Pierre J. Magistretti, MD, PhD

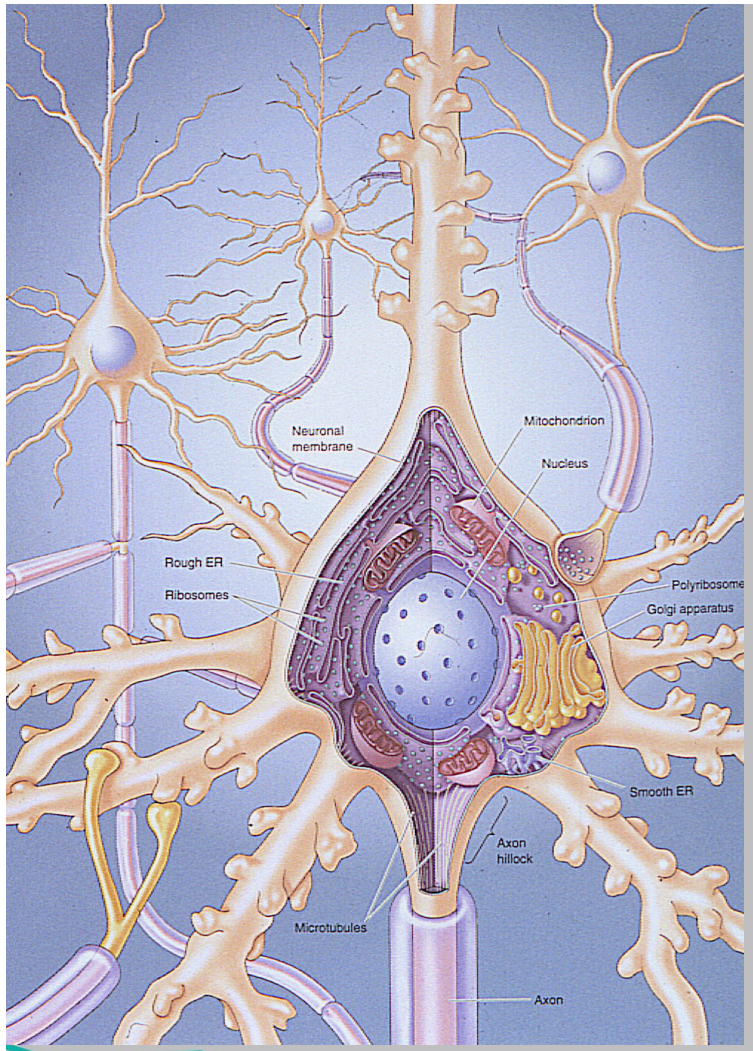
King Abdullah University of Science and Technology, KAUST

(Ecole Polytechnique Fédérale de Lausanne, EPFL)

Biennale Tecnologia, Tecnologia e Umanità
Torino, 19 aprile 2024

Svelare il futuro: Tecnologie per la cura delle persone

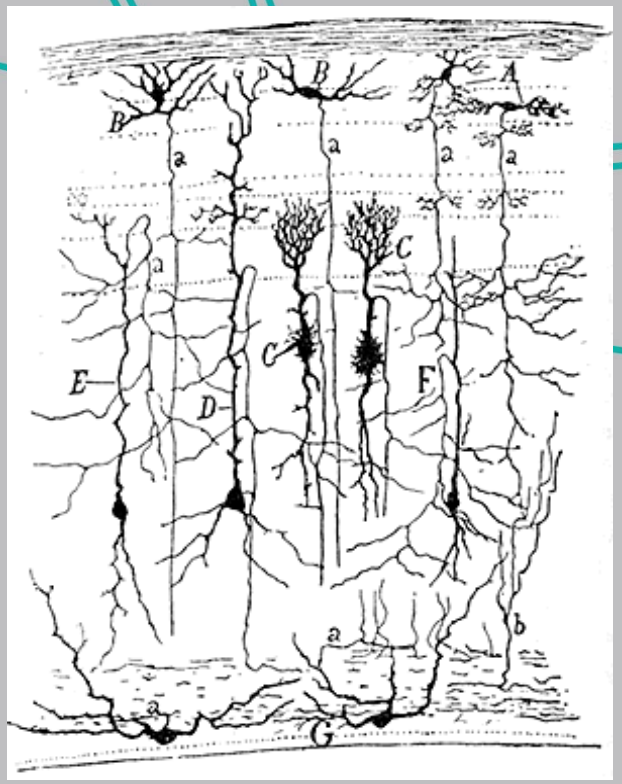
Le cellule gliali come target per la cura delle malattie del cervello



Neuroni

≈80 Miliardi

Santiago Ramon-y-Cajal
(Premio Nobel 1906)

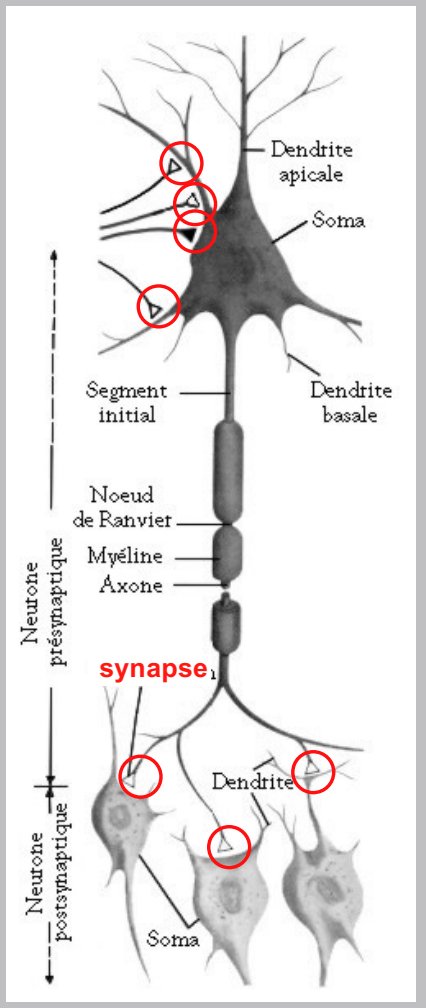


Come l'entomologi alla ricerca di farfalle multicolori, la mia attenzione si è portata sui giardini della materia grigia e sulle cellule dalle forme eleganti e delicate, le misteriose farfalle dell'anima,
sur des cellules aux formes délicates etélégantes, les mystérieux papillons de l'âme, dont le battement d'ailes nous révèlera peut-être un jour les secrets de l'esprit

Ramon y Cajal S.: Recuerdos de mi vida: Historia de mi labor cientifica.
Alianza Editorial, Madrid, p.98-99, 1984

Un singolo neurone può recevere fina a ***10'000 sinapsi***

10^{15} sinapsi ***(1000'000'000'000'000)***



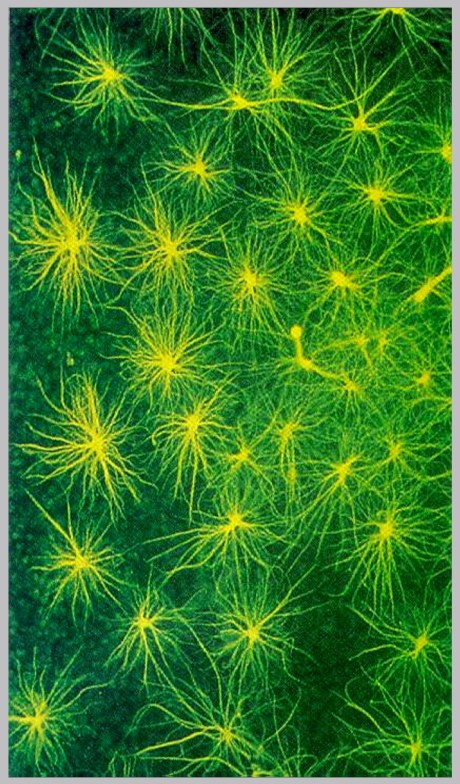
Direzionalità dei segnali elettrici

Ma non ci sono solo neuroni.

L’altra metà del cervello:
Le cellule gliali (glia)

Glia : “glu” “colla”

Rudolf Carl Virchow
(1821 – 1902)



Astrociti

Three main types of glial cells in the brain :

Astrocytes

Oligodendrocytes

Microglia

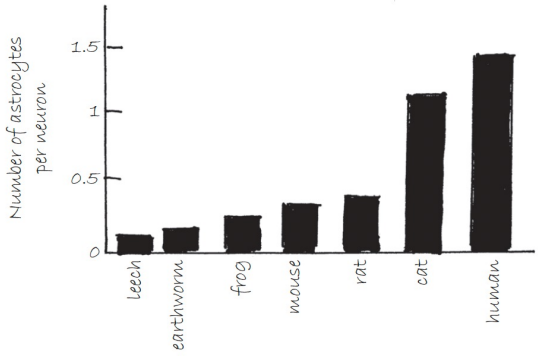
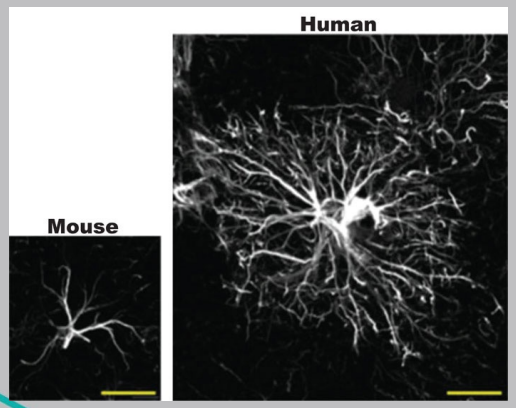
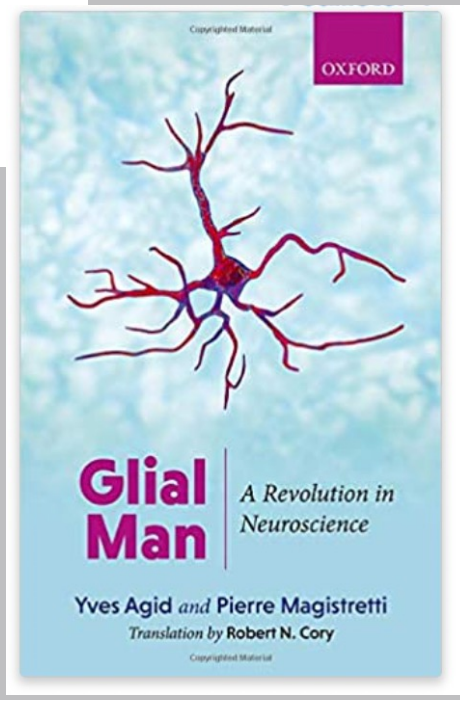


Figure 8 Astrocytes: a cognitive index of evolution?

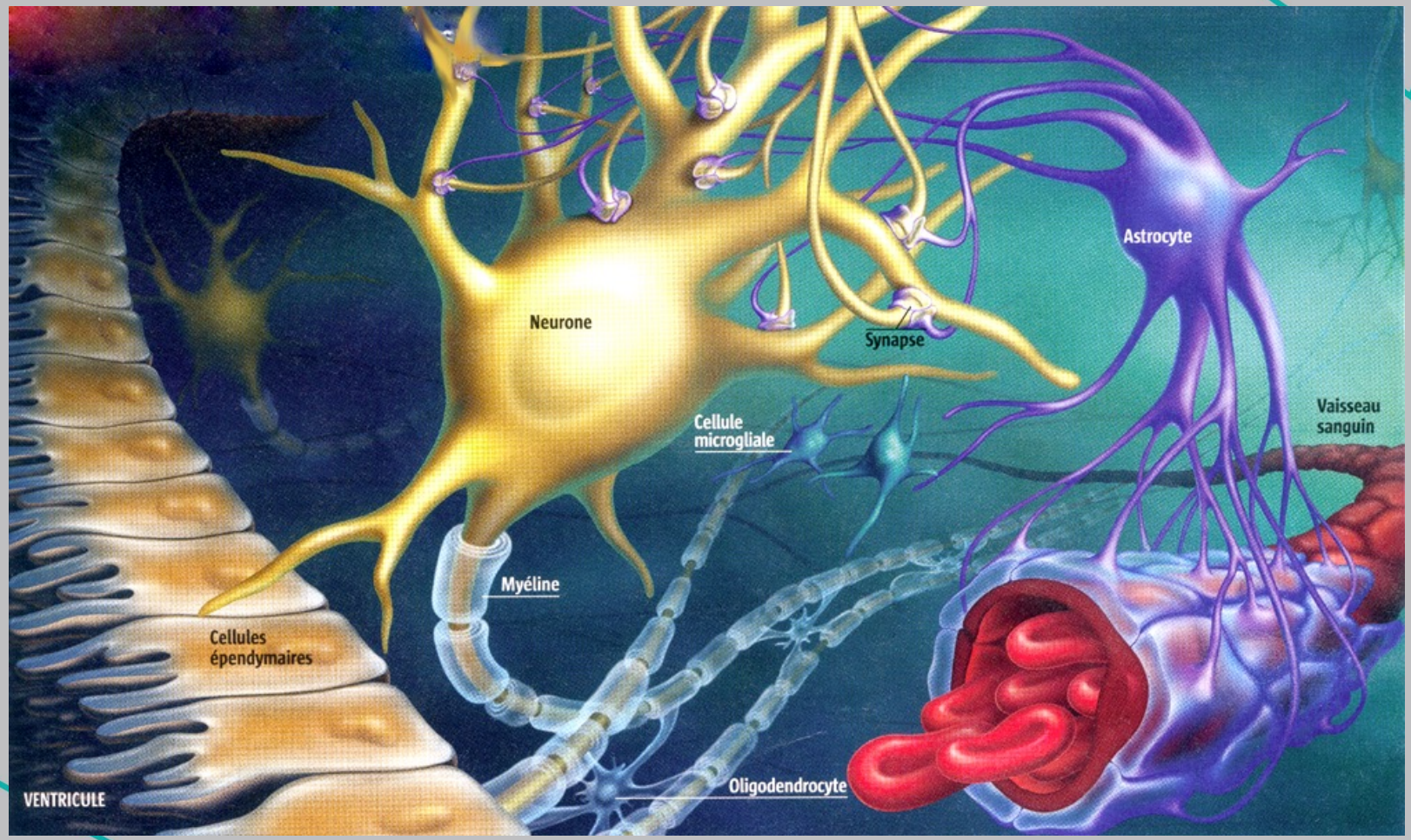
≈100 Billions



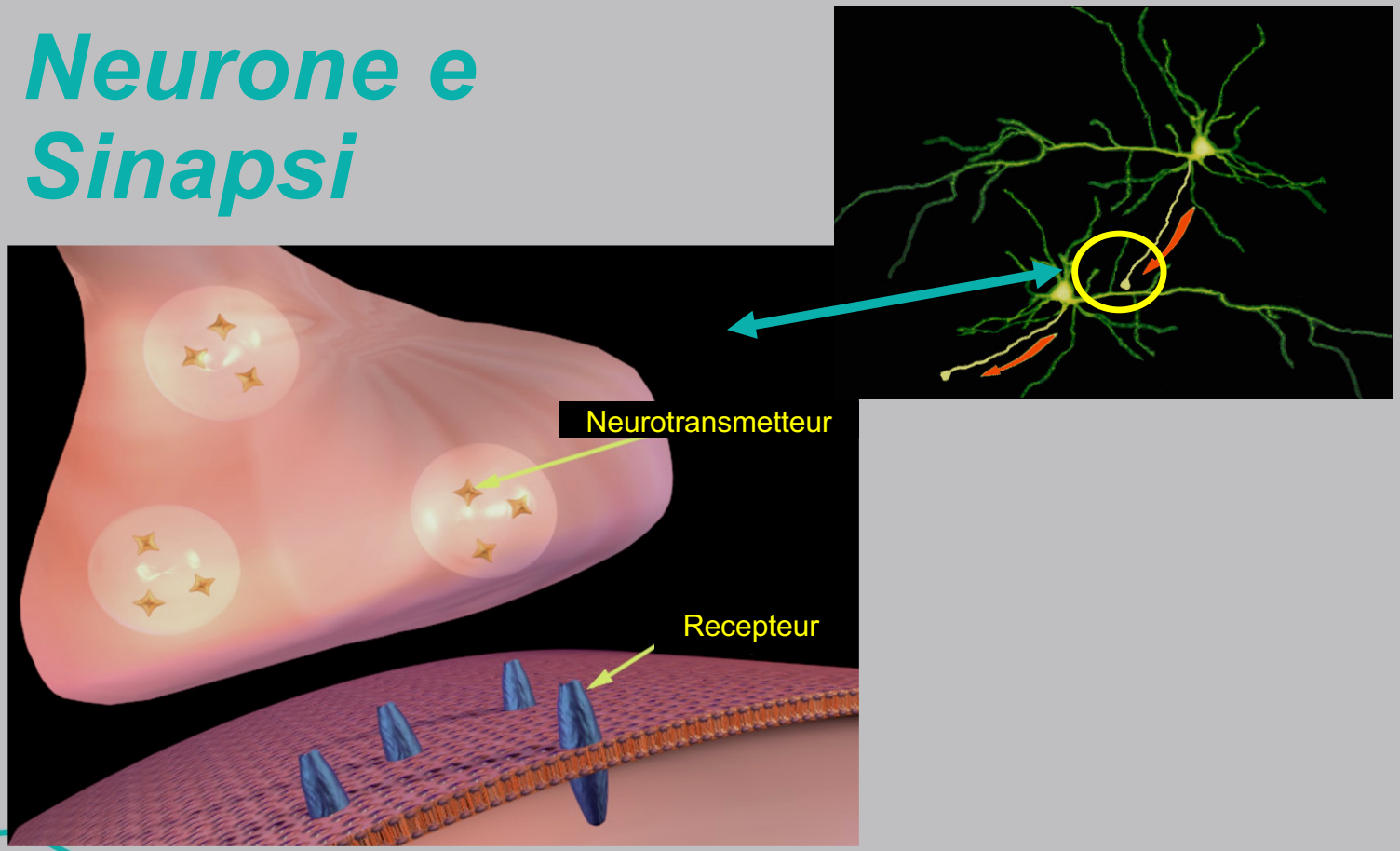
Astrociti



Un dialogo tra cellule



Neurone e Sinapsi



Quali neurotrasmettitori si conoscevano alla la fine degli anni 1970

- **Amine : noradrenalina, dopamina, acetilcolina**
- **Amino Acidi: GABA, glutammato (?)**
- **Peptidi : decine appena scoperti**

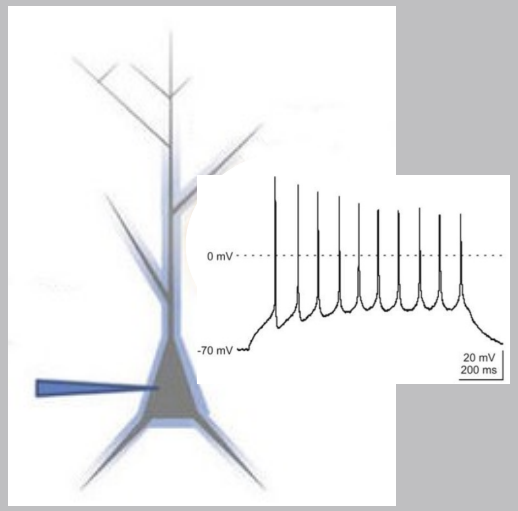
Roger Guillemin (Premio Nobel 1977)

Domanda :
Ruolo dei Neurotrasmettitori Peptidergici nel cervello ?

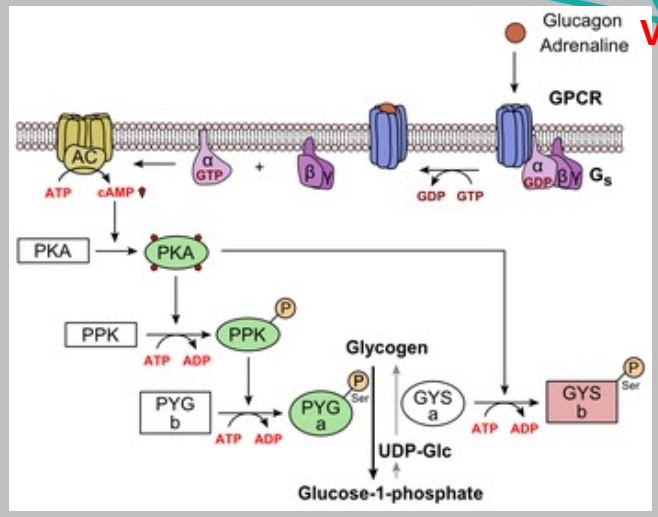
Tha Salk Insitute

Floyd Bloom

Ruolo del Vasoactive Intestinal Peptide (VIP) nel Cervello



Non un classico neurotrasmettitore



Glycogenolisi

Il mio ragionamento: Il VIP ha un effeto sul metabolismo energetico nel fegato e nel muscolo (mobilizza energia a partire dal glicogeno)
-> Dovrebbe avere un ruolo simile nel cervello

…. Ma ignoravo due dati importanti

- La concentrazione di glicogeno è molto bassa nel cervello
- Il glicogeno è contenuto solo nelle cellule gliali del cervello, che al tempo erano considerate
- Come una specie di “colla cellulare” (glue) del cervello

Proc. Natl. Acad. Sci. USA
Vol. 78, No. 10, pp. 6535–6539, October 1981
Neurobiology

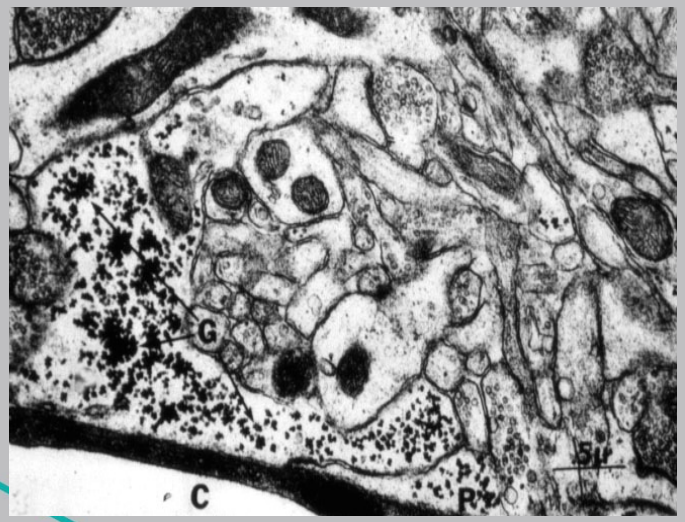
Vasoactive intestinal polypeptide induces glycogenolysis in mouse cortical slices: A possible regulatory mechanism for the local control of energy metabolism

(cerebral cortex/peptides/brain energy metabolism/glycogen/norepinephrine)

PIERRE J. MAGISTRETTI, JOHN H. MORRISON, WILLIAM J. SHOEMAKER, VIVECA SAPIN, AND FLOYD E. BLOOM

Arthur V. Davis Center for Behavioral Neurobiology, The Salk Institute, P.O. Box 85800, San Diego, California 92138

Contributed by Floyd E. Bloom, June 22, 1981



Neuron

Astrocyte

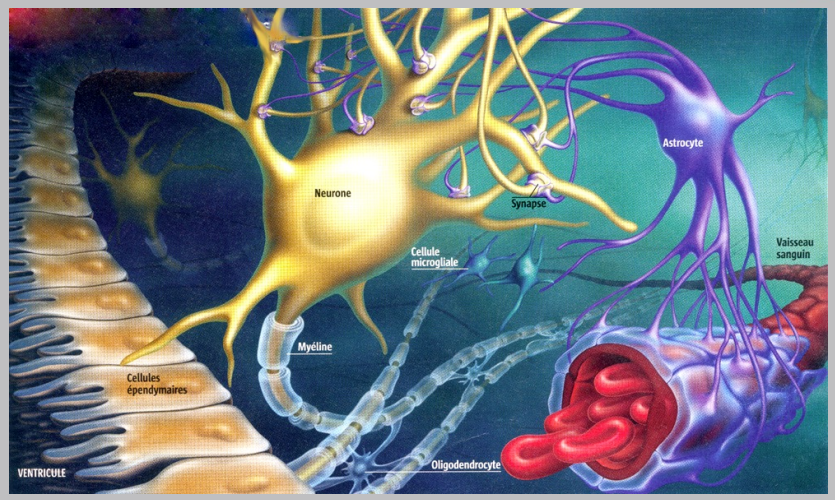
Noradrenaline

VIP

Glycogen

Glycolysis

Energy supply
to neurons



Prima dimostrazione che dei neurotrasmettitori potevano mandare segnali alle cellule gliali lequali rispondevano con un processo fisiologico (fornire energia)

Magistretti et al, PNAS, 1981

Circuiti contenenti Noradrenalina e VIP

Magistretti and Morrison,
Neuroscience, 1988
24: 367-378

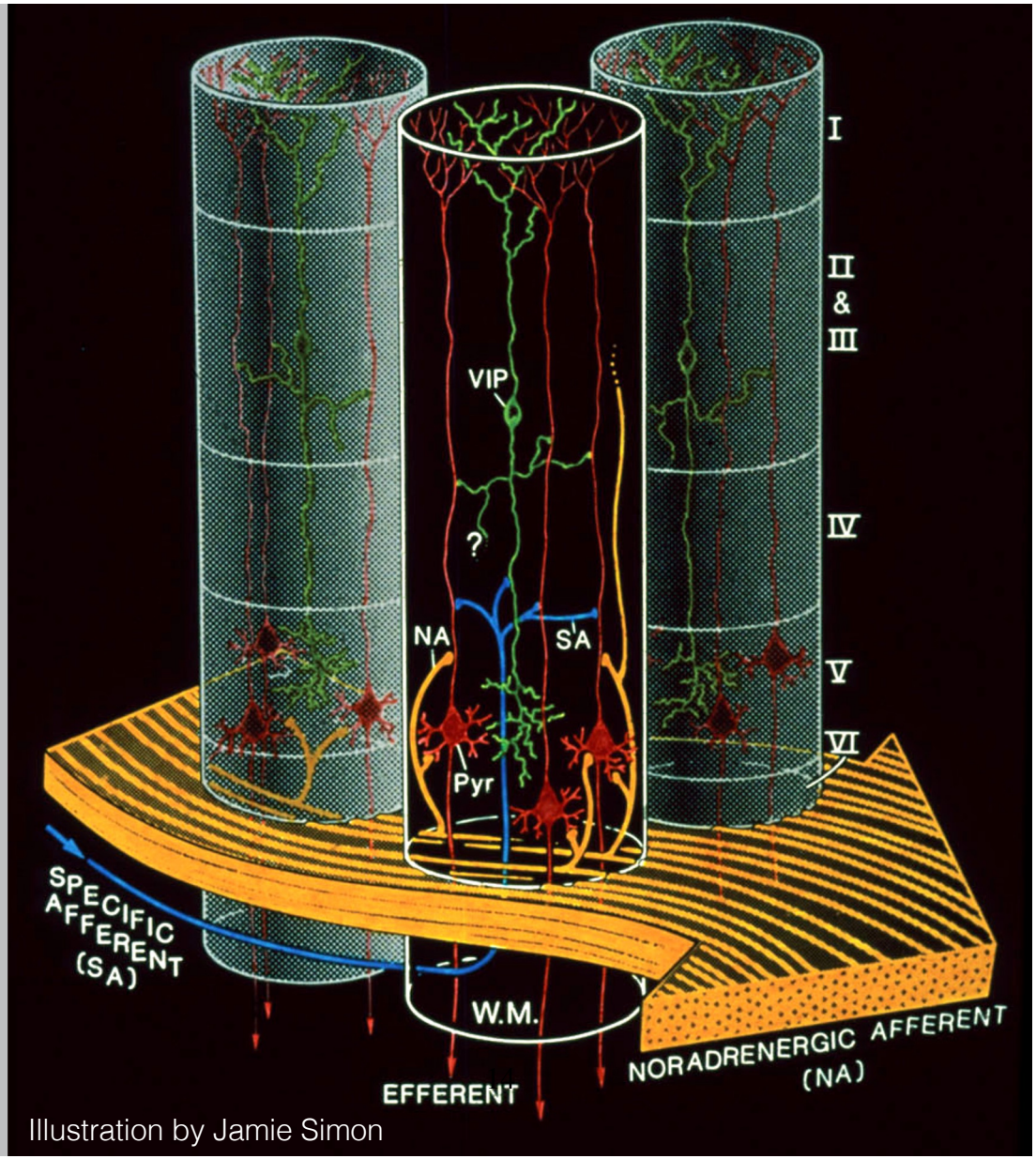


Illustration by Jamie Simon

Fine anni 1980

- Alcuni neurotrasmettitori liberati da circuiti neuronali specifici possono agire sulle cellule gliali

- Alcuni neurotrasmettitori possono esercitare effetti di tipo ormonale nel cervello, agendo sulle cellule gliali

- Dei neurotrasmettitori come il VIP e la noradrenalina mobilizzano l'energia depositata (glicogeno) nella glia (astrociti) per sostenere l'attività neuronale

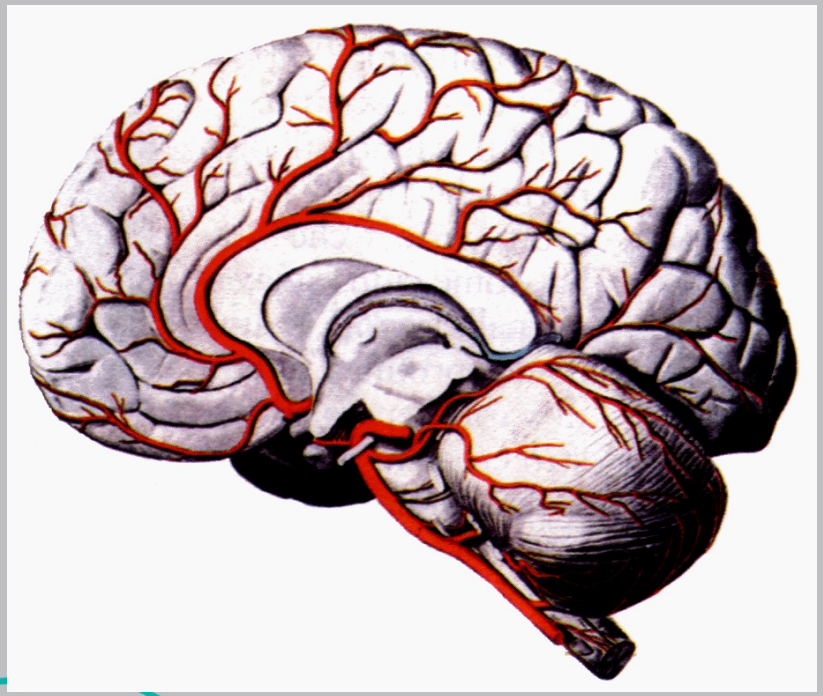
➔ Esiste un accoppiamento metabolico tra l'attività neuronale e il metabolism energetico gliale per fornire energia ai neuroni

Domanda:

Quali sono i meccanismi molecolari che Mediano l’accompiamento tra attività sinattica e risposte metaboliche gliali


PHYSIOLOGIE
1989 – 2004 :
Institute of Physiology, Faculty of Medicine,
University of Lausanne

Il cervello ha bisogni energetici importanti



- solo 2% della massa corporea

ma

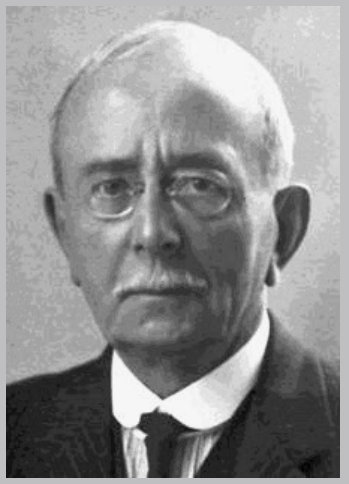
- 15% dell'output cardaico
- 25% del consumo energetico di glucosio dell'organismo
- 20% del consumo di ossigeno

ON THE REGULATION OF THE BLOOD-SUPPLY OF THE BRAIN. By C. S. ROY, M.D., F.R.S., *Professor of Pathology, University of Cambridge*, AND C. S. SHERRINGTON, M.B., M.A., *Fellow of Gonville and Caius College. Lecturer on Physiology in the School of St Thomas's Hospital, London.* Plates II., III. and IV.

From the Cambridge Pathological Laboratory.

We conclude then that the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brain can cause variations of the calibre of the cerebral vessels: that in this re-action *the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity.*

Journal of Physiology (London) 11:85-108 (1890)



Charles Sherrington
Nobel Laureate 1932

Louis Sokoloff

Neurochemical Research, Vol. 24, No. 2, 1999, pp. 321–329

Energetics of Functional Activation in Neural Tissues*

Louis Sokoloff[1,2]

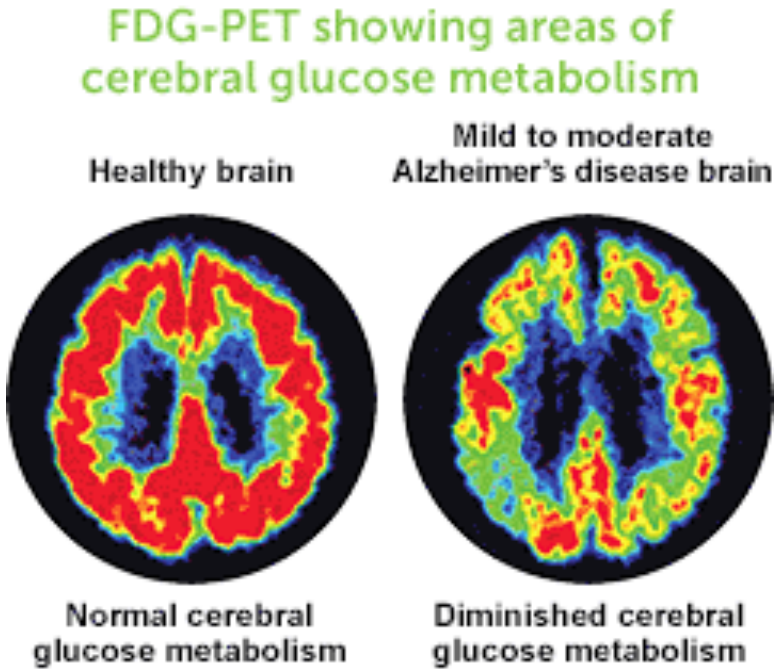


Image source: Small GW, Ercoli LM, Silverman DHS, et al. Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proc Natl Acad Sci USA*. 2000;97(11):6037-6042. Copyright 2013 National Academy of Sciences, U.S.A.

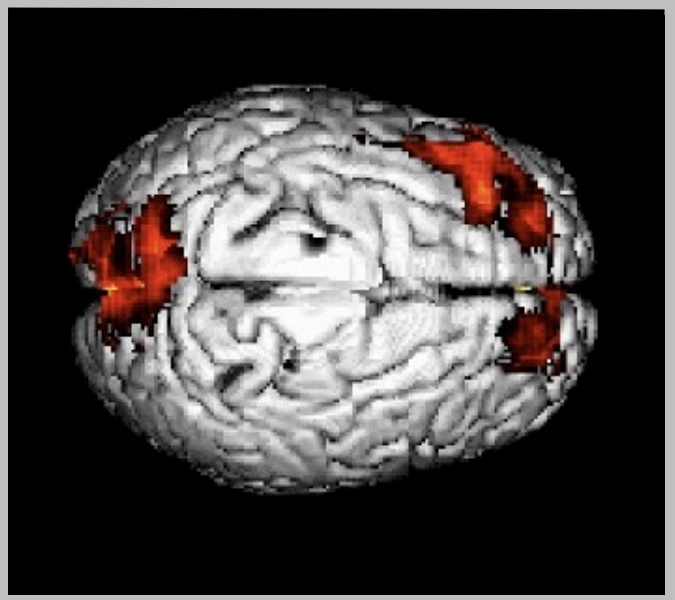
Tecniche per l' imaging cerebrale funzionale

Positron Emission Tomography (*PET*):

^{18}F-deoxyglucose
$^{15}O_2$
$H_2{}^{15}O_2$

Functional MRI (fMRI):

change in the ratio of
oxy-/deoxy hemoglobin

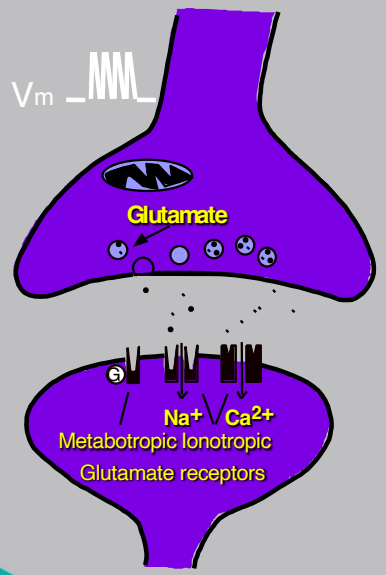


Mettono in evidenza dei signali legati al consumo di energia

Neuronal Activity

Metabolic Responses

- Functional Imaging
- Synaptic function



Coupling ?

Luc Pellerin

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 10625–10629, October 1994
Neurobiology

1994

Glutamate uptake into astrocytes stimulates aerobic glycolysis: A mechanism coupling neuronal activity to glucose utilization

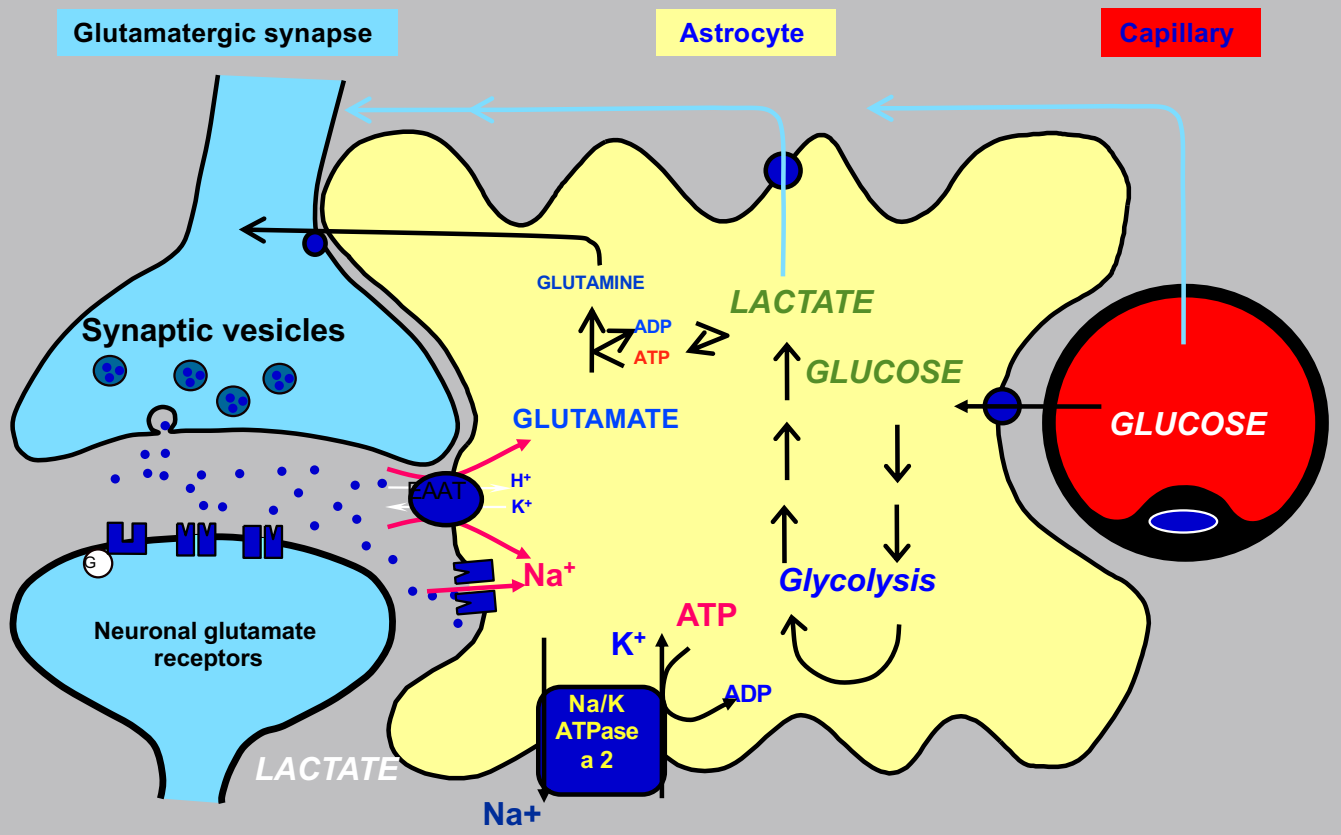
(glutamate transporter/Na^+/K^+-ATPase/2-deoxyglucose/positron-emission tomography/magnetic resonance imaging)

LUC PELLERIN AND PIERRE J. MAGISTRETTI

Institut de Physiologie, Université de Lausanne, CH-1005 Lausanne, Switzerland

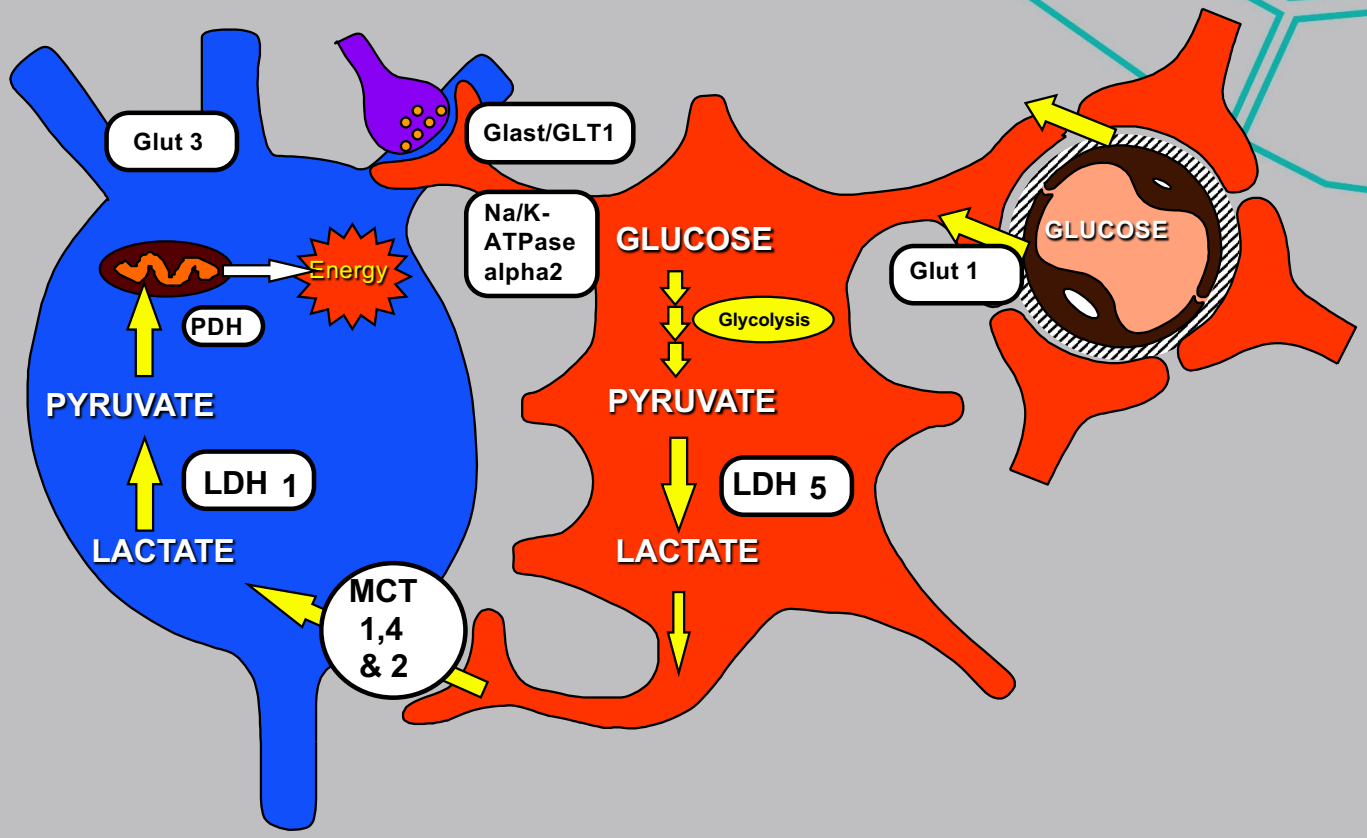
Communicated by Joseph F. Hoffman, June 28, 1994

Mechanism for Coupling Neuronal Activity
to Glucose Utilization



Reviewed in Magistretti and Allaman, *Nature Rev. Neuroscience*, 2018

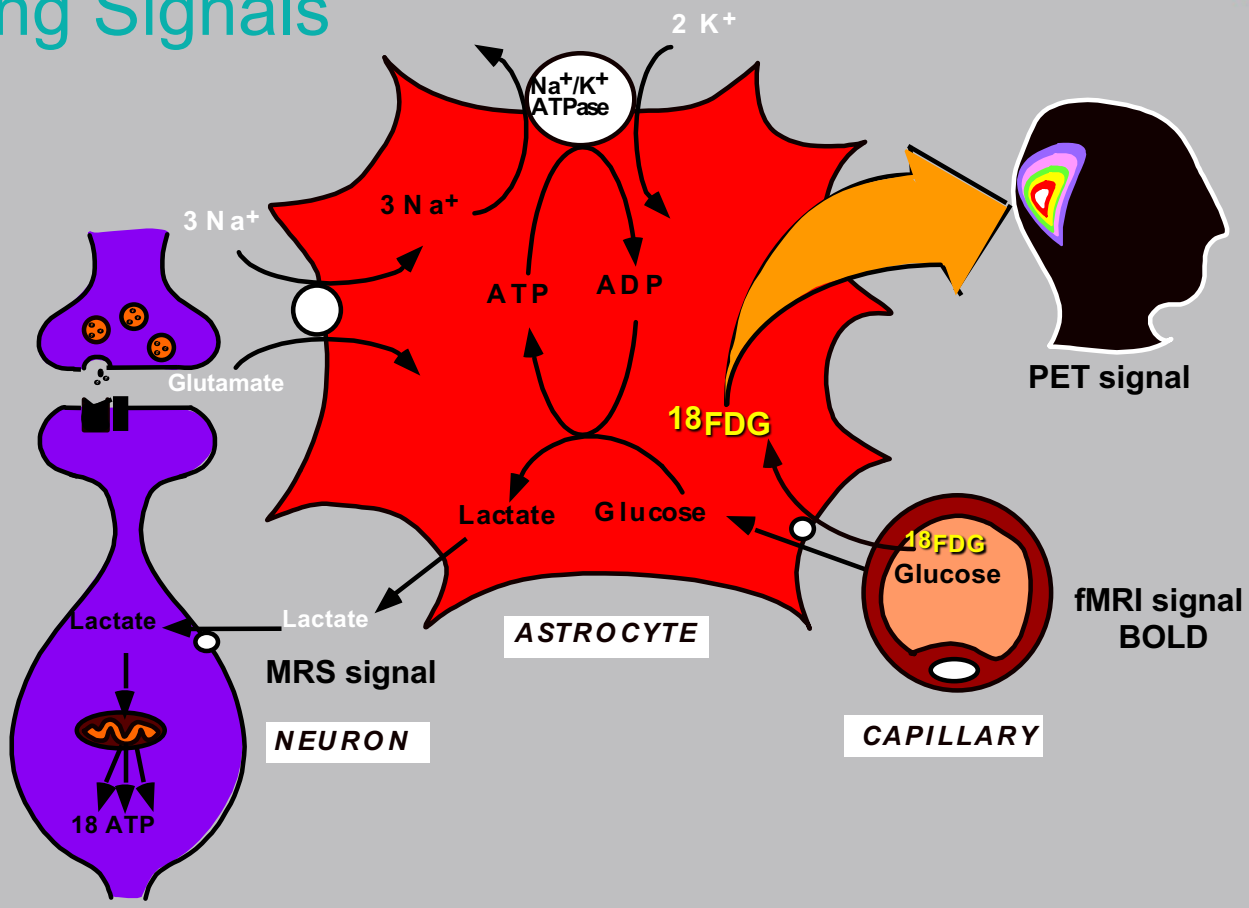
Astrocyte-Neuron Lactate Shuttle (ANLS)



Neurons are mainly oxidative

Astrocytes are mainly glycolytic

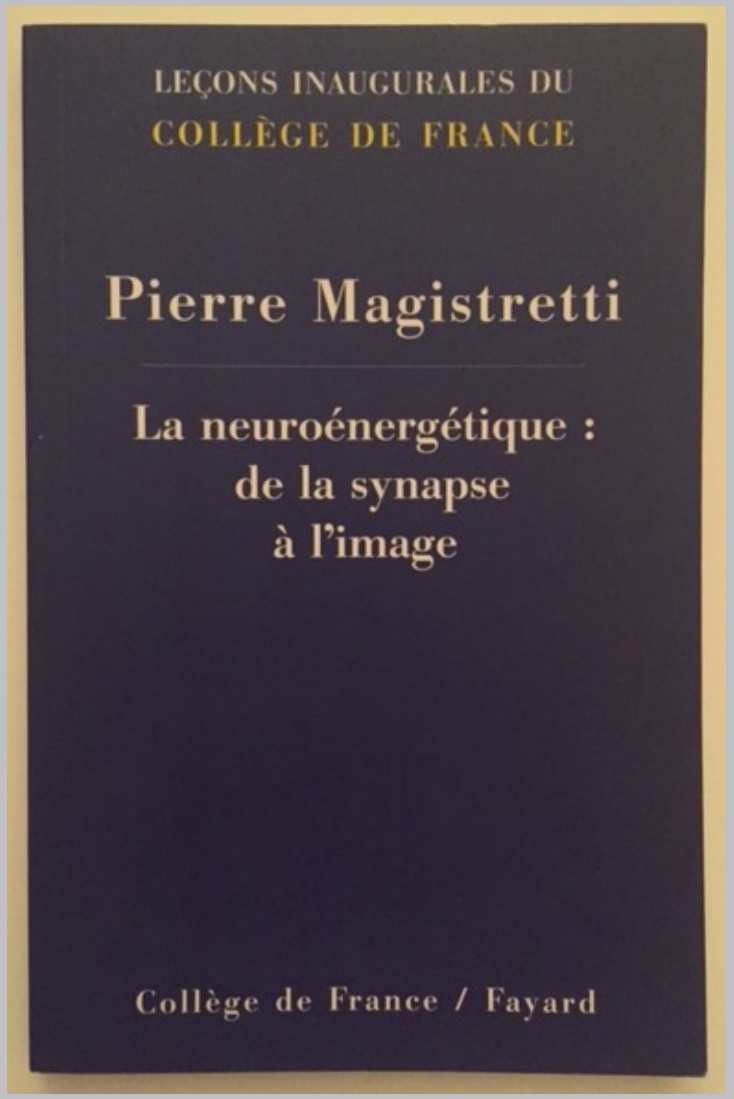
Role of Astrocytes
in Brain Imaging Signals



Fine anni 1990

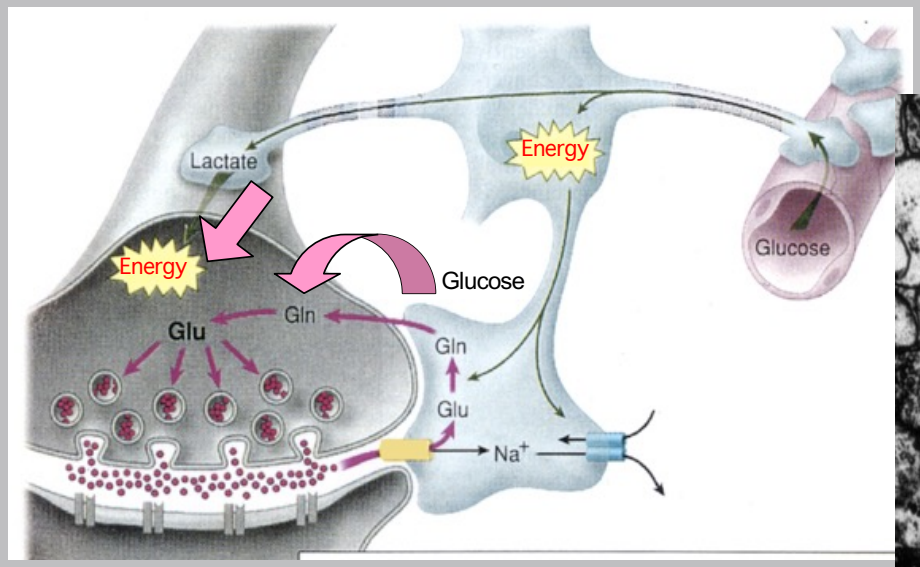
- Gli astrociti ripsondono al glutammato – il neurotrasmettitore che è liberato dall' 80% delle sinapsi
- Il glutammato attiva l'uptake di glucosio negli astrociti che lo trasformano in lattato che liberano **per fornire energia ai neuroni (glicolisi aerobica)**
- Questo meccanismo accoppia l'attività sinattica al metabolismo energetico e fornisce ai neuroni energia **quando e dove ne necessitano**
- **-> Questo meccanismo produce anche i segnali messi in evidenza dalle tecniche di imaging cerebrale fundzionale**

Magistretti et al, Science, 1999

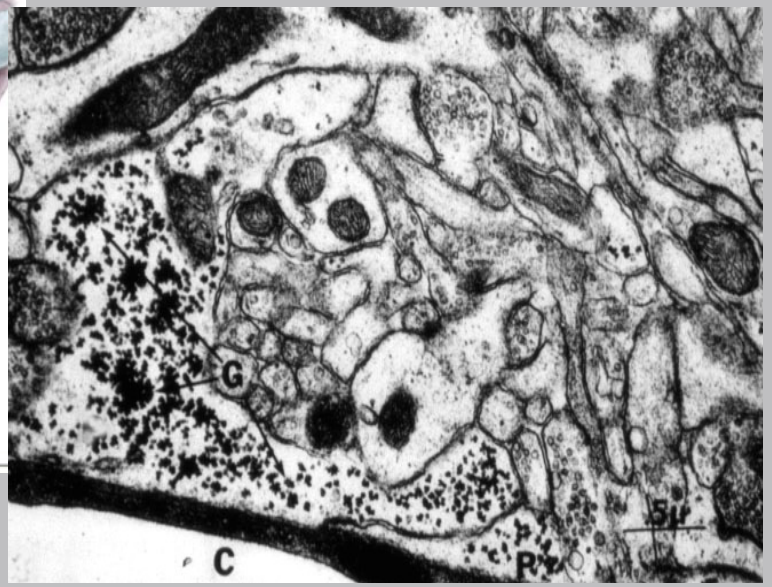


Leçon inaugurale
14 février 2008

La Astrocyte Neuron Lactate Shuttle e plasticità neuronale

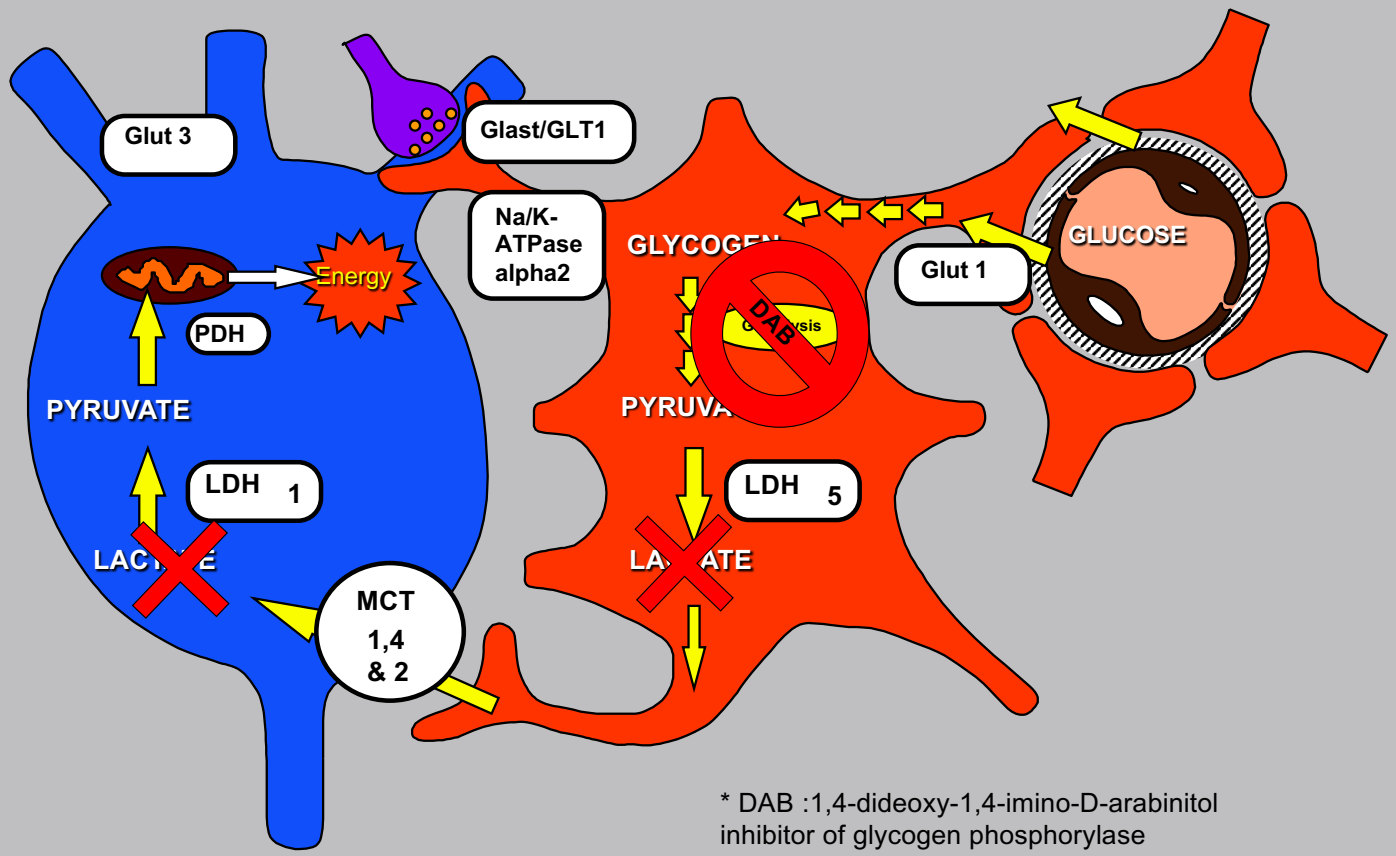


Glicogeno



Ruolo nella memoria?

Inibizione del metabolism del glicogeno durante l'apprendimento



* DAB :1,4-dideoxy-1,4-imino-D-arabinitol
inhibitor of glycogen phosphorylase

2011

Cell

Cell *144*, 810–823, March 4, 2011 ©2011 Elsevier Inc.

Astrocyte-Neuron Lactate Transport Is Required for Long-Term Memory Formation

Akinobu Suzuki,[1] Sarah A. Stern,[1,6] Ozlem Bozdagi,[1,2,6] George W. Huntley,[1] Ruth H. Walker,[3,4] Pierre J. Magistretti,[5,*] and Cristina M. Alberini[1,2,*]

Il lattato prodotto dal glicogeno astrocitario è necessario per la consolidazione della memoria !

Che sorpresa !

- **Un tipo cellulare considerate come una "colla cellulare"**
- **Un prodotto del metabolism energetico considerate come**
- **un "rifiuto"**

-> Hanno un ruolo fondamentale nella memoria

Cristina Alberini

Domanda:

L’effetto del lattato sulla memoria e “semplicemente” dovuto al suo effetto metabolico, o
Il lattato è anche una molecola di segnalizzazione?

12228–12233 | PNAS | August 19, 2014 | vol. 111 | no. 33

Lactate promotes plasticity gene expression by potentiating NMDA signaling in neurons

Jiangyan Yang[a,1], Evelyne Ruchti[a,b,c,1], Jean-Marie Petit[a,c], Pascal Jourdain[a,c], Gabriele Grenningloh[a], Igor Allaman[a,2,3], and Pierre J. Magistretti[b,c,a,2,3]

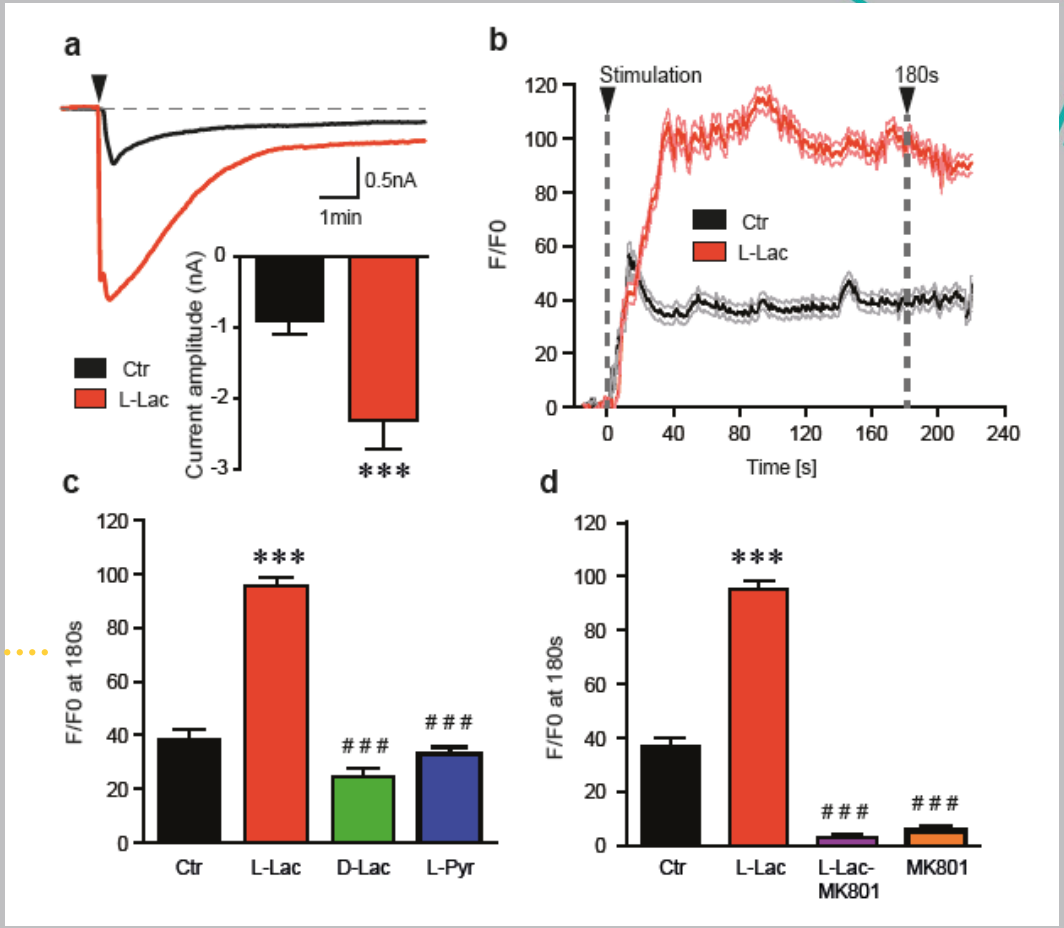
Igor Allaman

Significance

The transfer of lactate, a product of aerobic glycolysis, from astrocytes to neurons was recently shown to be necessary for the establishment of long-term memory and for the maintenance of in vivo long-term potentiation. Here, we report that lactate induces the expression of plasticity genes such as Arc, c-Fos, and Zif268 in neurons. The action of lactate is mediated by the modulation of NMDA receptor activity and the downstream Erk1/2 signaling cascade, through a mechanism associated with changes in the cellular redox state. These observations unveil an unexpected role of lactate as a signaling molecule in addition to its role in energy metabolism and open a previously unidentified research avenue for the study of neuronal plasticity and memory.

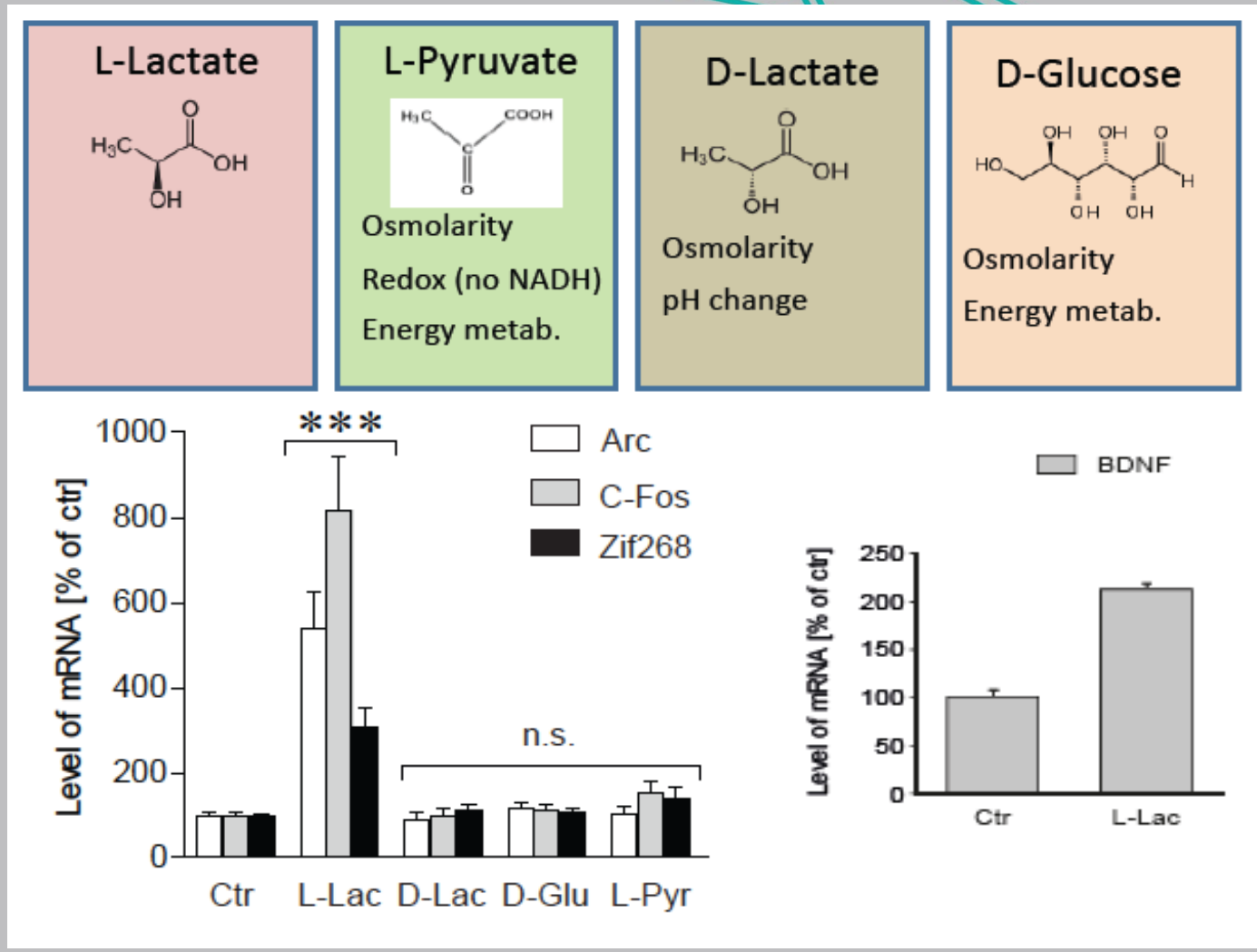
Evelyne Ruchti

Il Latatto potentenzia la trasmissioe sinattica médiata dal glutammato



Yang et al, *PNAS*, 2014

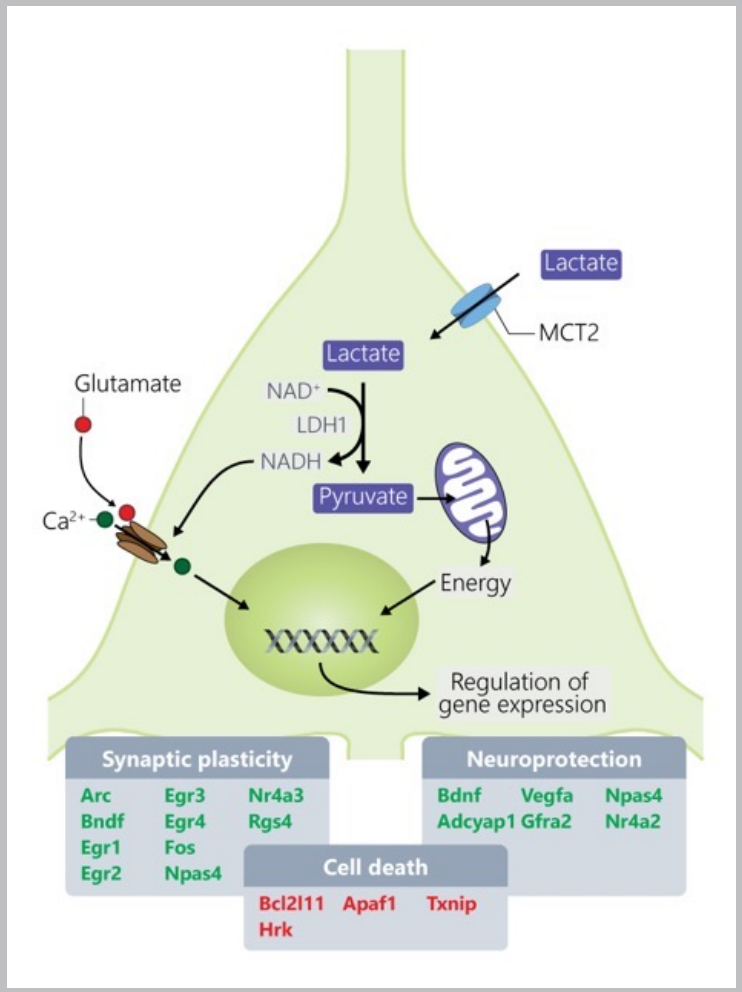
Increase in gene expression is specific to L-Lactate



Genes whose expression is upregulated (green) or downregulated (red) by L-Lactate

Michael Margineanu

Hubert Fiumelli



Margineanu et al, *Front in Neurosci, 2018*

Anni 2010 - 2020

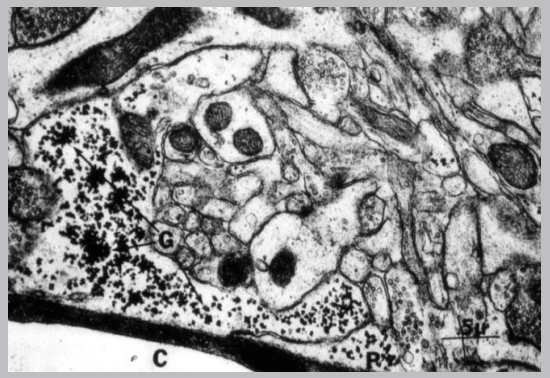
- Il lattato non è solamente un substrato energetico ma è anche un segnale per la comunicazione tra cellule del cervello
- Il lattato agisce come un “turbocharger” per il principale neurotrasmettitore, il glutammato
- Il lattato indice l’espressione di geni di plasticità e di neuroprotezione
- Una cooperazione tra un neurotrasmettitore (glutammato) e un gliotrasmettitore (lattato) è necessaria per la memoria

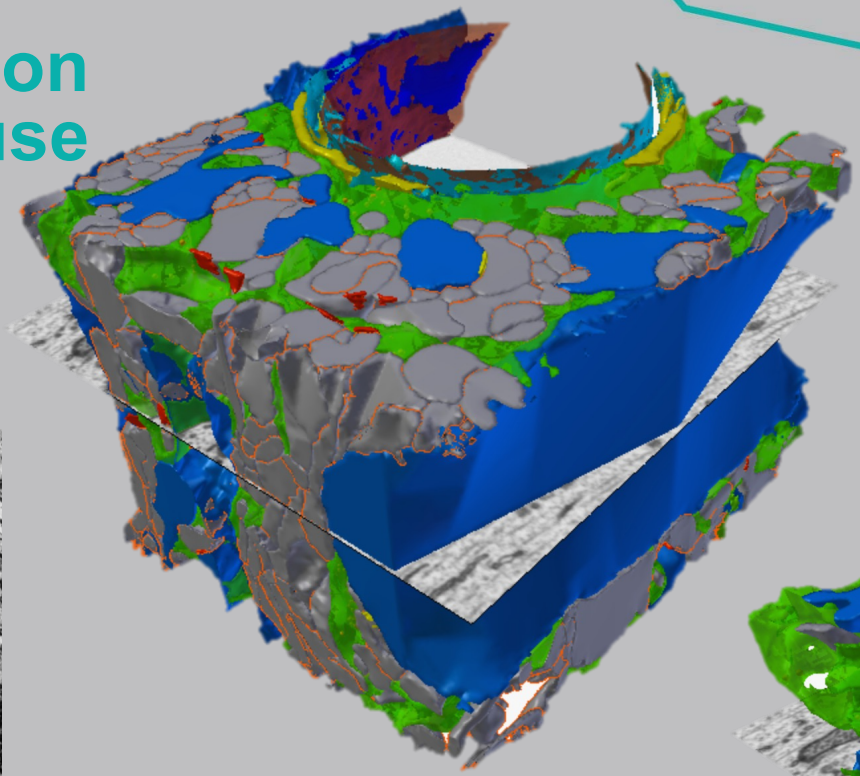
Visto il ruolo determinante del Glicogeno nella memoria:

Domanda :
Dove è localizzato il glicogeno negli astrociti rispetto ai contatti sinattici?

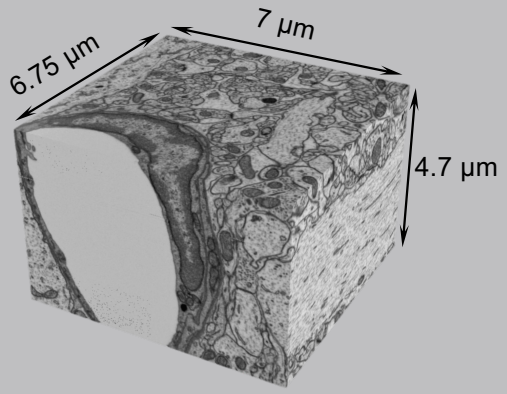
Corrado Cali

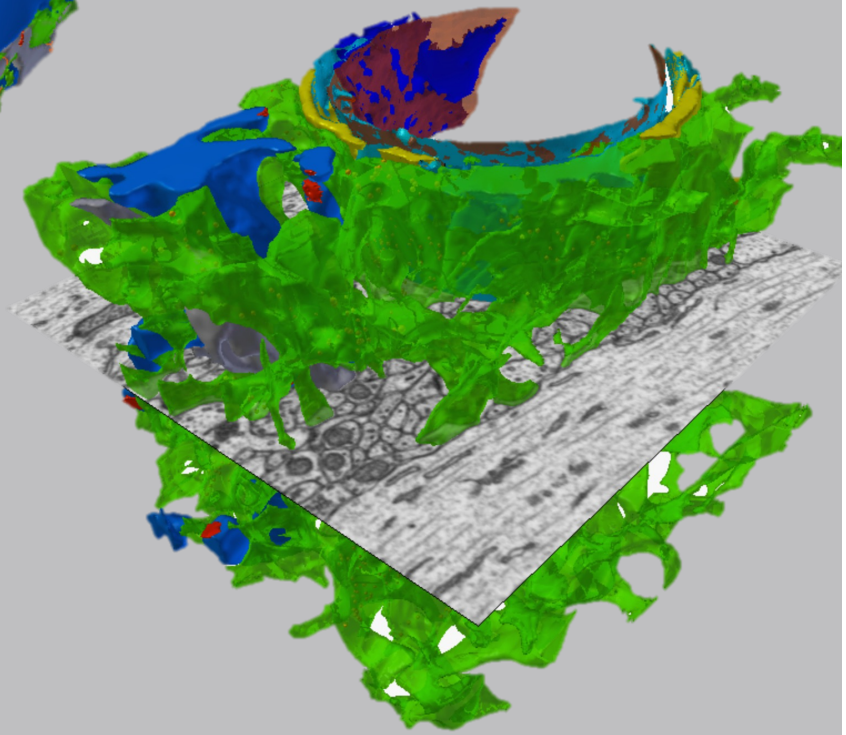
3D reconstruction of an adult mouse hippocampus



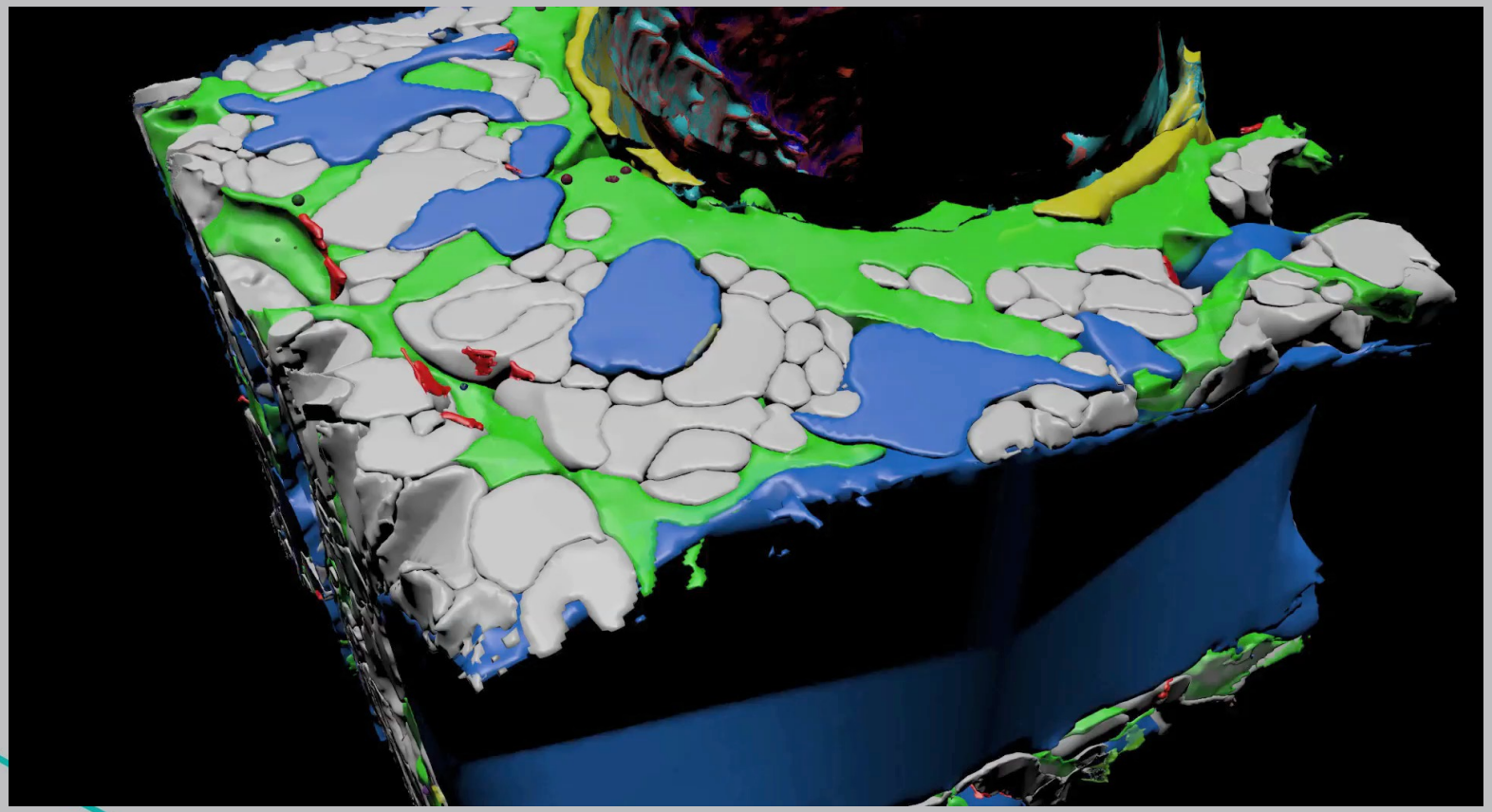


Axon
Dendrite
Synaptic Density
Astrocytic process

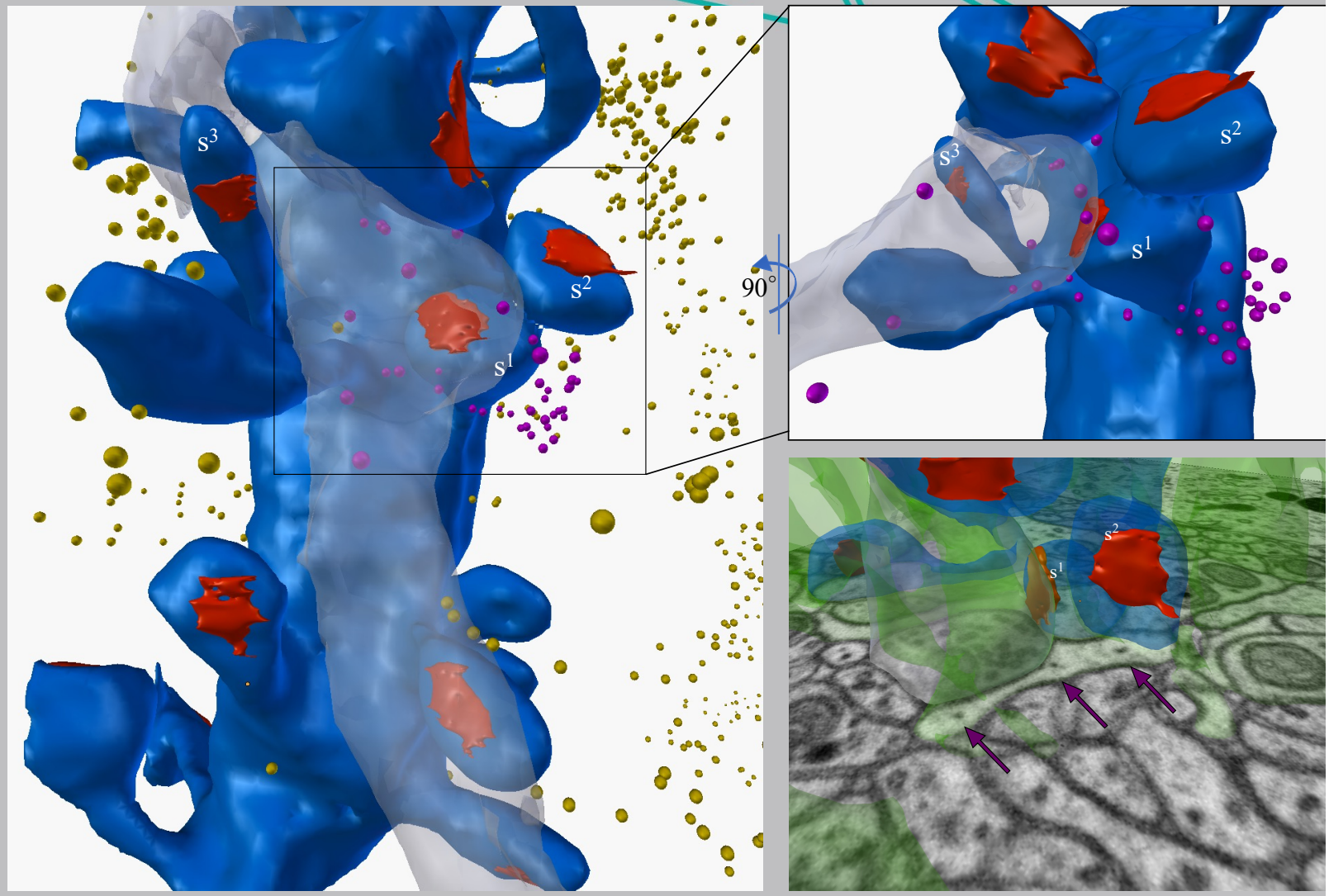




Analysis in a Virtual Reality environment



Example of glycogen clustering around a synapse



REVIEWS

Lactate in the brain: from metabolic end-product to signalling molecule

Pierre J. Magistretti[1,2,3] and Igor Allaman[2]*

Abstract | Lactate in the brain has long been associated with ischaemia; however, more recent evidence shows that it can be found there under physiological conditions. In the brain, lactate is formed predominantly in astrocytes from glucose or glycogen in response to neuronal activity signals. Thus, neurons and astrocytes show tight metabolic coupling. Lactate is transferred between astrocytes and neurons to match the neuronal energetic needs, and to provide signals that modulate neuronal functions, including excitability, plasticity and memory consolidation. In addition, lactate affects several homeostatic functions. Overall, lactate ensures adequate energy supply, modulates neuronal excitability levels and regulates adaptive functions in order to set the 'homeostatic tone' of the nervous system.

Nature Reviews Neuroscience, April;19(4) : 235-249, 2018

Domanda:

Ruolo dell’accopiamento metabolico tra astrociti e neuroni nelle patologie del cervello

Journal of Psychiatric Research 77 (2016) 42–51

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Exercise as a treatment for depression: A meta-analysis adjusting for publication bias

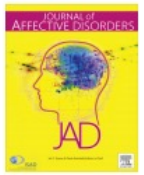
Felipe B. Schuch [a, b, *], Davy Vancampfort [c, d], Justin Richards [e], Simon Rosenbaum [f], Philip B. Ward [f], Brendon Stubbs [g, h]

Journal of Affective Disorders 202 (2016) 67–86

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad



Review article

Exercise as a treatment for depression: A meta-analysis

Siri Kvam [a,*], Catrine Lykkedrang Kleppe [b], Inger Hilde Nordhus [c], Anders Hovland [c,d]

Jean-Luc Martin in 2016 Anthony Carrard

2016

Molecular Psychiatry (2016) 00, 1–8

www.nature.com/mp

ORIGINAL ARTICLE

Peripheral administration of lactate produces antidepressant-like effects

A Carrard[1,4], M Elsayed[2,4], M Margineanu[3], B Boury-Jamot[1,2], L Fragnière[1], EM Meylan[1], J-M Petit[1,2], H Fiumelli[3], PJ Magistretti[1,2,3,5] and J-L Martin[1,5]

Jean-Luc Martin in 1986

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

campus biotech

GliaPharm

Target Glial Cells to Treat Neurons

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Commission for Technology and Innovation CTI

Sylvain Lengacher

Charles Finsterwald

Ambroise Magistretti

GLUT1-DS: A Genetic Model of Brain Hypometabolism

Metabolic monogenic disorder

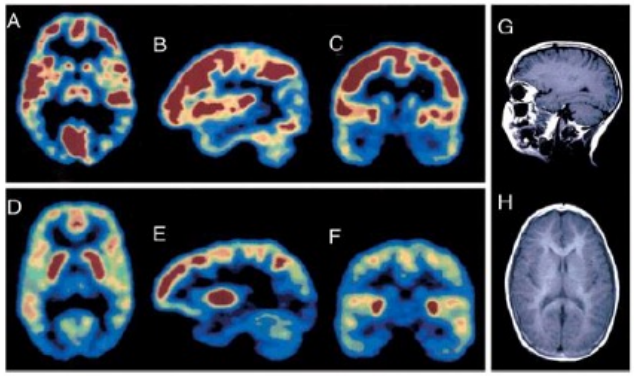
- Deficiency of glucose transporter 1 (GLUT1), described in 1991 by Dr. De Vivo.
- Heterozygous mutation of SLC2A1 gene coding for GLUT1, which is expressed on astrocytes and capillaries (neurons use GLUT3).
- Orphan disorder: incidence of 1.65 to 4.17 in 100,000 births. 130,000 to 328,000 estimated patients worldwide.
- Symptoms: infantile seizures refractory to anticonvulsants, cognitive and motor dysfunctions, developmental delays.
- Currently no efficient treatment.

GLUT1-DS: Hypometabolism is shown by FDG PET and CSF Levels of Glucose and Lactate

FDG PET scan

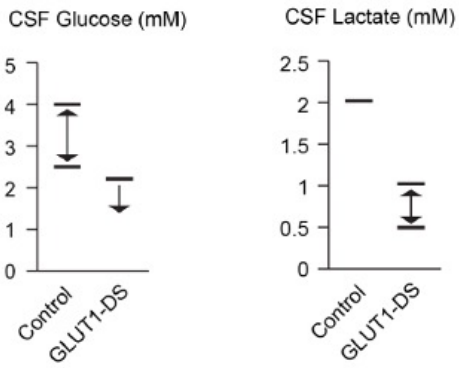
Control subject

GLUT1-DS

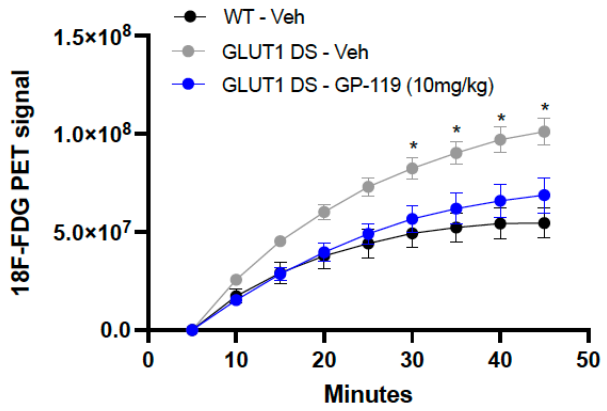


Pascual et al, Ann Neurol, 2002

CSF glucose and lactate levels



GLUT1-DS Mouse Model: Normalization of FDG PET Signal by GP-119

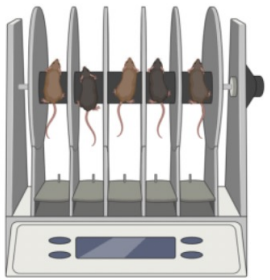


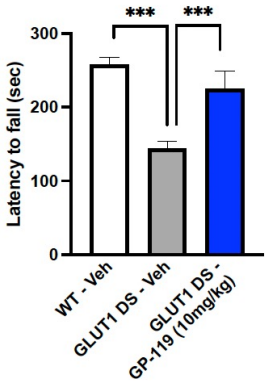
* statistically significant differences

- FDG PET signal to be used as a translational biomarker for target engagement in Phase Ib and subsequent clinical phases.
- Rapid action after oral administration.
- Durability of effect/signal.

GLUT1-DS: Preclinical Candidate GP-57-119 *In Vivo* Efficiency

Rotarod





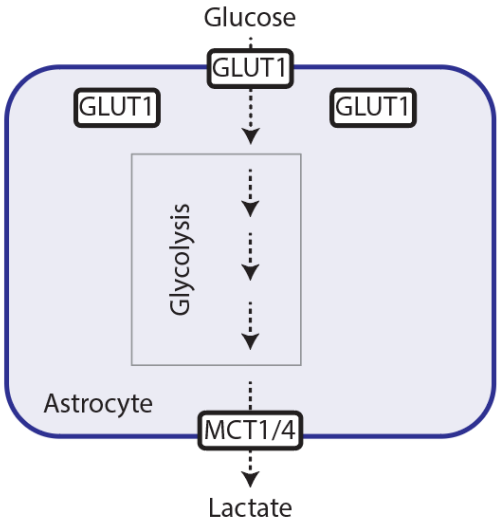
* statistically significant differences

Prof. De Vivo's mouse model of GLUT1-DS: GP-57-119 significantly corrects motor dysfunction in standardized test (rotarod)

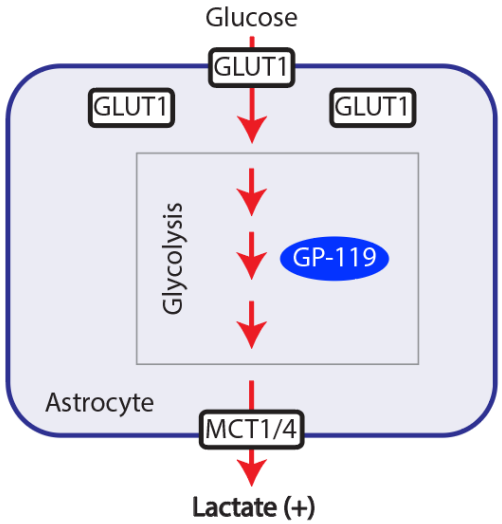
Improving motor coordination on the rotarod reflects potential positive effect on dyskinesias in human patients

GliaPharm's Lead Compound GP-119: Disease-Modifying Mode of Action

1 Astrocyte in pathological hypometabolic state

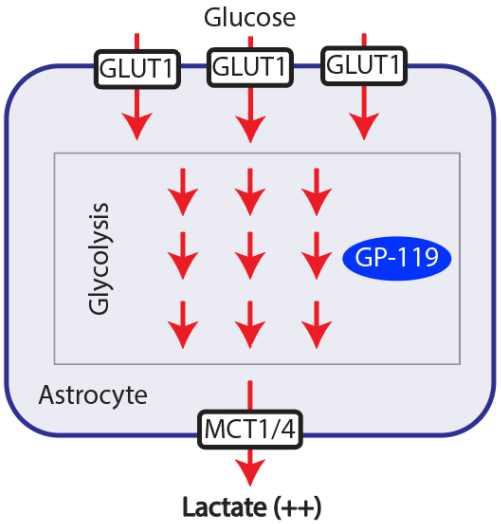


2 Short-term effect: Increased metabolic flux



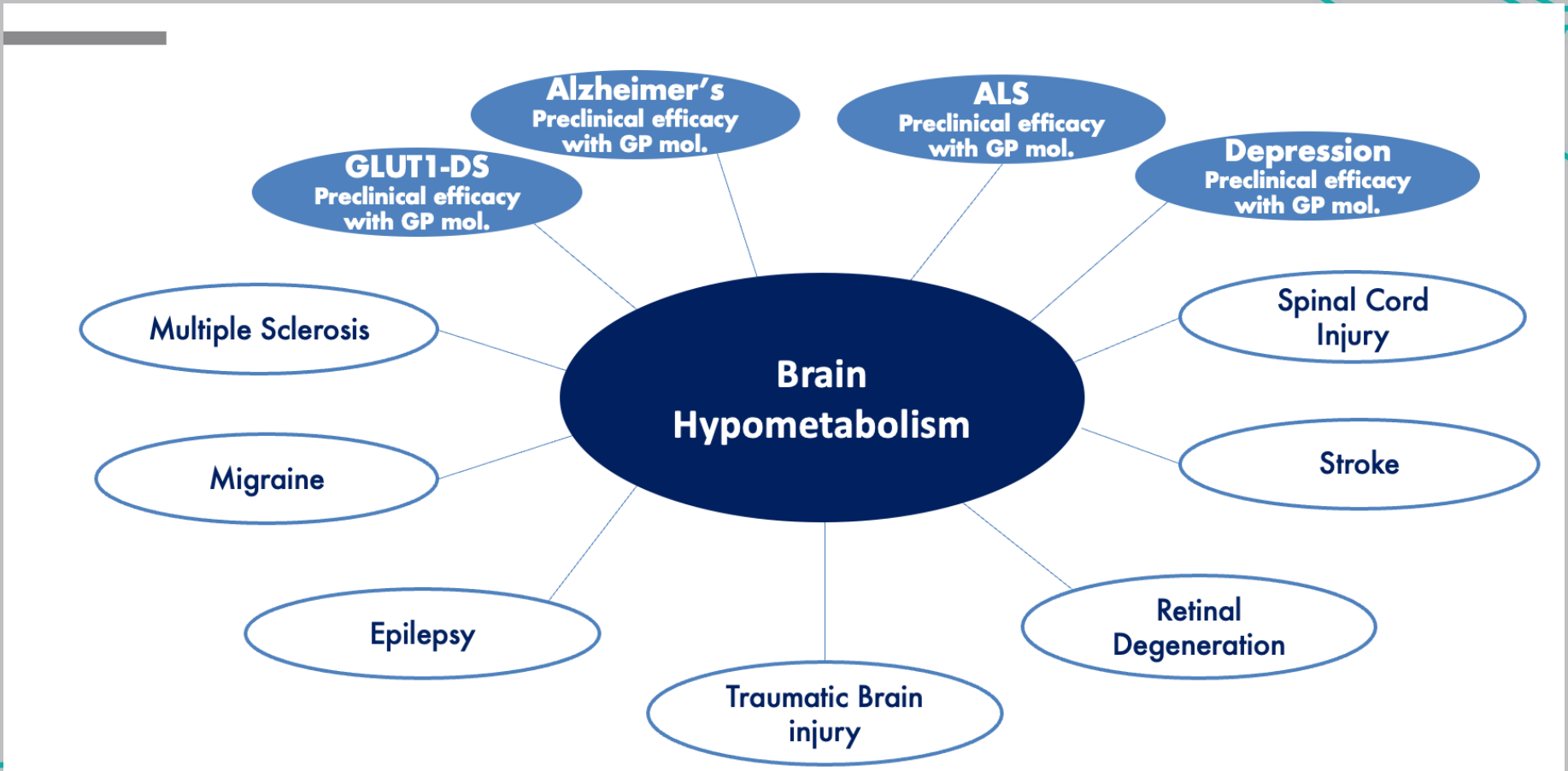
- GP-119 targets an identified **astrocytic glycolytic enzyme**
- GP-119 **stimulates glycolytic flux** in astrocytes
- GP-119 **increases glucose entry** and **lactate release**

3 Long-term effect: Metabolic reprogramming



- GP-119 induces **GLUT1 translocation** to the plasma membrane of both **astrocytes and capillaries**
- GP-119 **upregulates** the expression of astrocytic **glycolytic genes**

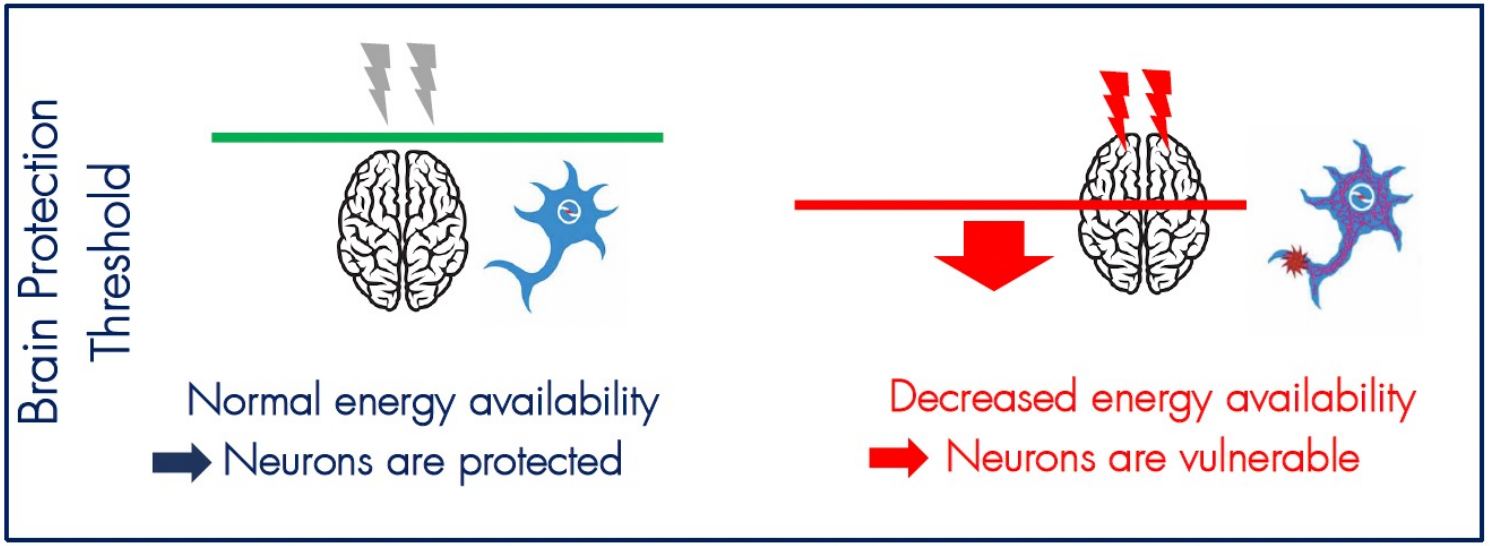
Diseases with identified abnormal brain energy metabolism



Maintaining Brain Energy Metabolism is Key to Brain Health

Normal brain energy metabolism
= Healthy brain

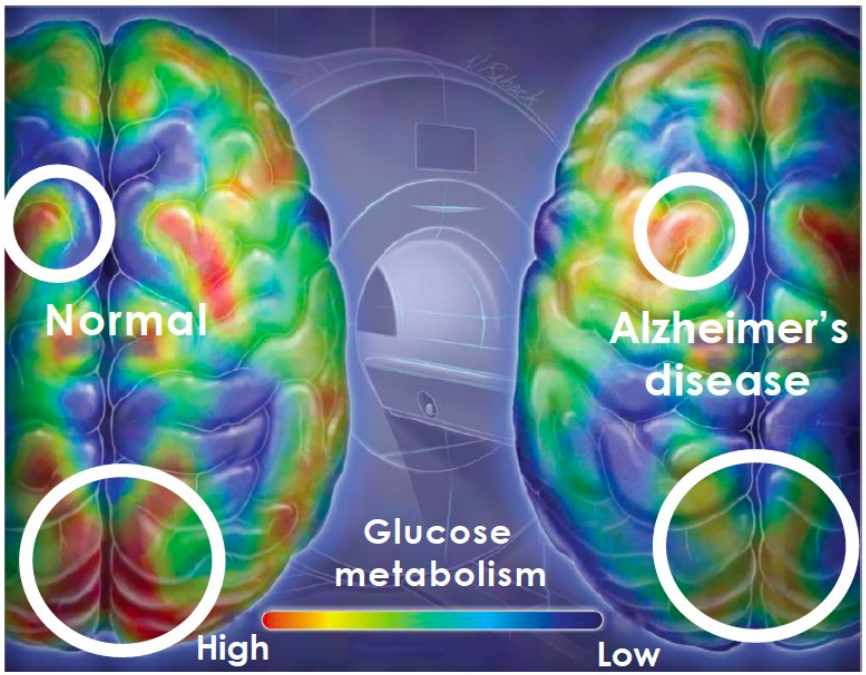
Brain hypometabolism
= Pathological brain



Brain hypometabolism is a significant contributing factor of ageing and neurodegenerative diseases. [1]

[1] Loss of Brain Aerobic Glycolysis in Normal Human Aging. Goyal et al., Cell Metabolism, 2017.

Targeting Brain Hypometabolism in Alzheimer's Disease



Modified from: Kuehn, JAMA, 2020

- Number of patients with Alzheimer's Disease in key markets:
  - US: 7.2M, EU: 19.5M and Japan: 5.2M
- Peak sales estimated to be USD 12B per year in US, EU and Japan combined.
- Abundant literature indicates **significantly reduced rates of glucose metabolism** in subjects with AD. [1-3]
- Brain hypometabolism is observed already **in pre-symptomatic state and correlates with primary risk factors** of AD: ageing and ApoE4 genotype (strongest genetic risk factor for AD). [4]

[1] In Alzheimer's Research, Glucose Metabolism Moves to Center Stage. Kuehn, JAMA, 2020
[2] Astrocyte contribution to dysfunction, risk and progression in neurodegenerative disorders. Allen, Nature Reviews Neuroscience, 2022
[3] Brain Energy Rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing. Cunnane et al., Nature Reviews Drug Discovery, 2020
[4] Correlations between apolipoprotein E4 gene dose and brain-imaging measurements of regional hypometabolism. Reiman et al., PNAS, 2005

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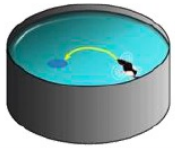
Memory Deficit is Restored in Old Mice with GP-119 (Lead Compound)

Morris Water Maze



Distance to reach the platform (1 day after training)

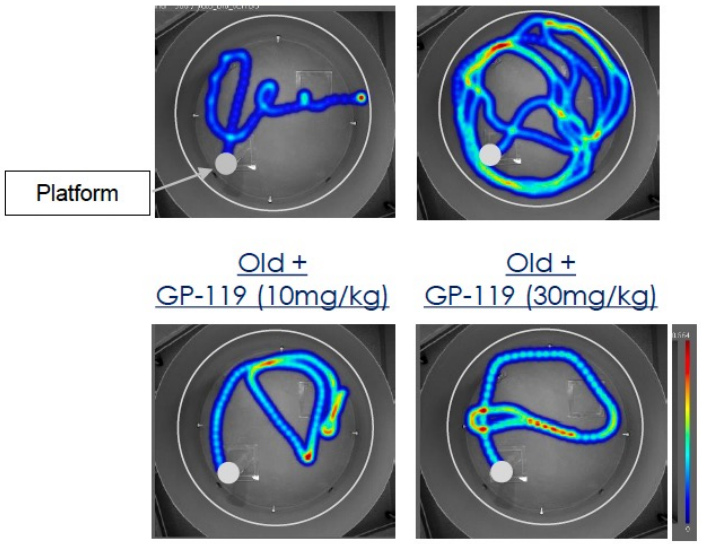
Young + Veh

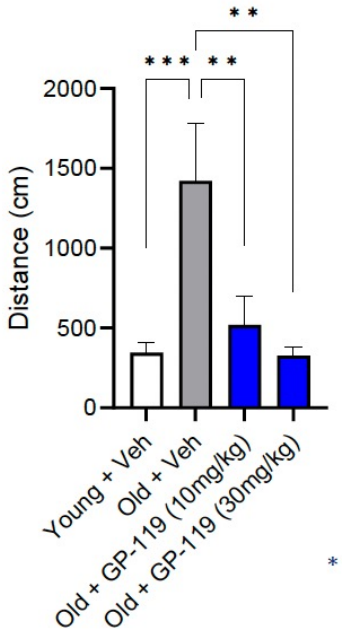
Old + Veh

Platform

Old + GP-119 (10mg/kg)

Old + GP-119 (30mg/kg)





* statistically significant differences

Short distance to reach the platform = better memory performance

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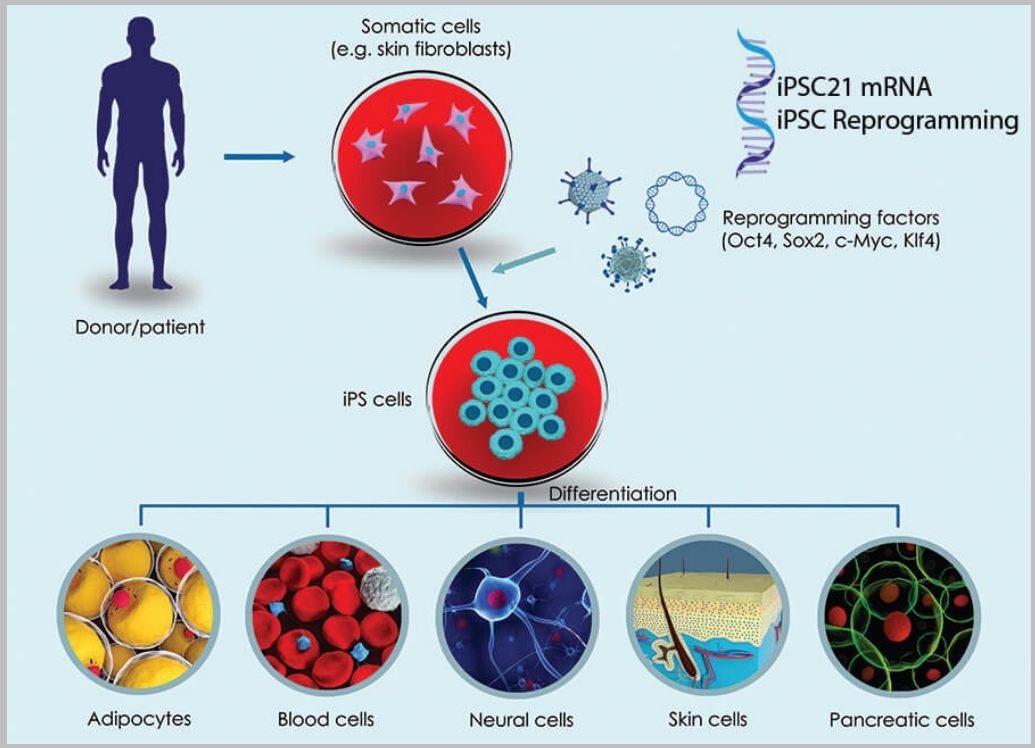
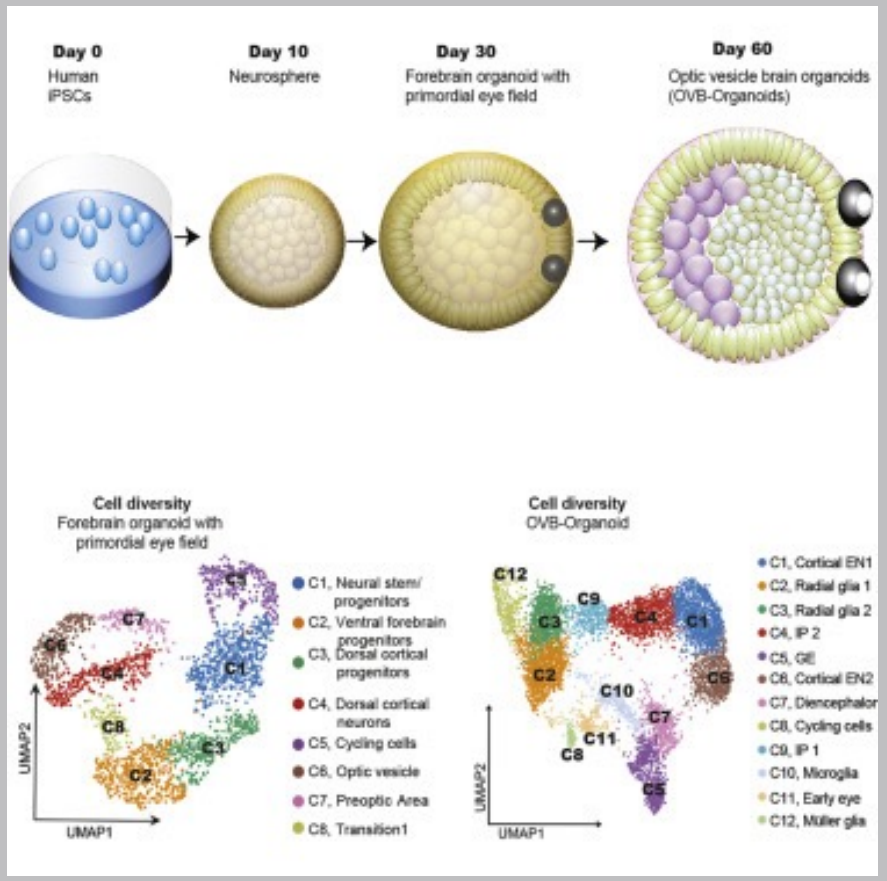
IPSC : Cellule Staminali Pluripotenti Induttibili



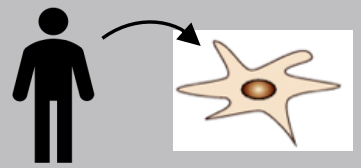
Organoidi cerebrali



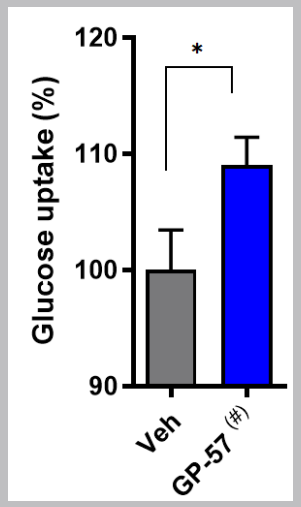
Alzheimer's Disease: *In Vitro* Efficacy (GP-57) [(#)]

Glucose uptake and lactate release are increased by GP-57 [(#)] in astrocytes from an APOE4(+) Alzheimer's patient

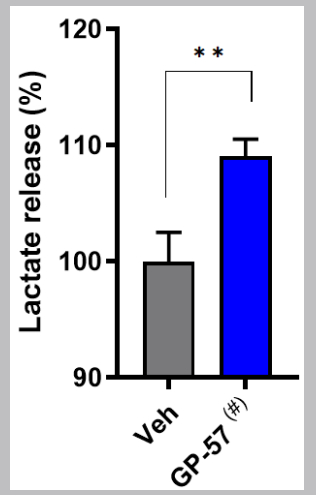
Human induced-pluripotent stem cells (iPSCs)-derived astrocytes



Glucose uptake



Lactate release



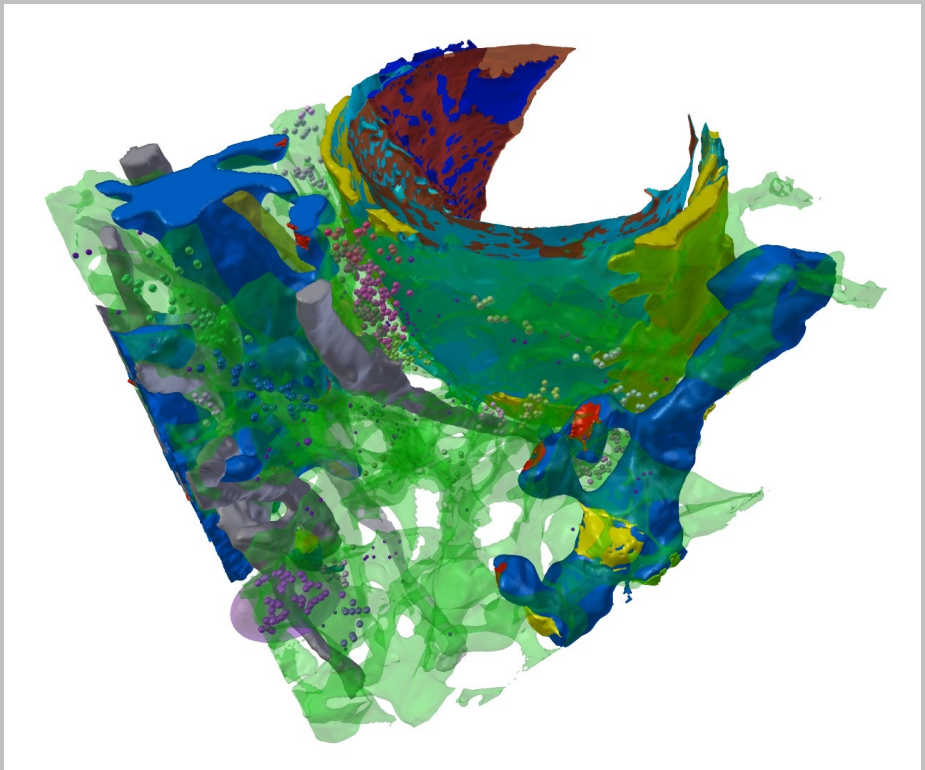
* p<0.05, ** p<0.01 (n=4-6)

[(#)] GP-57 is the tool compound from which GP-119 has been optimized

Glucose uptake and Lactate release are enhanced by GP-57 in human iPSCs-derived astrocytes from an Alzheimer's disease patient carrying APOE4 allele (hypometabolic hallmark)

Glycogen ➡ Astrocytes ➡ Lactate ➡ Plasticity

- ➡ Plasticity, Memory
- ➡ Neuroprotection



A 40 year journey

100 + collaborators over the years

Laboratory of Cellular Imaging and Energetics KAUST

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Arnaud Tauffenberger*

Fathia Ben Rached
Farah Shama
Reem Alkhater
Nadia Steiner
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Eleonora Curzi
Xiaoyan Lin
Ohood Alzahrani

Salam Almustafa
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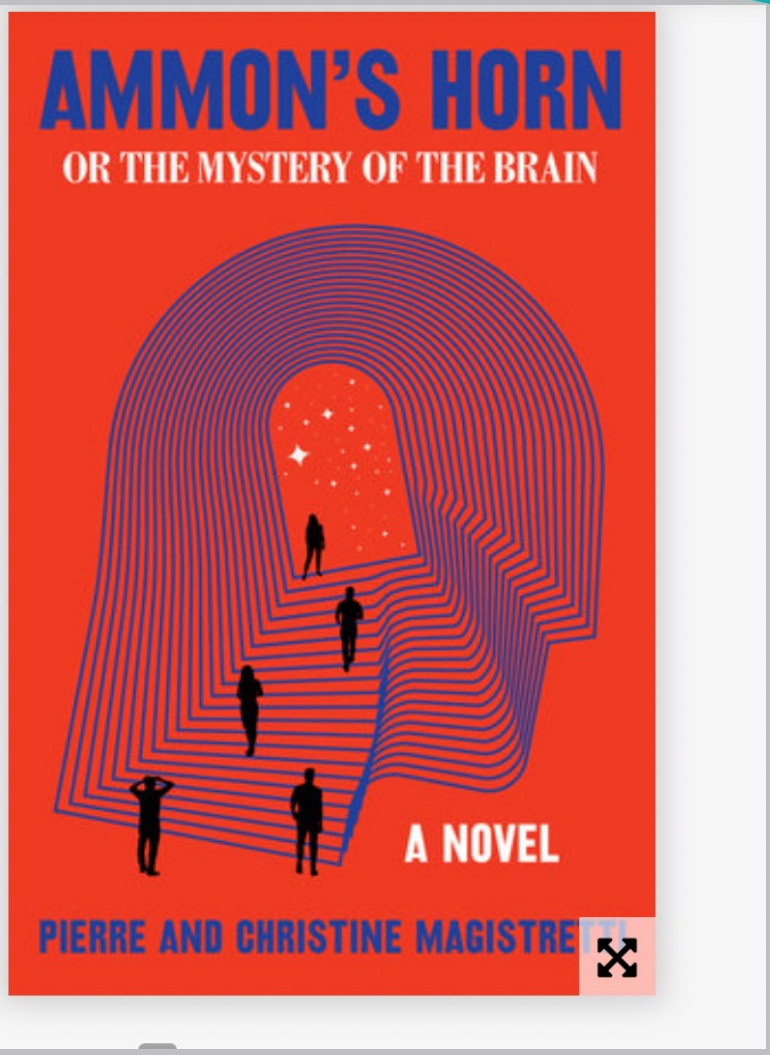
Sultan Albalawi


AMMON'S HORN
OR THE MYSTERY OF THE BRAIN
A NOVEL
PIERRE AND CHRISTINE MAGISTRETTI