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Journal of Gerontology & Geriatric Research
Review in 3 weeks Publishing in 72 hours Open Access
ISSN: 2167-7182

Aging and Neurodegenerative disease

AGING

Neurodegeneration

- Synaptic dysfunction
- Synapse loss
- Dendrite regression
- Impaired neurogenesis

Glial/Immuno alterations

- Cytokine cascade
- Microglial activation
- Impaired detoxification
- Demyelination

Neurons and glial cells may adapt to the adversities of aging. If adaptation is not successful, then molecular damage to neurons and inflammatory processes result in synaptic dysfunction and neuronal degeneration and death

Mattson M P et al. Physiol Rev 2002;82:637-672

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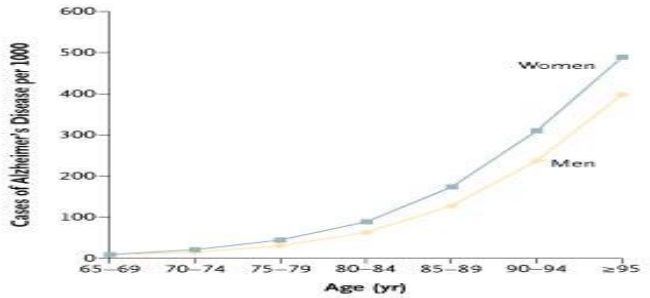
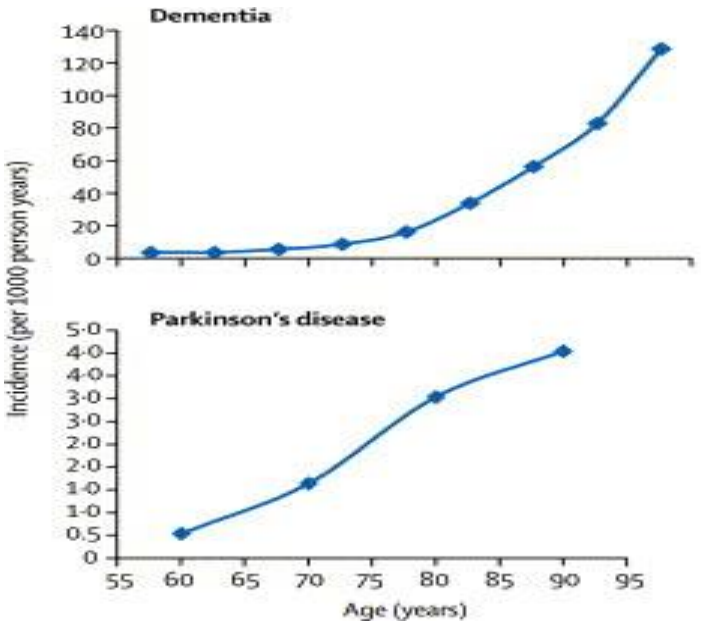
Neurodegenerative disease prevalence:

Alzheimer's disease:
1-2% age 65-75; 50% over age 85



Parkinson's disease:
0.5-1% age 60-69; 1-3% over age 80



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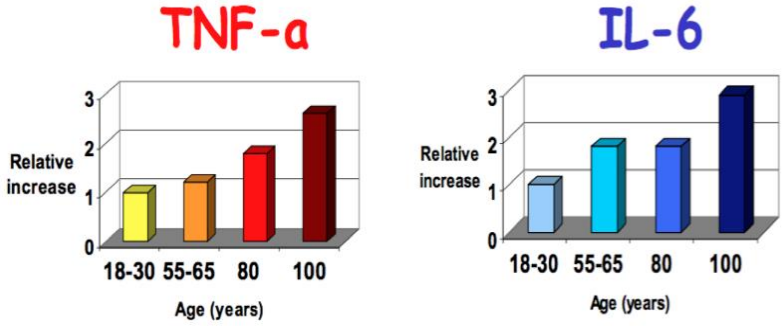
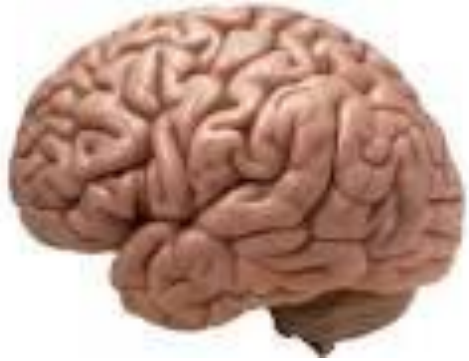
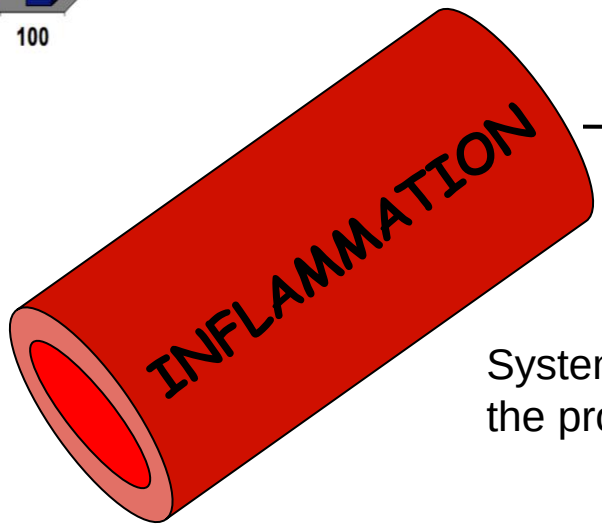
Inflammation in neurodegeneration: Cause, Effect, or Both?



Bruunsgaard, J Gerontol 2000





Aging is associated with systemic low-grade inflammation

Systemic inflammation can influence the progression of dementia

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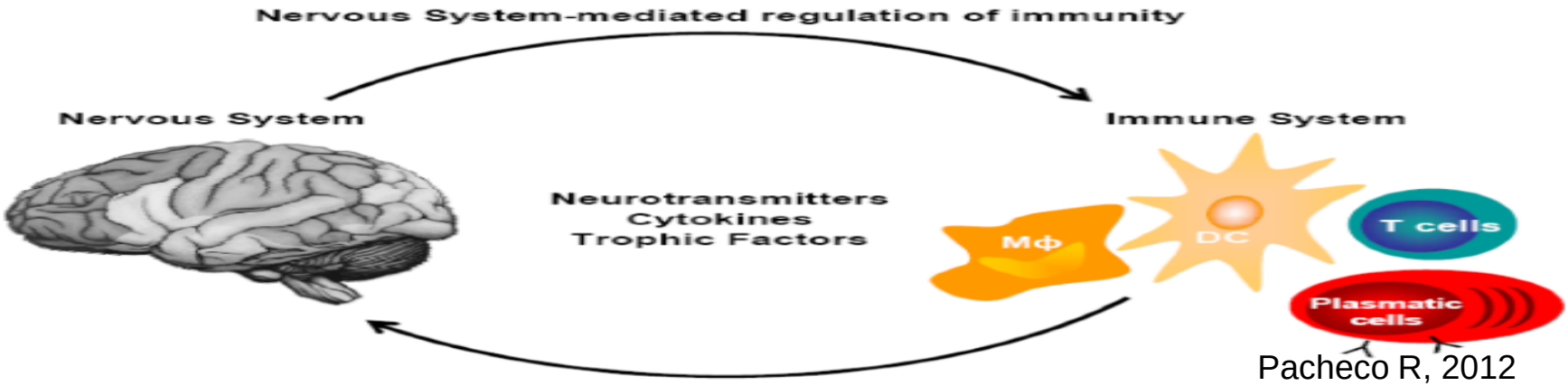
Bidirectional communication between nervous and immune system

bidirectional communication takes place between nervous and immune system in both health and disease.

The same molecules, including cytokines, neurotransmitters and trophic factors, participate as mediators in both directions.



Pacheco R, 2012

The brain responds to inflammation with sickness behavior

But also initiates an opposing, anti-inflammatory response to restore homeostasis

✓locally mediated through efferent autonomic nervous system (acetylcholine)

✓systemically mediated through activation of the HPA axis (glucocorticoids)

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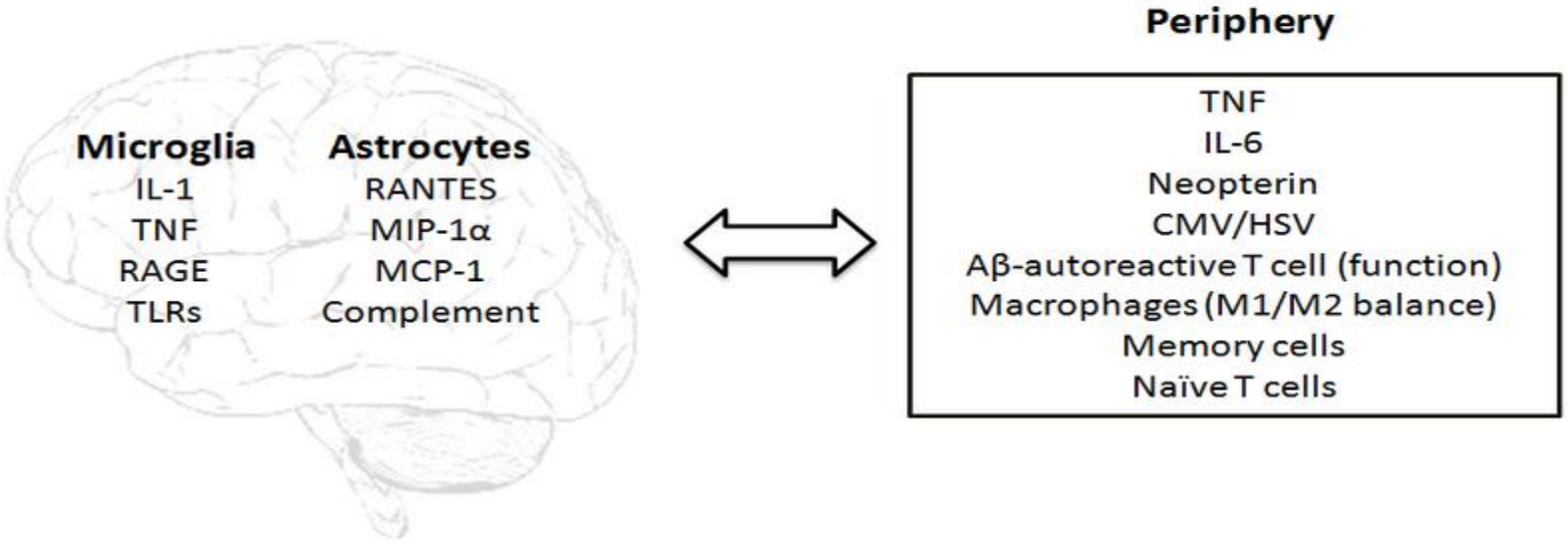
The immune response and AD



The inflammatory component is very strong in AD.
The main markers identified as associated or causative are shown not only for the brain but for the periphery as well.

Fulop et a. 2013

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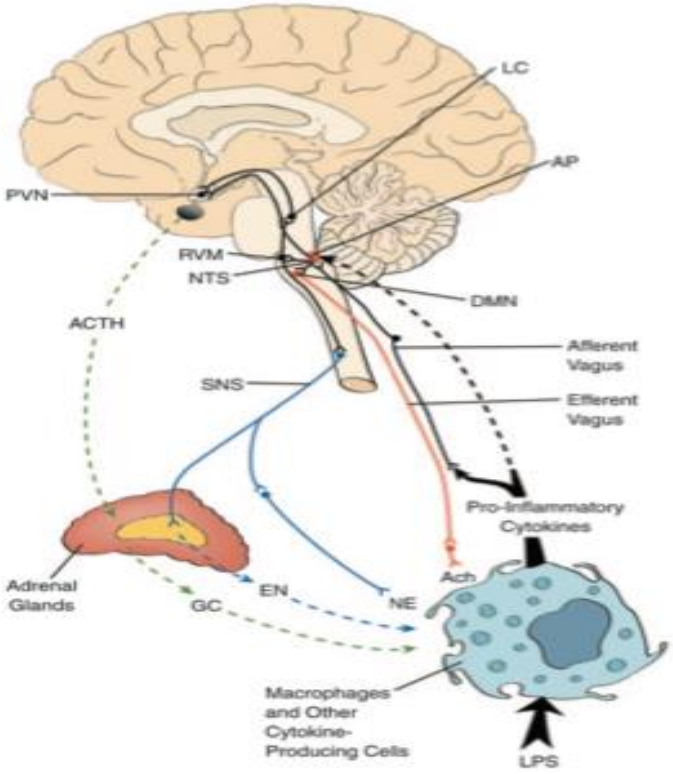
Routes of Communication between Brain and Immune system

SNS

Sympathetic fibers release Norepinephrine and innervate thymus, bone marrow, spleen, lymph nodes, and tissues exerts anti-inflammatory effects by interacting with adrenoceptors expressed on lymphocytes and macrophages. Adrenal medulla release Adrenaline



HPA axis

specialized neurons in the PVN synthesize CRH that induces the production of ACTH in the pituitary. Synthesis and release of glucocorticoids in the adrenalglands

SN sympathetic- vagus

the vagus innervating the reticuloendothelial system induce the release of acetylcholine

Pavlov V. et al. Mol. Med. 2003; 9,5-9:125

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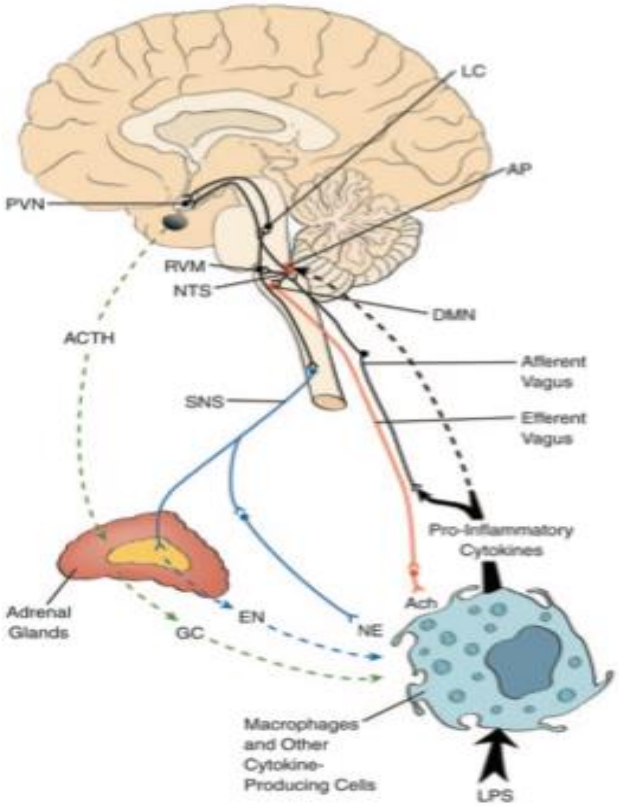
Routes of Communication between Immune system and Brain

Neural pathway
Activation of of vagus nerve afferent sensory fibers, directly by cytokines released from dendritic cells, macrophages, and other vagal-associated immune cells, or indirectly through the chemoreceptive cells located in vagal paraganglia, signal the brain that inflammation is occurring



Humoral pathway
Activated cells release cytokines that can cross the blood-brain barrier and enter cerebrospinal fluid and the interstitial fluid spaces of the brain were signal the brain for activation of immunomodulatory mechanisms.

Cytokine-to-brain communication also may occur via circum-ventricular organs such as AP, providing a way of signaling the SNS and HPA axis. Cytokine-induced production of prostaglandins may result in HPA axis activation

Pavlov V. et al. Mol. Med. 2003; 9,5-9:125

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Non-neuronal immune cholinergic system

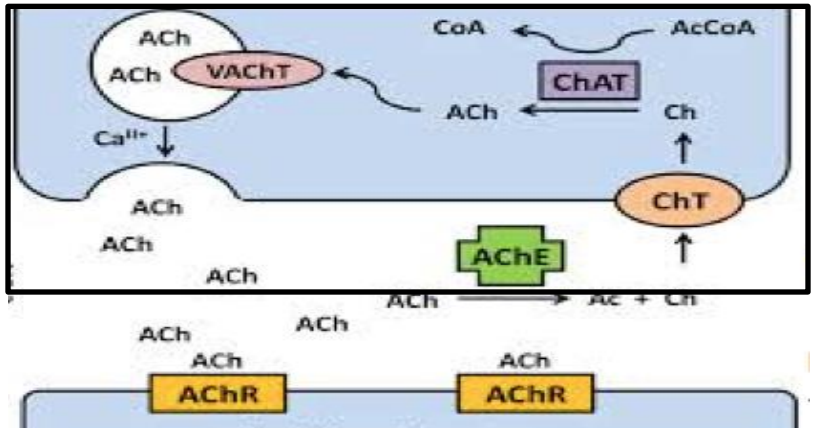
* Synthesis of ACh

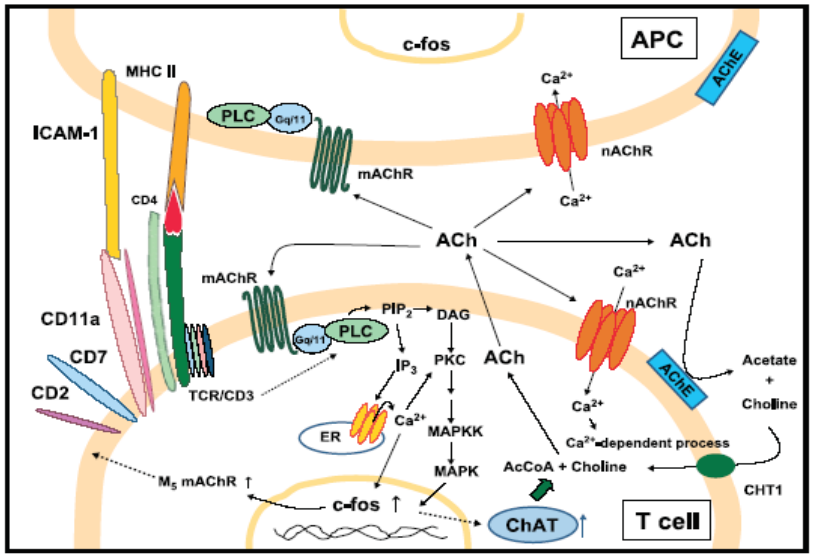
* Expression of the enzyme cholineacyltransferase (ChAT)

* Response to cholinergic signals; muscarnic and nicotinic

* Expression of α7 nicotinic acetylcholine receptor (AChR)

* Termination of cholinergic signals is mediated by AChE





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Cholinergic system and neuro-immune interactions

* The nervous system is a major producer of ACh
* The immune cholinergic system can mediate neuro-immune interactions
* or serve as an internal regulator of immune responses
* α7nAChR on macrophages and T-cells can be anti-inflammatory target
* Stimulation of M1/M5 mAChRs expressed on CD4+ T cells potentiates Th2 responses
* Stimulation of α7 nAChRs expressed on CD4+ T cells favors Th1 responses and impairs Th2 and Tregs differentiation.

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Functions of cytokines

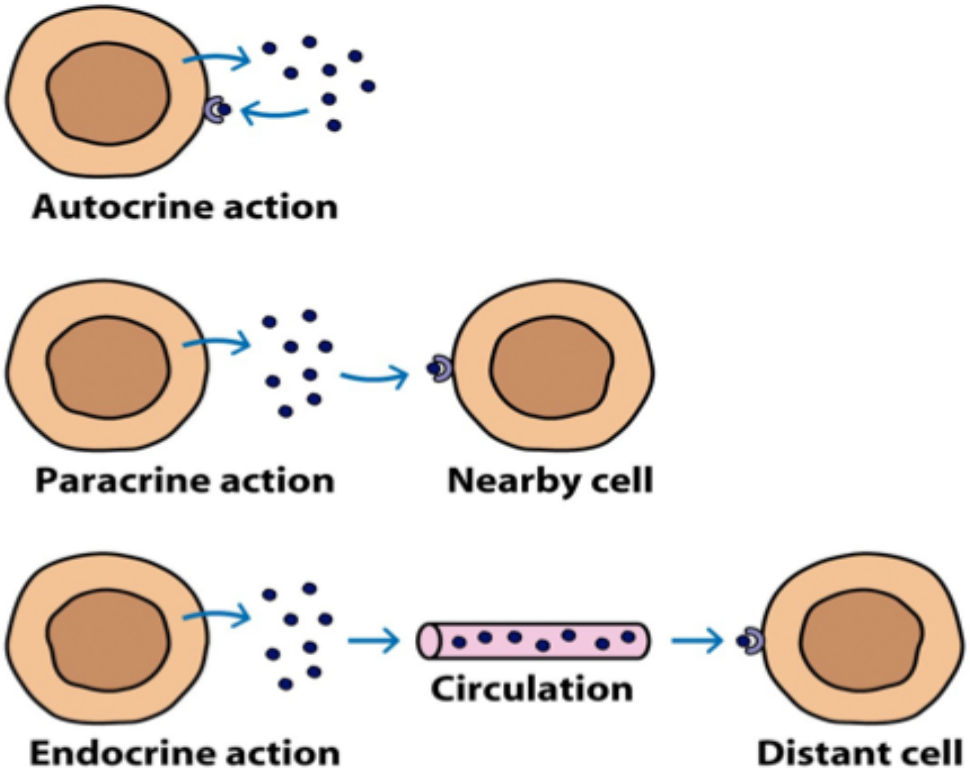

Figure 12-1b
Kuby IMMUNOLOGY, Sixth Edition

stimulation
inhibition
differentiation
cell death
chemoattract

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Cytokines

- A hierarchical order of cytokine actions has been observed with some early cytokines pre-activating cells so that they then can respond to late-acting cytokines
- Many cytokines induce the synthesis of novel gene products once they have bound to their respective receptors
- Cytokine mediators can be transported quickly to remote areas of a multicellular organism
- They can be degraded quickly.
- Concentration gradients can be used to elicit specific responses
- They also play a key role in neuroimmunological, neuroendocrinological, and neuroregulatory processes

Chemoattractant Cytokines were called Chemokines

- They are Small (8-10kd) secreted heparin-binding
- Promote recruitment and activation of leukocytes
- Can be divided into subclasses by virtue of structural properties:

✓ CC class – The first two cysteines are adjacent (example: MCP-1, RANTES)

✓ CXC class- The first two cysteines are not adjacent (example: IL-8)

✓ C class – Only has 2 cysteines not 4 (example: Lymphotactin)

✓ CX3C class – Has 3 amino acids between the first two cysteines and a different N-terminal

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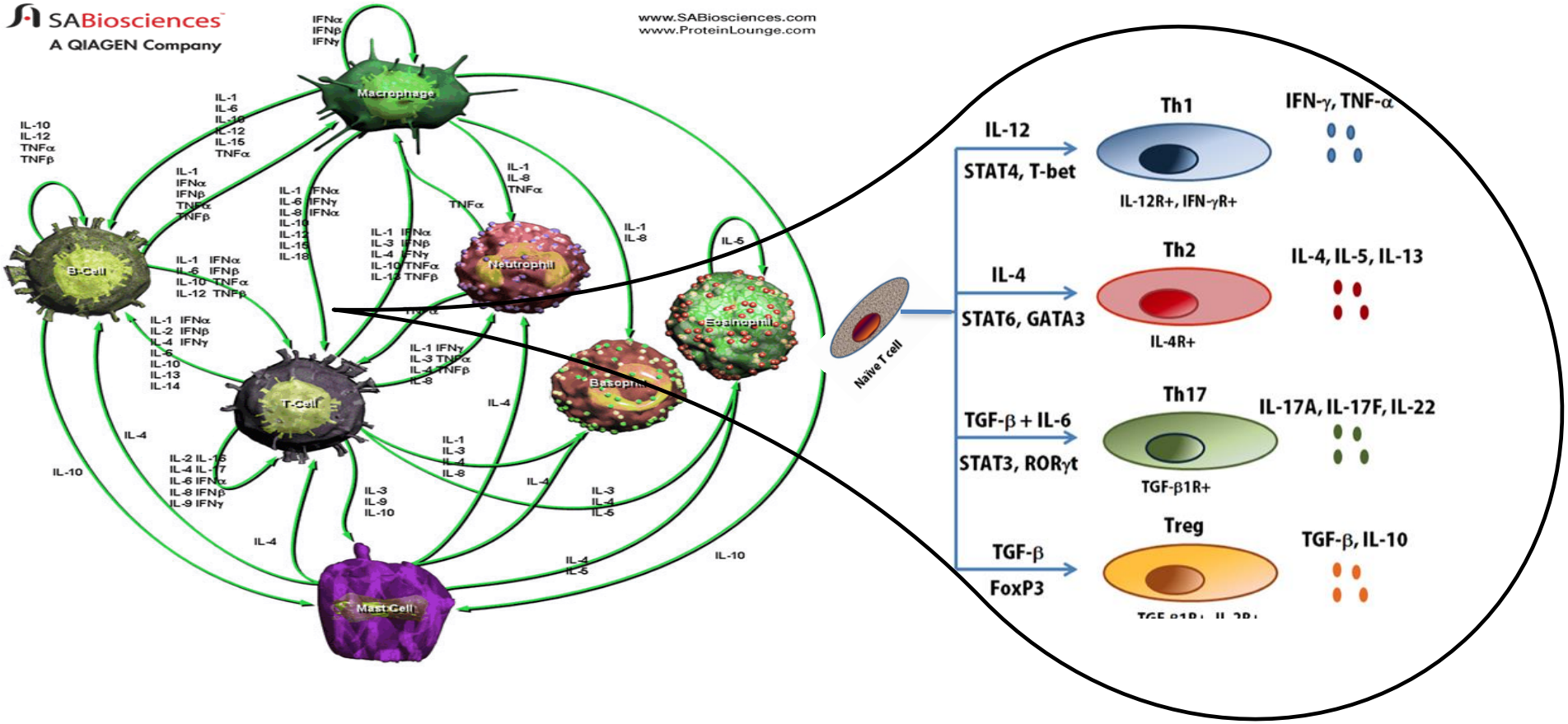
Cytokine network



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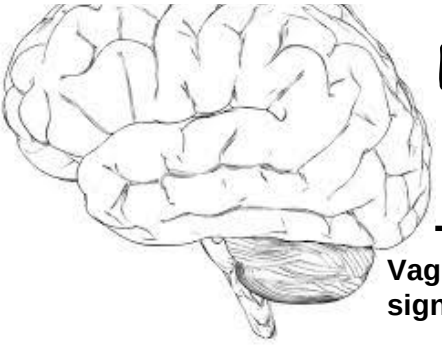
nergic anti-inflammatory pathway



Acetylcholine binding to α7 nAChR leads to the inhibition of the phosphorylation of inhibitor of NF-B (IkB), the downregulation of the activation of mitogen-activated protein kinases (MAPKs), inhibition of the release of intracellular Ca^{2+} stores and the formation of a heterodimeric protein complex with Janus kinase 1 (JAK2), which activates signal transducer and activator of transcription 2 (STAT3).

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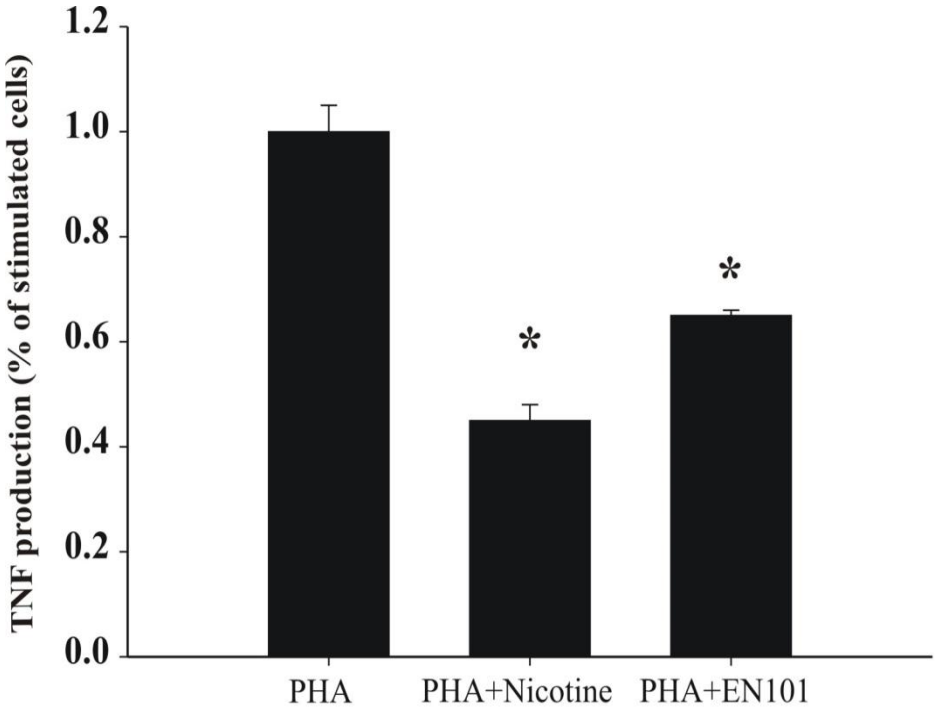
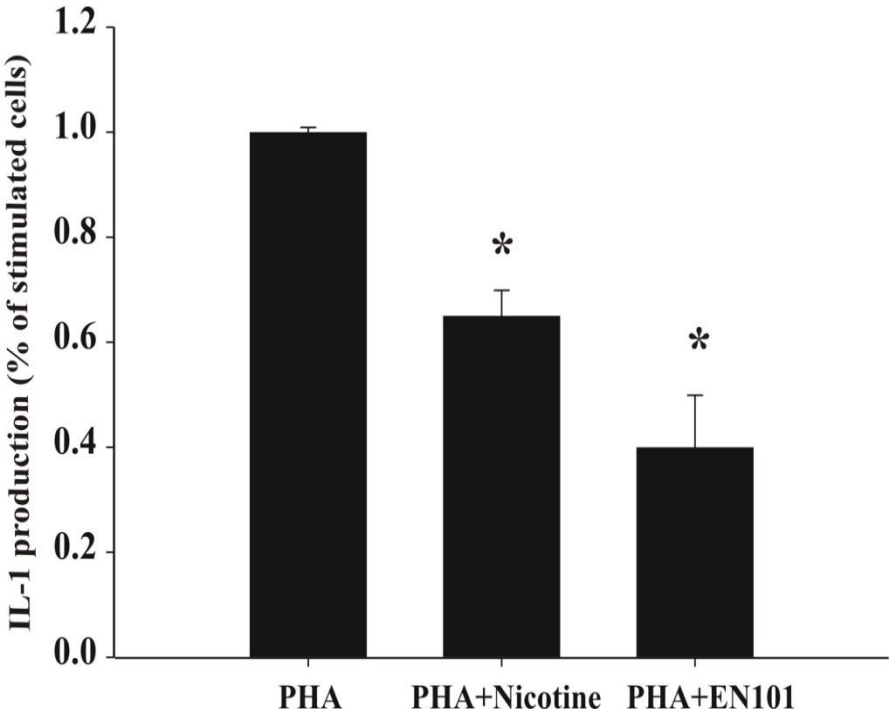
Attenuation of pro-inflammatory cytokine production by α7 nAChR activation





Nizri et al Neuropharmacology 2006

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Butyrylcholinesterase and Acetylcholinesterase

Butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) are members of the same family of enzymes

Both AChE and BuChE regulate the neurotransmitter acetylcholine (ACh) in the brain

Likely to play a key role (rather than just aback-up role) in improving cholinergic neurotransmission

Mesulam et al. 2002; Darvesh et al. 2003

Inhibition of either AChE or BuChE in the brain increases ACh concentration

AChE or BuChE specific inhibitors improve cognitive performance of elderly rats

Greig et al. 2001

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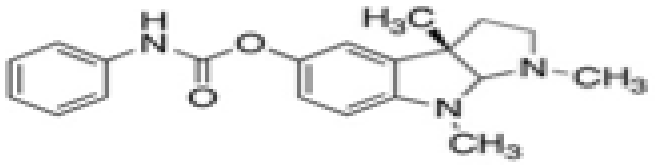
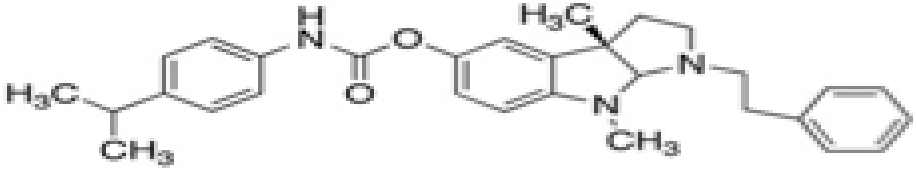
ChE inhibitors

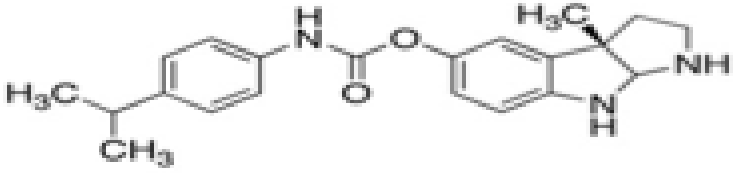
(-)-Phenserine (1)



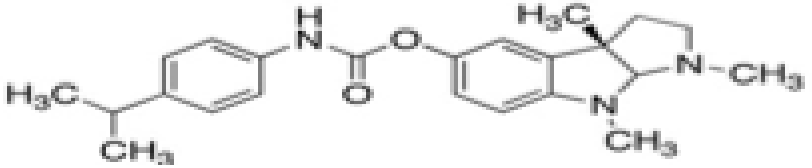
(-)-Phenethylcymserine (2)



(-)-Bisnorcymserine (3)



(-)-Cymserine (4)



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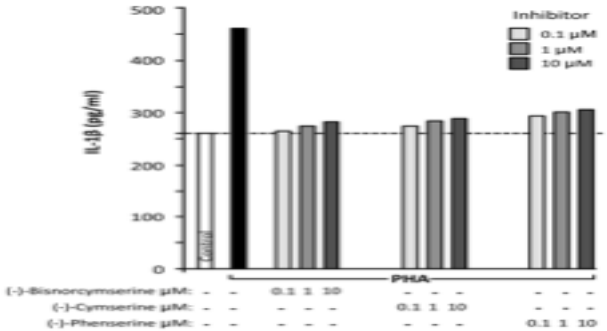
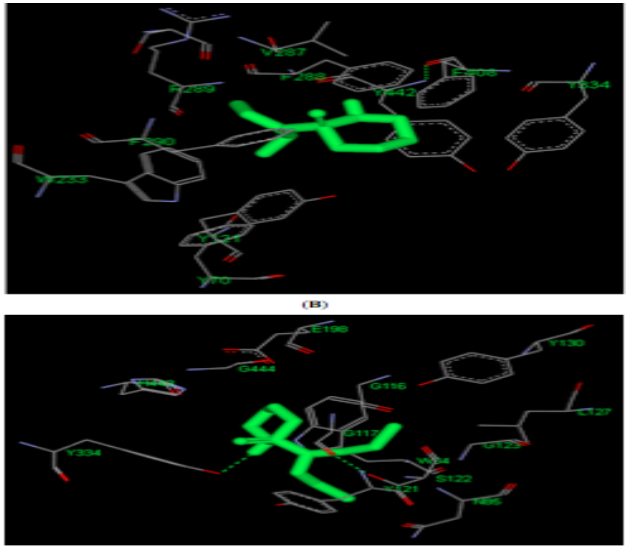


Selective Acetyl- and Butyrylcholinesterase Inhibitors Reduce Amyloid-β *Ex Vivo* Activation of Peripheral Chemo-cytokines From Alzheimer's Disease Subjects: Exploring the Cholinergic Anti-inflammatory Pathway

Marcella Reale[1,*], Marta Di Nicola[1], Lucia Velluto[2], Chiara D'Angelo[1], Erica Costantini[1], Debomoy K. Lahiri[3], Mohammad A. Kamal[4], Qian-sheng Yu[5] and Nigel H. Greig[5,*]



CNS & Neurological Disorders - Drug Targets, 2011, *10*, 000-000 928-935 1

Human Platelet Acetylcholinesterase Inhibition by Cyclophosphamide: A Combined Experimental and Computational Approach

Abdulaziz A. Al-Jafari[1], Shazi Shakil[2], Marcella Reale[3] and Mohammad A. Kamal[*,2]

Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 2013, *12*, 000-000 1

Synthesis of the Alzheimer Drug Posiphen into its Primary Metabolic Products (+)-N[1]-norPosiphen, (+)-N[8]-norPosiphen and (+)-N[1], N[8]-bisnorPosiphen, their Inhibition of Amyloid Precursor Protein, α-Synuclein Synthesis, Interleukin-1β Release, and Cholinergic Action

Qian-sheng Yu[1], Marcella Reale[2], Mohammad A. Kamal[3], Harold W. Holloway[1], Weiming Luo[1], Kumar Sambamurti[4], Balmiki Ray[5], Debomoy K. Lahiri[5], Jack T. Rogers[6] and Nigel H. Greig[1,*,#]

No.	Compound	% Inhibition Muscarinic Binding (at 10 µM test compound)					% Inhibition Nicotinic Binding (at 10 µM test compound)					
		M1	M2	M3	M4	M5	α2β2	α2β4	α3β2	α3β4	α4β2	α4β4
1	(+)-Posiphen	0	0	1.5	0	0	0	0	0	0.9	0.5	4.7
2	(-)-Phenserine	0	7.6	3.1	0.3	6.5	3.4	0	6.1	12.3	0.1	8.3
11	(+)-N[1],N[8]-BisnorPosiphen	0	9.8	0	0	0	0	0.5	0.8	0	2.6	5.1
15	(+)-N[1]-NorPosiphen	0	0.1	0	30	1.0	0	0	0	0	0	2.4
17	(+)-N[8]-NorPosiphen	0	0	4.5	0	0	0	0	0	0	0.2	1.1

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Neurodegenerative Diseases Alzheimer's Disease

A Pathophysiological Role for Selective Alteration of the Cytokine–Chemokine Network – Inflammatory Theory in Alzheimer's Disease

Domenico Gambi[1] and Marcella Reale[2]

International Journal of Alzheimer's Disease
Volume 2010, Article ID 974026, 2 pages
doi:10.4061/2010/974026

Editorial

Neuroinflammation, AD, and Dementia

Marcella Reale,[1] Talma Brenner,[2] Nigel H. Greig,[3] Nibaldo Inestrosa,[4] and Diana Paleacu[5]

Recent Patents on CNS Drug Discovery, 2013, *8*, 123-141 123

New Pharmacological Approaches to the Cholinergic System: An Overview on Muscarinic Receptor Ligands and Cholinesterase Inhibitors

Nigel H. Greig[1], Marcella Reale[2] and Ada M. Tata*[3]

Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 2013, *Vol. 12, No. 2* 1

Editorial

Modulation of Cholinergic System Activity in Neuronal and Non-Neuronal Tissues: Therapeutic Implications

Current Alzheimer Research, 2012, *9*, 447-457 447

Relationship between Inflammatory Mediators, Aβ Levels and ApoE Genotype in Alzheimer Disease

M. Reale[1,*], M.A. Kamal[2], L. Velluto[3], D. Gambi[1], M. Di Nicola[4] and N.H. Greig[5]

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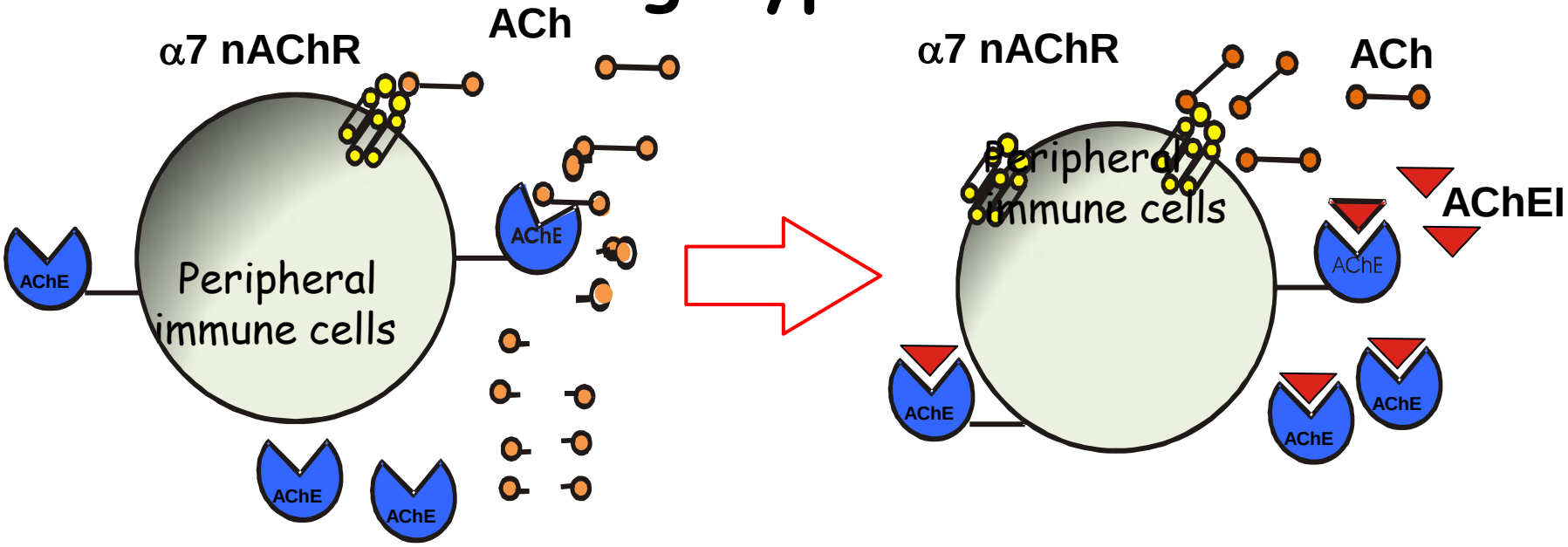
Working hypothesis:



Cholinergic up-regulation: inhibition of pro-inflammatory cytokine release

Inhibition of (extra-cellular) AChE: can activate the α7 nAChR

Activation of the α7 nAChR: anti-inflammatory effects

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- AChEI mediate anti-inflammatory effects: Suppression of cell activities, proliferation and pro-inflammatory cytokine production
- AChEI mechanism involves activation of α7nAChR
- Expression of α7nAChR on cell producing cytokines surface increases following stimulation
- Nicotine treatment reduced Th1 and Th17 activity and Th2 polarization with inhibition of NFkb induced signaling

Cholinergic up-regulation by treatment results in reduction of neuroinflammation and improvement of cognitive deficit

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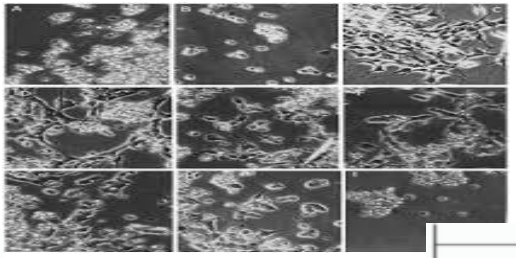
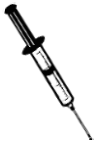
Methods

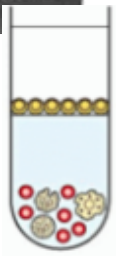


Cell lines:
SH-SY5Y
THP-1



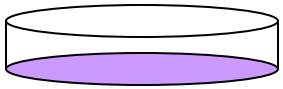
Collect whole blood

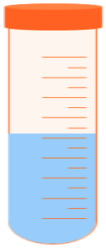
Centrifuge blood over a Ficoll-Hypaque gradient to isolate mononuclear cells



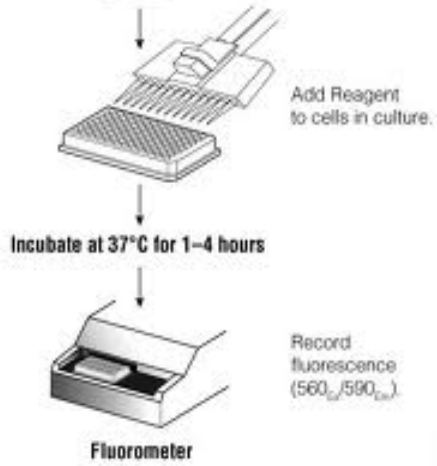
PBMCs

Place cells in culture tubes or disches , add ChEIs or agonist/antagonist of α7nAChR to study their effects on immune response



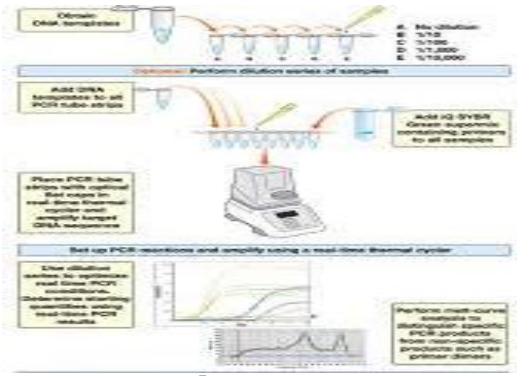


Cell Signaling and activities



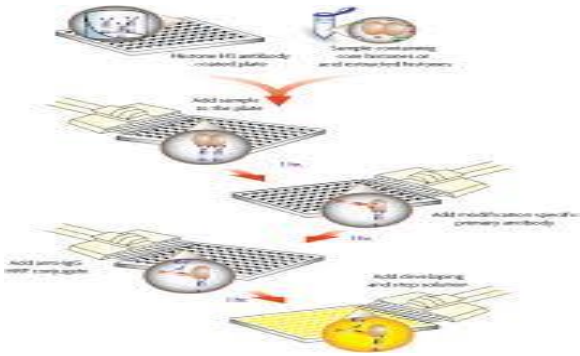
Cytokines assay

Transcription



Real time PCR

Secretion



Elisa Assay

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Conclusions

- The immune cholinergic system play a role in the immunomodulation
- Cholinergic up-regulation by AChEI treatment results in reduction of neuroinflammation and improvement of cognitive deficit
- Sustained inhibition of both AChE and BuChE is correlated with clinical benefit
- Selective BuChE inhibition reduces APP and Aβ levels
- AChE and BuChE inhibition versus AChE- specific inhibition currently being studied
- activation of ⟨7nAChR reduced Th1 and Th17 cytokine synthesis

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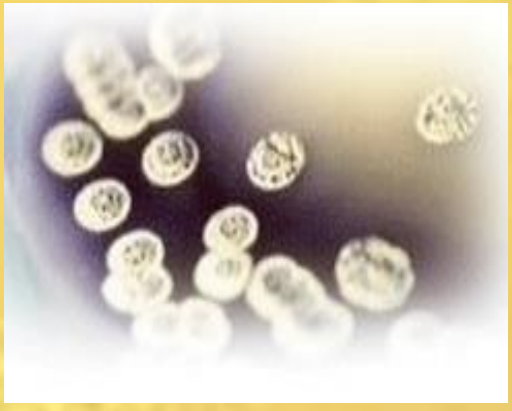

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