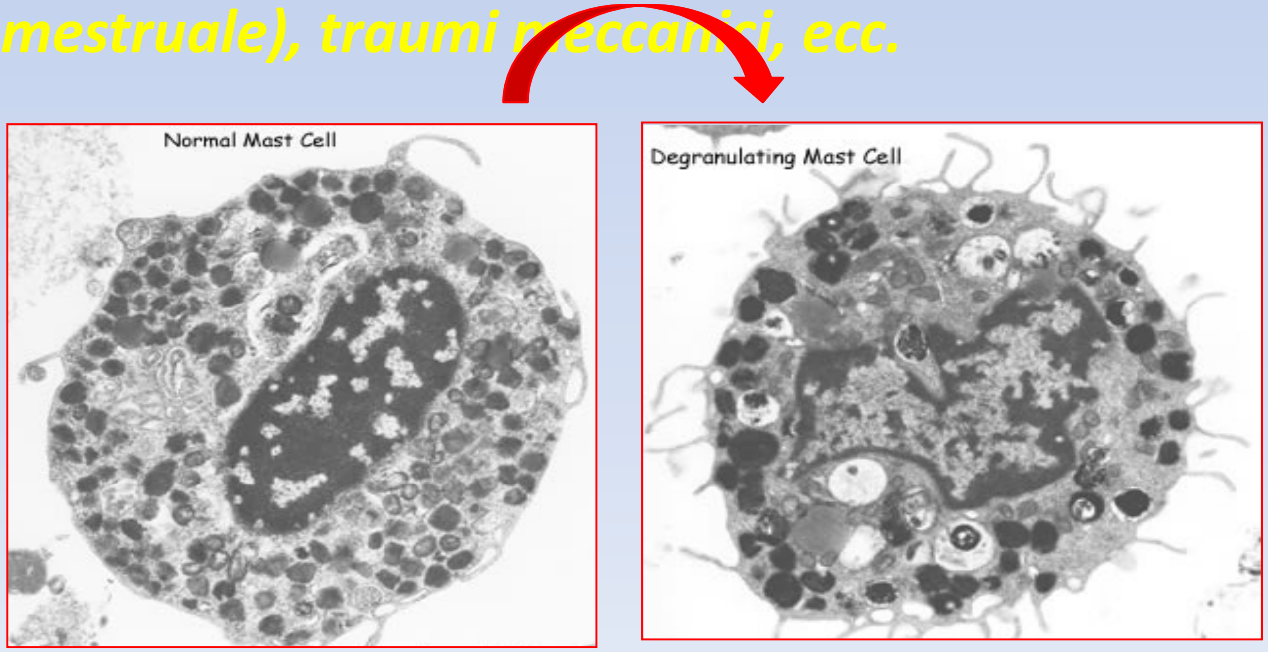
Kinet JP – ***The essential role of mast cells in orchestrating inflammation***
Immunological Reviews 2007;217:5-

Il mastocita

Il mastocita è una cellula specializzata fondamentale nella risposta infiammatoria e algica. Si ritiene oggi che la maggioranza dei quadri clinici caratterizzati da dolore siano sottesi da uno stato infiammatorio di cui il mastocita è il direttore generale. Il suo citoplasma contiene molteplici vescicole, che possono rilasciare nei tessuti, in modo selettivo, citochine infiammatorie,sostanza P, serotonina, fattori vasoattivi, fattori angiogenetici, neurotrofine (quali il Nerve Growth Factor), enzimi a varia azione litica sui connettivi (quali le eparanasi e le triptasi) e molti altri, responsabili di bruciore, dolore, calore, rossore, edema tessutale e lesione funzionale tipici dello stato infiammatorio. Il Nerve Growth Factor è responsabile della proliferazione delle terminazioni nervose del dolore, responsabili dell'iperalgesia periferica, nonché, probabilmente, dell'abbassamento della soglia centrale del dolore.

Il mastocita

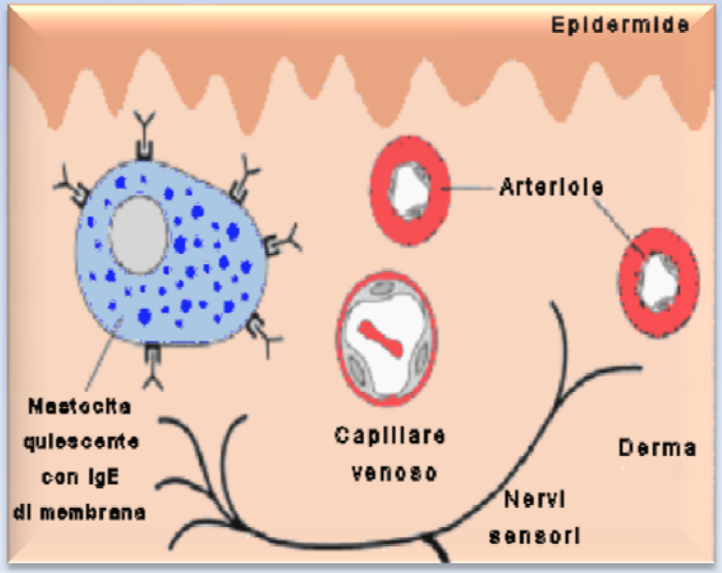
La degranulazione, ossia la liberazione nei tessuti del contenuto delle diverse vescicole, può essere attivata da una serie di stimoli agonisti rappresentati non solo da infezioni (candida, escherichia coli, chlamydia, ureaplasma etc), ma anche danni fisici o chimici (laser , radioterapia, chemioterapia, ecc), estrogeni (responsabili dei flares di dolore in fase premestruale), traumi meccanici, ecc.



Il mastocita

Vi sono sempre più evidenze che il ruolo di "grande trasformatore", di "regista" della Infiammazione Neurogenica" sia svolto dal "mastocita", una cellula immunitaria, contenente numerosi mediatori chimici, dotata di una attività straordinaria.

I mastociti, presenti in tutti i tessuti,mucose ed organi (es. vescica, organi genitali femminili e maschili, intestino, muscoli, etc.), sono localizzati nei tessuti in stretta connessione anatomica e funzionale con i vasi sanguigni e le terminazioni delle fibre nervose.



Il mastocita

Dobbiamo immaginare il mastocita come un'autocisterna che trasporta numerosi contenitori (vescicole) ripieni di diversi mediatori chimici, pronti ad essere rilasciati nei tessuti (degranulazione mastocitaria): citochine, ammine vasoattive, enzimi proteolitici, bradichinina, neuropeptidi, NGF – Nerve Growth Factor, triptasi, istamina, serotonina.

Questi potenti mediatori mastocitari, una volta rilasciati nell'ambiente circostante (tessuti e organi), innescano a cascata i successivi passaggi dell'infiammazione. In condizioni normali, il mastocita ricopre il delicato ruolo di "promotore/controllore" dell'infiammazione, un'azione di difesa utile all'organismo

Il mastocita

Ripetuti episodi infiammatori possono rappresentare fattori di "sovrastimolazione" mastocitaria.

I mastociti rispondono sia moltiplicando di migliaia di volte il loro numero e la loro concentrazione nei tessuti bersaglio, sia incrementando il processo di degranulazione delle vescicole, con conseguente liberazione di una grande quantità di mediatori mastocitari. A causa di tale sovrastimolazione,

il ruolo del mastocita si trasforma, da quello di fondamentale presidio del sistema di difesa, in quello di una "santabarbara in fiamme", in grado di sferrare nell'area tissutale un vero e proprio attacco di "guerra chimica", cioè di infiammazione.

Quali sono le conseguenze dell'infiammazione neurogenica mastocita-indotta a livello di cute e mucose ?

Richiamo di mastociti	→ Aumento del danno
Extravasazione di fluidi	→ Edema tissutale
Extravasazione di cellule infiammatorie	→ Innesco del processo infiammatorio tissutale
Neo-angiogenesi	→ Amplificazione
Abbassamento della soglia del dolore	→ Iperalgesia Allodinia
Neo-innervazione	→ Cronicizzazione

Mastociti: lavori presenti in letteratura



La scoperta del meccanismo ALIA è la conseguenza di un'idea straordinaria e straordinariamente logica suggerita, alla fine del 1991,

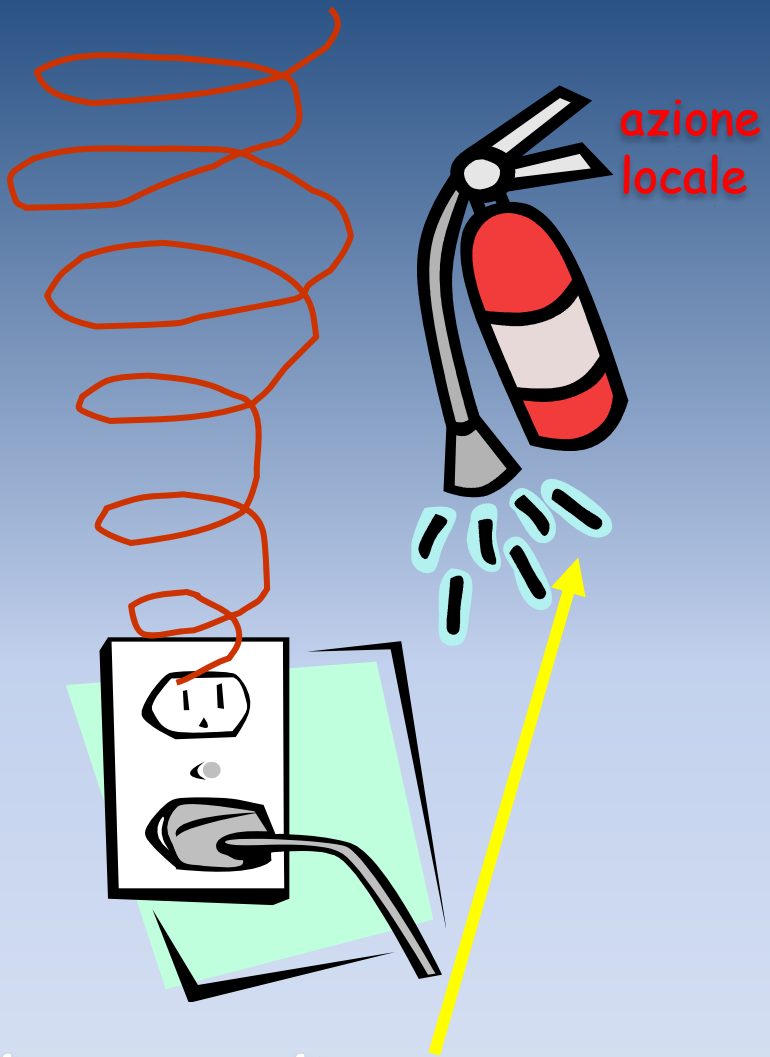


da
Rita Levi Montalcini
Premio Nobel 1986
per la Medicina

quando il fuoco è locale
non è opportuno
ed è anzi dannoso
chiamare
subito i pompieri !



azione
sistemica



azione
locale

è molto meglio tentare
prima di agire localmente
con un'estintore

Agents Actions 39, Special Conference Issue (1993)

0065-4299/93/03C145-03 $1.50 + 0.20/0

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A proposed autacoid mechanism controlling mastocyte behaviour

Luigi Aloe, Alberta Leon[1] and Rita Levi-Montalcini

Institute of Neurobiology, National Research Council, Rome, Italy and [1]Researchlife, Padua, Italy

Abstract

Evidence is provided here supporting the existence of a novel autacoid mechanism negatively modulating mast cell behaviour in response to noxious stimuli *in vivo*; hence, the denomination "autacoid local inflammation antagonism" (ALIA). In particular, as lipid amides of the *N*-acylethanolamine type have been reported to accumulate in tissues in degenerative inflammatory conditions, we examined whether these *N*-acylated lipids could exert regulatory effects on mast cell activation *in vivo*. The results reported show that both long- and short-chain *N*-acylethanolamines, when systemically administered, are effective in reducing mast cell degranulation induced by local injection of substance P in the ear *pinna* of developing rats. These and other data suggest that the endogenous production of *N*-acylethanolamines may constitute a local autocrine/paracrine response for the negative feedback control of mast cell responses to various activating signals. Such a process may be of physio-pathological relevance in the regulation of functional neuro-immune-mast cell interactions.

Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 3376–3380, April 1995
Pharmacology

Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide

L. FACCI, R. DAL TOSO, S. ROMANELLO, A. BURIANI, S. D. SKAPER, AND A. LEON*

Research*life*, 31033 Castelfranco Veneto (TV), Italy

Communicated by Rita Levi-Montalcini, Consiglio Nazionale Ricerche, Rome, Italy, January 9, 1995

ABSTRACT *Mast cells are multifunctional bone marrow-derived cells found in mucosal and connective tissues and in the nervous system, where they play important roles in tissue inflammation and in neuroimmune interactions. Very little is known about endogenous molecules and mechanisms capable of modulating mast cell activation. Palmitoylethanolamide, found in peripheral tissues, has been proposed to behave as a local autacoid capable of downregulating mast cell activation and inflammation. A cognate N-acylamide, anandamide, the ethanolamide of arachidonic acid, occurs in brain and is a candidate endogenous agonist for the central cannabinoid receptor (CB1). As a second cannabinoid receptor (CB2) has been found in peripheral tissues, the possible presence of CB2 receptors on mast cells and their interaction with N-acylamides was investigated. Here we report that mast cells express both the gene and a functional CB2 receptor protein with negative regulatory effects on mast cell activation. Although both palmitoylethanolamide and anandamide bind to the CB2 receptor, only the former downmodulates mast cell activation in vitro. Further, the functional effect of palmitoylethanolamide, as well as that of the active cannabinoids, was efficiently antagonized by anandamide. The results suggest that (i) peripheral cannabinoid CB2 receptors control, upon agonist binding, mast cell activation and therefore inflammation; (ii) palmitoylethanolamide, unlike anandamide, behaves as an endogenous agonist for the CB2 receptor on mast cells; (iii) modulatory activities on mast cells exerted by the naturally occurring molecule strengthen a proposed autacoid local inflammation antagonism (ALIA) mechanism; and (iv) palmitoylethanolamide and its derivatives may provide antiinflammatory therapeutic strategies specifically targeted to mast cells ("ALIAmides").*

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 3739–3743, April 1994
Neurobiology

Mast cells synthesize, store, and release nerve growth factor

(plasticity/inflammation/hyperalgesia/neuroimmune interactions)

A. LEON*†, A. BURIANI*, R. DAL TOSO*, M. FABRIS*, S. ROMANELLO*, L. ALOE‡, AND R. LEVI-MONTALCINI‡

*Researchlife, c/o Centro di Ricerca Biomedica, Ospedale Civile, 31033 Castelfranco Veneto, Italy; and ‡Institute of Neurobiology, National Research Council, 00137 Rome, Italy

Contributed by R. Levi-Montalcini, December 20, 1993

ABSTRACT **Mast cells and nerve growth factor (NGF) have both been reported to be involved in neuroimmune interactions and tissue inflammation. In many peripheral tissues, mast cells interact with the innervating fibers. Changes in the behaviors of both of these elements occur after tissue injury/inflammation. As such conditions are typically associated with rapid mast cell activation and NGF accumulation in inflammatory exudates, we hypothesized that mast cells may be capable of producing NGF. Here we report that (*i*) NGF mRNA is expressed in adult rat peritoneal mast cells; (*ii*) anti-NGF antibodies clearly stain vesicular compartments of purified mast cells and mast cells in histological sections of adult rodent mesenchymal tissues; and (*iii*) medium conditioned by peritoneal mast cells contains biologically active NGF. Mast cells thus represent a newly recognized source of NGF. The known actions of NGF on peripheral nerve fibers and immune cells suggest that mast cell-derived NGF may control adaptive/reactive responses of the nervous and immune systems toward noxious tissue perturbations. Conversely, alterations in normal mast cell behaviors may provoke maladaptive neuroimmune tissue responses whose consequences could have profound implications in inflammatory disease states, including those of an autoimmune nature.**

Nerve growth factor: from neurotrophin to neurokine

Rita Levi-Montalcini, Stephen D. Skaper, Roberto Dal Toso, Lucia Petrelli and Alberta Leon

Nerve growth factor (NGF) is largely known as a target-derived factor responsible for the survival and maintenance of the phenotype of specific subsets of peripheral neurones and basal forebrain cholinergic nuclei during development and maturation. However, NGF also exerts a modulatory role on sensory, nociceptive nerve physiology during adulthood that appears to correlate with hyperalgesic phenomena occurring in tissue inflammation. Other NGF-responsive cells are now recognized as belonging to the haemopoietic–immune system and to populations in the brain involved in neuroendocrine functions. The concentration of NGF is elevated in a number of inflammatory and autoimmune states in conjunction with an increased accumulation of mast cells. Mast cells and NGF appear to be involved in neuroimmune interactions and tissue inflammation, with NGF acting as a general 'alert' molecule capable of recruiting and priming tissue defence processes following insult as well as systemic defensive mechanisms. Moreover, mast cells themselves produce NGF, suggesting that alterations in normal mast cell behaviours can provoke maladaptive neuroimmune tissue responses whose consequences could have profound implications in inflammatory disease states. This review discusses recent discoveries involving novel and diverse biological activities of this fascinating molecule.

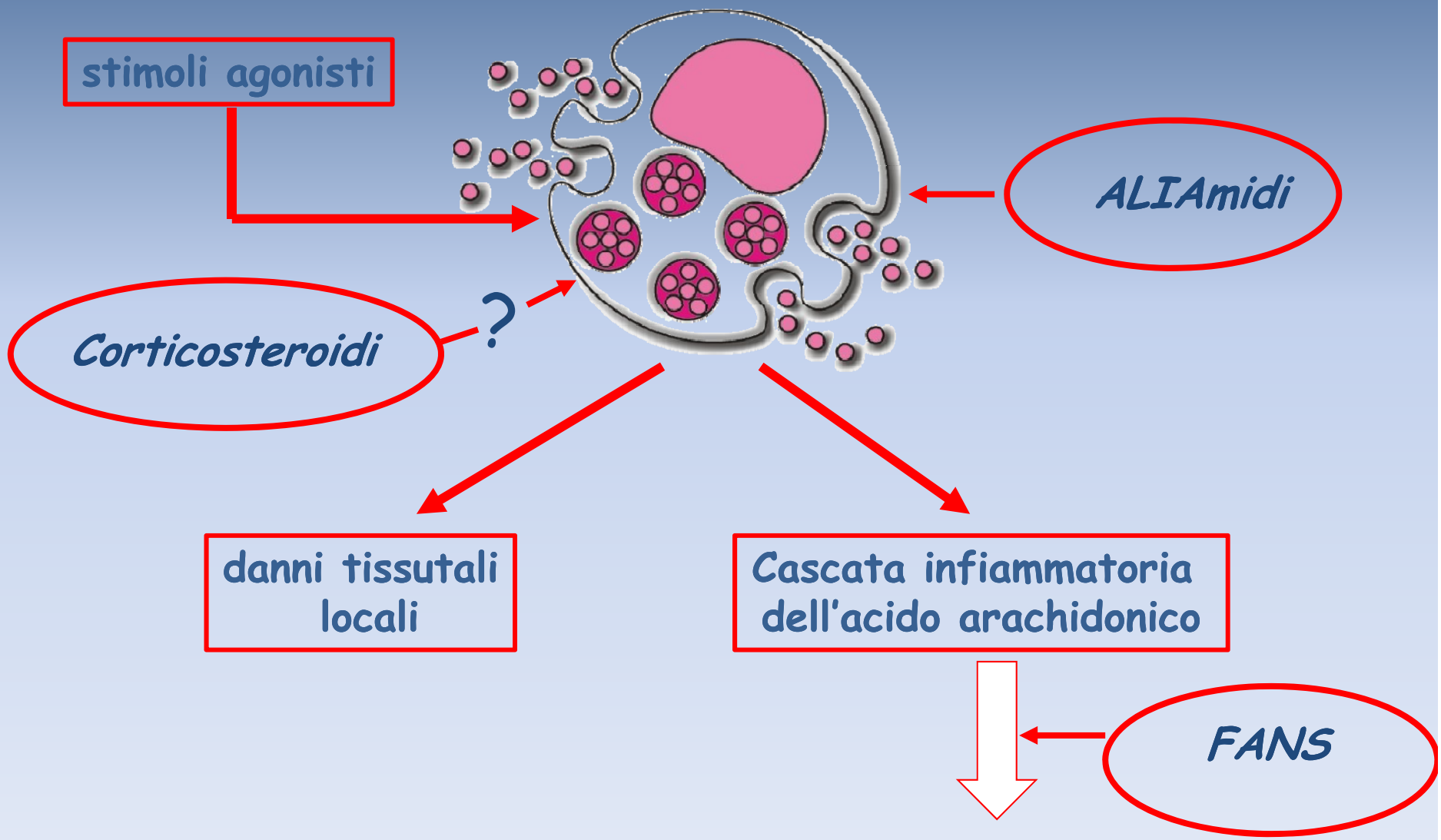
Trends Neurosci. (1996) 19, 514–520



Il meccanismo ALIA

(Autacoid Local Injury Antagonism)

Le possibili strategie terapeutiche in infiammazione tissutale



Fenomeno dello *sprouting*

iper-algesia

normo-algesia

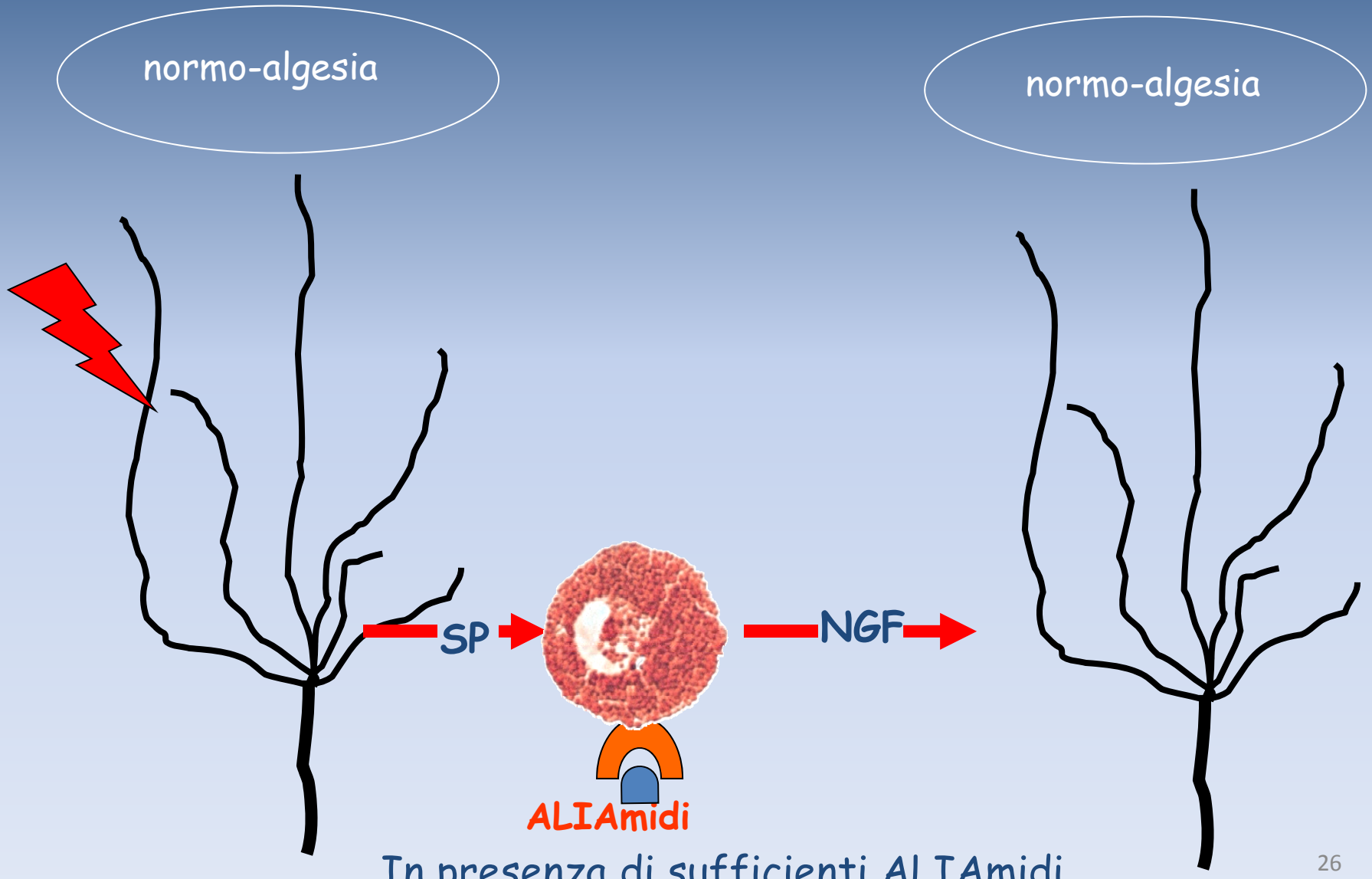


SP

NGF

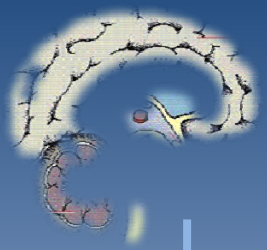
In mancanza/carenza di ALIAmidi

… che non avviene in presenza di sufficiente ALIAmide



In presenza di sufficienti ALIAmidi

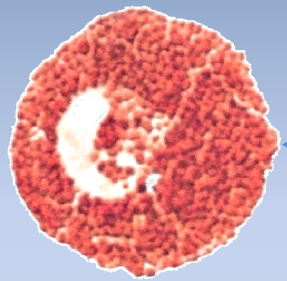
BRAIN - SKIN CONNECTION



Stress Psicologici

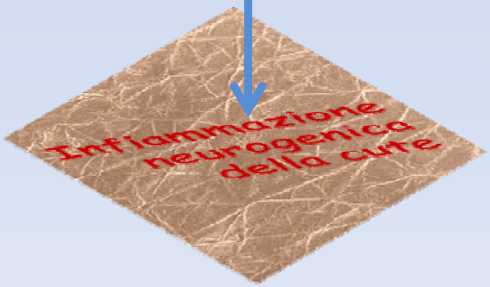
CRH

Fattori stressogeni esogeni



Fattori stressogeni endogeni

Degranulazione

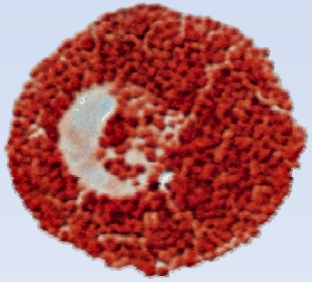


Arck P.C. et al – Neuroimmunology of Stress: Skin Takes Center Stage – J Inv Dermatol.(2006);126:1697-1704

IPER-REATTIVITÀ TISSUTALE

definizione

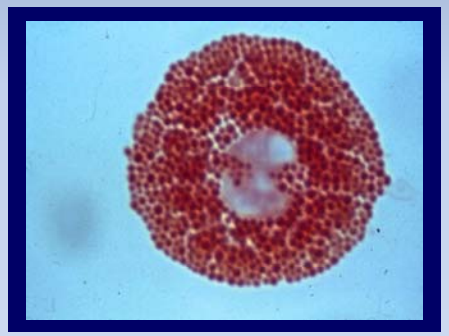
Scompenso della
normoreattività adattativa
di un tessuto (es: cute e mucose)
a causa di
stimolazioni anomale
per qualità, quantità e durata
provocata e/o amplificata da…



IPERDEGRANULAZIONE DEI MASTOCITI LOCALI

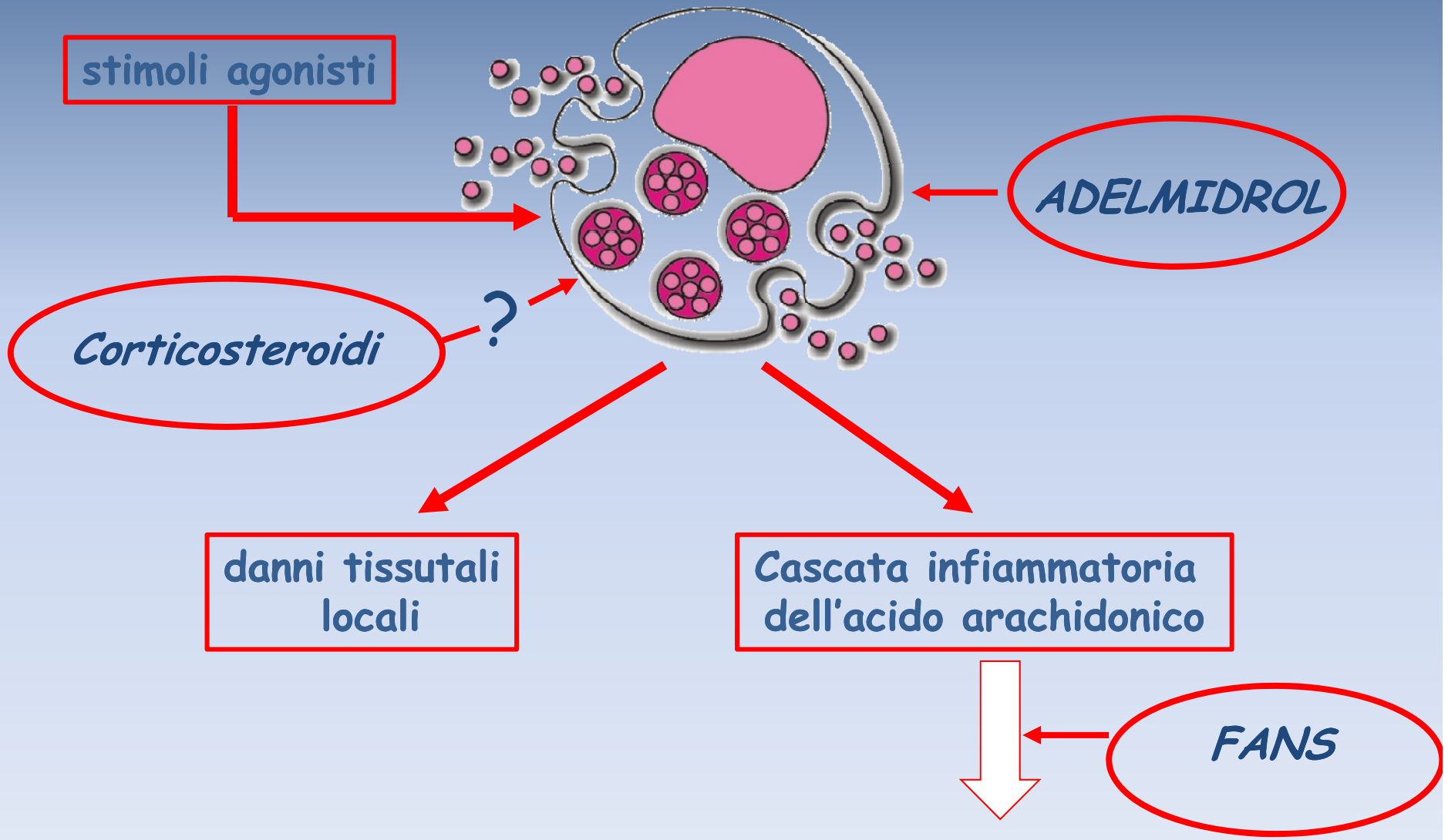
In conclusione :

Il mastocita
regola la reattività del tessuto



controllare la reattività del mastocita
corrisponde a controllare
la reattività del tessuto

La strategie terapeutica in corso di infiammazione tissutale in carenza di anandamide



Patologie & parafisiologie sostenute da iper-reattività mastocitaria

Progetto Again Life

- Cute
  - Sist.Epidermico
    - Dermatiti eritemato-squamose
    - Dermatiti & pruriti dell'anziano
    - Dermatiti da radio-chemio
    - Dermatofitosi
  - Sist. Dermo-epidermico
    - Fenomeni irritativi zona anale
    - Fimosi & fenomeni fibrotici
- Annessi cutanei
  - App. Ungueale
    - Onicomicosi - Onicodistrofie
  - App. Pilifero
    - Alteraz. bulbo pilifero da radio-chemio
  - App. Ghiandolare
    - Iperidrosi & Bromidrosi
- Mucose
  - Sist. Mucosale Orale
    - Mucositi da radio-chemio
    - Fenom.Infiammatori tessuti orali
    - Vulviti e vaginiti da radio-chemio
  - Sist. Mucosale Genitale
    - Balaniti e balanopost. radio-chemio
    - Fenom.Infiammat. tessuti genitali

Grazie
dell'attenzione