« Homéostasie cérébrale & neuroinflammation »

David BLUM

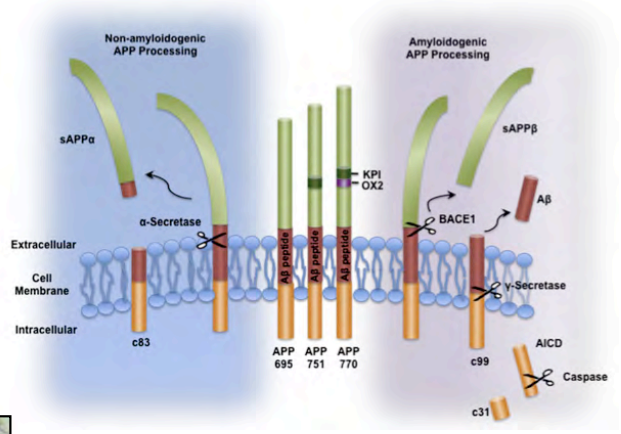
Inserm UMR-S 1172

« Alzheimer & Tauopathies »

DIU MA2

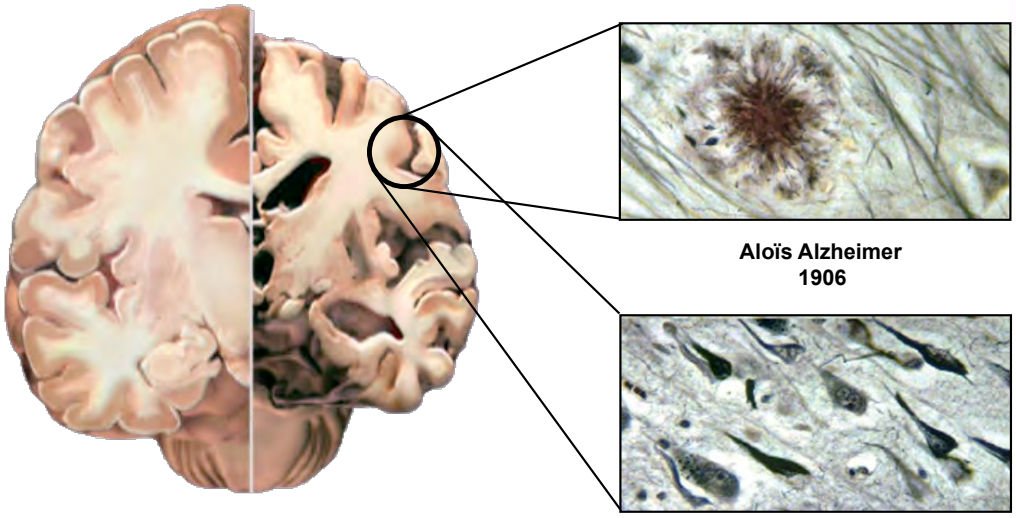
Neuroinflammation and Alzheimer's Disease

Alzheimer's disease: lesions



healthy brain

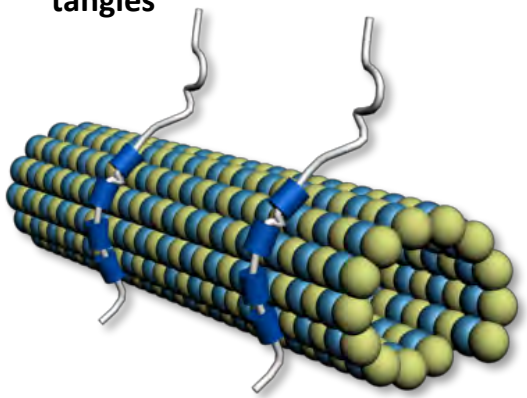
advanced Alzheimer's



Aloïs Alzheimer
1906

Senile plaques

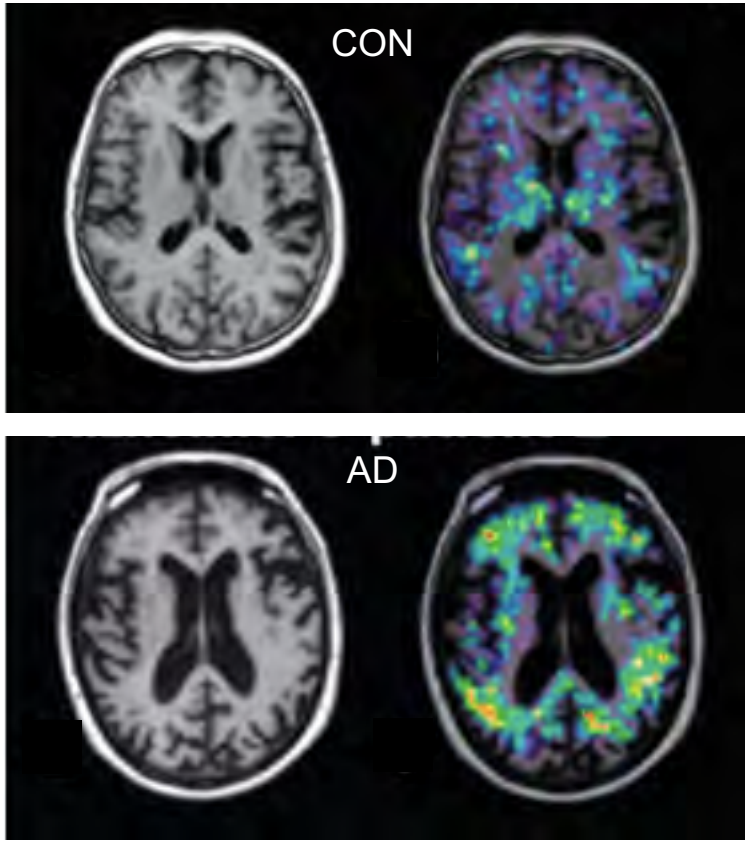
Neurofibrillary tangles



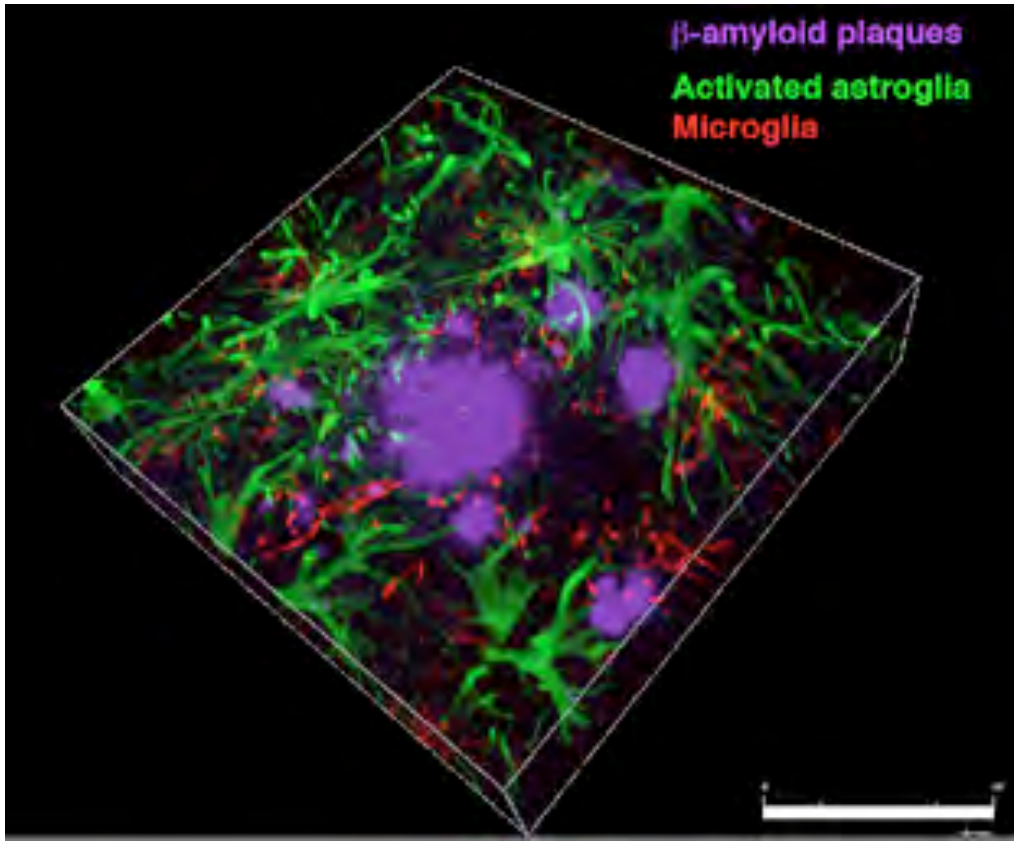
Inflammation is central in Alzheimer's Disease

Imaging and histology

[11C](R)-PK11195 binding



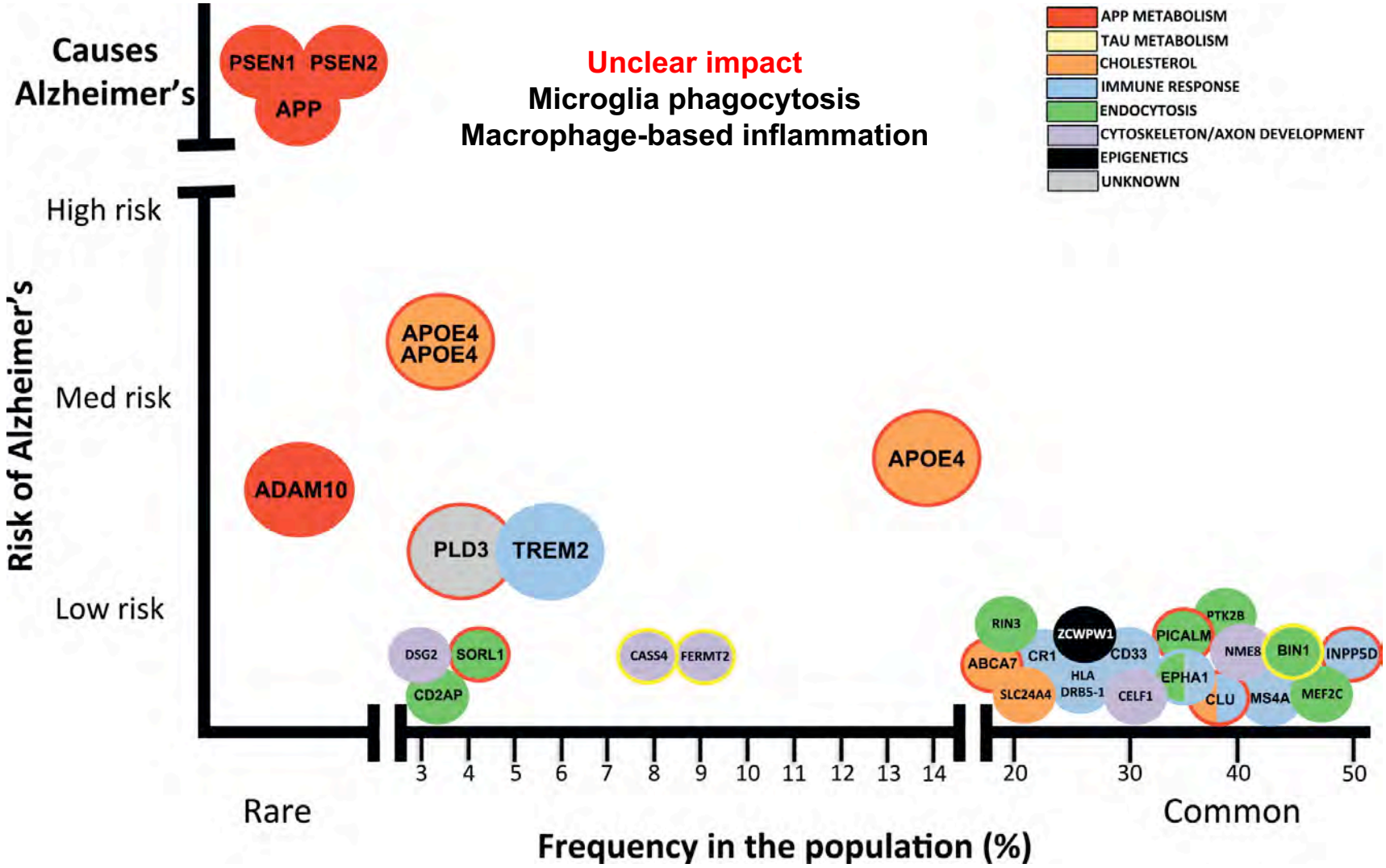
Cagnin et al.



Tsuneya Ikezu

Innate immunity is central in Alzheimer's Disease

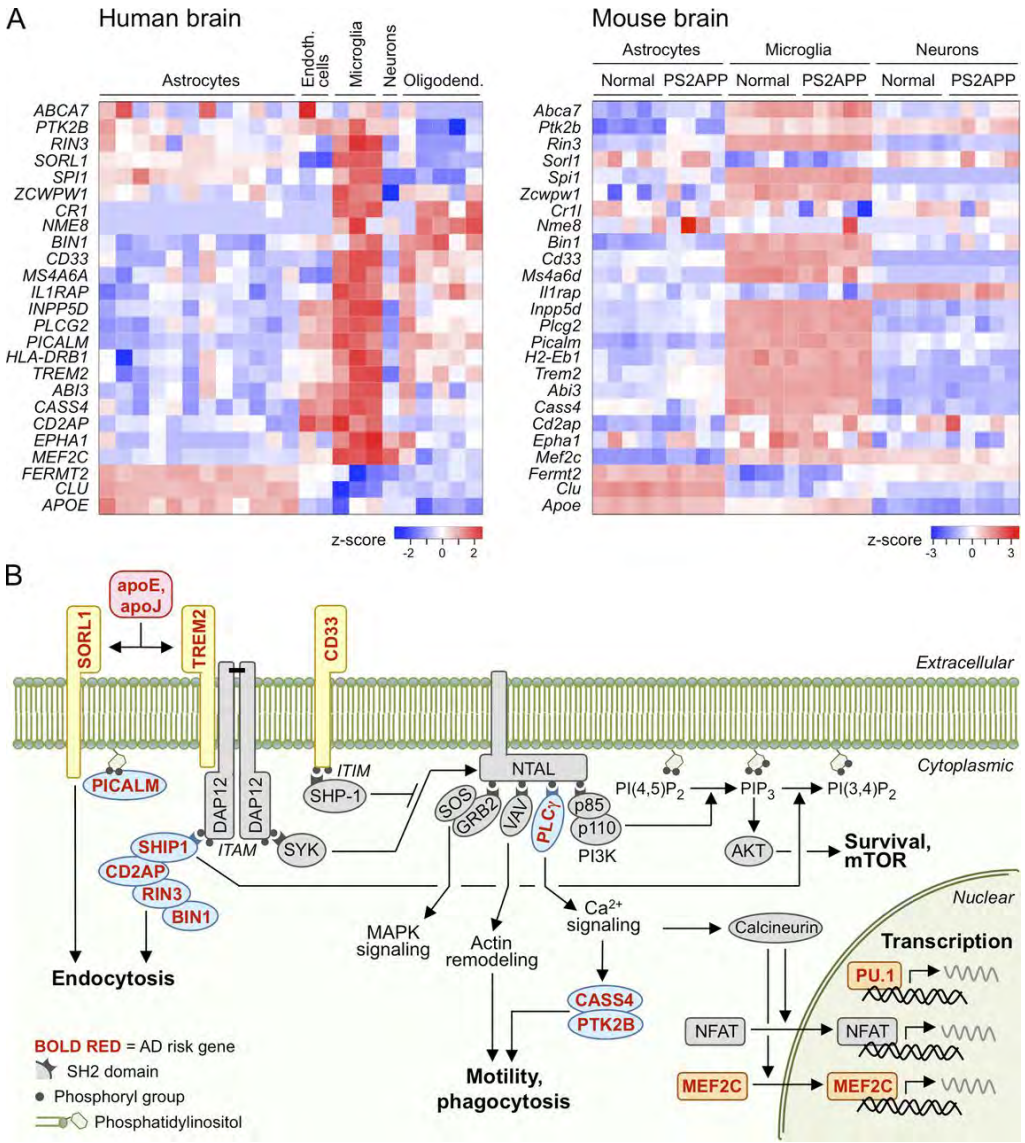
GWAS



Neurosciences, neurologie, psychiatrie Inserm

Karch & Goate, 2015

Many GWAS genes are enriched in microglia and interact



David V. Hansen et al. J Cell Biol doi:10.1083/jcb.201709069

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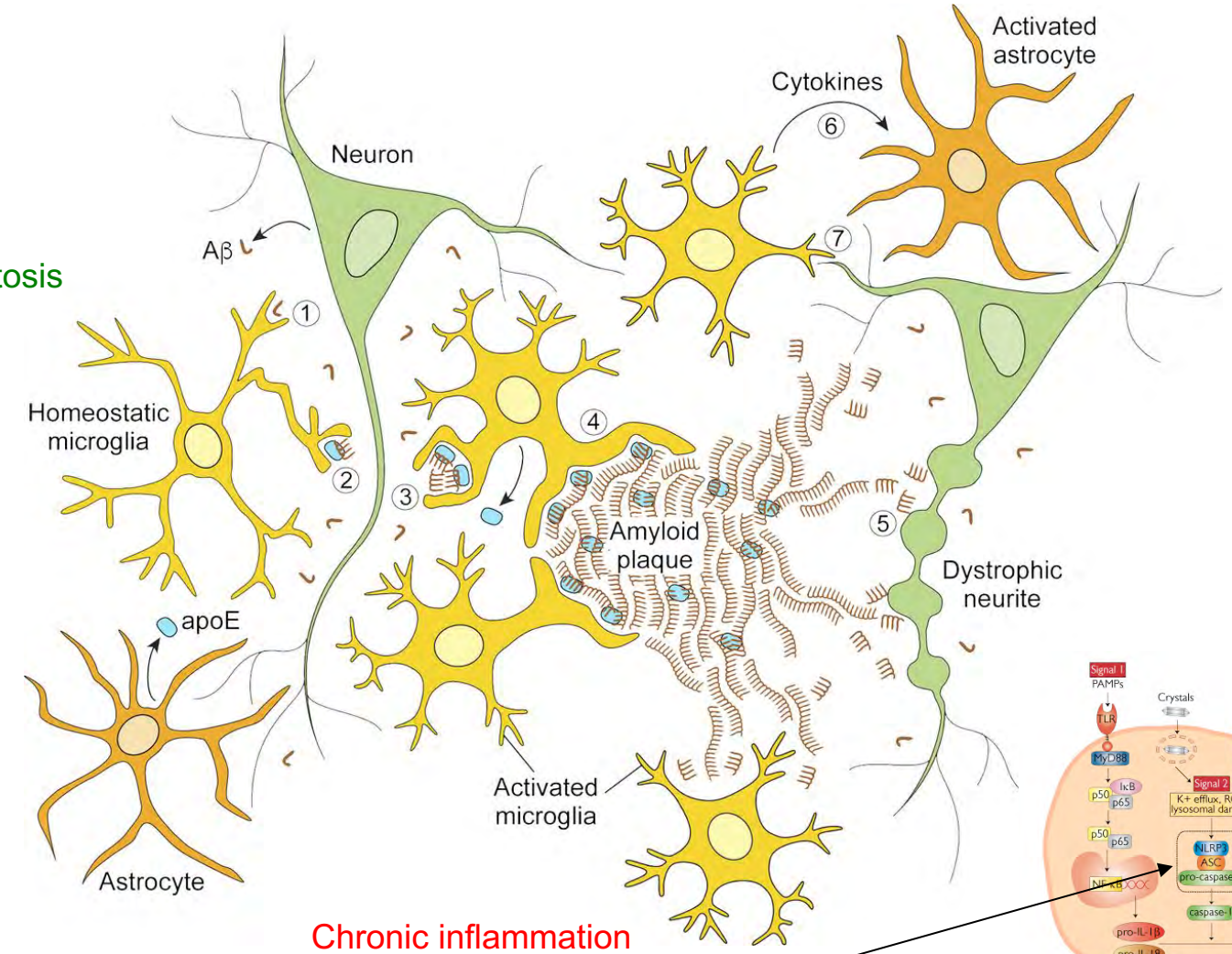
Enhanced microglial activation contribute to amyloid pathology

Phagocytosis

Aβ clearance

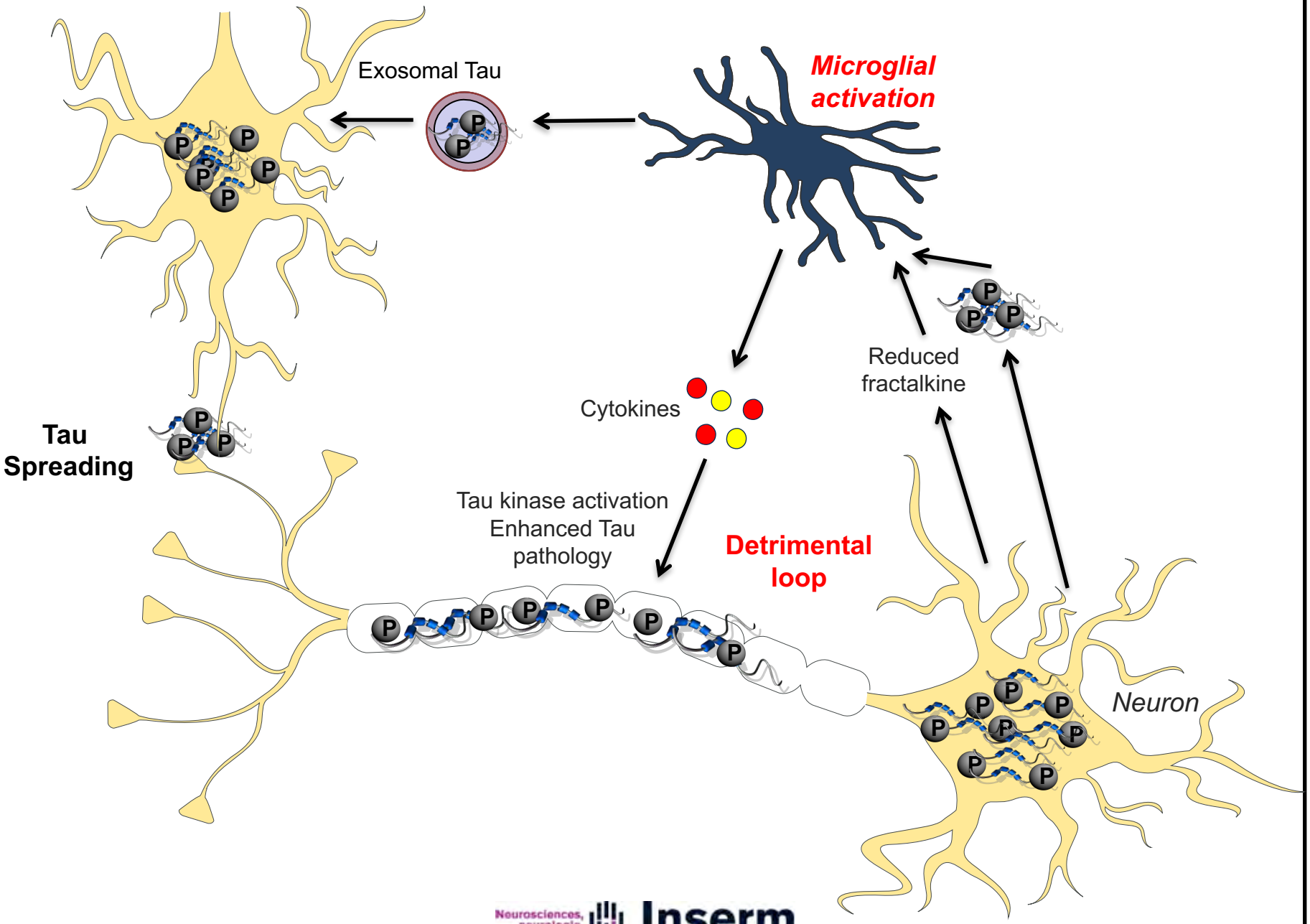


Chronic inflammation
Activation of microglial inflammasome
Clearance inhibition

Neurosciences, neurologie, psychiatrie — Inserm

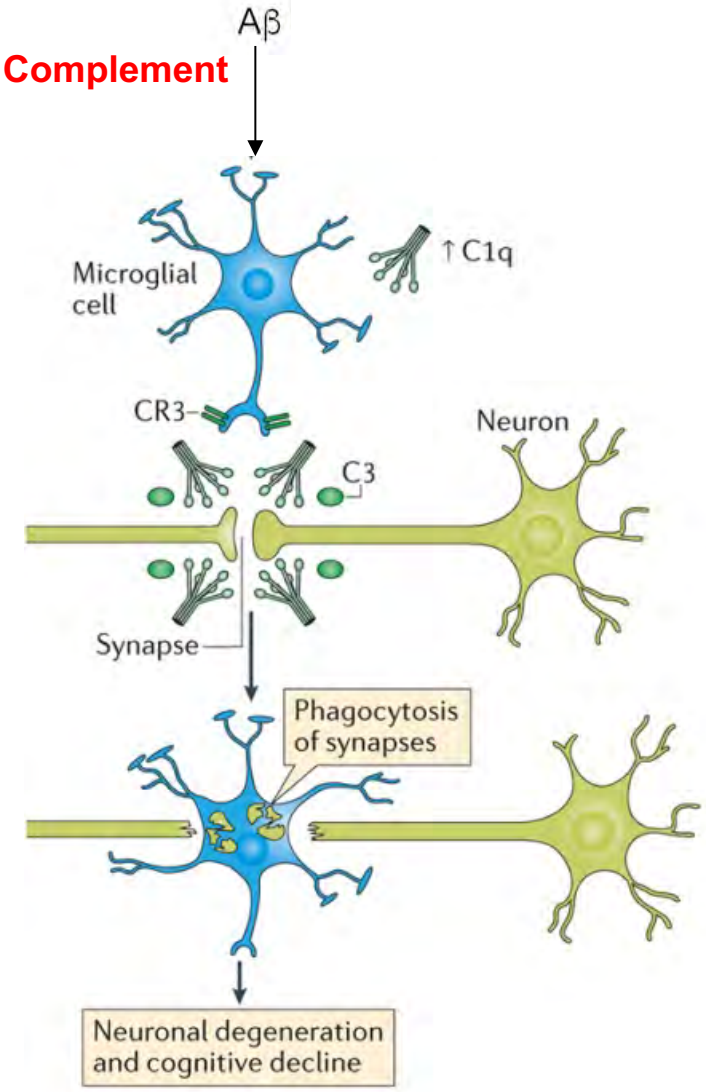
David V. Hansen et al. J Cell Biol 2017

Enhanced microglial activation contribute to Tau pathology



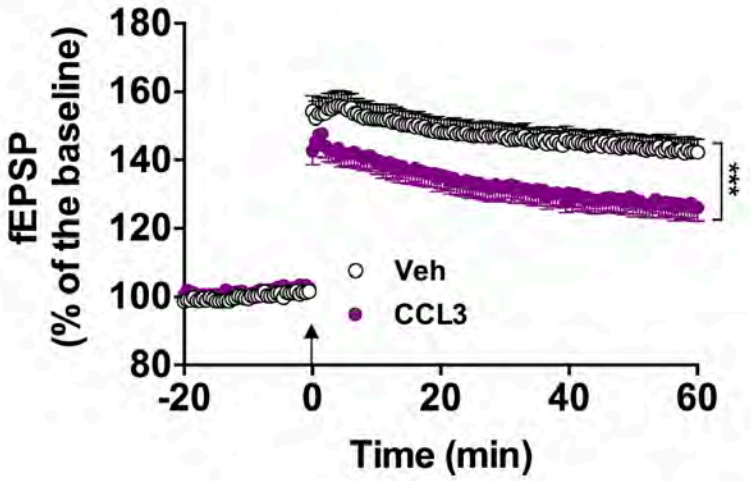
Microglial factors directly impair synapses: examples

Complement



Hong et al., Science 2016

Cytokines



OPEN

The Chemokine MIP-1α/CCL3 impairs mouse hippocampal synaptic transmission, plasticity and memory

Received: 19 June 2015
Accepted: 05 October 2015
Published: 29 October 2015

Elodie Marciniak[1,2,3], Emilie Faivre[1,2,3], Patrick Dutar[4], Claire Alves Pires[1,2,3], Dominique Demeyer[1,2,3], Raphaëlle Caillierez[1,2,3], Charlotte Laloux[1,5], Luc Buée[1,2,3], David Blum[1,2,3,*] & Sandrine Humez[1,2,3,*]

Adaptive immunity may play a role

Journal of Alzheimer's Disease 20 (2010) 1107–1118
DOI 10.3233/JAD-2010-100018
IOS Press

Implication of the Immune System in Alzheimer's Disease: Evidence from Genome-Wide Pathway Analysis

Jean-Charles Lambert[a,b,c,*], Benjamin Grenier-Boley[a,b,c], Vincent Chouraki[a,b,c], Simon Heath[d], Diana Zelenika[d], Nathalie Fievet[a,b], Didier Hannequin[e], Florence Pasquier[c,f], Olivier Hanon[g], Alexis Brice[h], Jacques Epelbaum[g], Claudine Berr[i], Jean-Francois Dartigues[j], Christophe Tzourio[k,l], Dominique Campion[e], Mark Lathrop[d,m] and Philippe Amouyel[a,b,c,f]

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[m]*Fondation Jean Dausset- CEPH, Paris, France*

List of the most signifcantly overrepresented GO categories at different P value criterion for SNPs association with AD risk unsing ALIGATOR

P value Criterion For SNPs	GO ID	Type	Total genes in category	Nb of genes on list	Category-specific p-value	Study wide p-value[1]	Function
$P < 0.01$	48261	Biological process	5	3	0.00012	0.2	Negative regulation of receptor-mediated endocytosis
	32395	Molecular function	8	6	0.00052	0.532	MHC class II receptor activity
	3918	Molecular function	4	3	0.00086	0.703	DNA topoisomerase (ATP-hydrolyzing) activity
	42613	Cellular component	12	7	0.00118	0.806	MHC class II protein complex
	43190	Cellular component	9	4	0.0014	0.846	ATP-binding cassette (ABC) transporter complex
	31307	Cellular component	6	3	0.00154	0.871	Integral to mitochondrial outer membrane
	2504	Biological process	15	7	0.0017	0.893	Antigen processing and presentation of peptide or polysaccharide antigen via MHC class II
	5132	Molecular function	8	3	0.00184	0.904	Interferon-alpha/beta receptor binding
	6268	Biological process	13	4	0.0019	0.914	DNA unwinding during replication
	6955	Biological process	542	73	0.00212	0.947	Immune response
$P < 0.001$	33344	Biological process	13	4	0.00004	0.14	Cholesterol efflux
	42613	Cellular component	12	4	0.00018	0.4	MHC class II protein complex
	2504	Biological process	15	4	0.00022	0.49	Antigen processing and presentation of peptide or polysaccharide antigen via MHC class II
	2455	Biological process	30	4	0.00096	2.05	Humoral immune response mediated by circulating immunoglobulin
	34379	Biological process	5	2	0.0012	2.53	Very-low-density lipoprotein particle assembly
	34377	Biological process	7	2	0.00158	3.33	Plasma lipoprotein particle assembly
	65005	Biological process	8	2	0.00162	3.41	Protein-lipid complex assembly
	32395	Molecular function	8	3	0.00162	3.41	MHC class II receptor activity
	5319	Molecular function	55	7	0.00174	3.69	Lipid transporter activity
	31490	Molecular function	6	2	0.0023	4.8	Chromatin DNA binding
$P < 0.0001$	2455	Biological process	30	3	0.00002	0.054	Humoral immune response mediated by circulating immunoglobulin
	19724	Biological process	48	3	0.00012	0.136	B cell mediated immunity
	16064	Biological process	46	3	0.00012	0.136	Immunoglobulin mediated immune response
	51235	Biological process	47	3	0.00024	0.209	Maintenance of location
	2449	Biological process	58	3	0.00034	0.267	Lymphocyte mediated immunity
	2460	Biological process	64	3	0.00034	0.267	Adaptive immune response based on somatic recombination of immune receptors built from immuno
	2250	Biological process	64	3	0.00034	0.267	Adaptive immune response
	2443	Biological process	64	3	0.00048	0.344	Leukocyte mediated immunity
	6959	Biological process	64	3	0.00092	0.478	Humoral immune response
	17038	Biological process	93	3	0.00108	0.519	Protein import
	50778	Biological process	83	3	0.00116	0.539	Positive regulation of immune response

[1]P values indicated whether the signifcantly GO pathways were potentially identified by chance.

Polymorphisms in genes associated with antigen presentation to T cells were identified as susceptibility loci for Alzheimer's disease

Neurosciences, neurologie, psychiatrie Inserm

T Cell infiltration related to Tau pathology

Table 3 Results of correlation analyses within non-immunized Alzheimer's disease control group – Spearman's ρ and *P*-values

cAD	Phospho-tau load	CD68 load	CD64 load	CD32 load	MSR load	MSR clusters	Iba-1 load	Iba-1 + cells	IgG load	C1q load	CD3 + cells
Amyloid-β_{42} load	$\rho = -0.2$ $P = 0.428$	$\rho = -0.3$ $P = 0.091$	$\rho = -0.1$ $P = 0.477$	**$\rho = -0.6$** **$P < 0.001$**	$\rho = -0.2$ $P = 0.438$	$\rho = 0.1$ $P = 0.660$	**$\rho = -0.6$** **$P = 0.001$**	**$\rho = -0.4$** **$P = 0.026$**	$\rho = -0.2$ $P = 0.370$	$\rho = -0.2$ $P = 0.258$	$\rho = -0.1$ $P = 0.553$
Phospho-tau load		**$\rho = 0.4$** **$P = 0.036$**	**$\rho = 0.5$** **$P = 0.010$**	**$\rho = 0.4$** **$P = 0.032$**	**$\rho = 0.4$** **$P = 0.045$**	$\rho < 0.1$ $P = 0.936$	**$\rho = 0.4$** **$P = 0.046$**	$\rho = 0.3$ $P = 0.151$	**$\rho = 0.4$** **$P = 0.030$**	**$\rho = 0.6$** **$P = 0.003$**	**$\rho = 0.4$** **$P = 0.026$**
CD68 load			**$\rho = 0.7$** **$P < 0.001$**	**$\rho = 0.7$** **$P < 0.001$**	**$\rho = 0.6$** **$P < 0.001$**	$\rho = 0.2$ $P = 0.441$	**$\rho = 0.5$** **$P = 0.004$**	$\rho = 0.1$ $P = 0.586$	**$\rho = 0.7$** **$P < 0.001$**	**$\rho = 0.5$** **$P = 0.012$**	$\rho = 0.2$ $P = 0.244$
CD64 load				**$\rho = 0.6$** **$P = 0.001$**	**$\rho = 0.5$** **$P = 0.003$**	$\rho = 0.2$ $P = 0.387$	**$\rho = 0.5$** **$P = 0.007$**	$\rho = 0.2$ $P = 0.444$	**$\rho = 0.7$** **$P < 0.001$**	**$\rho = 0.6$** **$P = 0.001$**	$\rho = 0.3$ $P = 0.095$
CD32 load					$\rho = 0.4$ $P = 0.052$	$\rho < 0.1$ $P = 0.912$	**$\rho = 0.7$** **$P < 0.001$**	**$\rho = 0.5$** **$P = 0.011$**	**$\rho = 0.5$** **$P = 0.003$**	**$\rho = 0.7$** **$P < 0.001$**	$\rho = 0.1$ $P = 0.446$
MSR load						**$\rho = 0.5$** **$P = 0.002$**	$\rho = 0.4$ $P = 0.054$	$\rho = -0.1$ $P = 0.725$	**$\rho = 0.6$** **$P = 0.001$**	**$\rho = 0.4$** **$P = 0.036$**	$\rho < 0.1$ $P = 0.899$
MSR clusters							$\rho = 0.1$ $P = 0.750$	$\rho = -0.1$ $P = 0.524$	$\rho = 0.1$ $P = 0.459$	$\rho < 0.1$ $P = 0.801$	$\rho = -0.2$ $P = 0.208$
Iba-1 load								**$\rho = 0.7$** **$P < 0.001$**	**$\rho = 0.4$** **$P = 0.036$**	**$\rho = 0.5$** **$P < 0.017$**	$\rho < 0.1$ $P = 0.818$
Iba-1 + cells									$\rho = -0.1$ $P = 0.701$	$\rho = 0.3$ $P = 0.165$	$\rho = 0.1$ $P = 0.750$
IgG load										**$\rho = 0.7$** **$P < 0.001$**	**$\rho = 0.4$** **$P = 0.030$**
C1q load											$\rho = 0.3$ $P = 0.141$

cAD = non-immunized Alzheimer's disease control

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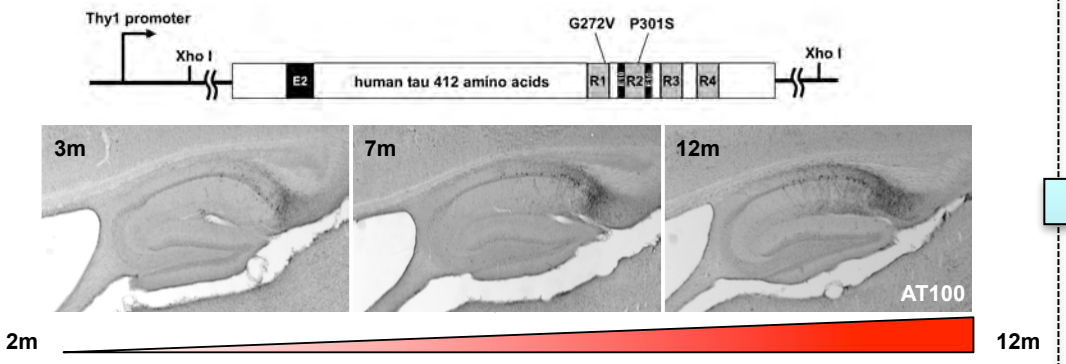
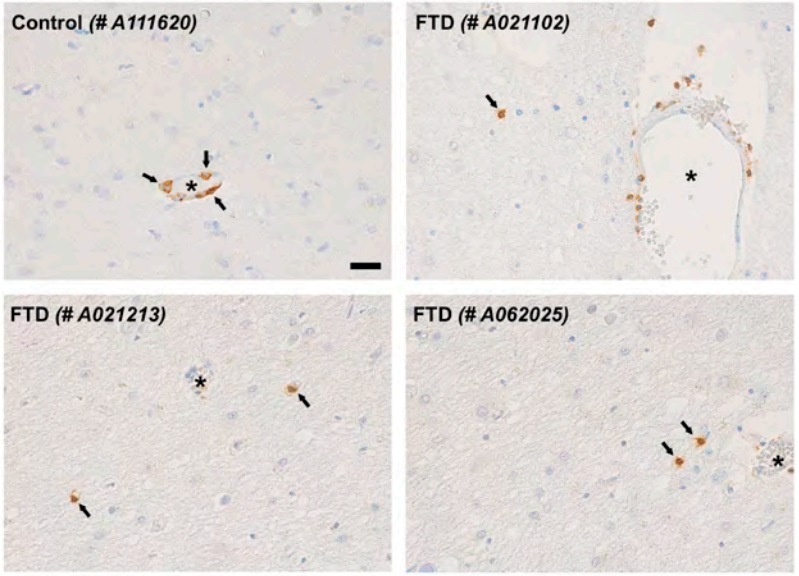
Zotova et al., Brain 2013

T Cell infiltration related to Tau pathology

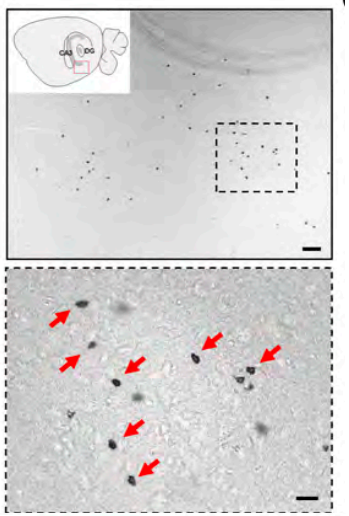


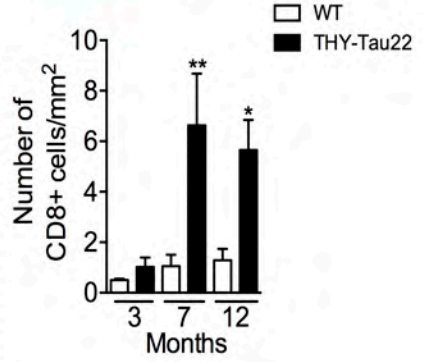
Memory deficits

FTLD MAPT



THY-Tau22





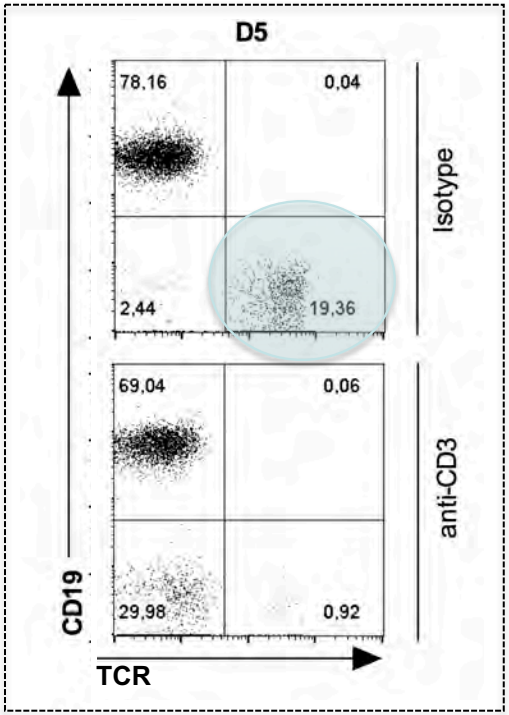
Relationship between Tauopathy and CD8+ T-Cell brain infiltration

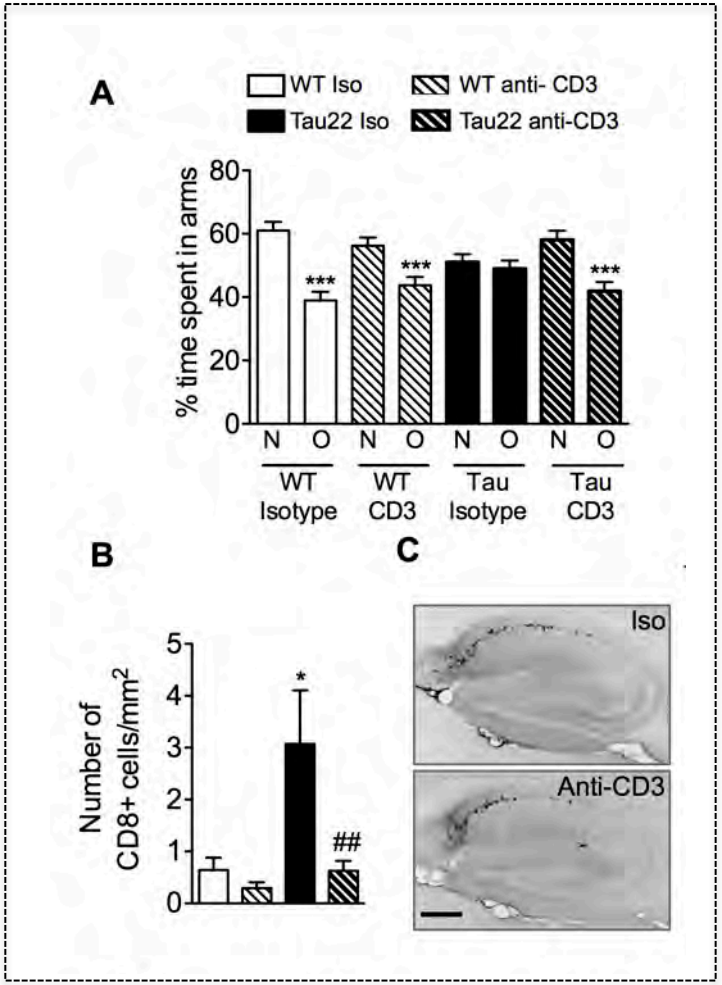
Neurosciences, neurologie, psychiatrie — Inserm

Laurent et al., Brain 2017

T Cell infiltration instrumental to Tau pathology-induced cognitive deficits

Chronic Anti-CD3 injections
in Tau mice





T Cell depletion improves memory in THY-Tau22 mice

Neurosciences, neurologie, psychiatrie Inserm

Laurent et al., Brain 2017

Targeting immunosuppressive T regulatory cells

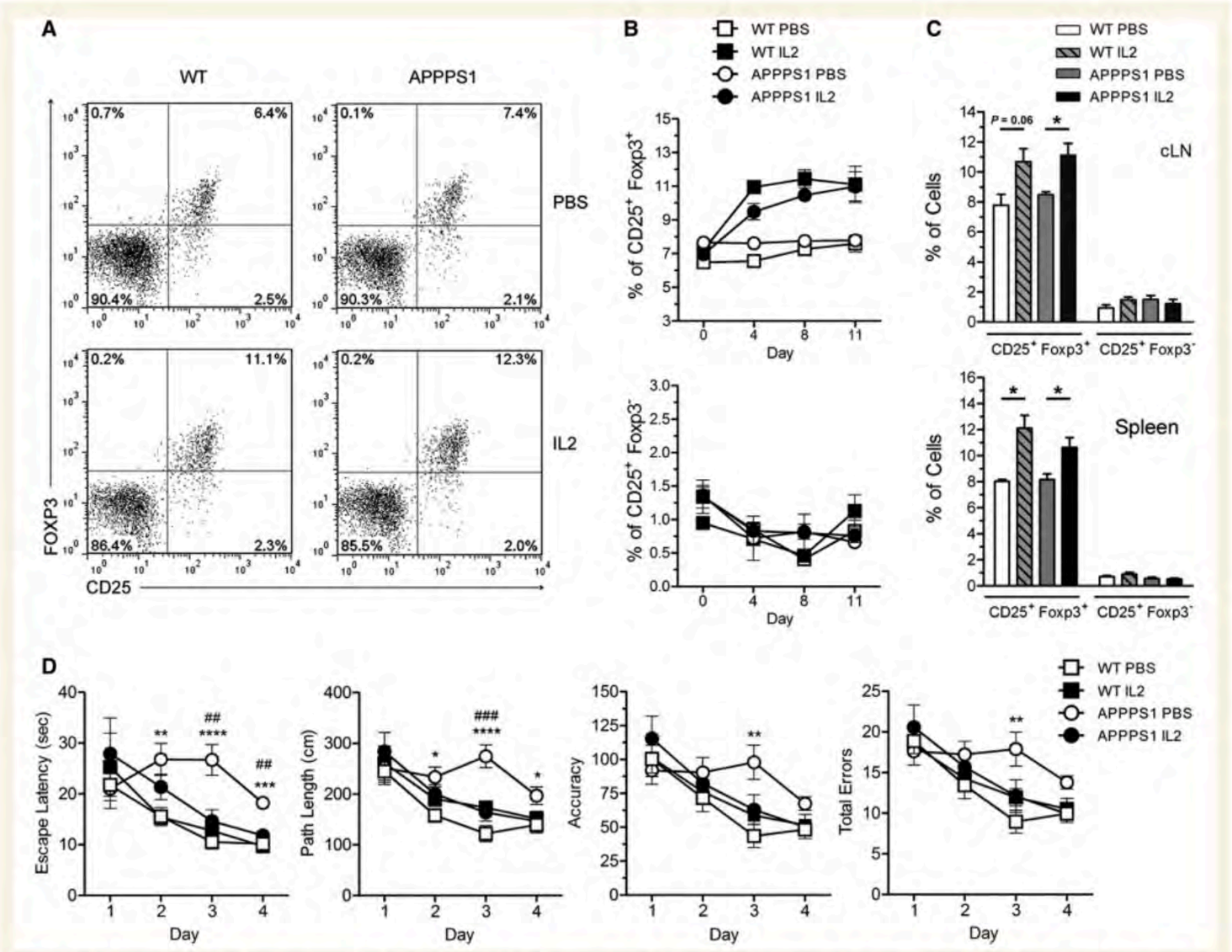


Figure 5 Low-dose IL-2 treatment selectively amplifies Tregs and restores cognitive functions in APPPS1 mice. Six-week-old

Dansokho et al., Brain 2016

Link between neuroinflammation and brain insulin resistance

Origin of insulin in the brain

Diabetologia
DOI 10.1007/s00125-017-4285-4

ARTICLE

Unravelling the regulation of insulin transport across the brain endothelial cell

Sarah M. Gray[1] · Kevin W. Aylor[2] · Eugene J. Barrett[1,2]

Abstract

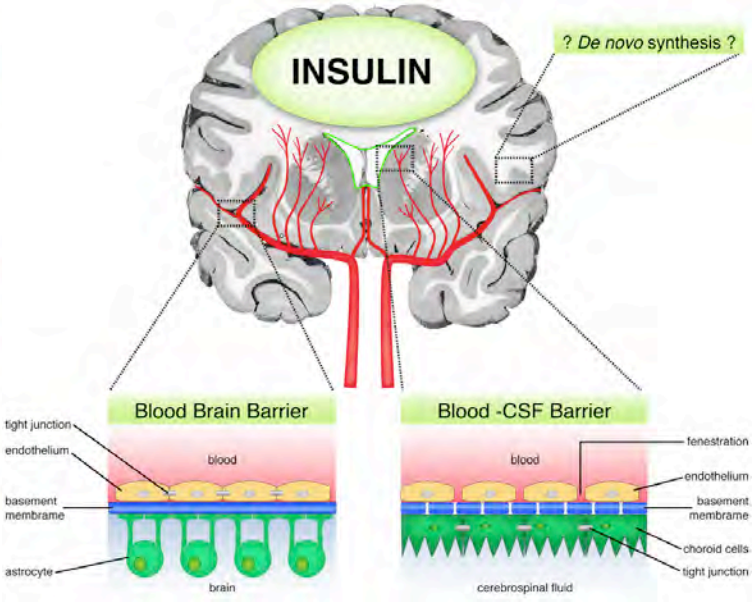
Aims/hypothesis For circulating insulin to act on the brain it must cross the blood–brain barrier (BBB). Remarkably little is known about how circulating insulin crosses the BBB's highly restrictive brain endothelial cells (BECs). Therefore, we examined potential mechanisms regulating BEC insulin uptake, signalling and degradation during BEC transcytosis, and how transport is affected by a high-fat diet (HFD) and by astrocyte activity.

Methods ^{125}I–TyrA14-insulin uptake and transcytosis, and the effects of insulin receptor (IR) blockade, inhibition of insulin signalling, astrocyte stimulation and an HFD were tested using purified isolated BECs (iBECs) in monoculture and co-cultured with astrocytes.

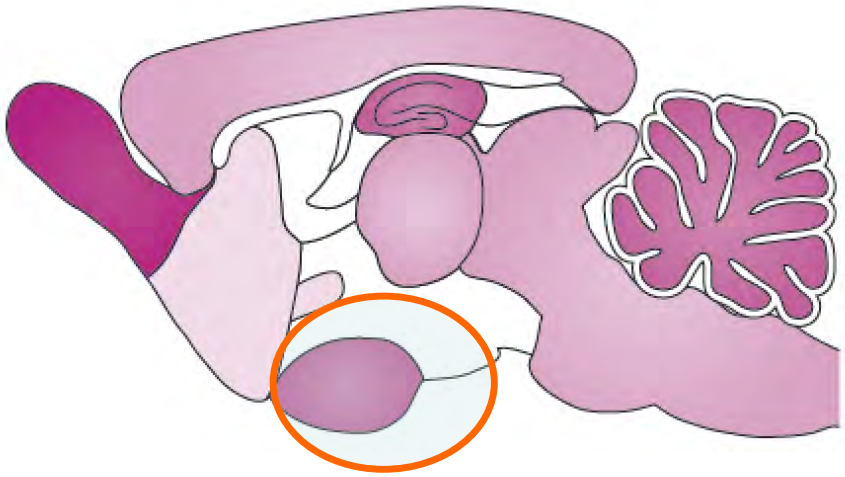
Results At physiological insulin concentrations, the IR, not the IGF-1 receptor, facilitated BEC insulin uptake, which required lipid raft-mediated endocytosis, but did not require insulin action on phosphoinositide-3-kinase (PI3K) or mitogen-activated protein kinase kinase (MEK). Feeding rats an HFD for 4 weeks decreased iBEC insulin uptake and increased NF-κB binding activity without affecting insulin PI3K signalling, IR expression or content, or insulin degrading enzyme expression. Using an in vitro BBB (co-culture of iBECs and astrocytes), we found insulin was not degraded during transcytosis, and that stimulating astrocytes with L-glutamate increased transcytosis, while inhibiting nitric oxide synthase decreased insulin transcytosis.

Conclusions/interpretation Insulin crosses the BBB intact via an IR-specific, vesicle-mediated transport process in the BECs. HFD feeding, nitric oxide inhibition and astrocyte stimulation can regulate BEC insulin uptake and transcytosis.

Brain insulin is mostly derived from periphery
Saturable transport by EC



Role of insulin in the brain: energy homeostasis



Insulin receptor is
highly expressed in the hypothalamus
Regulate food intake & peripheral metabolism
Energy expenditure & HPG

Intraventricular insulin and leptin reduce food intake and body weight in C57BL/6J mice

Lynda M. Brown *, Deborah J. Clegg, Stephen C. Benoit, Stephen C. Woods

Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio 45237, USA

Received 7 April 2006; received in revised form 29 July 2006; accepted 7 August 2006

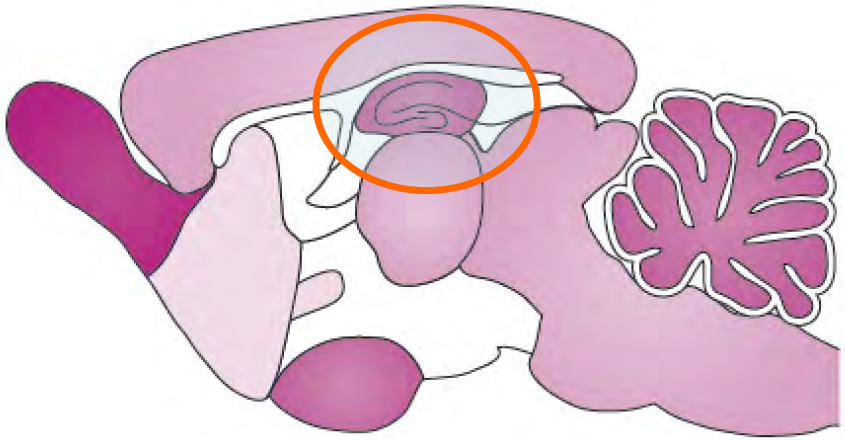
Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats

Silvana Obici[1], Zhaohui Feng[1], George Karkanias[1], Denis G. Baskin[2] and Luciano Rossetti[1]

Role of Brain Insulin Receptor in Control of Body Weight and Reproduction

Jens C. Brüning,[1]* Dinesh Gautam,[1] Deborah J. Burks,[2] Jennifer Gillette,[1] Markus Schubert,[1] Paul C. Orban,[3]† Rüdiger Klein,[3] Wilhelm Krone,[1] Dirk Müller-Wieland,[1] C. Ronald Kahn[2]*

Role of insulin in the brain: learning and memory

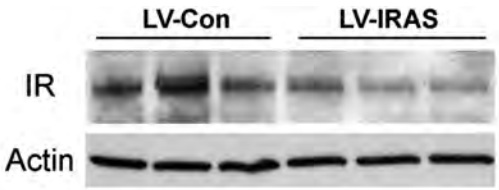


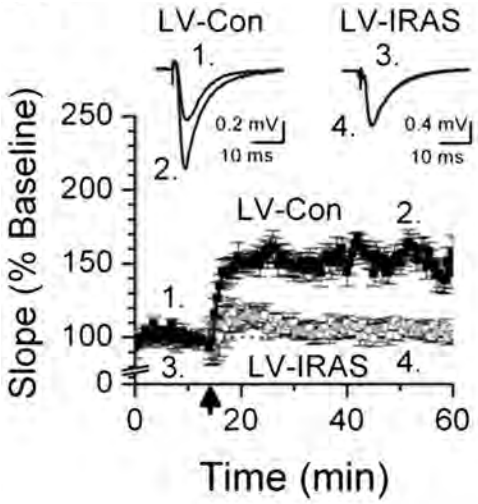
Insulin receptor is expressed in the brain
Highly expressed in hippocampus
Important for memory and plasticity

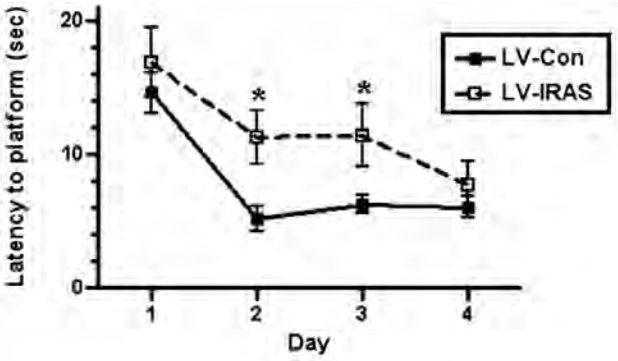
Claudia A. Grillo,[1] Gerardo G. Piroli,[1] Robert C. Lawrence,[1,2] Shayna A. Wrighten,[1] Adrienne J. Green,[1] Steven P. Wilson,[1] Randall R. Sakai,[3] Sandra J. Kelly,[1,2] Marlene A. Wilson,[1,4] David D. Mott,[1] and Lawrence P. Reagan[1,4]

Hippocampal Insulin Resistance Impairs Spatial Learning and Synaptic Plasticity

Diabetes 2015;64:3927–3936 | DOI: 10.2337/db15-0596

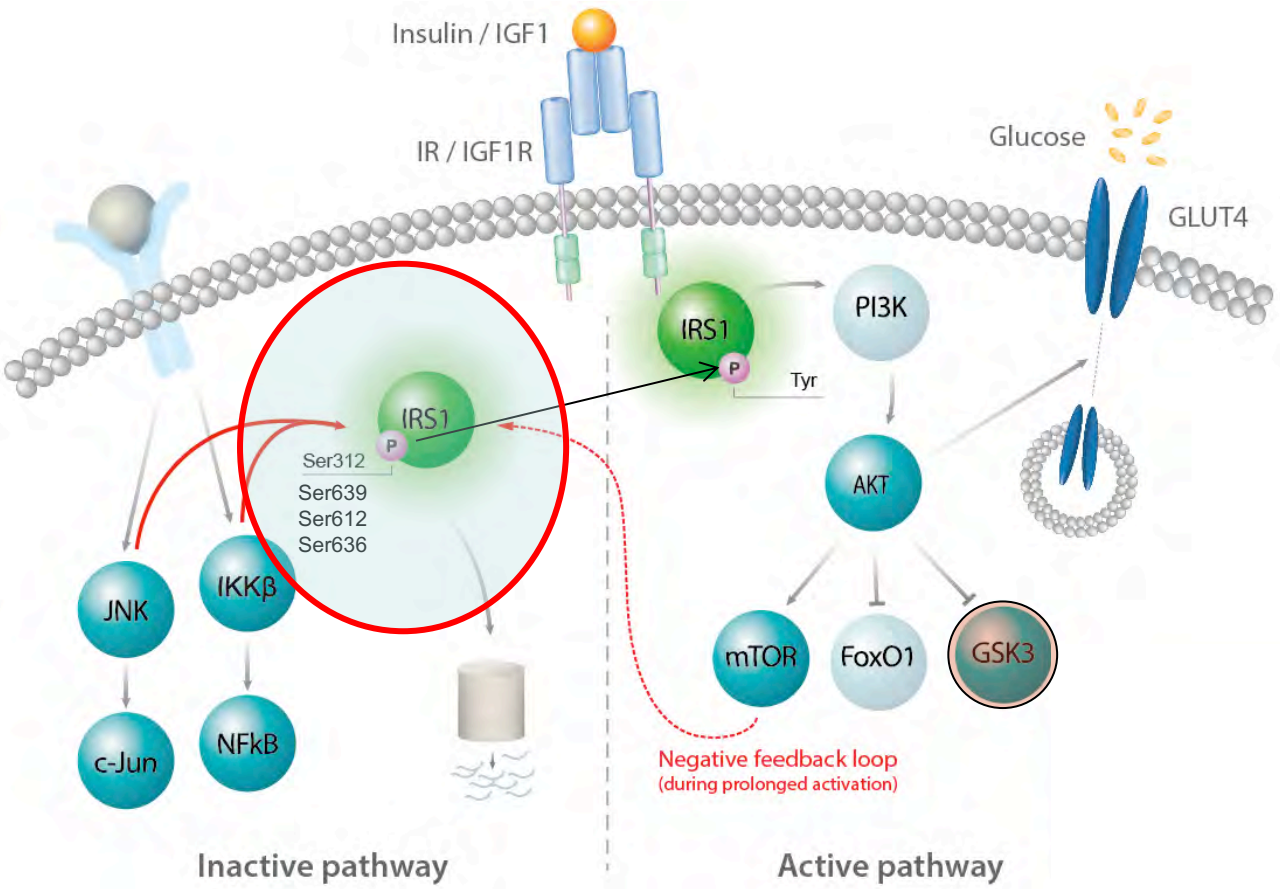






Fernandez and Torres-Alemán, 2012
Grillo et al., 2015

Insulin signaling



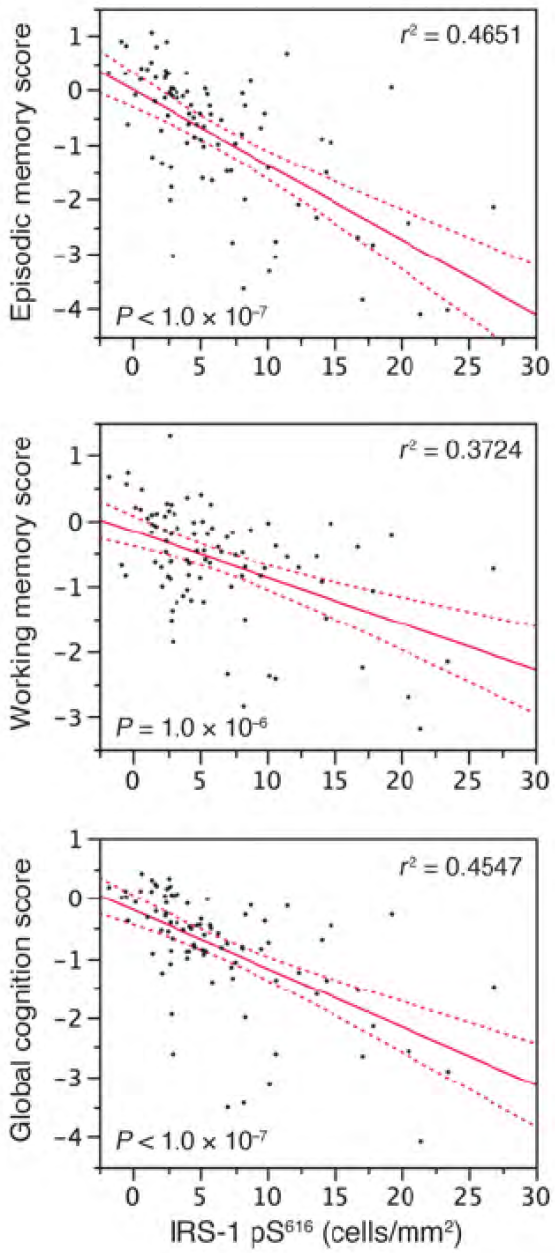
Alzheimer's Disease: a « type 3 diabetes »

Changes in insulin and insulin signaling in Alzheimer's disease: cause or consequence?

Molly Stanley, Shannon L. Macauley, and David M. Holtzman

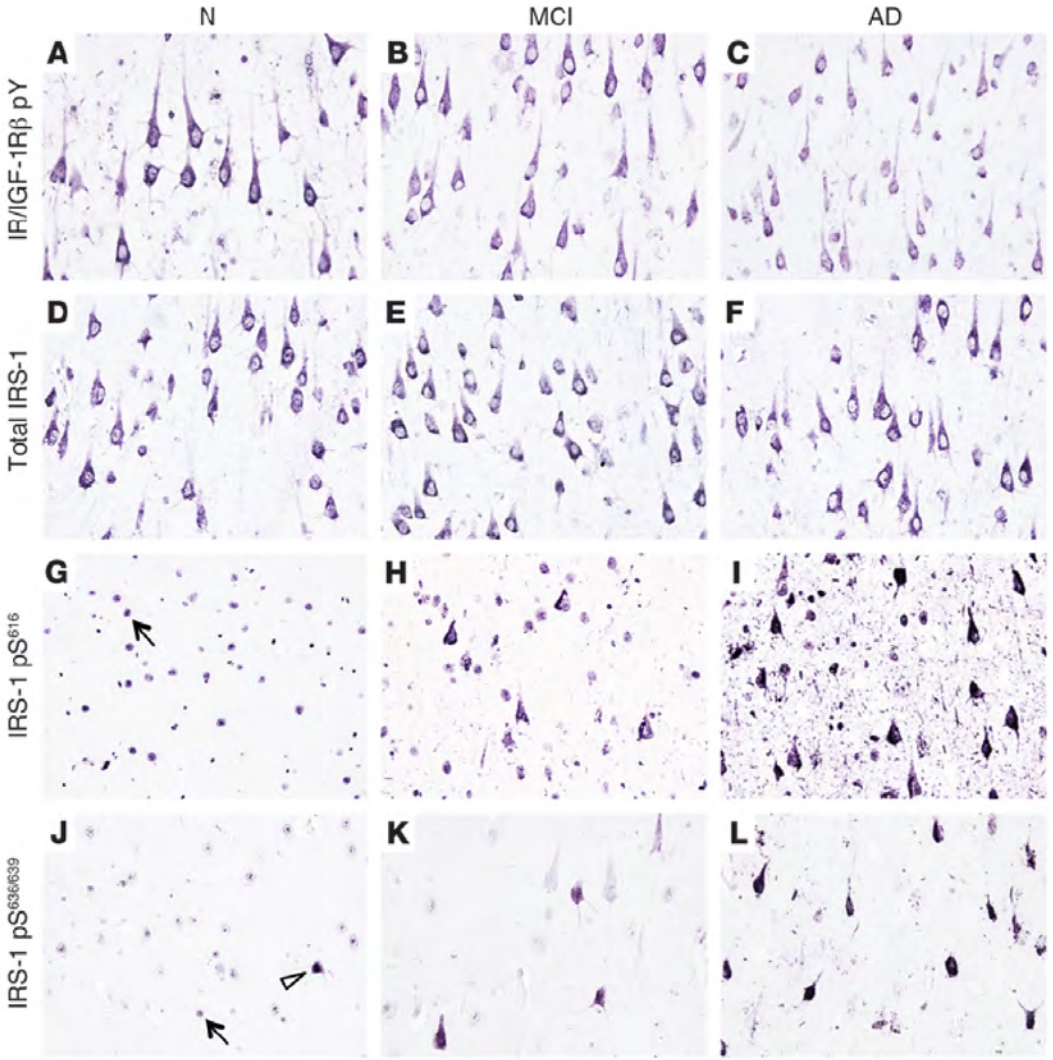
Parameter	AD ↑ ↓	Study	Details
Blood insulin	↑	Bucht et al., 1983; Fujisawa et al., 1991; Stolk et al., 1997; Craft et al., 1998; Ma et al., 2016	-Fasting or after glucose tolerance test -In women only (1 study) -Only in non-APOE4 and moderate/severe AD (1 study) -Meta-analysis of 11 studies: 5 report overall ↑, 1 ↑ in women, 1 ↑ with advanced stage (Ma et al., 2016)
CSF insulin	↑	Fujisawa et al., 1991	-Also found small increase with vascular dementia
	↓	Craft et al., 1998; Gil-Bea et al., 2010	-Only in non-APOE4 and moderate/severe AD -No relationship to APOE or AD severity
	No change	Molina et al., 2002	-No relationship with AD severity or cognition
Brain insulin	No change	Frölich et al., 1998	-Comparing controls >65 y/o and AD patients
	↓	Frölich et al., 1998; Rivera et al., 2005; Steen et al., 2005	-Comparing controls <65 y/o and AD patients -mRNA: in hippocampus and hypothalamus -mRNA: progressive reduction with Braak stage
Brain IR (total)	↓	Frölich et al., 1998; Rivera et al., 2005; Steen et al., 2005	-Comparing controls <65 y/o and AD patients -mRNA and protein -mRNA: progressive reduction with Braak stage
	↑	Frölich et al., 1998	-Comparing controls >65 y/o and AD patients
	No change	Moloney et al., 2010; Liu et al., 2011; Ho et al., 2012; Talbot et al., 2012	-Potential changes in cellular distribution -Also no change in p-IR -Only reduced in patients with T2D and AD
Brain p-IR and activity	↓	Frölich et al., 1998; Rivera et al., 2005; Steen et al., 2005	-In hippocampus -Reduced insulin binding -TK activity reduced compared to all controls
Brain IRS1 (total)	↓	Steen et al., 2005; Moloney et al., 2010	-mRNA in 3 regions -Also reductions in IRS2
	No change	Liu et al., 2011; Talbot et al., 2012	-Also no change in IRS2 -Only reduced in patients with T2D and AD
Brain p(Ser)-IRS1	↑	Moloney et al., 2010 Talbot et al., 2012 Bomfim et al., 2012 Yarchoan et al., 2014	-Regardless of APOE status and reduced ex vivo insulin stimulation -Highest in AD, but also elevated in some tauopathies
Brain AKT (total)	↓	Griffin et al., 2005; Liu et al., 2011	-Reduced in AD and in patients with T2D and AD
	No change	Steen et al., 2005; Talbot et al., 2012	
Brain p-AKT	↑	Pei et al., 2003; Griffin et al., 2005; Talbot et al., 2012; Yarchoan et al., 2014	-Associated with tangles
	↓	Steen et al., 2005	-In hippocampus
	No change	Liu et al., 2011	-Only reduced in patients with T2D and AD
Brain GSK3 (total)	↓	Ho et al., 2012	-With advanced AD
	No change	Steen et al., 2005; Liu et al., 2011; Talbot et al., 2012	-Only reduced in patients with T2D or T2D and AD
Brain p(Ser)-GSK3	↓	Steen et al., 2005 Griffin et al., 2005	-In hippocampus
	No change	Liu et al., 2011	-Only reduced in patients with T2D or T2D and AD
Brain p-GSK3	↑	Pei et al., 2003	-Associated with tangles
Brain p-JNK	↑	Bomfim et al., 2012; Talbot et al., 2012	
Other IR signaling molecules	↓	Griffin et al., 2005; Liu et al., 2011; Talbot et al., 2012	-PDK1, p-PDK1 and p-PI3K -PIP3, PKC, p-mTOR, p-ERK2 -PTEN

Alzheimer's Disease: a « type 3 diabetes »



Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline

Konrad Talbot,[1] Hoau-Yan Wang,[2] Hala Kazi,[1] Li-Ying Han,[1] Kalindi P. Bakshi,[2] Andres Stucky,[2] Robert L. Fuino,[1] Krista R. Kawaguchi,[1] Andrew J. Samoyedny,[1] Robert S. Wilson,[3]

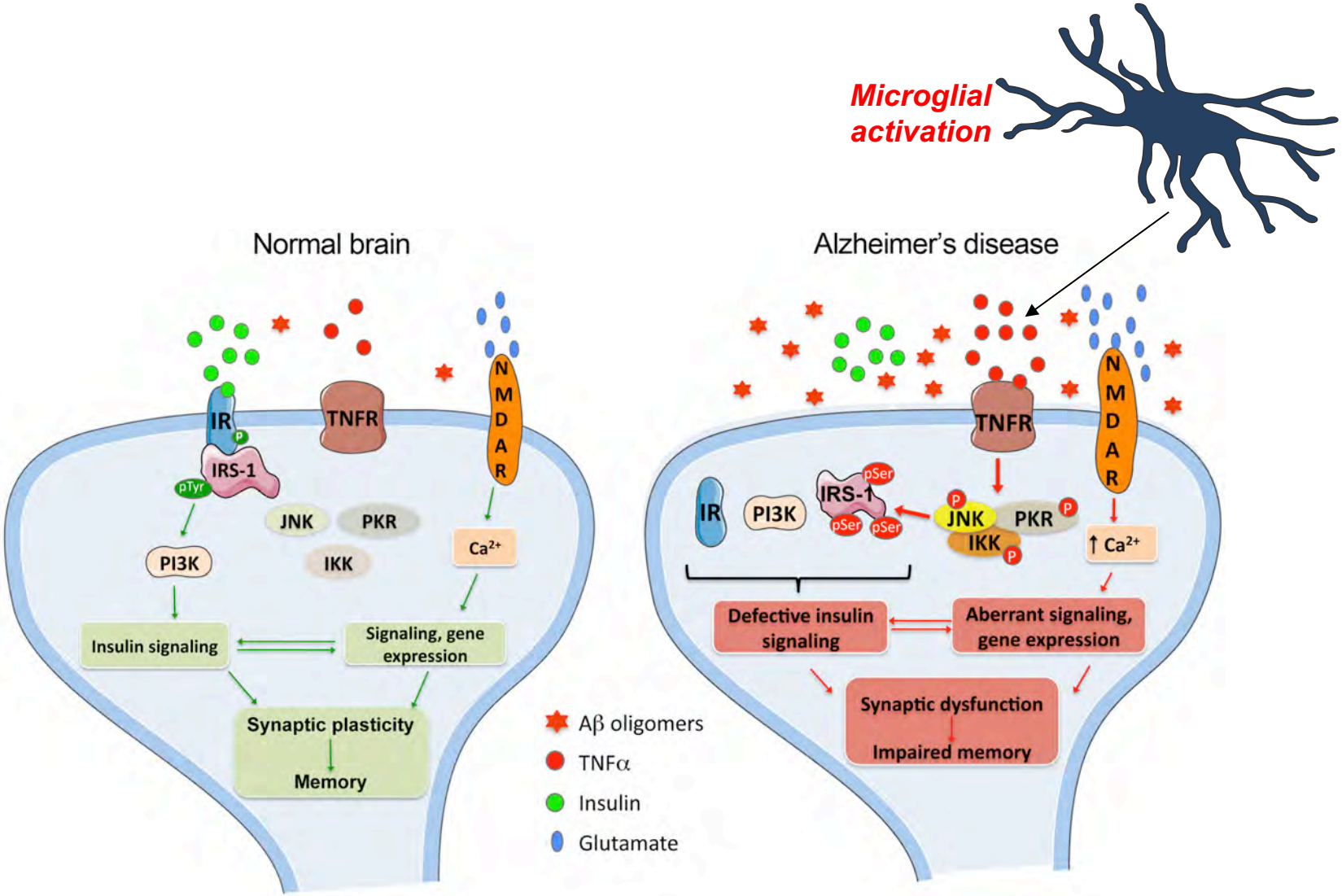


Neurosciences, neurologie, psychiatrie

inserm

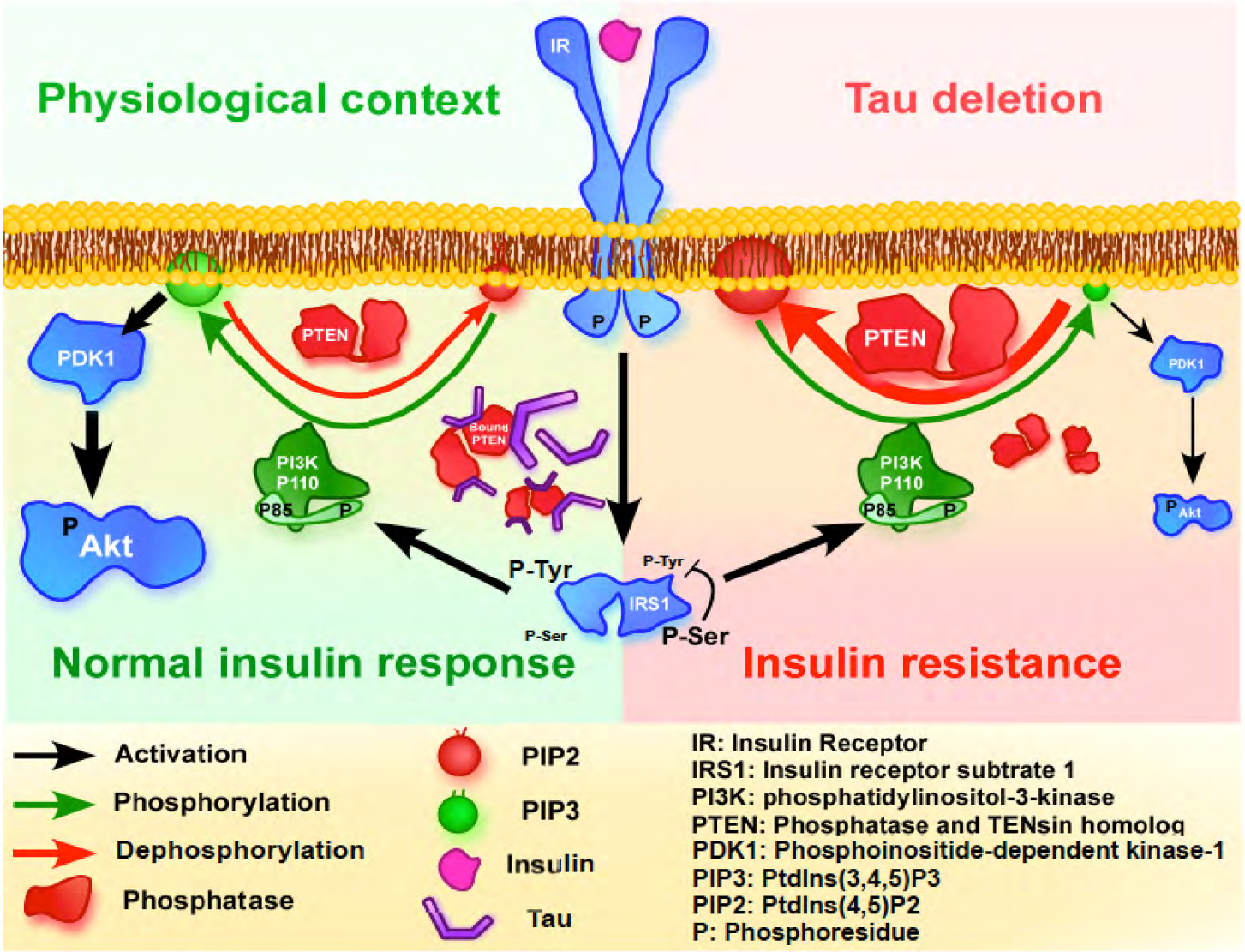
Impact of AD lesions upon brain insulin signalling

Aβ oligomer-induced neuroinflammation leads to insulin resistance



De Felice et al.

Involvement of Tau



Neurosciences, neurologie, psychiatrie Inserm

Marciniak et al., *J Exp Med* 2017

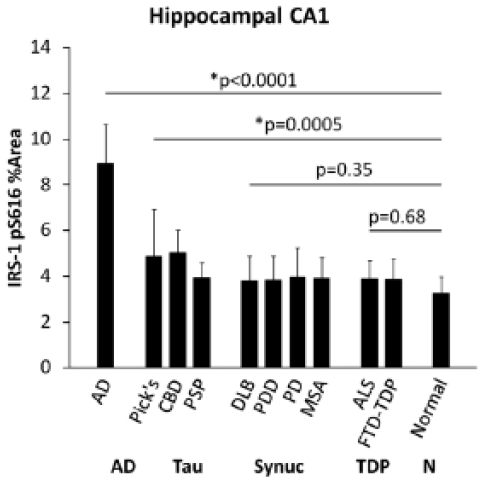
Involvement of Tau

Acta Neuropathol (2014) 128:679–689
DOI 10.1007/s00401-014-1328-5

ORIGINAL PAPER

Abnormal serine phosphorylation of insulin receptor substrate 1 is associated with tau pathology in Alzheimer's disease and tauopathies

Mark Yarchoan · Jon B. Toledo · Edward B. Lee · Zoe Arvanitakis · Hala Kazi · Li-Ying Han · Natalia Louneva · Virginia M.-Y. Lee · Sangwon F. Kim · John Q. Trojanowski · Steven E. Arnold



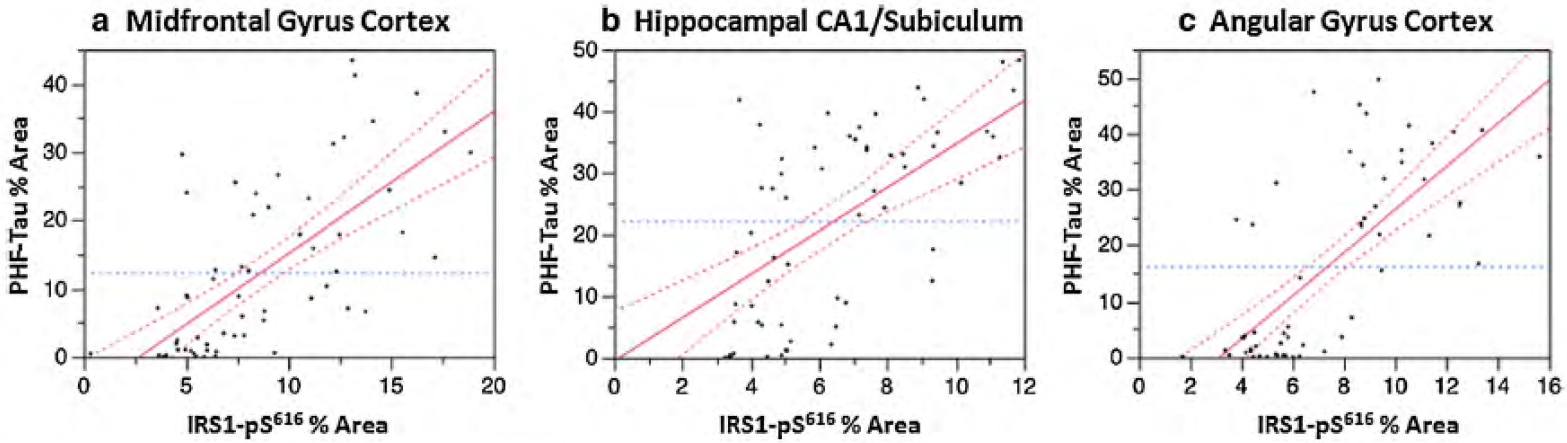


Fig. 2 Regression plots of IRS1-pS^{616} and PHF-Tau percent area of immunolabeled cells and neurites in AD and other tauopathies in (a) midfrontal gyrus cortex, (b) hippocampal CA1/subiculum and (c) angular gyrus cortex in AD and other tauopathies. All p values were <0.0001

Impact of AD lesions upon brain insulin signalling

Amyloïd and Tau lesions (through Tau loss of function) are responsible for brain insulin resistance

...explaining cognitive but also glucose homeostasis impairments of AD patients

Increased Risk of Type 2 Diabetes in Alzheimer Disease

Juliette Janson,[1,2] Thomas Laedtke,[1] Joseph E. Parisi,[2] Peter O'Brien,[3] Ronald C. Petersen,[4] and Peter C. Butler[5]

Alterations in Glucose Metabolism in Patients with Alzheimer's Disease

Graydon S. Meneilly, MD and Amanda Hill, MD

P1-347

INDIVIDUALS WITH ALZHEIMER'S DISEASE EXHIBIT A HIGH PREVALENCE OF UNDIAGNOSED IMPAIRED GLUCOSE TOLERANCE AND TYPE 2 DIABETES MELLITUS

Raymond Turner[1], Suzanne Craft[2], Paul Aisen[3], *[1]Georgetown University, Washington, D.C., United States; [2]Stitch Center on Aging, Winston-Salem, North Carolina, United States; [3]UCSD, La Jolla, California, United States. Contact e-mail: rst36@georgetown.edu*

BIOL PSYCHIATRY 1991;30:1219–1228

Increased Insulin Levels after OGTT Load in Peripheral Blood and Cerebrospinal Fluid of Patients with Dementia of Alzheimer Type

Yoshikatsu Fujisawa, Ken Sasaki, and Kazufumi Akiyama

Age and Ageing 1994;23:390–395

Hyperinsulinaemia and Alzheimer's Disease

GEORGE RAZAY, GORDON K. WILCOCP

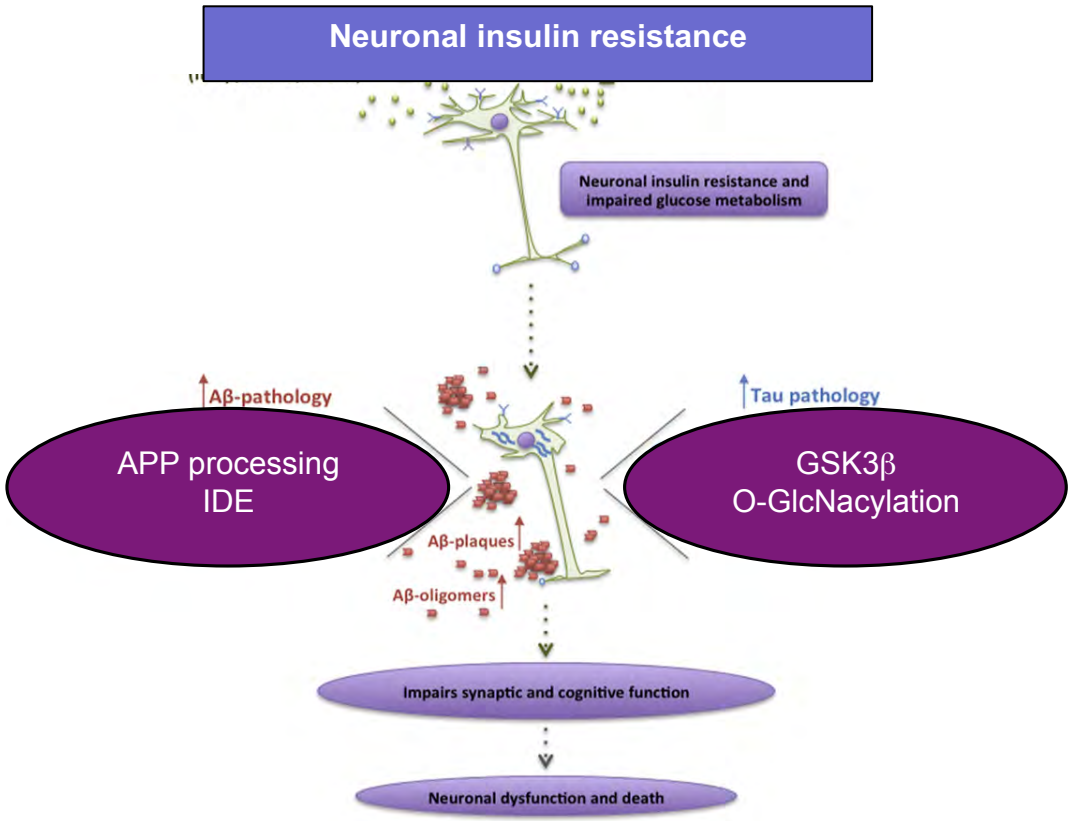
J Clin Exp Neuropsychol. 1992 Mar;14(2):253-67.

Glucose and memory in mild senile dementia of the Alzheimer type.

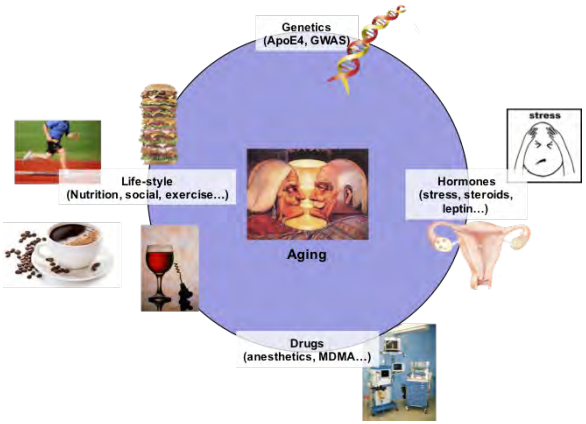
Craft S[1], Zallen G, Baker LD.

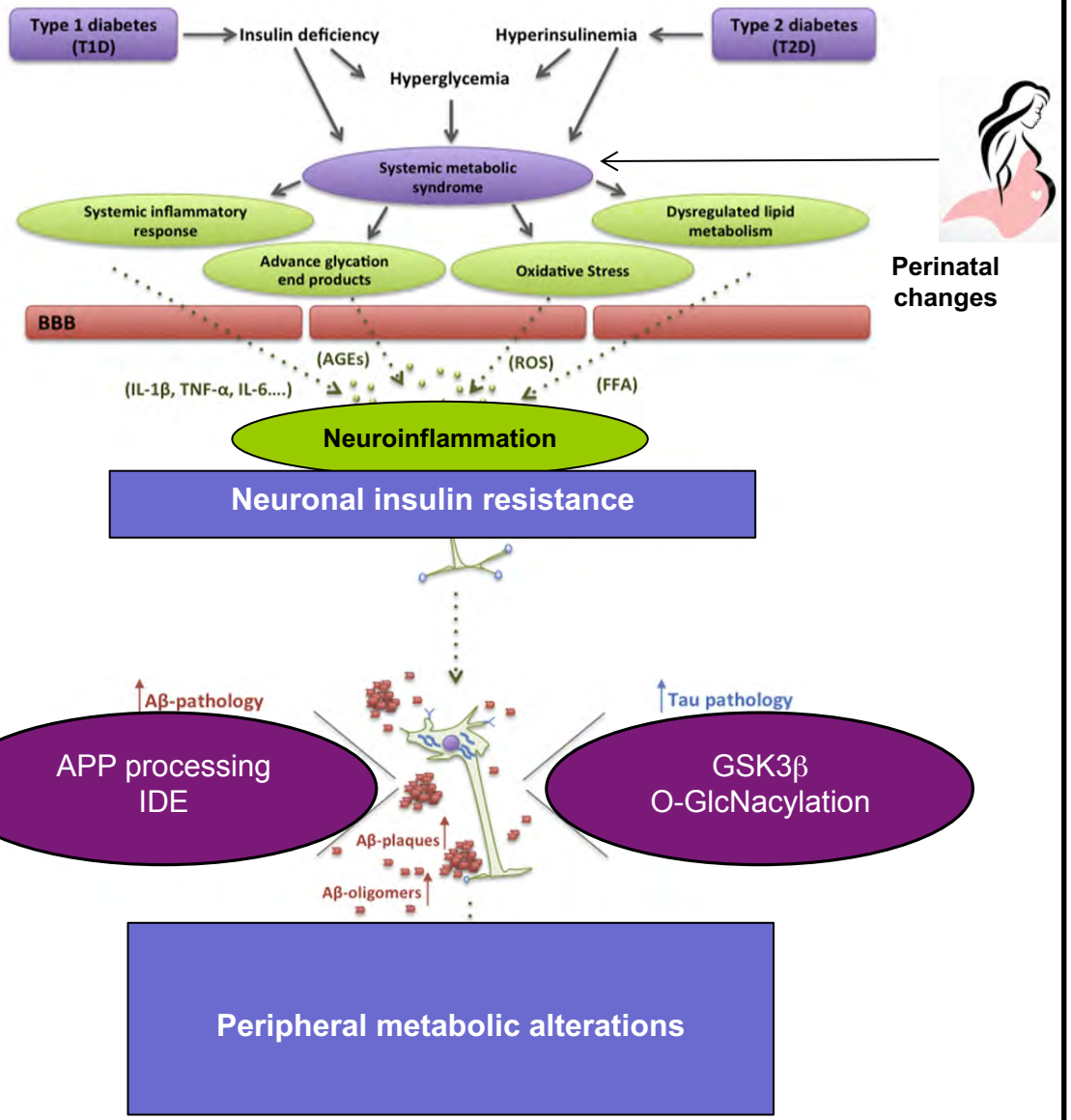
Author information

Impact of insulin resistance on lesions



Impact of diabetes and peripheral insulin resistance





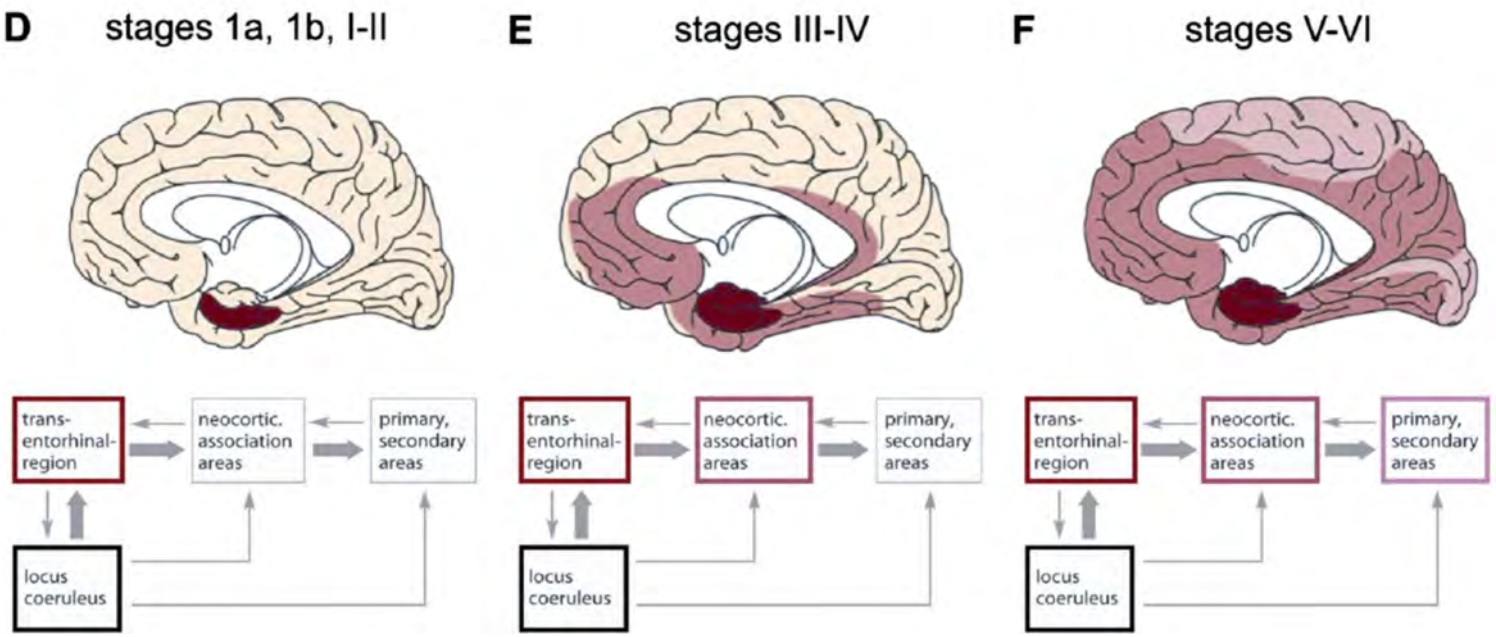
Detrimental loop !!

Link between neuroinflammation and neuromodulation

Main neurotransmitter systems are affected in AD

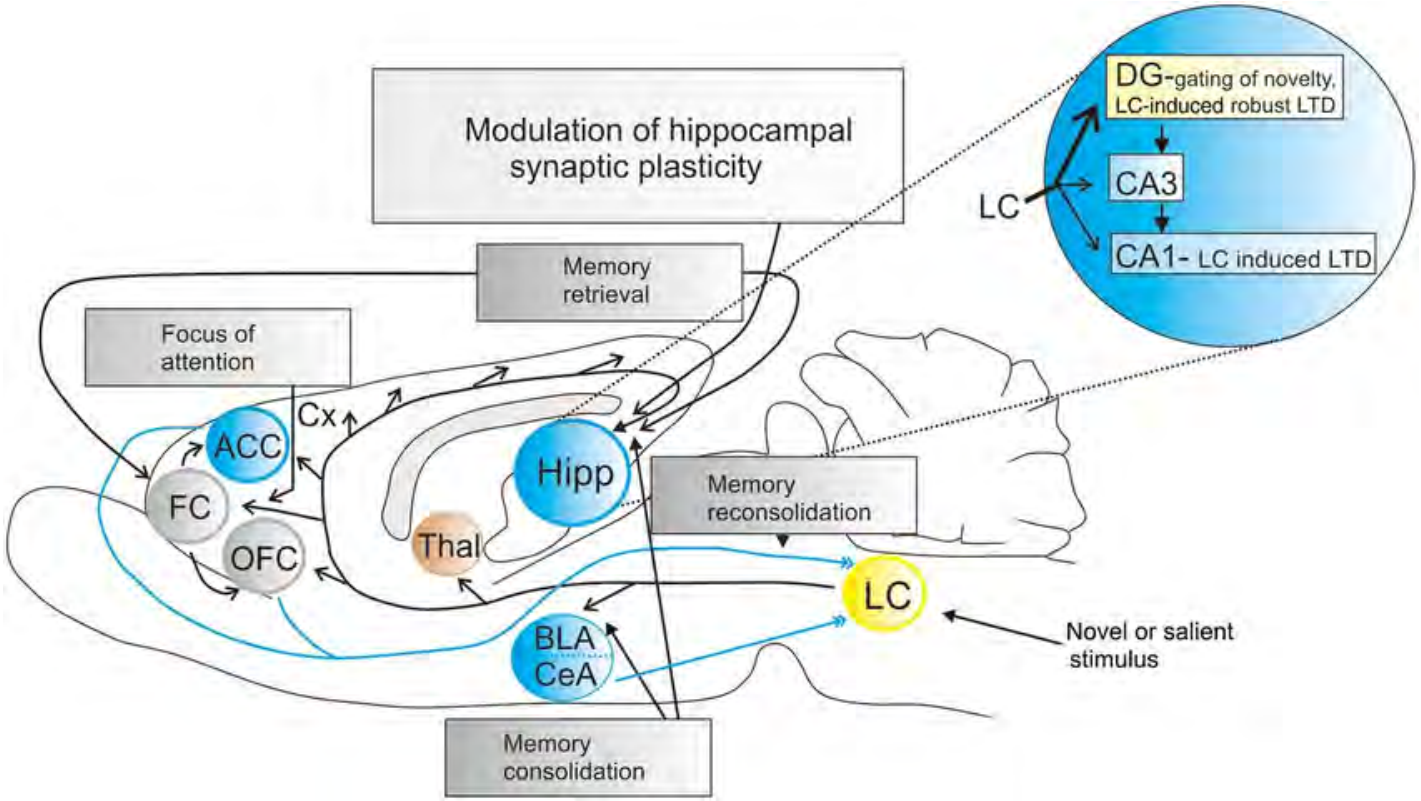
Glutamate/GABA
Cholinergic system
Monominergic systems (5HT, NA…)
Adenosinergic system

Locus coeruleus is early affected in AD



Braak et al., 2011

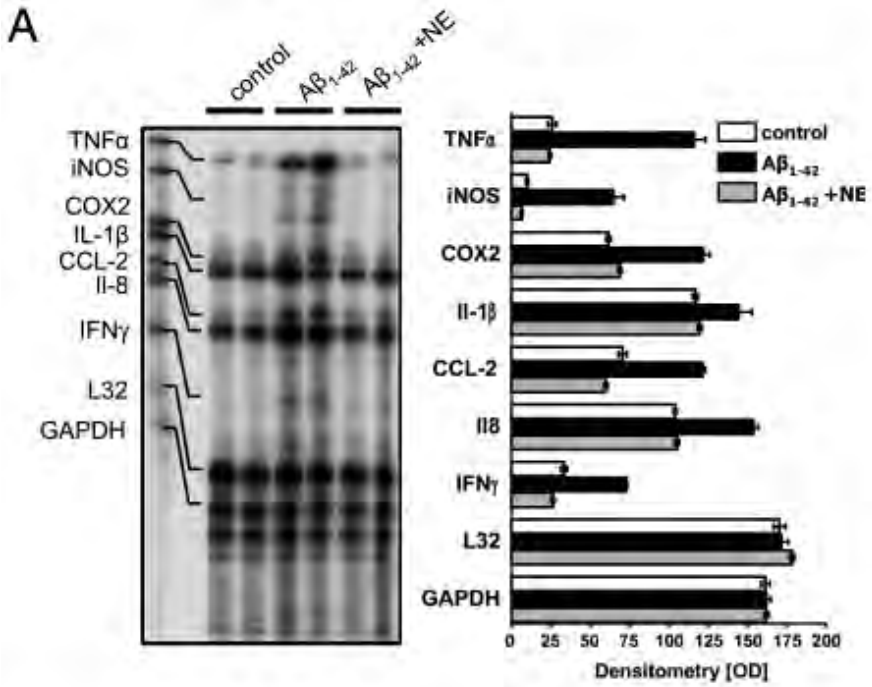
NA is important for plasticity

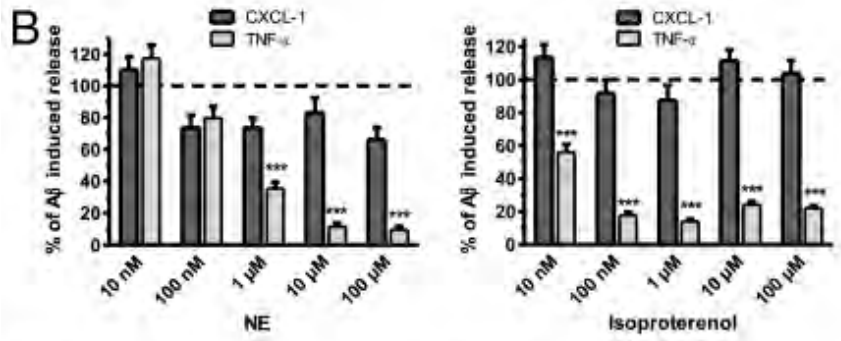


Hagena et al., *2016*

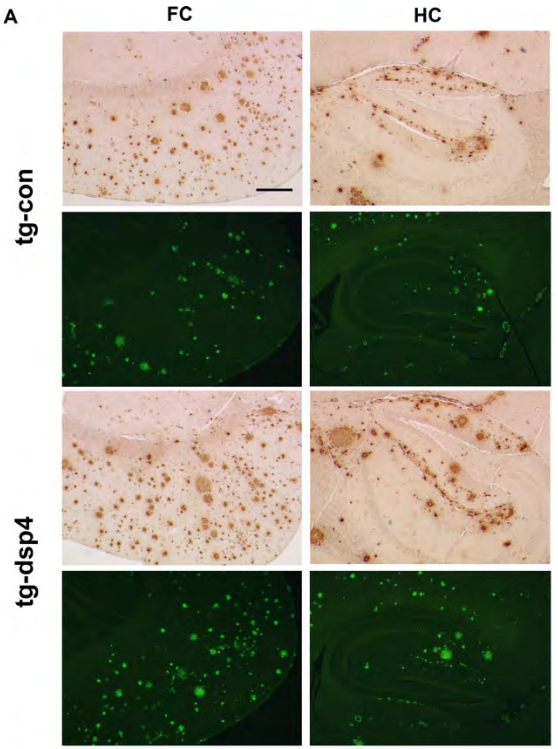
LC degeneration impacts microglia and AD lesions

Heneka et al., 20





Heneka et al., 2010



LC lesions exacerbate inflammation, amyloid burden and cognitive deficits in amyloid models

Locus coeruleus ablation exacerbates cognitive deficits, neuropathology, and lethality in P301S tau transgenic mice

Termpanit Chalermpalanupap[1], Jason P. Schroeder[1], Jacki M. Rorabaugh[1], L. Cameron Liles[1], James J. Lah[2], Allan I. Levey[2] and David Weinshenker[1]

[1]*Departments of Human Genetics*
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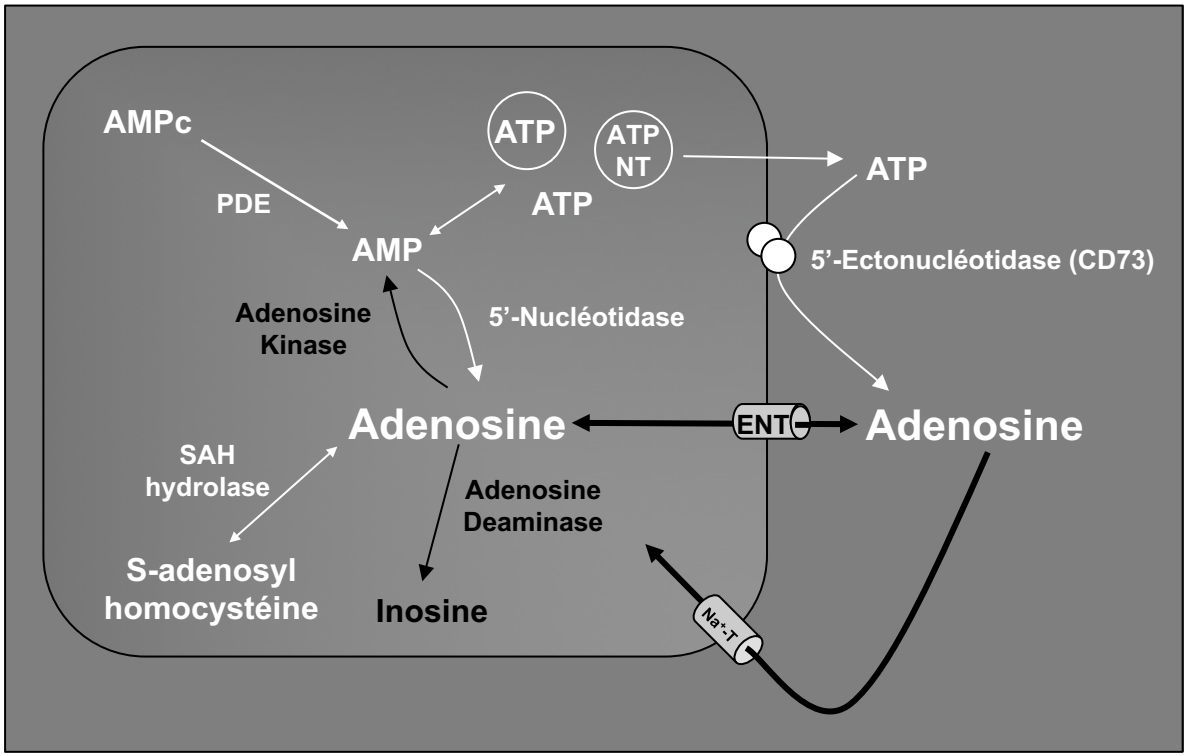
Published: 13 November 2017

LC lesions in Tau mice exacerbate inflammation, pTau and cognitive deficits

The case of adenosine



Increases in metabolically stressful conditions (nM to mM)

OPEN

Citation: Cell Death and Disease (2015) 6, e1629; doi:10.1038/cddis.2014.576
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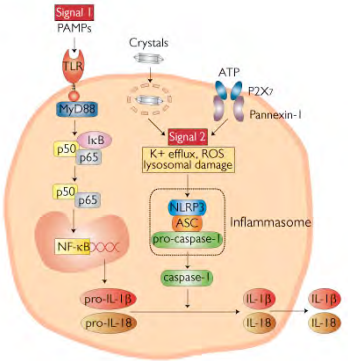
www.nature.com/cddis

The NLRP3 inflammasome is activated by nanoparticles through ATP, ADP and adenosine

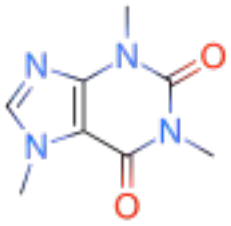
L Baron[1], A Gombault[1], M Fanny[1], B Villeret[1], F Savigny[1], N Guillou[1], C Panek[1], M Le Bert[1], V Lagente[2], F Rassendren[3], N Riteau[1] and I Couillin[1]



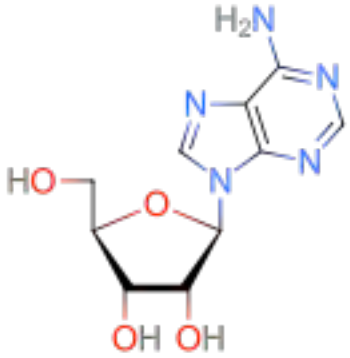
Adenosine receptors

A_1	A_{2A}	A_{2B}	A_3
326aa	410aa	332aa	320aa
G_i, G_o	G_s, G_{olf}	G_s, G_q	G_i
cAMP(-), PLC(+) Canaux K(+) PI3K(+)	cAMP(+) PLC(+)	cAMP(+) PLC(+) AA(+)	cAMP(-) PLC(+) PLD(+)

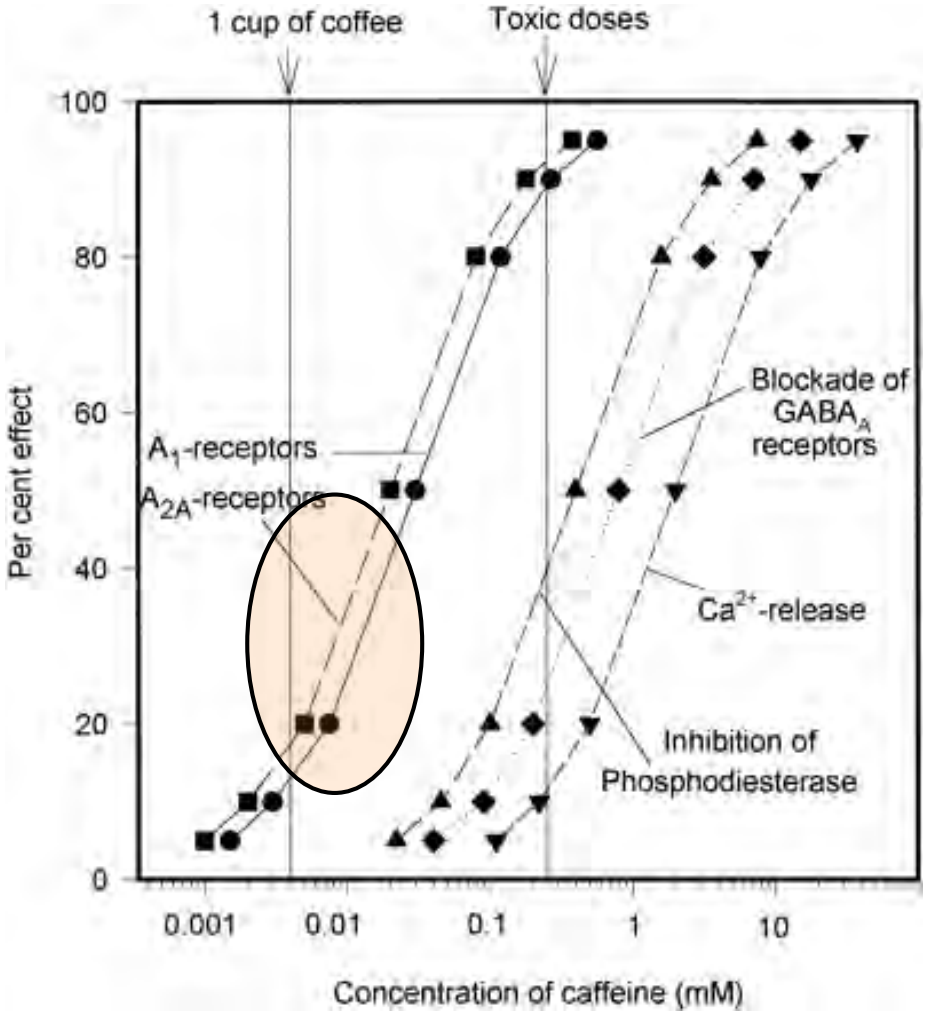
Caffeine is an antagonist of adenosine receptors



Caffeine



Adenosine



Caffeine influences AD risk

Life-style
(Nutrition, social, exercise…)

Ageing

Does caffeine intake protect from Alzheimer's disease?

L. Maia and A. de Mendonça
Dementia Clinics, Hospital of Santa Maria and Laboratory of Neurosciences, Faculty of Medicine of Lisbon, Portugal

Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study

BM van Gelder[1], B Buijsse[2,3], M Tijhuis[1,*], S Kalmijn[4], S Giampaoli[5], A Nissinen[6,7] and D Kromhout[3]

Midlife Coffee and Tea Drinking and the Risk of Late-Life Dementia: A Population-Based CAIDE Study

Marjo H. Eskelinen[a,*], Tiia Ngandu[a,b], Jaakko Tuomilehto[c,d,e], Hilkka Soininen[a,f] and Miia Kivipelto[a,b,*]

The neuroprotective effects of caffeine

A prospective population study (the Three City Study)

Contents lists available at ScienceDirect
Neurobiology of Aging
journal homepage: www.elsevier.com/locate/neuaging

Beneficial effects of caffeine in a transgenic model of Alzheimer's disease-like tau pathology

Cyril Laurent[a,b], Sabiha Eddarkaoui[a,b], Maxime Derisbourg[a,b], Antoine Leboucher[a,b], Dominique Demeyer[a,b], Sébastien Carrier[a,b], Marion Schneider[c], Malika Hamdane[a,b], Christa E. Müller[c], Luc Buée[a,b,d], David Blum[a,b,d,*]

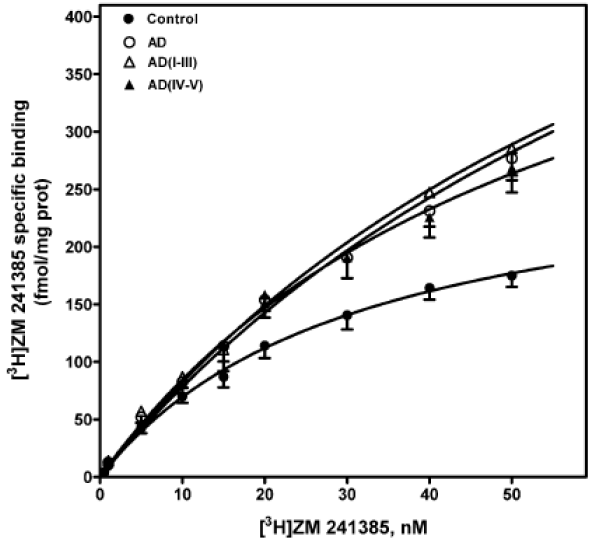
Caffeine reduces inflammation & Tau pathology
as well as improves memory in AD models

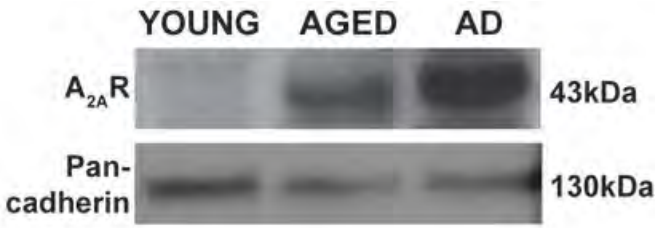
Neuronal A_{2A}Rs are dysregulated in AD brain

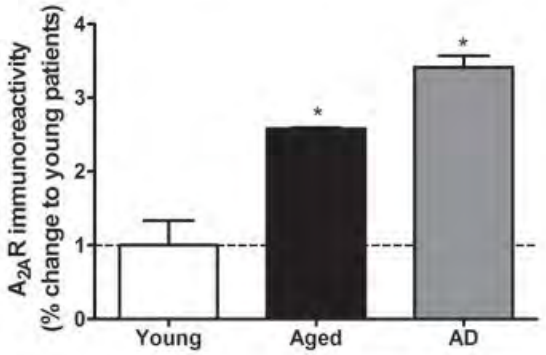
RESEARCH ARTICLE

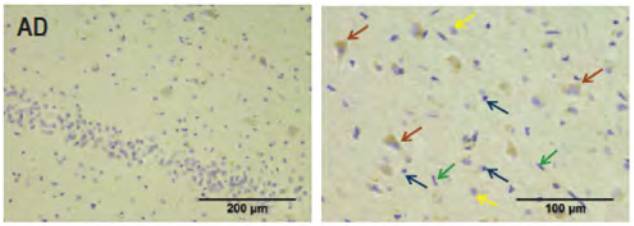
Up-regulation of Adenosine Receptors in the Frontal Cortex in Alzheimer's Disease

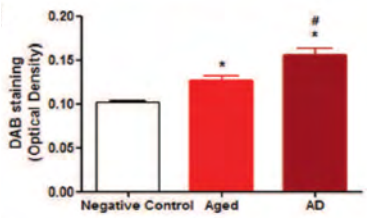
José L. Albasanz, PhD[1]; Sandra Perez[2]; Marta Barrachina, PhD[2]; Isidro Ferrer, MD[2,3]; PhD; Mairena Martín, PhD[1]

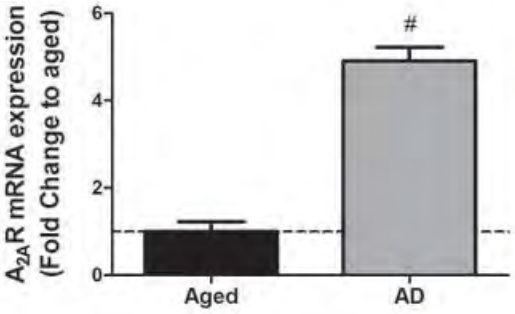












Neurosciences, neurologie, psychiatrie Inserm

Temido et al., submitted

Impact of neuronal $A_{2A}R$ activation in AD models

Neuronal activation of $A_{2A}R$ impairs plasticity

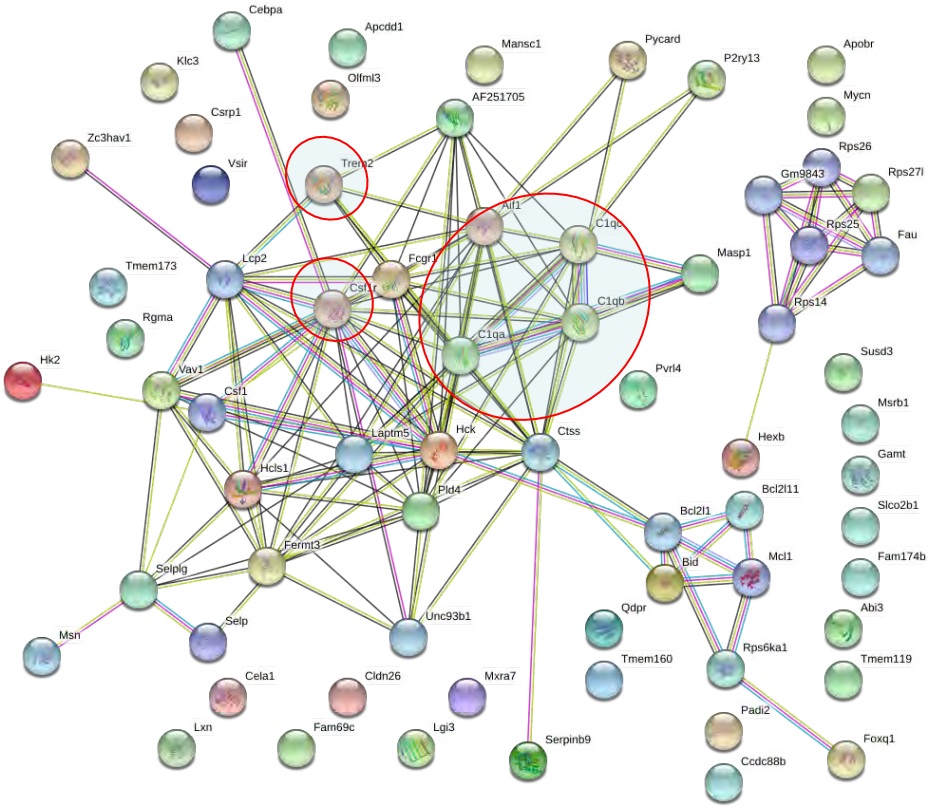
ARTICLE

Received 29 Feb 2016 | Accepted 12 May 2016 | Published 17 Jun 2016 DOI: 10.1038/ncomms11915 OPEN

Early synaptic deficits in the APP/PS1 mouse model of Alzheimer's disease involve neuronal adenosine A_{2A} receptors

Silvia Viana da Silva[1,2], Matthias Georg Haberl[3,*], Pei Zhang[1,*], Philipp Bethge[1], Cristina Lemos[4], Nélio Gonçalves[4], Adam Gorlewicz[1], Meryl Malezieux[1], Francisco Q. Gonçalves[4], Noëlle Grosjean[1], Christophe Blanchet[1], Andreas Frick[3], U Valentin Nägerl[1], Rodrigo A. Cunha[4,5] & Christophe Mulle[1]

Neuronal activation of $A_{2A}R$ activate microglial pathways

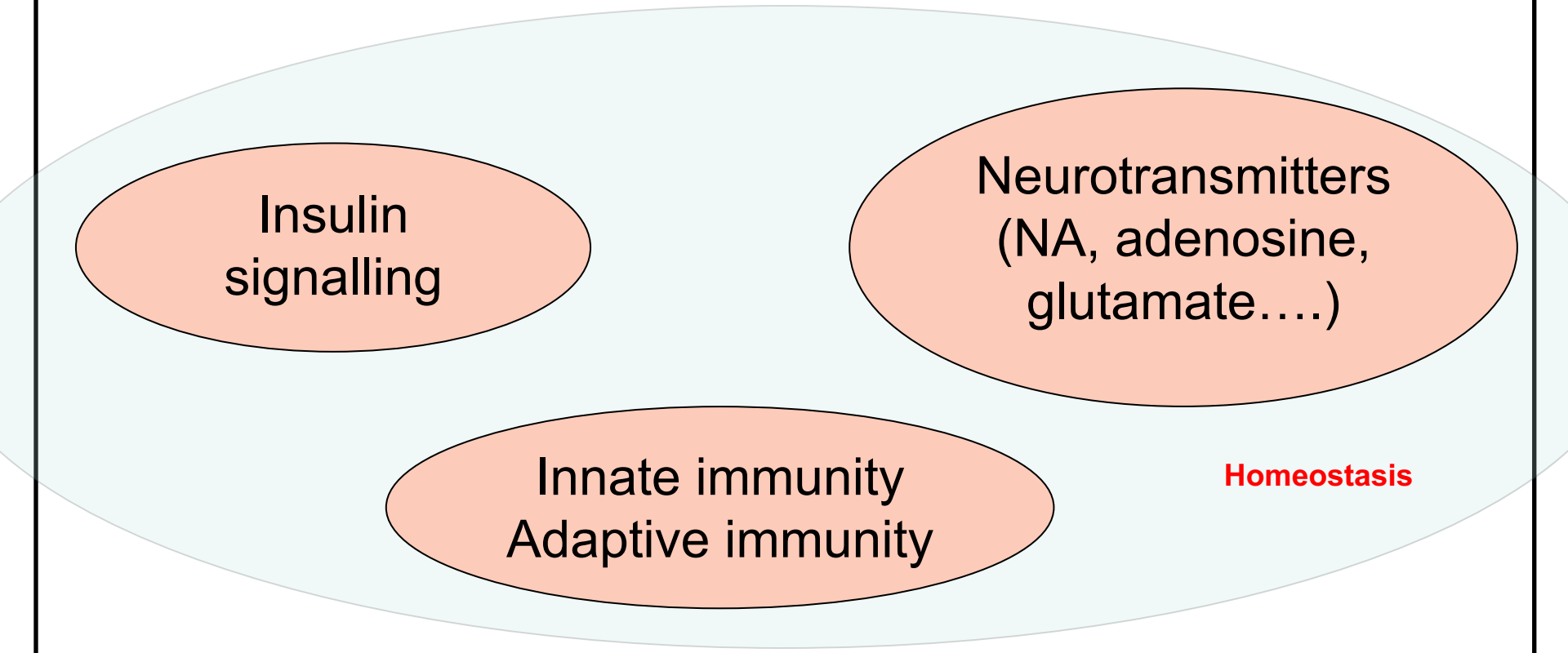


Memory defects

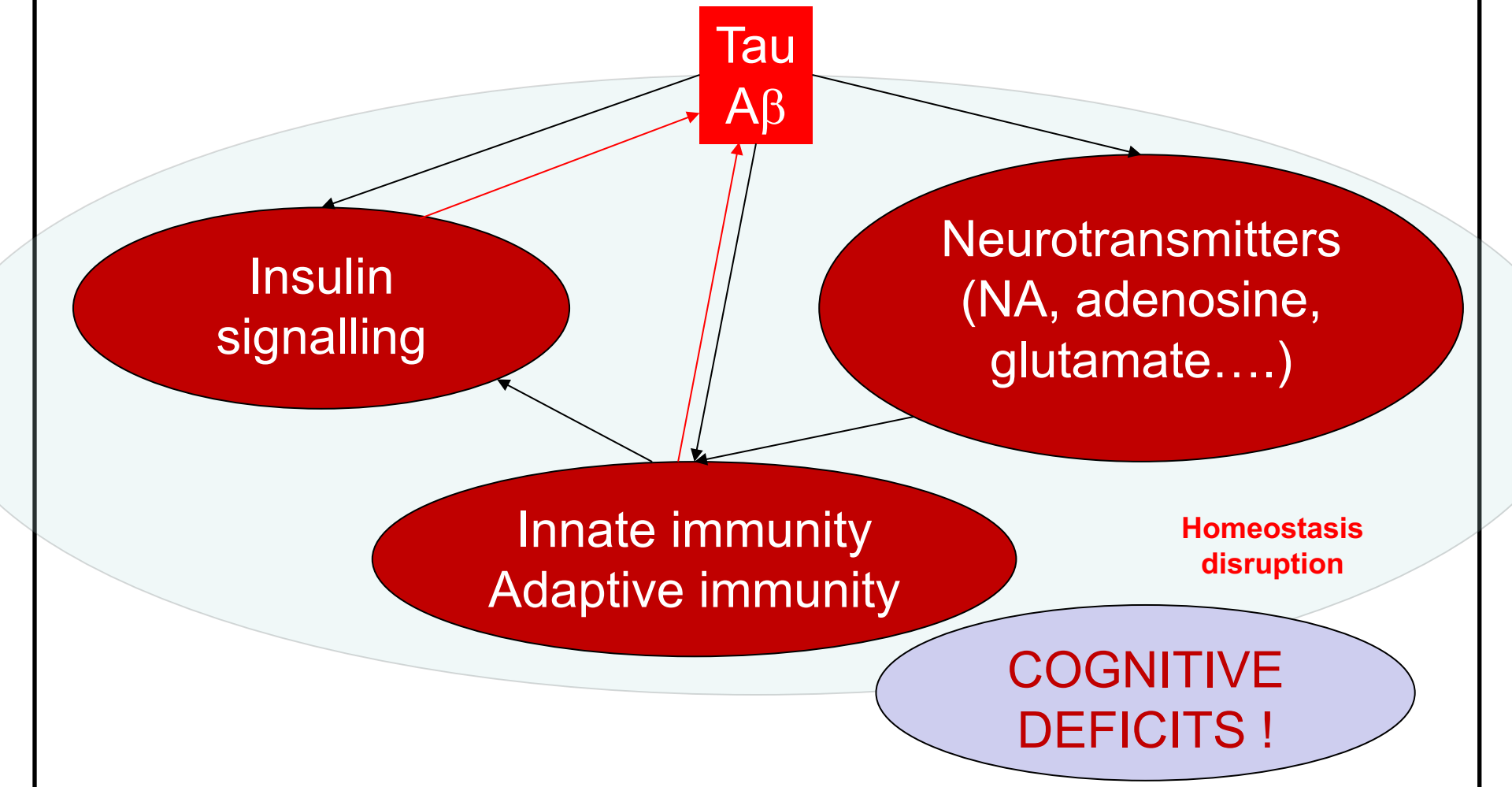
Blocking $A_{2A}Rs$ improves memory in AD models

Neurosciences, neurologie, psychiatrie Inserm

Conclusion


Insulin signalling
Neurotransmitters (NA, adenosine, glutamate….)
Innate immunity
Adaptive immunity
Homeostasis

Conclusion



AD lesions disrupt brain homeostasis leading to cognitive deficits and amplifying lesions