LA "TERAPIA MULTIFATTORIALE" NEL DETERIORAMENTO COGNITIVO DELL'ANZIANO: QUALI EVIDENZE ?

Ferrara , 24 ottobre 2014

Alimenti (AFSM) e neuroinfiammazione: la palmitoiletanolamide

Lucio Luchetti
Consultorio Aziendale per i Disturbi Cognitivi
U.O. di Geriatria - Ospedale Guglielmo da Saliceto
AUSL di Piacenza

Piacenza Primogenita
150 anni dell'Unità d'Italia

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Alzheimer's Disease

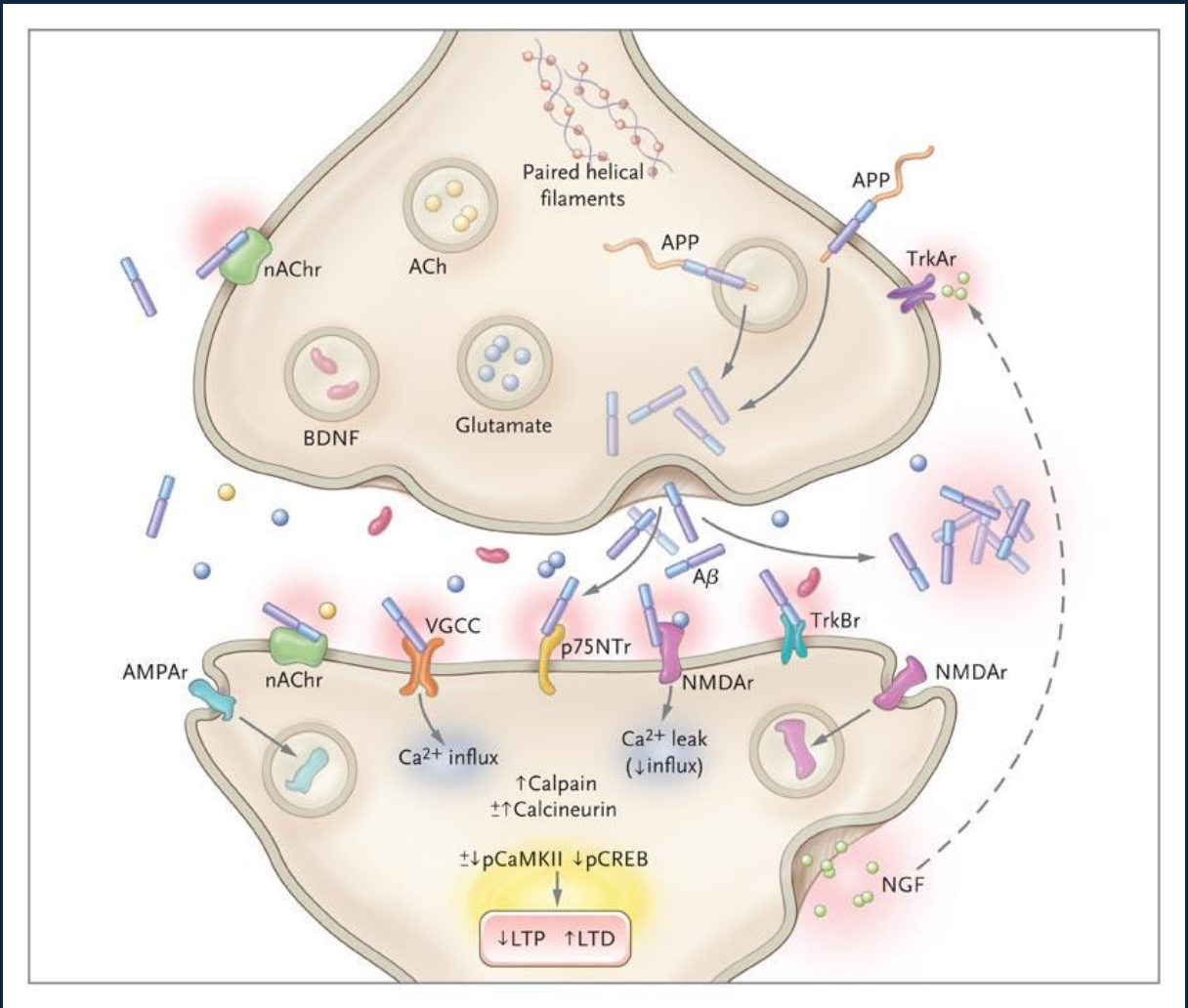
Henry W. Querfurth, M.D., Ph.D., and Frank M. LaFerla, Ph.D.

N Engl J Med 2010;362:329-44.

Outline

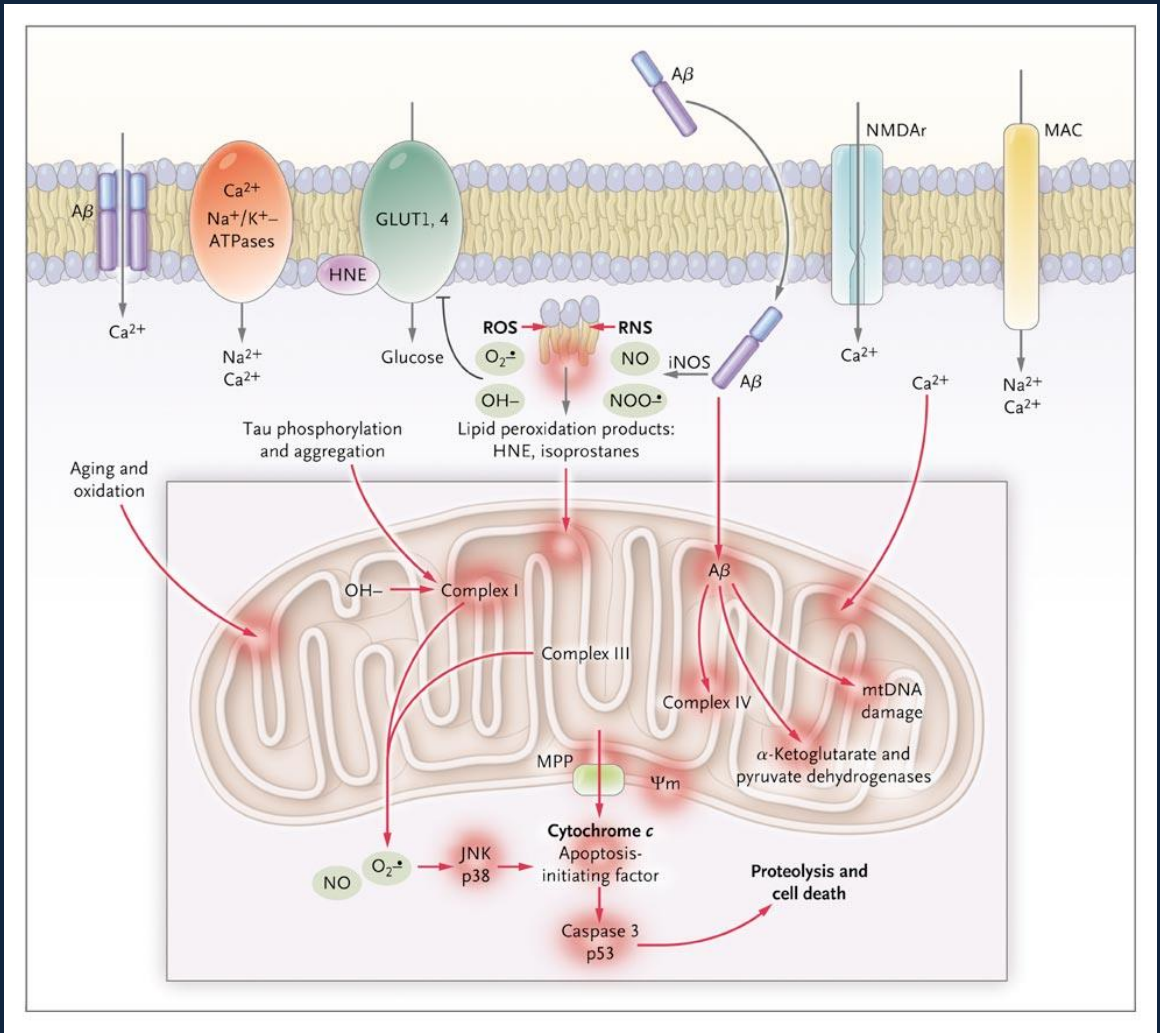
- Protein Abnormalities in Alzheimer's Disease
  - ß-Amyloid
  - Tau
- The Synapse in Alzheimer's Disease
  - Synaptic Failure
  - Depletion of Neurotrophin and Neurotransmitters
- Mitochondrial Dysfunction
  - Oxidative Stress
  - Insulin-Signaling Pathway
  - Vascular Effects
  - Inflammation
  - Calcium
  - Axonal-Transport Deficits
  - Aberrant Cell-Cycle Reentry
  - Cholesterol Metabolism

Synaptic Dysfunction in Alzheimer's Disease



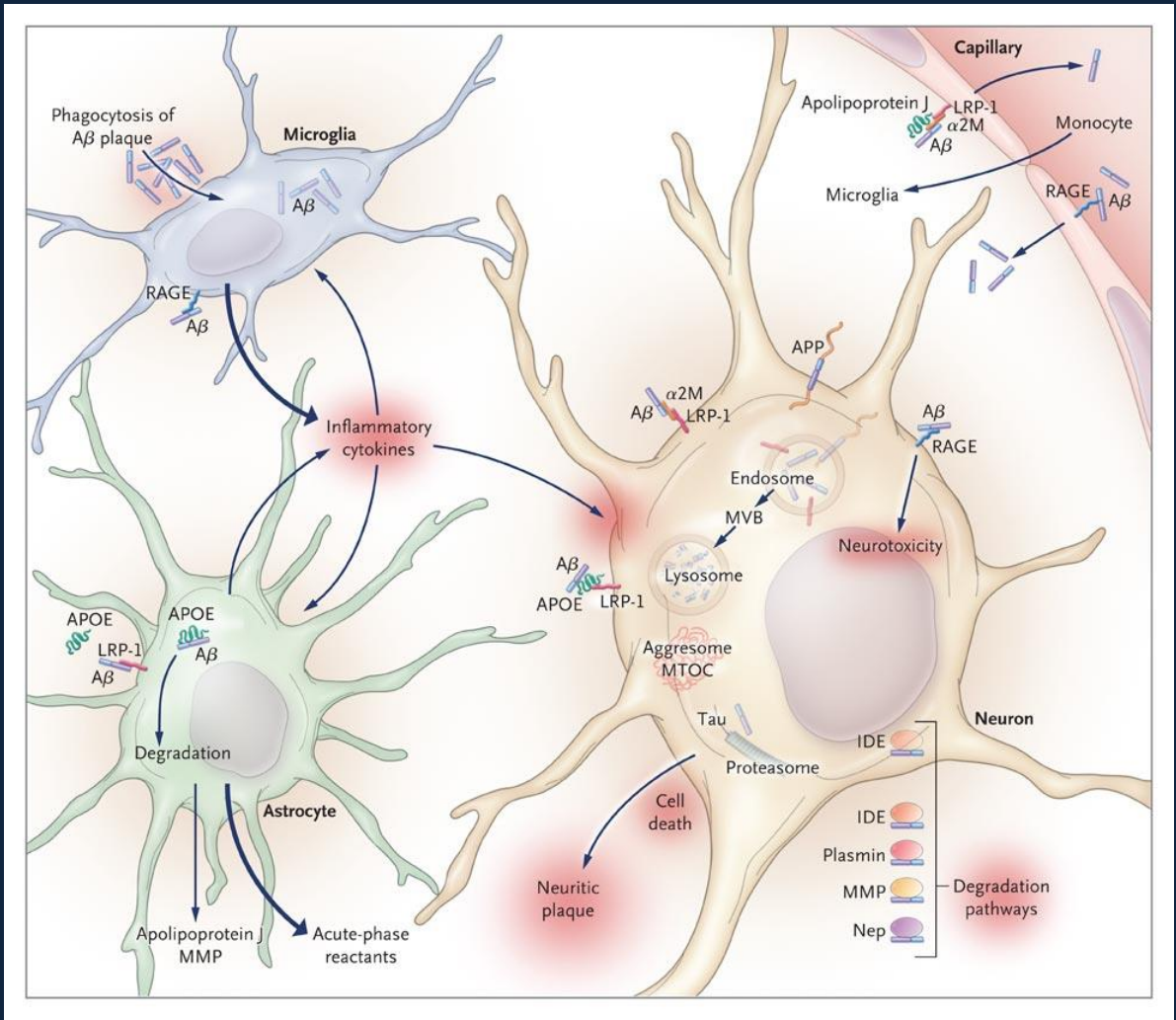
Querfurth H, LaFerla F. N Engl J Med 2010;362:329-344

Oxidative Stress and Mitochondrial Failure



Querfurth H, LaFerla F. N Engl J Med 2010;362:329-344

Inflammation and Mechanisms of Aß Clearance



Querfurth H, LaFerla F. N Engl J Med 2010;362:329-344

CONCLUSIONS

An effective treatment for sporadic Alzheimer's disease rests on the translation of the disease pathways we have discussed, as well as additional molecular mechanisms or new risk genes defined by gene-expression profiling and whole-genome association studies, into specific pharmacologic targets.

However, their underlying mechanisms are diverse, and whether any of these factors lead to amyloid deposition and tauopathy in humans is unknown.

Thus, the development of a multitargeted approach to prevent or symptomatically treat Alzheimer's disease, as used in current practice for other multigenic disorders, is needed.

N Engl J Med 2010;362:329-44.

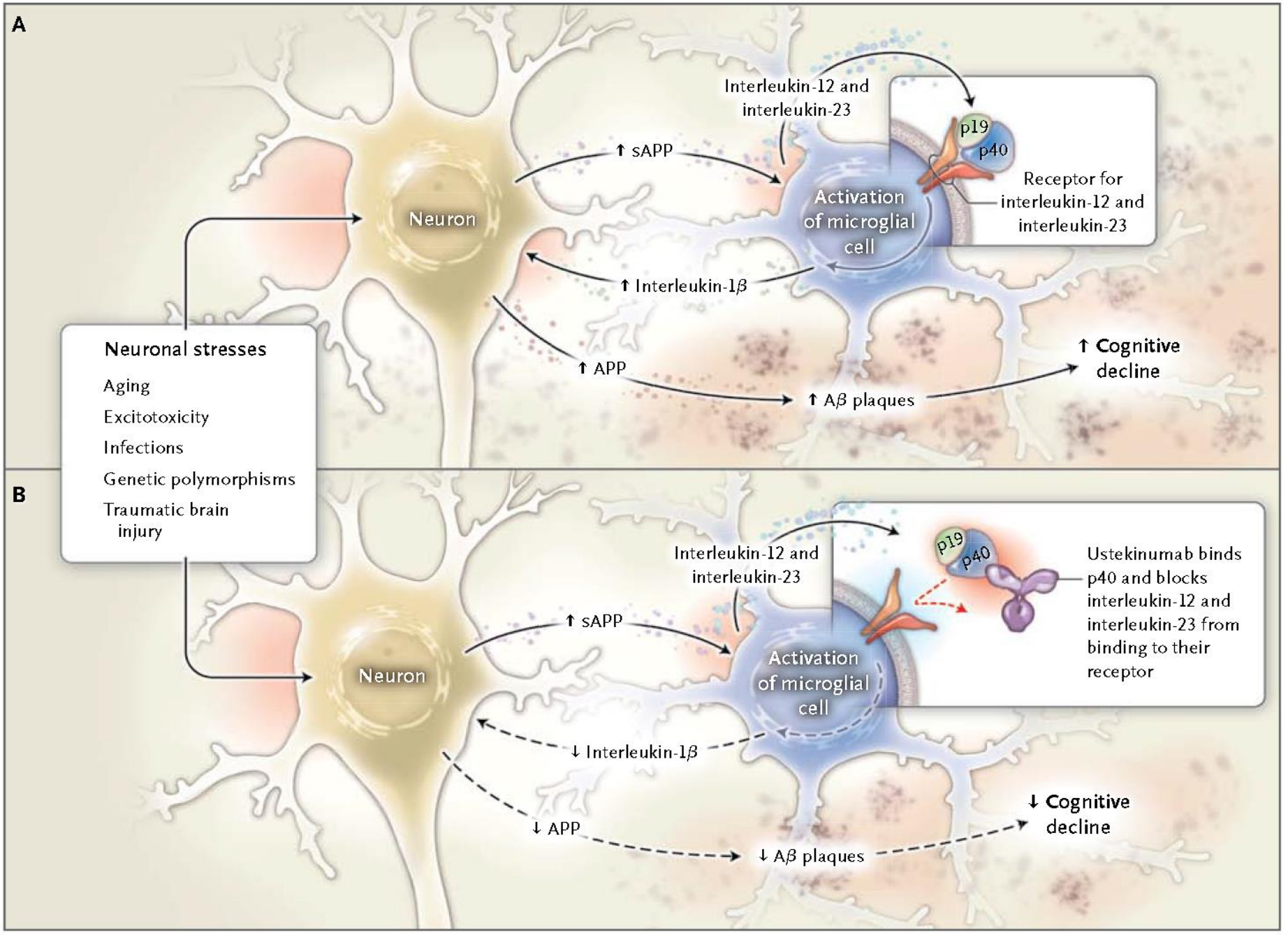
The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Neuroinflammatory Cytokine Signaling and Alzheimer's Disease

W. Sue T. Griffin, Ph.D.

N ENGL J MED 368;8 NEJM.ORG FEBRUARY 21, 2013


A
Interleukin-12 and interleukin-23
p19
p40
↑ sAPP
Receptor for interleukin-12 and interleukin-23
Neuron
Activation of microglial cell
↑ Interleukin-1β
Neuronal stresses
Aging
Excitotoxicity
Infections
Genetic polymorphisms
Traumatic brain injury
↑ APP
↑ Cognitive decline
↑ Aβ plaques
B
Interleukin-12 and interleukin-23
p19
p40
Ustekinumab binds p40 and blocks interleukin-12 and interleukin-23 from binding to their receptor
↑ sAPP
Neuron
Activation of microglial cell
↓ Interleukin-1β
↓ APP
↓ Cognitive decline
↓ Aβ plaques

1. **Neuroinflammation, expressed as frank microglial activation with excessive expression of immune cytokines, is fast acquiring the status of "principal culprit" in the unresolved connection between an elevated risk for the development of sporadic Alzheimer's disease and traumatic brain injury, systemic infections, normal aging, and several neurologic disorders.**

Neuroinflammation also appears to be a substantial contributor to Alzheimer's disease in persons with Down's syndrome (owing to the excess gene dosage that is characteristic of the syndrome) and in persons with genetic mutations that affect the amyloid precursor protein (APP) or presenilin.

2. An advance in this area has been described by Vom Berg et al., who used a mouse model of Alzheimer's disease to investigate the role of proinflammatory cytokines in disease pathogenesis.

Their results show that damping the expression and signaling of the cytokines interleukin-12 and interleukin-23 in the mouse model is associated with decreases in microglial activation, in the level of soluble β-amyloid (Aβ), and in the overall Aβ plaque burden.

These findings are consistent with earlier studies that linked microglial activation with excess expression of interleukin-1 (which regulates interleukin-12–interleukin-23 signaling) and expression of APP (which when cleaved generates Aβ), the development of Aβ plaques, and the activation of microglia in the brains of patients with Alzheimer's disease.

3. **These observations suggest that the suppression of signaling by interleukin-12, interleukin-23, or other inflammatory cytokines may prevent or delay the onset of Alzheimer's disease and, for patients already undergoing the cognitive decline of Alzheimer's disease, may halt such decline.**

The NEW ENGLAND JOURNAL of MEDICINE

Antiamyloid Therapy for Alzheimer's Disease — Are We on the Right Road?

Eric Karran, Ph.D., and John Hardy, Ph.D.

N ENGL J MED 370;4 NEJM.ORG JANUARY 23, 2014

Most pharmaceutical companies seeking disease-modifying treatments for Alzheimer's disease have investigated Aβ-centric therapeutics.

In summary, both the **bapineuzumab** trials and the **solanezumab** trials have provided valuable information.
They have brought into question the interpretation placed on some biomarkers — especially the CSF level of phospho-tau, but also brain volume.

We advocate continuing to investigate ways to modulate Aβ levels in the brain while accepting that we lack clarity on the roles that different forms of Aβ play in the disease.

N ENGL J MED 370;4 NEJM.ORG JANUARY 23, 2014

EDITORIAL

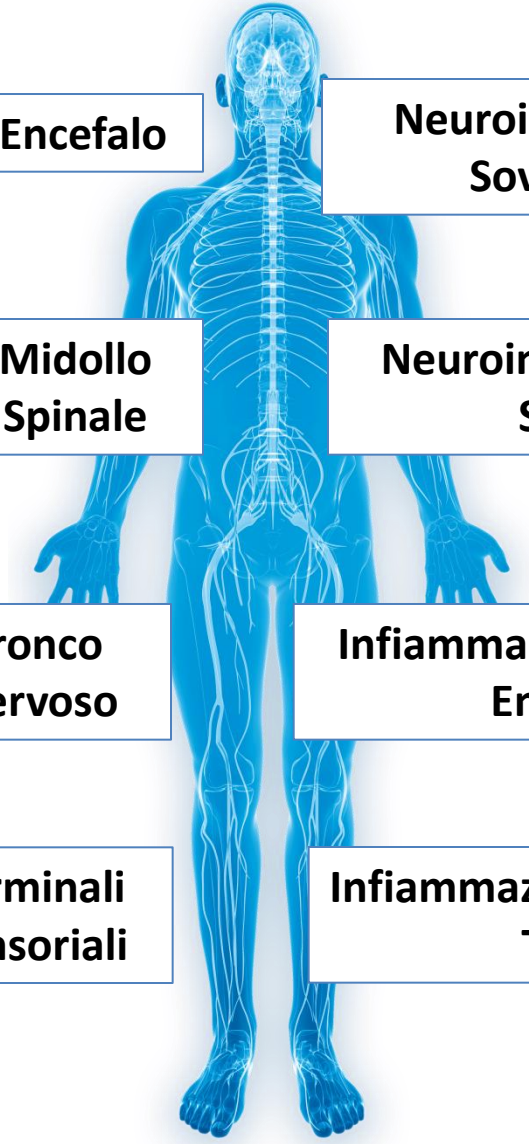
nature neuroscience

Focus on neuro-immune interactions

In this issue, *Nature Neuroscience* presents a focus on neuro-immune interactions.

"The work described by the reviews and perspectives presented in this focus issue has vastly improved our understanding of the **intricate and often reciprocal relationship between the neural and immune systems**. Once thought to be separate and distinct entities, **it is becoming increasingly clear that a number of diverse functions, including endogenous host-defense, disease response and postinfection or -injury repair depend on the activity and interplay of these systems**".

“neuroinfiammazione” a differenti livelli



Encefalo

Neuroinfiammazione Sovra-spinale

Midollo Spinale

Neuroinfiammazione Spinale

Tronco Nervoso

Infiammazione Neurogenica Endoneurale

Terminali sensoriali

Infiammazione Neurogenica Tissutale

NEUROINFIAMMAZIONE

Boche D Nicoll JA. Neuropathol Appl Neurobiol. 2013; 39(1):1-2.

Modulare per via farmacologica i meccanismi causali regolatori che innescano, sostengono, amplificano e cronicizzano il *loop* eziopatogenetico della sofferenza neuronale nel SNP e nel SNC

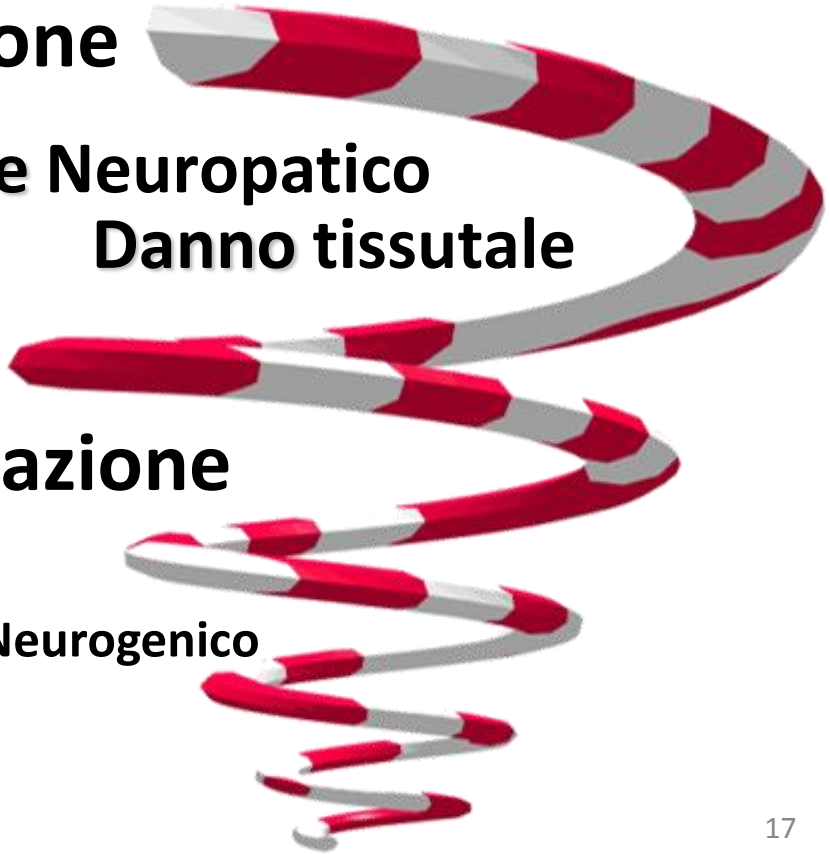
Neurodegenerazione

Dolore Neuropatico

Danno tissutale

Neuroinfiammazione

Dolore Neurogenico

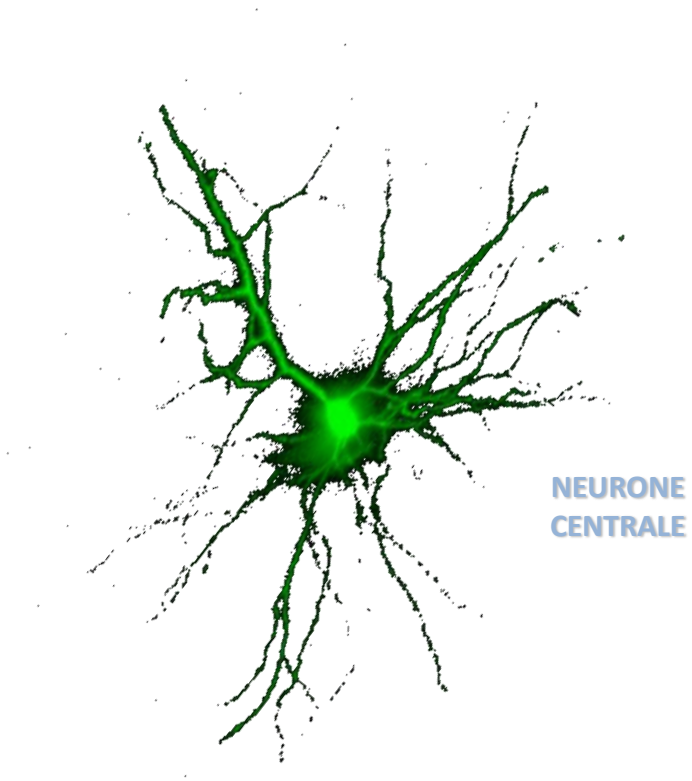


ASN NEURO REVIEW ARTICLE

ASN NEURO 4(3):art:e00082.doi:10.1042/AN20120010

Neurological diseases as primary gliopathies: a reassessment of neurocentrism

Alexei Verkhratsky*[,†,‡,1], Michael V. Sofroniew[§], Albee Messing[¶], Nihal C. deLanerolle[‖], David Rempe[**], José Julio Rodríguez[†,‡,††] and Maiken Nedergaard[‡‡,1]



NEURONE CENTRALE

The majority of therapeutic drugs currently in clinical use target neuronal receptors, channels or transporters.

Verkhratsky A, Sofroniew MV, Messing A, de Lanerolle NC, Rempe D, Rodríguez JJ, Nedergaard M.
ASN Neuro 2012; 4(3).

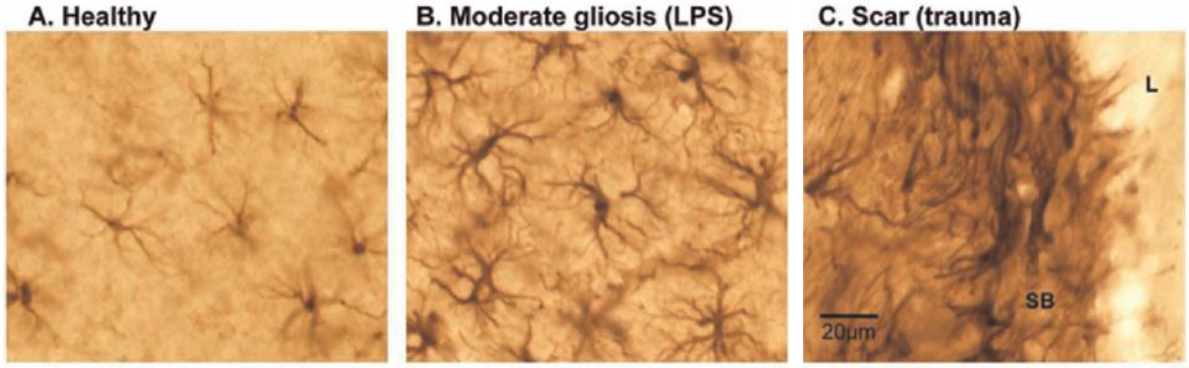
ASN NEURO REVIEW ARTICLE

ASN NEURO 4(3):art:e00082.doi:10.1042/AN20120010

Neurological diseases as primary gliopathies: a reassessment of neurocentrism

Alexei Verkhratsky[*,†,‡1], Michael V. Sofroniew[§], Albee Messing[¶], Nihal C. deLanerolle[||], David Rempe[**], José Julio Rodríguez[†,‡,††] and Maiken Nedergaard[‡‡1]

Future therapeutic efforts may benefit by a stronger focus on the supportive homoeostatic functions of astrocytes.



Verkhratsky A, Sofroniew MV, Messing A, de Lanerolle NC, Rempe D, Rodríguez JJ, Nedergaard M.
ASN Neuro 2012;4(3).

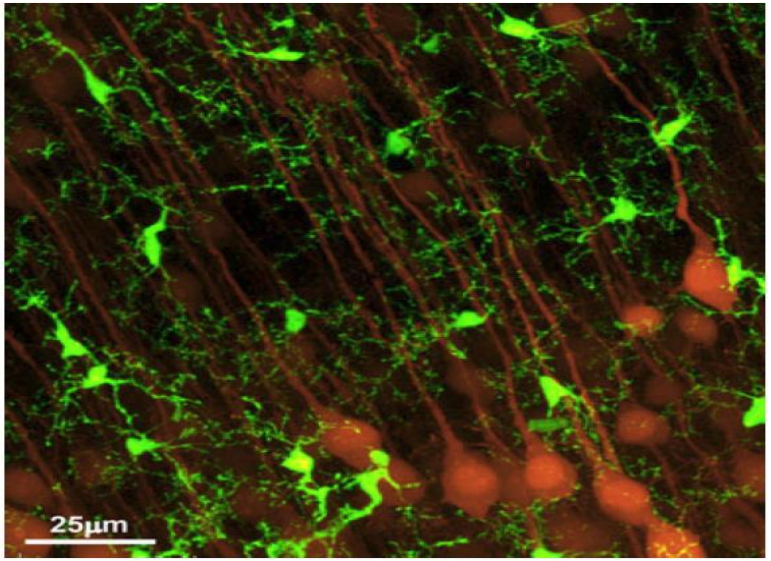
J Neuroimmune Pharmacol
DOI 10.1007/s11481-013-9434-z

INVITED REVIEW

Microglia: Key Elements in Neural Development, Plasticity, and Pathology

Ukpong B. Eyo · Michael E. Dailey

…microglia play important developmental roles in synapse remodeling, developmental apoptosis, phagocytic clearance, and angiogenesis.



…microglia also contribute to pathology, including neurodevelopmental and neurobehavioral disorders, ischemic injury, and neuropathic pain

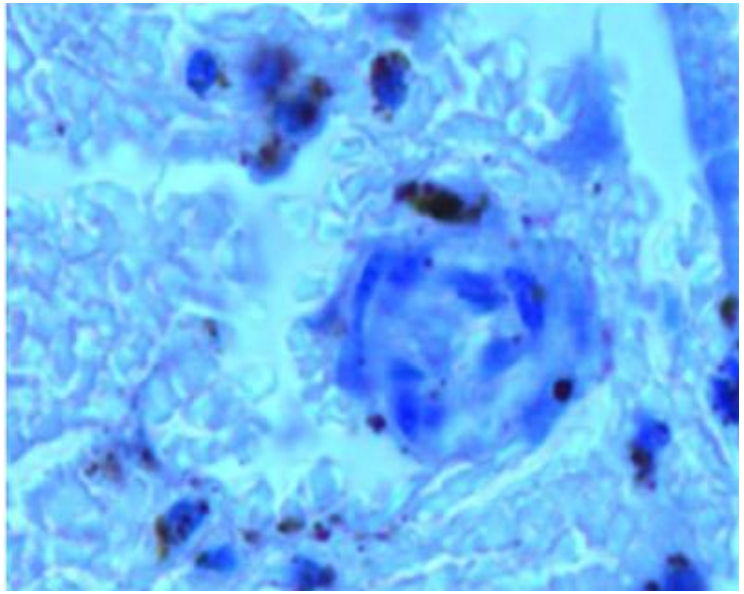
Eyo UB, Dailey ME.
J Neuroimmune Pharmacol. 2013;8(3):494-509.

Acta Neuropathol
DOI 10.1007/s00401-013-1092-y

REVIEW

The role of mast cells in neuroinflammation

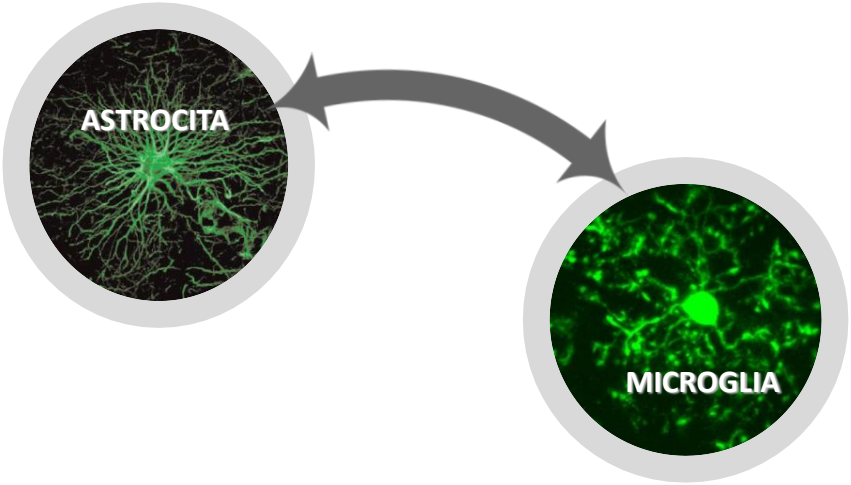
Sofie Nelissen · Evi Lemmens · Nathalie Geurts · Peter Kramer · Marcus Maurer · Jerome Hendriks · Sven Hendrix

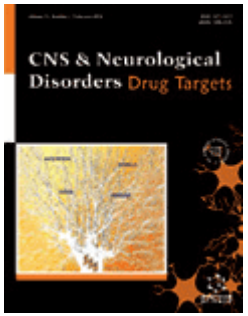


Mast cells and their secreted mediators modulate neuroinflammatory processes in multiple CNS pathologies and can thereby either contribute to neurological damage or confer neuroprotection.

Nelissen S, Lemmens E, Geurts N, Kramer P, Maurer M, Hendriks J, Hendrix S. Acta Neuropathol 2013.

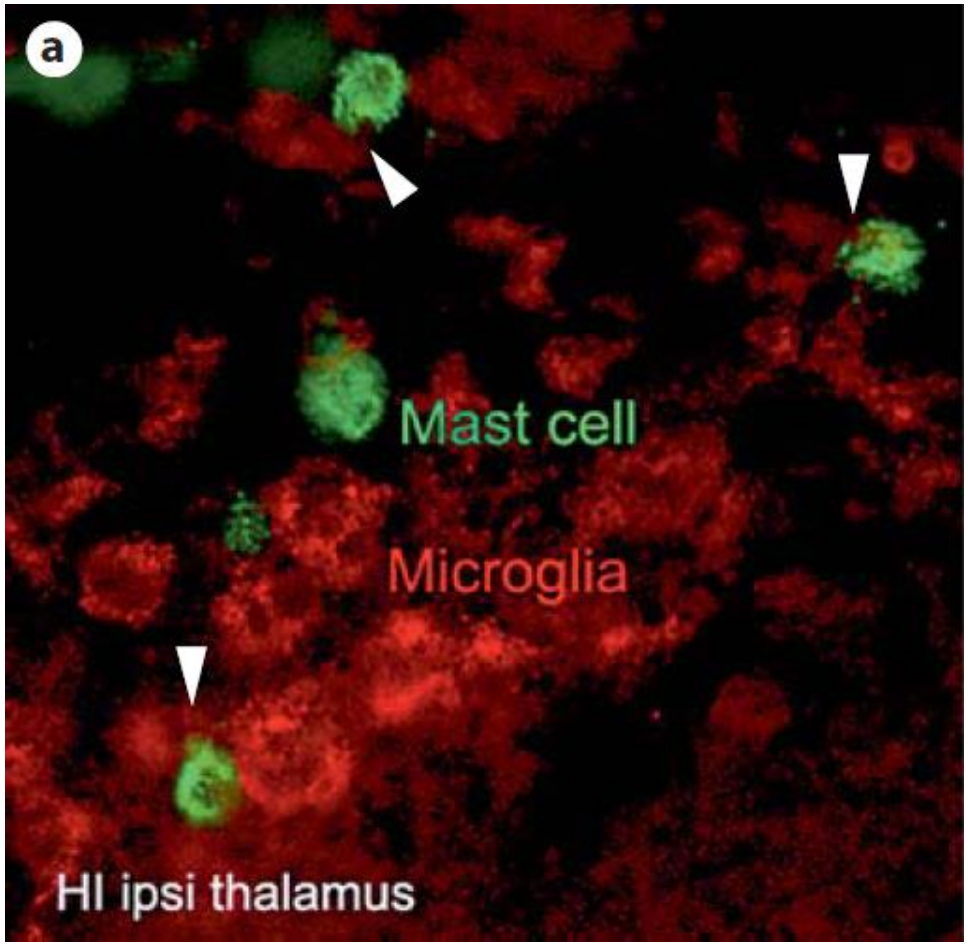
Il *cross-talk* tra Astrocita e Microglia



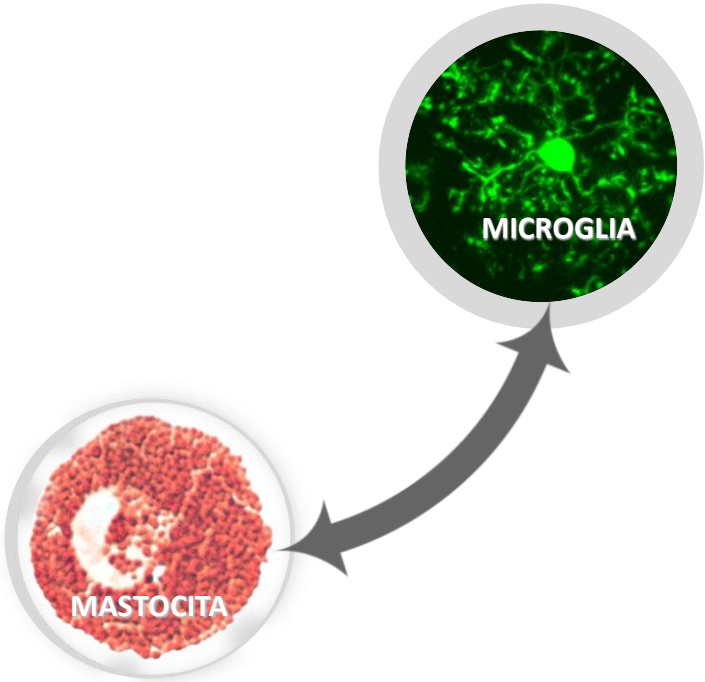


Astrocyte-Microglia Cooperation in the Expression of a Pro-Inflammatory Phenotype.
Barbierato M, Facci L, Argentini C, Marinelli C, Skaper SD, Giusti P.
CNS Neurol Disord Drug Targets 2013.

Il *cross-talk* tra Microglia e Mastocita

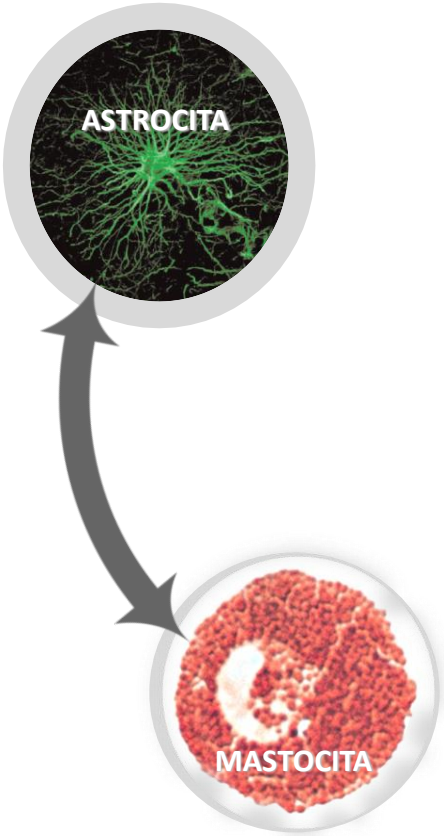


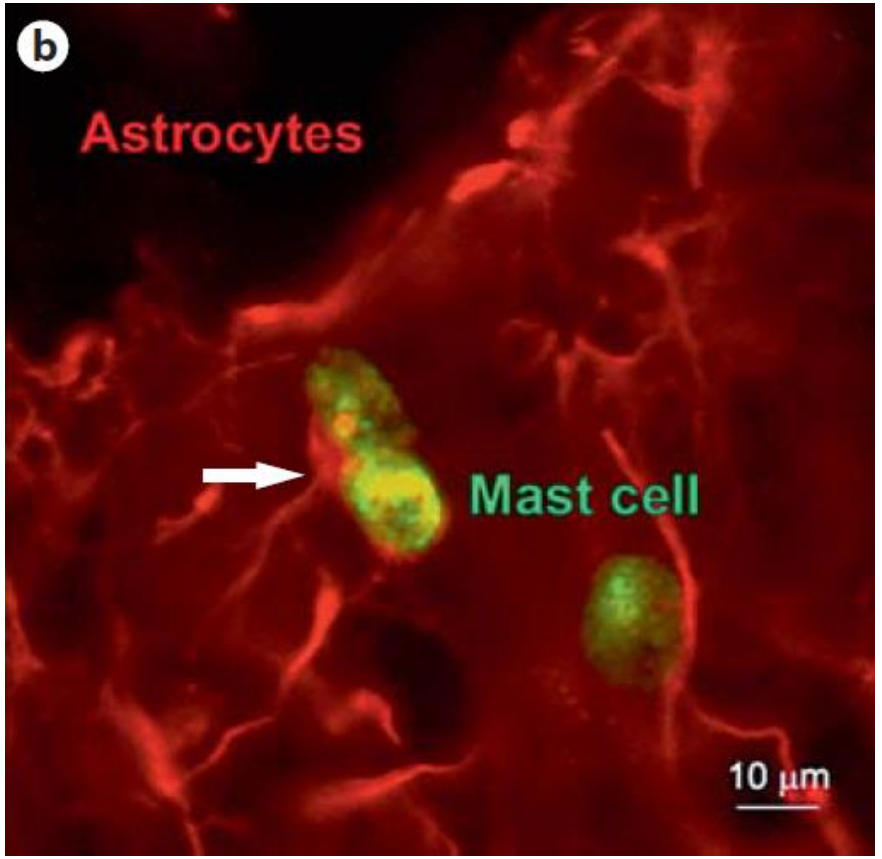
Mast cell stabilization limits hypoxic-ischemic brain damage in the immature rat.
Jin Y, Silverman AJ, Vannucci SJ.
Dev Neurosci 2007;29(4-5):373-84.



P2 receptor-mediated signaling in mast cell biology.
Bulanova E, Bulfone-Paus S.
Purinergic Signal 2010;6(1):3-17.

Il *cross-talk* tra Mastocita e Astrocita

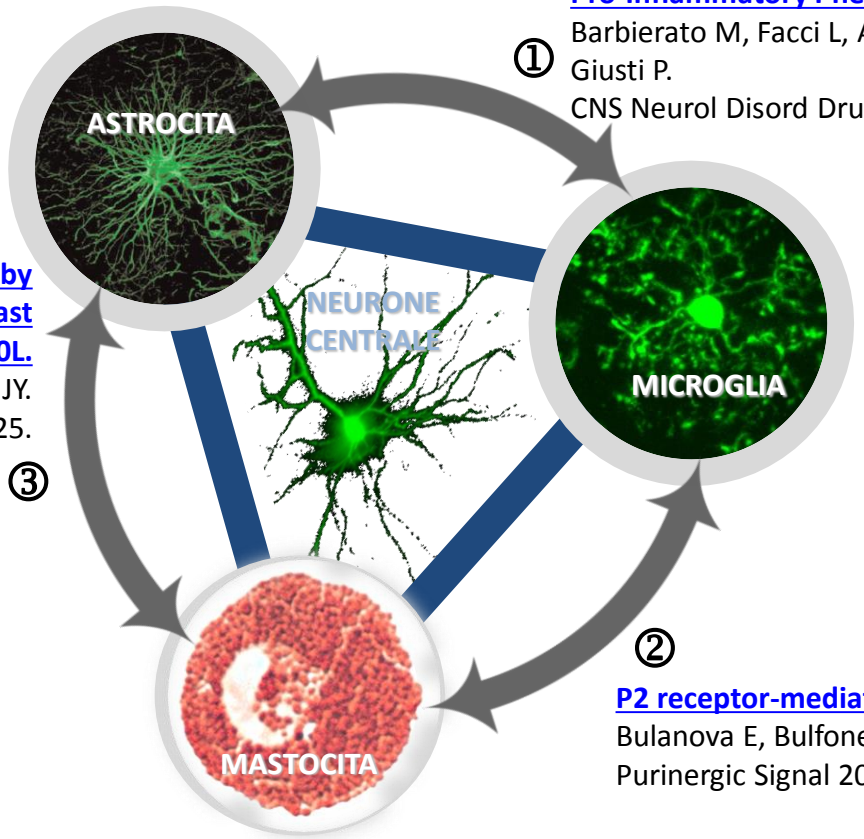




Signal pathways in astrocytes activated by cross-talk between of astrocytes and mast cells through CD40-CD40L.
Kim DY, Hong GU, Ro JY.
J Neuroinflammation. 2011;16:8:25.

Mast cell stabilization limits hypoxic-ischemic brain damage in the immature rat.
Jin Y, Silverman AJ, Vannucci SJ.
Dev Neurosci. 2007;29(4-5):373-84.

Il *cross-talk* tra cellule non neuronali nel CNS



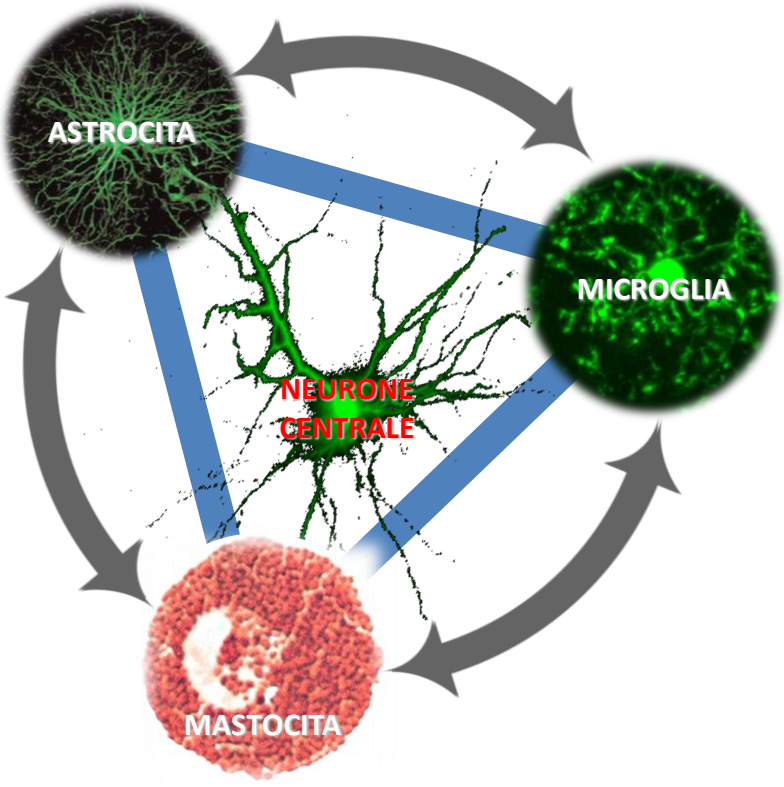
① [Astrocyte-Microglia Cooperation in the Expression of a Pro-Inflammatory Phenotype.](#)
Barbierato M, Facci L, Argentini C, Marinelli C, Skaper SD, Giusti P.
CNS Neurol Disord Drug Targets 2013.

② [P2 receptor-mediated signaling in mast cell biology.](#)
Bulanova E, Bulfone-Paus S.
Purinergic Signal 2010;6(1):3-17.

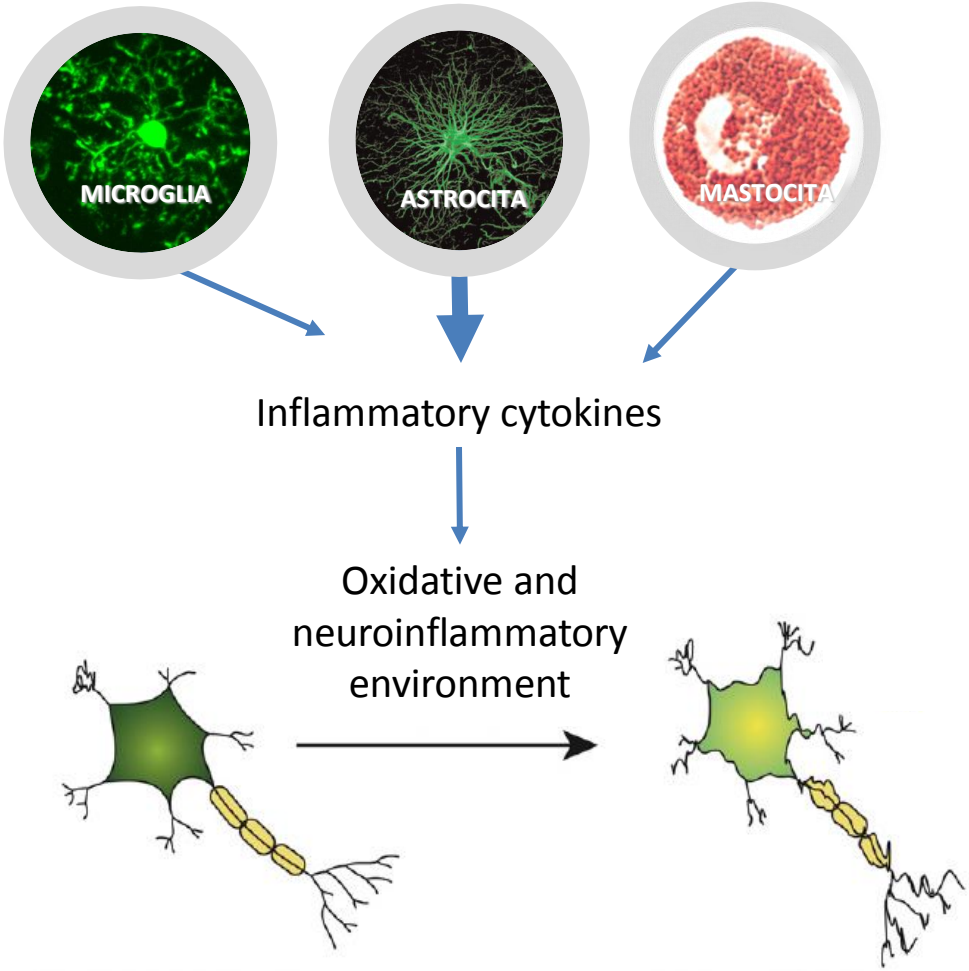
③ [Signal pathways in astrocytes activated by cross-talk between of astrocytes and mast cells through CD40-CD40L.](#)
Kim DY, Hong GU, Ro JY.
J Neuroinflammation 2011;16:8-25.

Unità Morfofunzionale Dinamica - UMD

Queste cellule operano in sinergia come Unità Morfofunzionale Dinamica - UMD con l'obiettivo fondamentale di mantenere l'equilibrio omeostatico/ omeodinamico cerebrale



Neuroinfiammazione e Stress Ossidativo



It is becoming increasingly evident that neuroinflammation and **oxidative stress** play a critical role in the aetiology of degenerative diseases

Both neuroinflammation and oxidative stress share common linkages and influence each other greatly

Neuroinflammation and oxidative stress: Co-conspirators in the pathology of degenerative diseases

Neuroinflammation and oxidative stress: Co-conspiration in the pathology of Parkinson Disease
Taylor JM, Main BS, Crack PJ.
Neurochem Int. 2013;62(5):803-19.

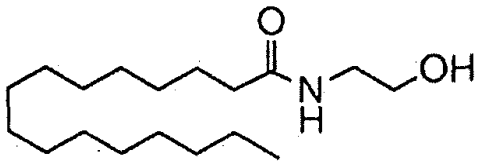
Gli **alimenti a fini medici speciali (AFMS**) sono destinati alla dieta di soggetti con disturbi particolari o affetti da patologie. **Sono disciplinati dalla direttiva 99/21/CE, attuata a livello nazionale con il DPR 20 marzo 2002, n. 57 e soggetti alla procedura di notifica al Ministero della salute.**

Data la loro **eterogeneità**, per l'ampia variabilità della possibile destinazione nonché per la diversità del contributo calorico-nutritivo offerto alla razione alimentare giornaliera, la normativa specifica sopra citata non contiene disposizioni sui requisiti nutrizionali della composizione e si limita, per tale aspetto, a fornire indicazioni sulle vitamine e i minerali ammessi con i relativi tenori per 100 kcal.

Può infatti trattarsi di alimenti completi o incompleti dal punto di vista nutrizionale, la cui formulazione può essere di tipo standard per distribuzione energetica e densità nutrizionale o presentare anche adattamenti mirati alle specifiche esigenze dei soggetti nelle condizioni sopra citate.

I prodotti destinati a fini medici speciali, ai fini di una corretta utilizzazione, vanno impiegati su indicazione e controllo del medico; tale avvertenza deve essere obbligatoriamente riportata in etichetta.

Il meccanismo endogeno di regolazione delle cellule non-neuronali



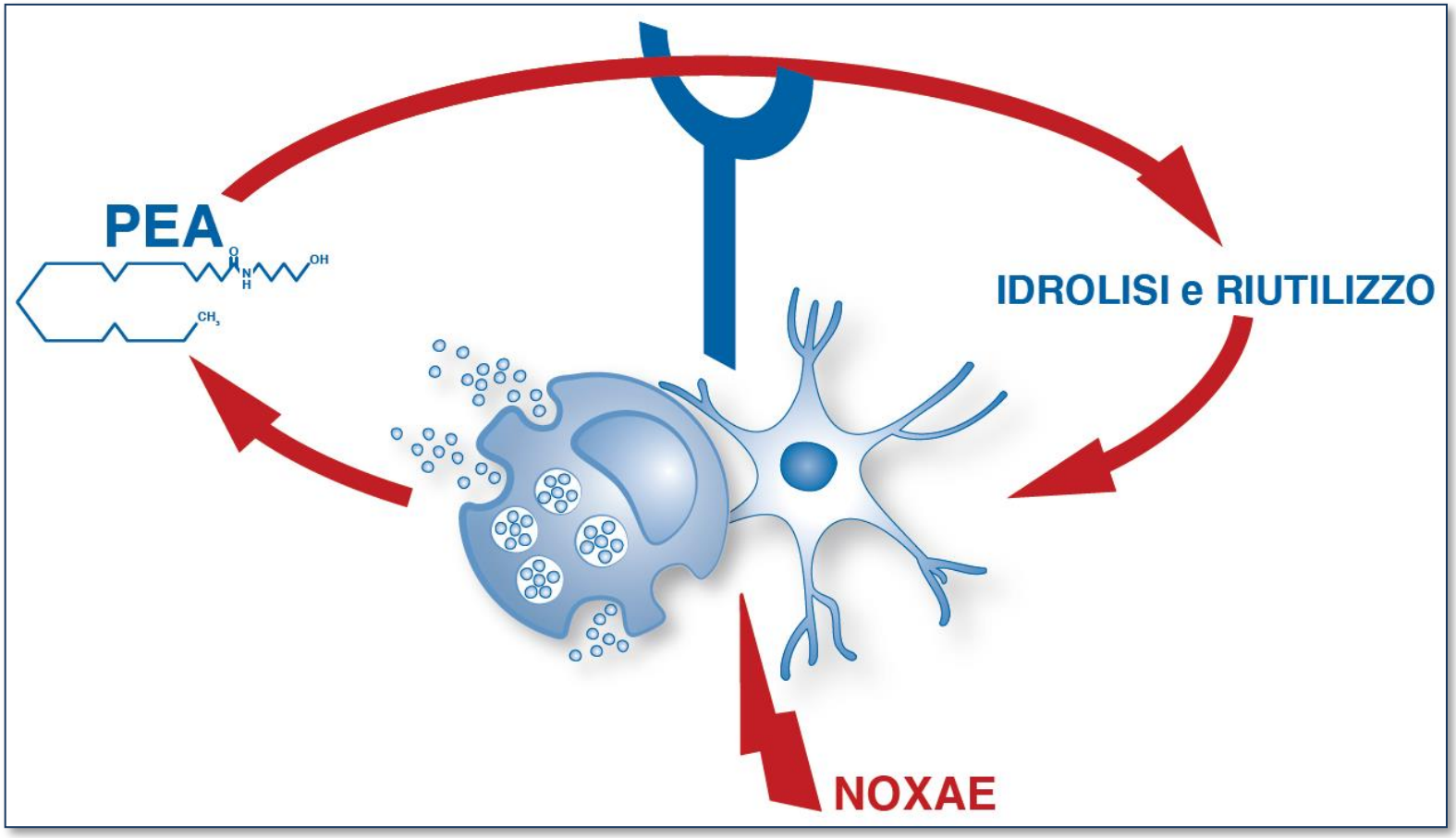
La Palmitoiletanolamide (**PEA**), attraverso una azione recettoriale pleiotropica controlla fisiologicamente la normale reattività dei tre stipiti cellulari

Palmitoylethanolamide exerts neuroprotective effects in mixed neuroglial cultures and organotypic hippocampal slices via peroxisome proliferator-activated receptor-α.
Scuderi C, Valenza M, Stecca C, Esposito G, Carratù MR, Steardo L.
J Neuroinflammation 2012;9:9-49.

Palmitoylethanolamide is a new possible pharmacological treatment for the inflammation associated with trauma.
Esposito E, Cuzzocrea S.
Mini Rev Med Chem 2013;13(2):237-55.

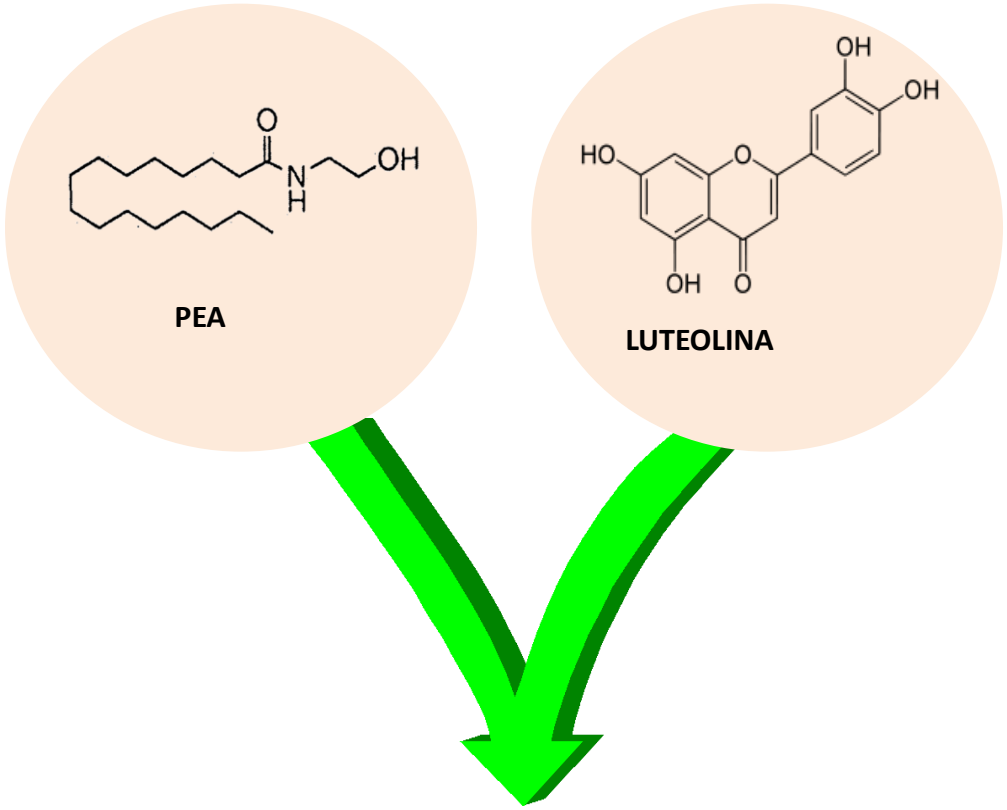
Mast cell-glia axis in neuroinflammation and therapeutic potential of the anandamide congener palmitoylethanolamide.
Skaper SD, Facci L.
Philos Trans R Soc Lond B Biol Sci. 2012 5;367(1607):3312-25.

La regolazione endogena di cellule non-neuronali:
il Meccanismo ALIA - *Autacoid Local Injury Antagonism*

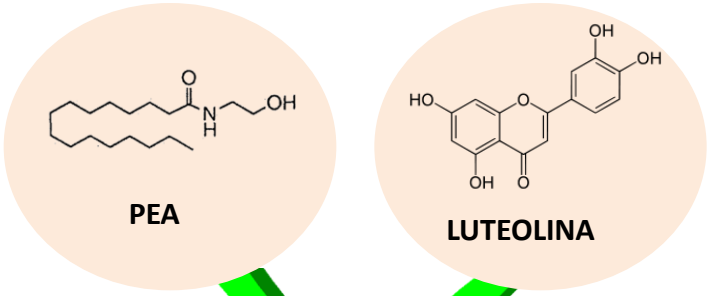


Nerve growth factor: from neurotrophin to neurokine.
Levi-Montalcini R, Skaper SD, Dal Toso R, Petrelli L, Leon A.
Trends Neurosci 1996;19(11):514-20

Azione sincronica tra PEA e Luteolina



Ultra-microcomposito PEALUT®



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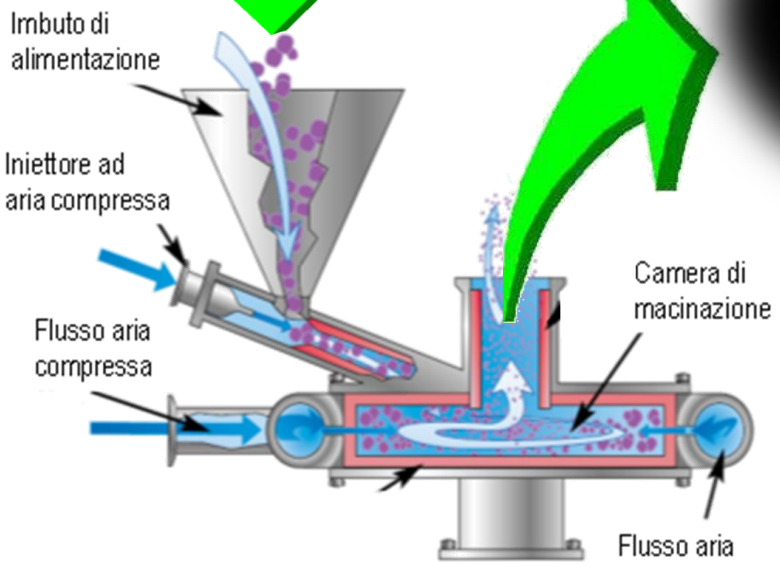
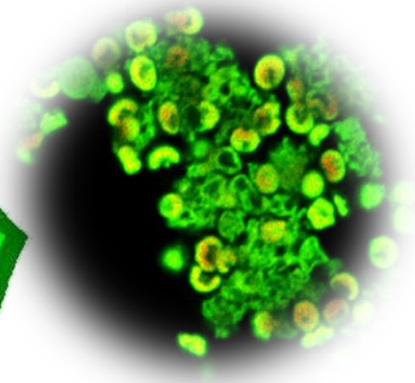
Premiscelazione





Ultra-microcomposito **PEA-LUT®** microparticelle miste da 0,5÷ 2,0 micron in grado di attraversare la BBB

Malattia di Alzheimer

La **PEA** contrasta la neurotossicità indotta dal peptide dell'amiloide Aβ *(1-42)* sia nelle colture primarie di astrociti cerebrali che nelle colture organotipiche di ippocampo *(Scuderi C et al, 2011; Scuderi C et al, 2012)*.

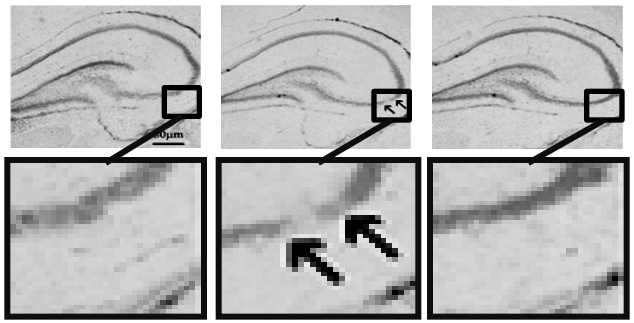
La **PEA** riduce lo sviluppo dei deficit cognitivi e mnemonici indotti dall'Aβ *(1-42)*; questo effetto è associato anche ad un ridotto *stress* ossidativo *(D'Agostino G et al, 2012)*.

La **Luteolina** riduce la neurotossicità indotta dall'Aβ(25-35) favorendo un recupero delle capacità di apprendimento e memorizzazione (Liu R et al, 2009; Xu B et al, 2010; Cheng HY et al, 2010). L'effetto della **Luteolina** è associato a:

- un minore danno ossidativo *(Liu R et al, 2009; Tsai FS et al, 2010)*;
- ridotta fosforilazione delle proteine tau *(Zhou F et al, 2012)*;
- ridotto danno ai neuroni colinergici;
- ripristino della memoria spaziale negli animali invecchiati *(Schmitt-Schillig S et al, 2005; Jang S et al, 2010)*;
- ridotto *deficit* mnemonico nell'invecchiamento cerebrale *(Schmitt-Schillig S et al, 2005; Jang S et al, 2010)*.

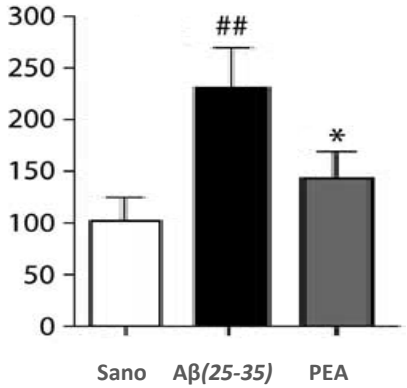
PEALUT® riduce la neurotossicità dell' Aβ 1-42 in colture organotipiche di ippocampo *(Esposito E et al, 2013 in progress)*.

Neuroni in colture organotipiche di ippocampo



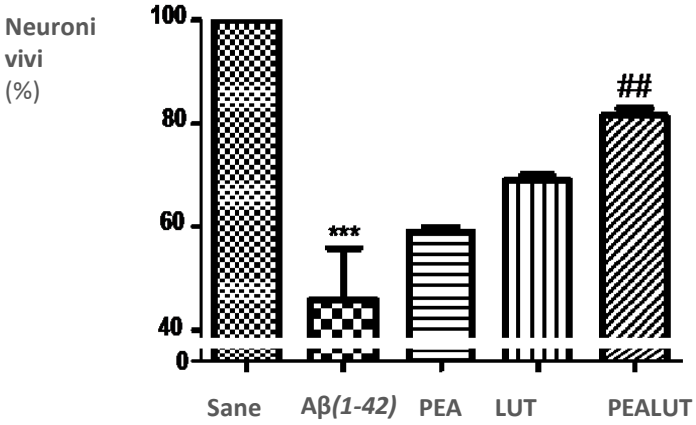
Scuderi et al. 2012

Stress ossidativo



D'Agostino et al. 2012

"**PEALUT** riduce la neurotossicità dell' Aβ*(1-42)* in colture organotipiche di ippocampo"



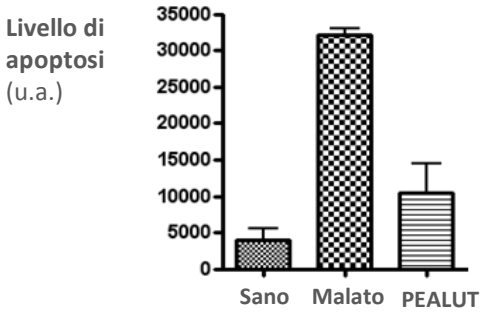
Esposito et al. 2013

Stati di alterazione dell'umore

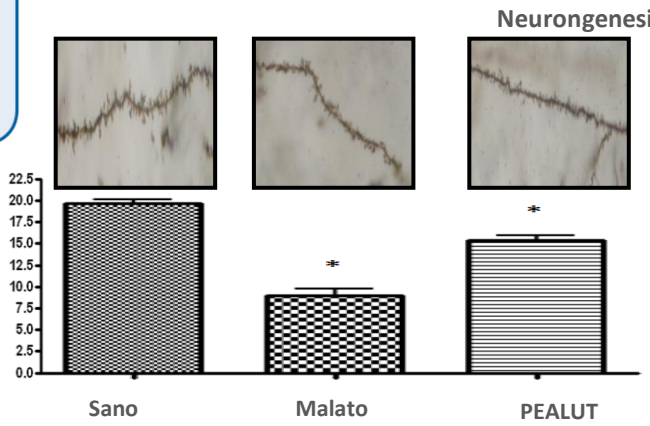
La **Luteolina** esercita un effetto di tipo antidepressivo correlabile a inibizione della morte cellulare indotta dal danno al reticolo endoplasmatico *(Ishisaka M et al, 2011)*

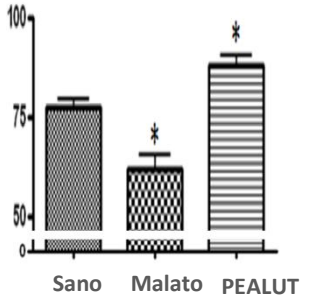
La **PEA** esplica un effetto di tipo antidepressivo dose-dipendente *(Yu HL et al, 2011)*; l'effetto antidepressivo è stato riconfermato e valutato anche con *test* per l'ansia. *(Crupi R et al, 2013)*

PEALUT® riduce i comportamenti ansiosi e i sintomi di depressione, effetti correlati ad un ad una normalizzazione dei livelli del fattore neurotrofico BDNF, ad una ridotta morte neuronale ed una aumentata neurogenesi *(Crupi R et al, 2013)*.



"effetti correlati a ridotta morte neuronale ed aumentata neurogenesi"



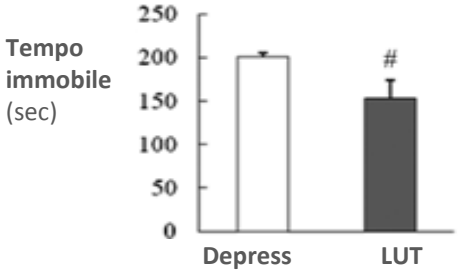


Crupi et al. 2013

"**LUT** esercita un effetto di tipo antidepressivo"

Test della "coda sospesa"

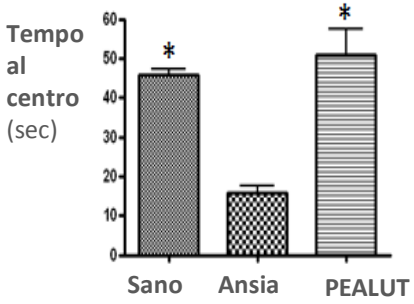
Test del "nuoto forzato"



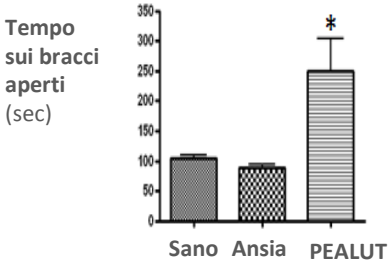
Ishisaka et al. 2011

"**PEALUT** riduce i comportamenti ansiosi e i sintomi di depressione"

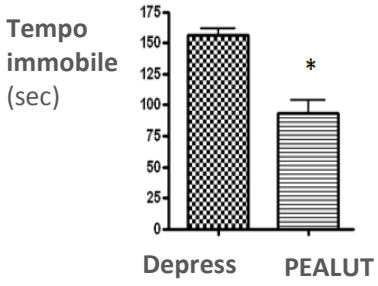
Test dello "spazio aperto"



Test del "labirinto sospeso"



Test del "nuoto forzato"



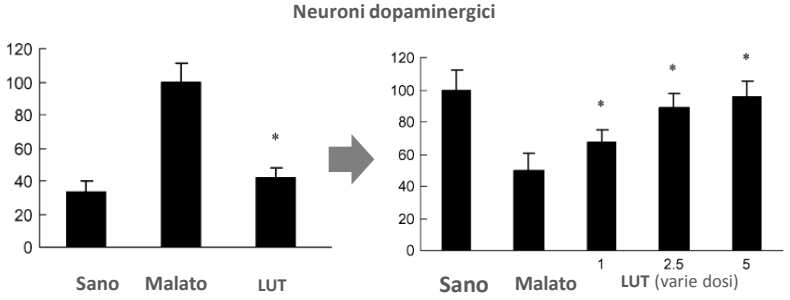
Crupi et al. 2013

Malattia di Parkinson

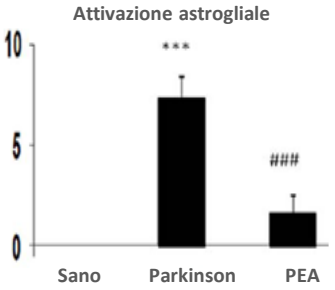
La **PEA** contrasta lo sviluppo delle alterazioni comportamentali e biochimico-morfologiche nel modello sperimentale di malattia di Parkinson (MPTP); gli effetti della **PEA** sono associati a una:

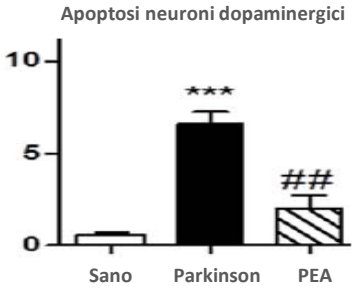
- minore attivazione microgliale ed astrogliale e ridotta produzione di *marker* pro-infiammatori;
- maggiore sopravvivenza dei neuroni dopaminergici nella *substantia nigra (Esposito E et al, 2012).*

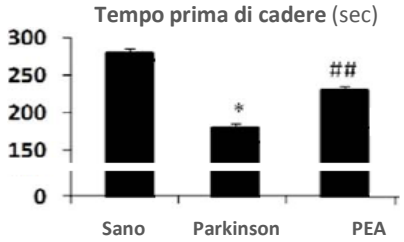
La **Luteolina** contrasta le alterazioni dei neuroni dopaminergici danneggiati dall'attivazione microgliale (Chen HQ et al, 2008).

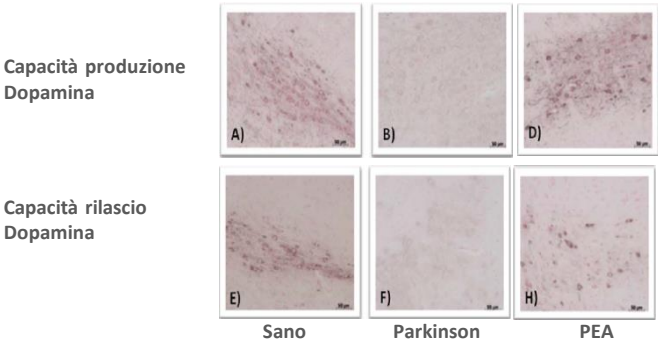


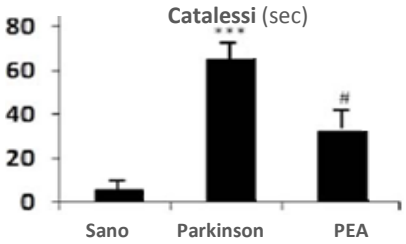
Chen et al. 2008











Esposito et al. 2012

Stati di sofferenza ischemica

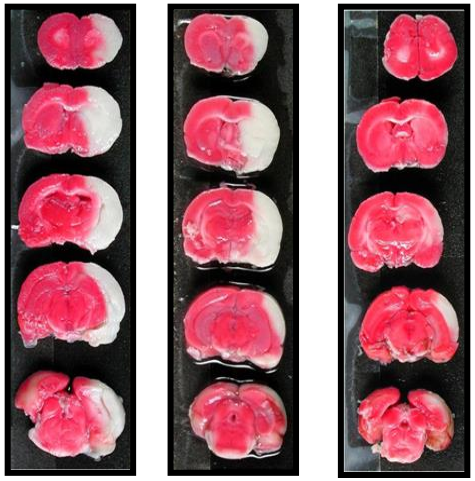
In seguito ad occlusione transitoria dell'arteria cerebrale media (tMCAO), la **PEA** riduce il volume d'infarto in modo dose-dipendente *(Schomacher M et al, 2008)*. L'effetto è:

- correlato ad un minor *deficit* neurologico e a una *downregulation* di mediatori infiammatori *(Garg P et al, 2010)*;
- associato ad una ridotta attivazione astrocitaria e minore reclutamento dei mastociti *(Ahmad A et al, 2012)*.

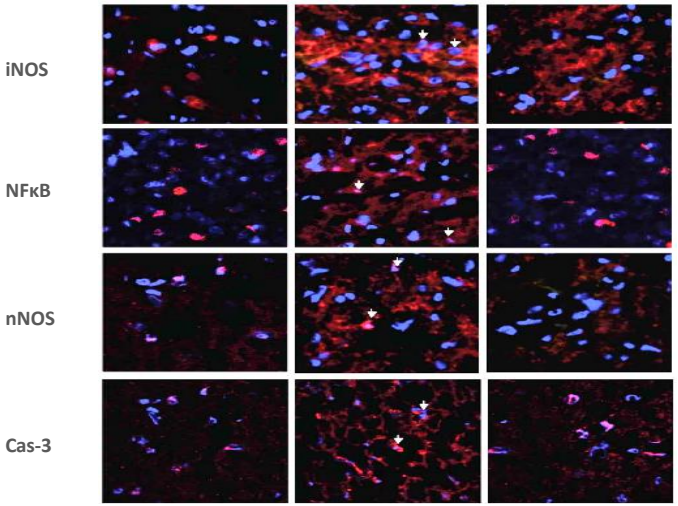
Dopo occlusione dell'arteria cerebrale media, la **Luteolina** riduce il *deficit* neurologico, il danno tissutale, il volume d'infarto, l'edema *(Qiao H et al, 2012)*. L'effetto della **Luteolina** è associato a:

- una *downregulation* dei processi infiammatori e dello *stress* ossidativo *(Qiao H et al, 2012a)*
- riduzione della morte neuronale *(Zhao G et al, 2011)*;

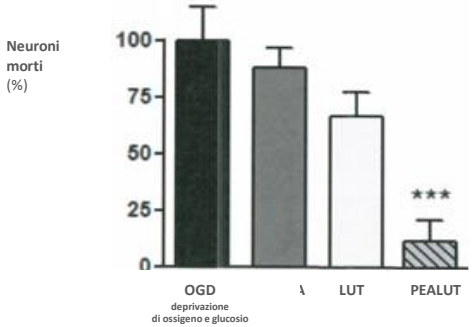
In colture di neuroni corticali sottoposte a deprivazione di ossigeno e glucosio (OGD) l'ultramicrocomposito **PEALUT®** protegge completamente i neuroni dalla morte determinando un potente effetto sinergico tra le due molecole *(Pizzi M et al, 2013; in progress)*.



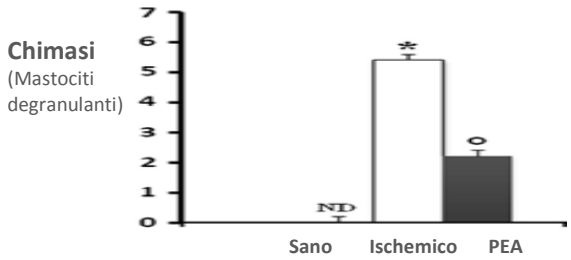
Schomacher et al. 2008

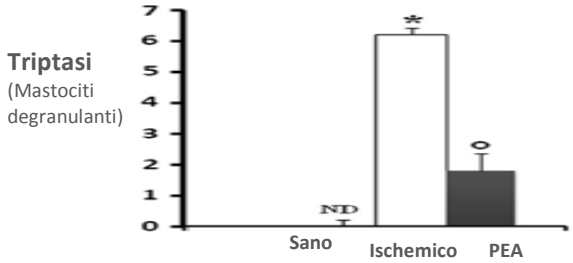


Garg et al. 2008



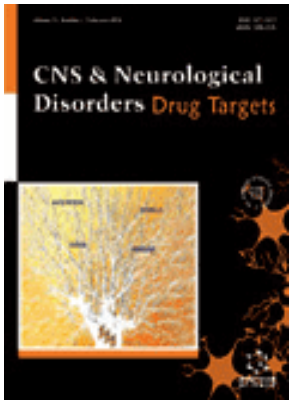
Pizzi et al. 2013





Ahmad et al. 2012

CNS Neurol Disord Drug Targets. **2013** Feb 1;12(1):62-9.



Neuroglial roots of neurodegenerative diseases: therapeutic potential of palmitoylethanolamide in models of Alzheimer's disease.

Scuderi C, Steardo L.

Abstract

The growth of knowledge about the molecular mechanisms underlying Alzheimer's disease (AD) has highlighted the role of neuroinflammation in the pathophysiology of this disorder. AD is classically characterized by the deposit of misfolded proteins: the extracellular accumulation of beta amyloid peptide (Aβ), and the formation of intracellular neurofibrillary tangles. However, it is clear that many other cellular dysfunctions occur. **Among these, a prominent role is exerted by the inflammatory process which is a consequence of the over-activation of glial cells.** Indeed, several models of AD have demonstrated that glia modify their functions, losing the physiological supportive role. **These cells instead acquire a pro-inflammatory phenotype, thus contributing to exacerbate Aβ toxicity. The relationship between neurodegeneration and neuroinflammation is strictly interdependent**, and research efforts are now addressed to antagonize both processes simultaneously. Along this line **palmitoylethanolamide (PEA) has attracted much attention because of its numerous pharmacological properties, particularly those related to the modulation of peripheral inflammation through the peroxisome proliferator activated receptor-α involvement**. In light of these considerations, we explored the antiinflammatory and neuroprotective effects of PEA in rat neuronal cultures and organotypic hippocampal slices challenged with Aβ, and treated with PEA in the presence or absence of a selective peroxisome proliferator activated receptor-α antagonist. **The data indicate that PEA is able to blunt Aβ-induced astrocyte activation and to exert a marked protective effect on neurons.** These findings highlight new pharmacological properties of PEA and suggest that this compound may provide an effective strategy for AD.

Biochem Soc Trans. 2013 Dec;41(6):1583-7.

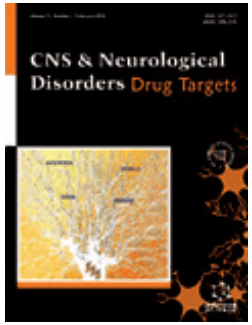
Endocannabinoid signalling in Alzheimer's disease.

Maroof N[1], Pardon MC, Kendall DA.

Abstract

The ECs (endocannabinoids) AEA (anandamide) and 2-AG (2-arachidonoylglycerol) and their lipid congeners OEA (N-oleoylethanolamide) and PEA (N-palmitoylethanolamide) are multifunctional lipophilic signalling molecules. **The ECs, OEA and PEA have multiple physiological roles including involvement in learning and memory, neuroinflammation, oxidative stress, neuroprotection and neurogenesis.** They have also been implicated in the pathology of, or perhaps protective responses to, neurodegenerative diseases. This is particularly the case with Alzheimer's disease, the most common age-related dementia associated with impairments in learning and memory accompanied by neuroinflammation, oxidative stress and neurodegeneration. The present mini-review examines **the evidence supporting the roles that ECs appear to play in Alzheimer's disease and the potential for beneficial therapeutic manipulation of the EC signalling system.**

CNS Neurol Disord Drug Targets. 2014 Aug 6. [Epub ahead of print]



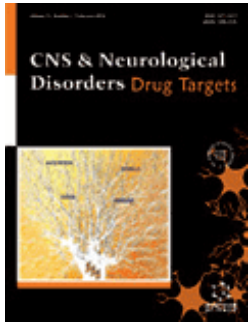
Neuroprotection by Association of Palmitoylethanolamide with Luteolin in Experimental Alzheimer's Disease Models: the Control of Neuroinflammation.

Paterniti I, Cordaro M, Campolo M, Siracusa R, Cornelius C, Navarra M, Cuzzocrea S, Esposito E

Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder. Its neuropathological hallmarks include deposition of beta amyloid (Aβ) fibrils in senile plaques. Numerous biochemical events, leading to Aβ neurotoxicity in AD, have been proposed and it seems that neuroinflammation plays a prominent role among these. Thus**, since inflammatory processes and oxidative stress are considered to play an important role in neuroinflammatory disorders and in AD pathology**, in the present work we decided to test a new composite, which is a formulation constituted of an **anti-inflammatory compound such as palmitoylethanolamide (PEA)** and the well recognized **antioxidant flavonoid luteolin (Lut)**, **subjected to an ultra-micronization process, here designated co-ultraPEALut**. We investigated the effect of co-ultraPEALut in both an **in vitro and ex vivo organotypic model of AD**.

CNS Neurol Disord Drug Targets. **2014** Aug 6. [Epub ahead of print]

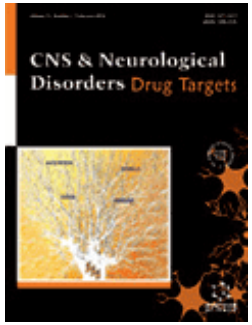


Neuroprotection by Association of Palmitoylethanolamide with Luteolin in Experimental Alzheimer's Disease Models: the Control of Neuroinflammation.

Paterniti I, Cordaro M, Campolo M, Siracusa R, Cornelius C, Navarra M, Cuzzocrea S, Esposito E

1. For the **in vitro model**, we used **human neuronal cells**, **obtained by differentiating SH-SY5Y neuroblastoma cells** into sustainable neuronal morphology. These well differentiated cells express features specific to mature neurons, such as synaptic structures and functional axonal vesicle transport, making this new concept for in vitro differentiation valuable for many neuroscientific research areas, including AD.
Differentiated SH-SY5Y cells were pre-treated with co-ultraPEALut (reference concentrations: 27, 2.7 and 0.27 µM PEA) for 2 h. AD features were induced by Aβ1-42 stimulation (1 µM). Twenty-four hours later cell vitality was evaluated by the colorimetric MTT assay, whereas the neuroinflammation underling AD was observed by Western blot analysis for IκBα degradation and nuclear factor-κB traslocation, as well as glial fibrillary acidic protein expression.

CNS Neurol Disord Drug Targets. 2014 Aug 6. [Epub ahead of print]



Neuroprotection by Association of Palmitoylethanolamide with Luteolin in Experimental Alzheimer's Disease Models: the Control of Neuroinflammation.

Paterniti I, Cordaro M, Campolo M, Siracusa R, Cornelius C, Navarra M, Cuzzocrea S, Esposito E

2. For the **organotypic model of AD**, **hippocampal slice cultures were prepared from mice** at postnatal day 6 and after 21 days of culturing the slices were pre-treated with co-ultraPEALut (reference concentrations: 27, 2.7 and 0.27 µM PEA) for 2 h and then incubated with Aβ1-42 (1 µg/ml) for 24 h.

Pre-treatment with co-ultraPEALut significantly reduced inducible nitric oxide synthase and glial fibrillary acidic protein expression, restored neuronal nitric oxide synthase and brain-derived neurotrophic factor and reduced the apoptosis.

Taken together our results clearly showed that co-ultraPEALut is able to blunt Aβ-induced astrocyte activation and to exert a marked protective effect on glial cells.
These findings suggest that the association of co-ultraPEALut may provide an effective strategy for AD.

Pharmacol Res. 2014 Aug;86C:32-41.

Palmitoylethanolamide in CNS health and disease.

Mattace Raso G, Russo R, Calignano A, Meli R.

Abstract

The existence of acylethanolamides (AEs) in the mammalian brain has been known for decades. Among AEs, palmitoylethanolamide (PEA) is abundant in the central nervous system (CNS) and conspicuously produced by neurons and glial cells. **Antihyperalgesic and neuroprotective properties of PEA have been mainly related to the reduction of neuronal firing and to control of inflammation.** Growing evidence suggest that PEA may be neuroprotective during CNS neurodegenerative diseases. Advances in the understanding of the physiology and pharmacology of PEA have potentiated its interest as useful biological tool for disease management.

Several rapid non-genomic and delayed genomic mechanisms of action have been identified for PEA as peroxisome proliferator-activated receptor (PPAR)-α dependent.

Pharmacol Res. 2014 Aug;86C:32-41.

Palmitoylethanolamide in CNS health and disease.

Mattace Raso G, Russo R, Calignano A, Meli R.

Several rapid non-genomic and delayed genomic mechanisms of action have been identified for PEA as peroxisome proliferator-activated receptor (PPAR)-α dependent.

First, an early molecular control, through Ca+2-activated intermediate- and/or big-conductance K+ channels opening, drives to rapid neuronal hyperpolarization. This is reinforced by the increase of the inward Cl− currents due to the modulation of the gamma aminobutyric acid A receptor and by the desensitization of the transient receptor potential channel type V1.
Moreover, the gene transcription-mediated mechanism sustains the long-term anti-inflammatory effects, by reducing pro-inflammatory enzyme expression and increasing neurosteroid synthesis.

Overall, the integration of these different modes of action allows PEA to exert an immediate and prolonged efficacious control in neuron signaling either on inflammatory process or neuronal excitability, maintaining cellular homeostasis.
In this review, we will discuss the effect of PEA on metabolism, behavior, inflammation and pain perception, related to the control of central functions **and the emerging evidence demonstrating its therapeutic efficacy in several neurodegenerative diseases.**

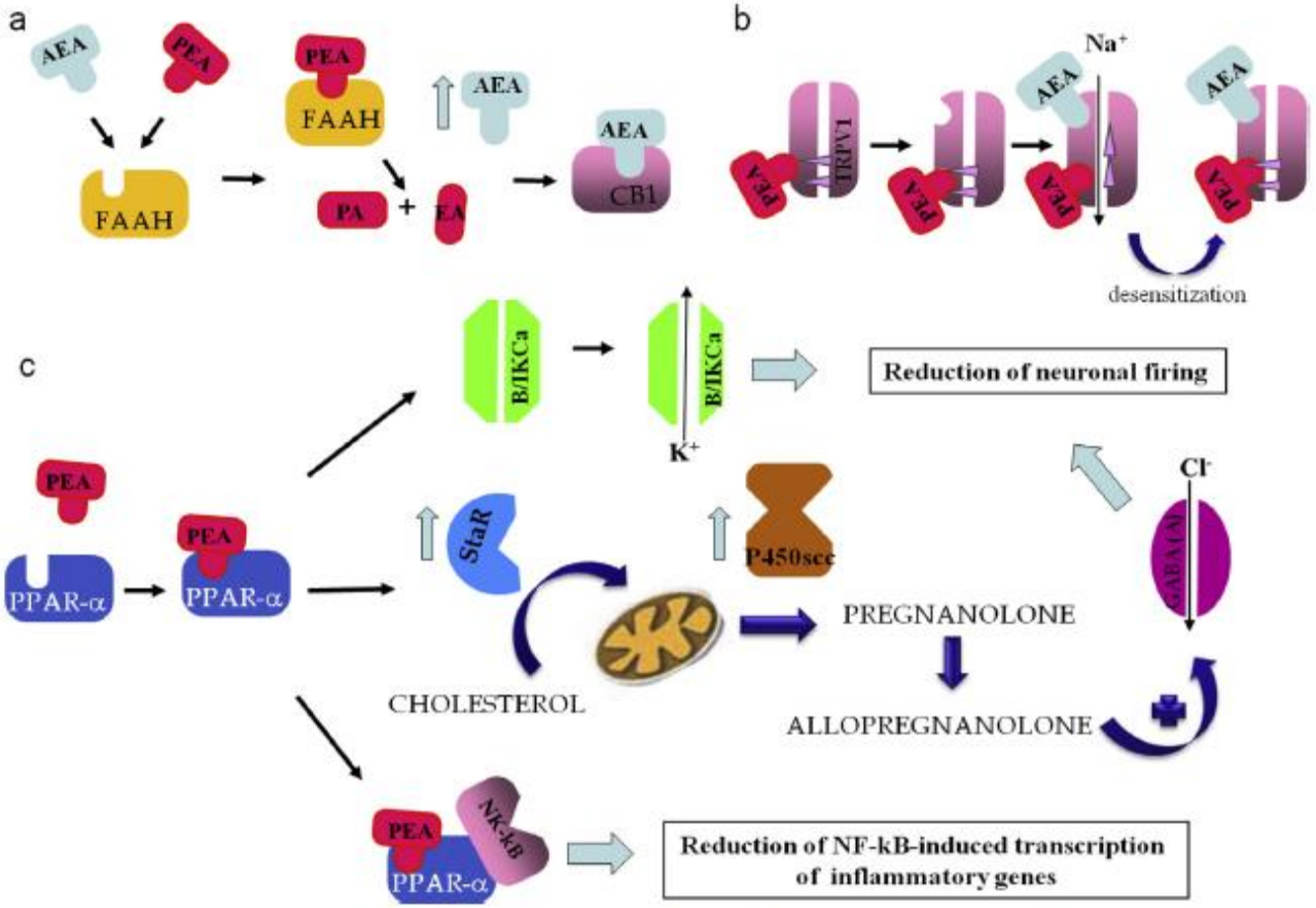


Fig. 1. Direct and indirect mechanisms of action of PEA. The indirect mechanism would involve PEA potentiation of AEA effects through (a) a competitive inhibition of AEA metabolism by FAAH, leading to an increase in AEA levels and its binding to CB1 (b); an allosteric activity on TRPV1, increasing AEA affinity to this receptor, and inducing later TRPV1 desensitization. (c) Through a PPAR-α dependent non-genomic mechanism, PEA increases the gating properties of IKCa and BKCa channels, resulting in a fast reduction of neuronal firing. Moreover, PPAR-α activation, through a genomic mechanism, increases the expression of StaR and P450scc, involved in cholesterol transfer into the mitochondria and its metabolism in pregnanolone, respectively. The resulting increase in allopregnanolone levels leads to a positive allosteric activation of GABA(A) receptors, an increase in Cl^- currents and a reinforcing effect on the reduction of neuronal firing. PEA anti-inflammatory effect appears to be related to a cytoplasmatic complex, that reduces NF-κB transcription activity, dampening the transcription of pro-inflammatory gene. PEA, palmitoylethanolamine; AEA, anandamide; FAAH, fatty acid amide hydrolase; PA palmitic acid, EA, ethanolamine; CB1, cannabinoid receptor 1; TRPV1, transient receptor potential channel type V1; PPAR-α, peroxisome proliferator-activated receptor-α; I/BKCa, calcium-activated intermediate- or big-conductance potassium channels; StaR, steroidogenic acute regulatory protein; P450scc, cytochrome P450 side-chain cleavage; GAGA-A, gamma-aminobutyric acid receptor A; NF-κB, nuclear factor-κB.

Clinical studies demonstrating anti-nociceptive/anti-hyperalgesic effects of PEA, reduction in disability, improvement of neurological functions and quality of life

	Source of pain (n=patient number)	Study Design	n	Regimen of PEA administration	PEA effects	Ref
Postsurgery pain	Lower third molar extraction	Single-blind, randomized, split-mouth. micronized PEA	30	300 mg/bid for 15 days (6 before, 9 after surgery)	post surgery pain relief	Bacci et al 2011
Osteoarthritis	Temporomandibular joint	Double-blind randomized; micronized PEA vs ibuprofen	24	900 mg/day for 7 days; + 300 mg/bid for next 7 days vs ibuprofen 1800 mg/day for 14 days	greater score pain reduction better maximum mouth opening greater tolerability	Marini et al 2012
Chronic pain	Lumbosciatica	Double-blind, randomized, two doses of micronized PEA vs placebo	636	1st arm: 300 mg/die x 3 weeks; 2nd arm: 600 mg/die for 3 weeks	score pain reduction reduced disability	Guida et al 2010
	Lumbosciatica	Double-blind, randomized, two doses of micronized PEA vs placebo	111	1st arm: 300 mg/die x 3 weeks 2nd arm: 600 mg/die for 3 weeks	score pain reduction reduced exposure to anti-inflammatory or analgesic drugs	Canteri et al 2010
	Radiculopathy (331) Osteoarthritis (54) Herpes Zoster (44) Diab. Neuropaty (32) FBSS (76) Oncologic (22) Other diseases (51)	Open (ultramicronized PEA ± analgesics)	610	600 mg bid for 3 weeks + 600 mg/die for next 4 weeks ± standard analgesics	score pain reduction	Gatti et al 2012

Clinical studies demonstrating anti-nociceptive/anti-hyperalgesic effects of PEA, reduction in disability, improvement of neurological functions and quality of life

	Source of pain (n=patient number)	Study Design	n	Regimen of PEA administration	PEA effects	Ref
Chronic pain	Cervicobrachial or sciatical pain	Open micronized PEA ± acupuncture)	30	300 mg/bid for 8 weeks	reduced chronic pain score reduced pain impact on emotional state reduced pain impact on employment	Crestani et al 2013
	Low back pain	Open ultramicronized PEA+oxycodone	20	PEA 600 mg/bid +oxycodone* for 30 days	score pain reduction reduces disability	Desio, 2011
	Diabetic neuropathy (11) Postherpetic neuralgia (19)	Open ultramicronized PEA+pregabalin	30	PEA 600 mg/bid +pregabalin* for 45 days	score pain reduction reduces disability	Desio, 2010
	Trigeminal neuralgia	Open ultramicronized PEA+carbamazepin	31	PEA 600 mg/bid + carbamazepin* for 45 days	score pain reduction reduces disability	Desio, 2012
	Diabetic neuropathy + carpal tunnel syndrome .	Group-controlled, randomized, micronized PEA vs standard care	50	600 mg/bid for 60 days	score pain reduction improved sensory conduction velocity	Assini et al 2010
	Carpal tunnel syndrome	Group-controlled, randomized, two doses of micronized PEA vs no-treated patients	26	1st arm: 300 mg/bid for 30 days 2nd arm: 600 mg/bid for 30 days	reduced median nerve latency time minor Tinel's sign presence reduced discomfort	Conigliaro et al 2011
	Endometriosis	Open (case series) micronized PEA	4	200 mg/bid (+polydatin 20 mg/bid) for 3 months	decreased pelvic pains: CPP dyspareunia dysmenorrhea decreased use of analgesics	Indraccolo & Barbieri, 2010
	Endometriosis	Double-blind, randomized parallel-group, micronized PEA vs placebo	61	400 mg/tid (+ 40 mg/ tid polydatin) for 3 months vs celecoxib 200 mg/bid for 7 days	decreased pelvic pains: CPP dyspareunia dysmenorrhea	Cobellis et al 2011

Clinical studies demonstrating anti-nociceptive/anti-hyperalgesic effects of PEA, reduction in disability, improvement of neurological functions and quality of life

	Source of pain (n=patient number)	Study Design	n	Regimen of PEA administration	PEA effects	Ref
Chronic Pain	Endometriosis: • recto-vaginal septum (19) • ovary (28)	Prospective micronized PEA	47	400 mg/bid (+polydatin 20 mg/bid) for 3 months	decreased pelvic pains: CPP dyspareunia dysmenorrheal dyschezia	Giuglian et al al 2013
	Primary dysmenorrhoea	Open micronized PEA	20	400 mg/bid (+ polydatin 40 mg/bid) for 6 months	decreased pelvic pain	Fulghesu et al 2010
	Pudendal neuralgia	Case Report micronized PEA	1	300 mg/tid gradually decreasing to 300 mg/die for1 year	resolution of pain	Calabrò, 2010
	Post-stroke patients	Open Controlled ultra-micronized PEA + physiotherapy. vs physiotherapy	20	600 mg/bid for 60 days + 600 mg/die for next 30 days	pain intensity reduction spasticity reduction	Russo and Parabita, 2011
Neuropathic pain	Chemotherapy-induced neuropathy	Open micronized PEA	20	300 mg/bid for two months	pain score reduction increased amplitude of foot-LEPs, sural-SNAPs, peroneal-CMAPs	Truiniet al 2011
	Multiple sclerosis	Case Report: micronized PEA + acupuncture	1	900 mg daily for five weeks	persistent reduction of pain intensity	Kopsky and Hesselink, 2012
	Lumbosciatica	Group-controlled, randomized, micronized PEA +standard analgesic therapies vs standard analgesic therapies	118	300 mg/bid for 30 days	pain score reduction quality life improvement	Dominguez et al 2012
	Diabetic polyneuropathy	Open micronized PEA	30	300 mg/bid for 60 days	pain relief; reduced neuropathic symptoms	Schifilliti et al 2011

Conclusioni

- Il controllo della neuroinfiammazione nel Sistema Nervoso Centrale può rallentare lo sviluppo della neurodegenerazione
- E' possibile modulare per via farmacologica i meccanismi causali regolatori che innescano, sostengono, amplificano e cronicizzano il *loop* eziopatogenetico della sofferenza neuronale nel SNC e nel SNP
- PEA + Luteolina potrebbero giocare un ruolo nella riduzione della neurotossicità indotta da Aβ e nello sviluppo dei deficit cognitivi
- **"Thus, the development of a multitargeted approach to prevent or symptomatically treat Alzheimer's disease, as used in current practice for other multigenic disorders, is needed"** *(N Engl J Med Volume 2010; 362(4):329-344).*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