



**Pierre J. Magistretti, MD, PhD**

Division of Biological and Environmental Sciences and Engineering, KAUST  
Department of Psychiatry, University of Lausanne  
Brain Mind Institute, EPFL

**Neuron-glia metabolic coupling  
mediated by lactate:  
Role in plasticity and pathology**

---

**Beyond the Symptom : The Biology of Fatigue Workshop  
Virtual Meeting, NINDS  
September 27-28 2021**

# The brain has considerable energetic requirements

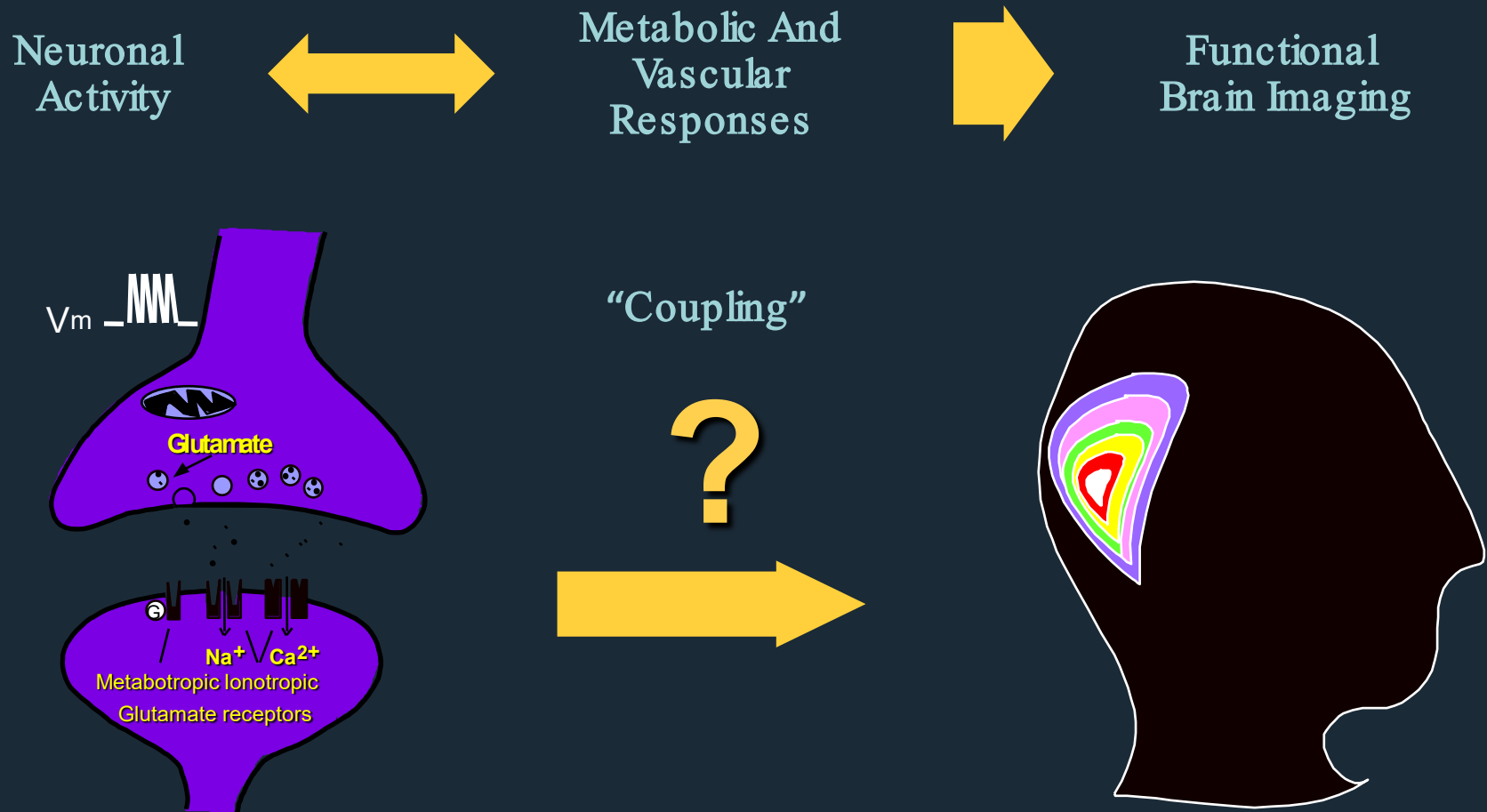
---

- 2% of body mass
- yet
- 15% of cardiac output
- 25% of whole body glucose utilization
- 20% of oxygen consumption



# Which are the cellular and molecular mechanisms that underlie the coupling of synaptic activity with metabolic and vascular responses?

---





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.

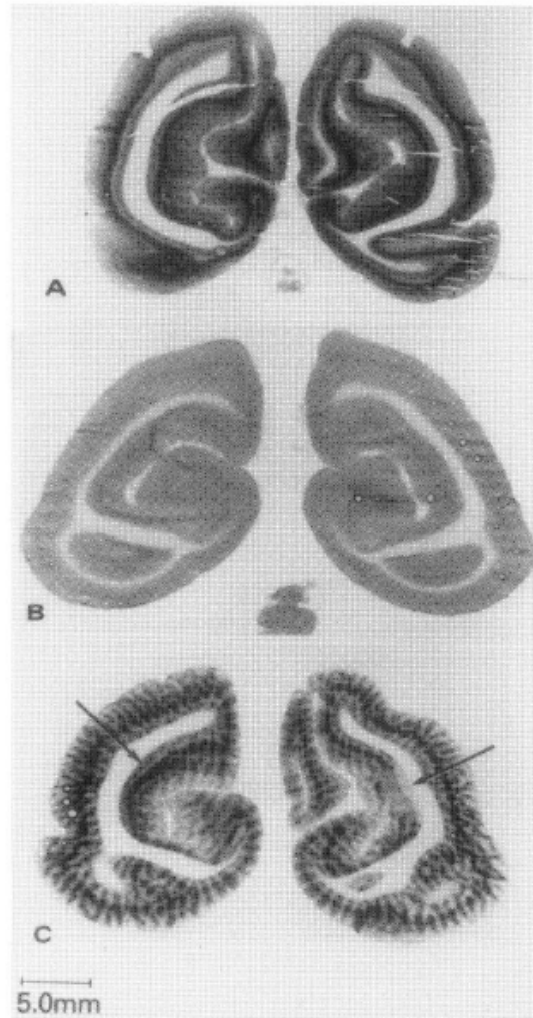
*From the Cambridge Pathological Laboratory.*

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.*

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

## **Energetics of Functional Activation in Neural Tissues\***

**Louis Sokoloff<sup>1,2</sup>**



# Which are the cellular and molecular mechanisms that underlie the coupling of synaptic activity with metabolic responses?

.....

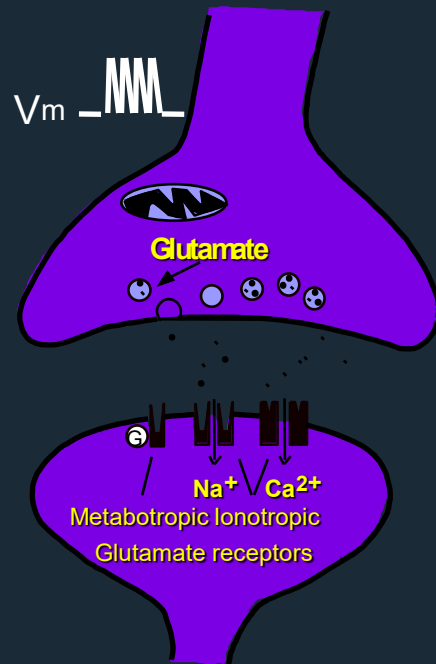
Neuronal  
Activity



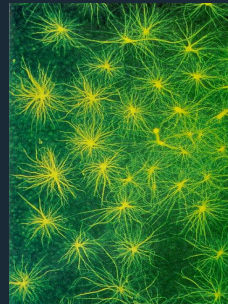
Metabolic  
Responses



- Functional Imaging
- Synaptic function



Coupling

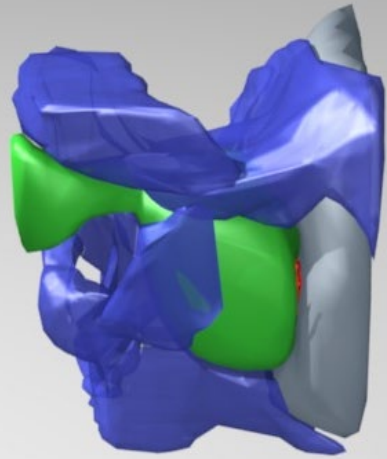


Astrocytes

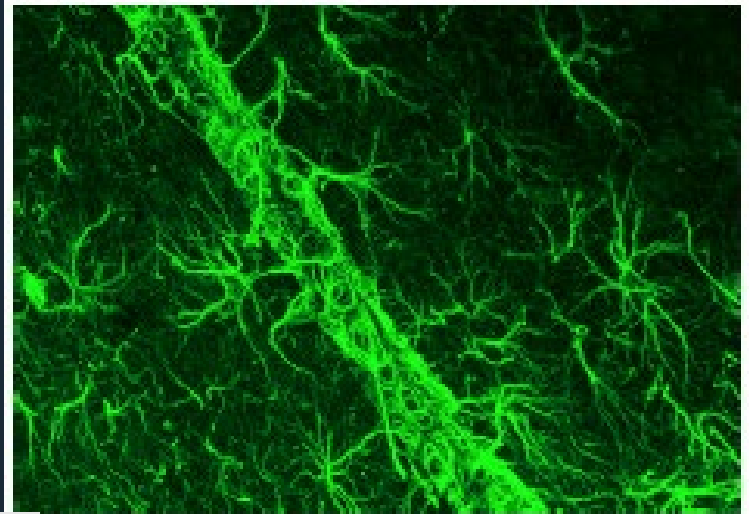


- Neuroenergetics
- Neuronal plasticity
- Disease

# Cytological features of astrocytes



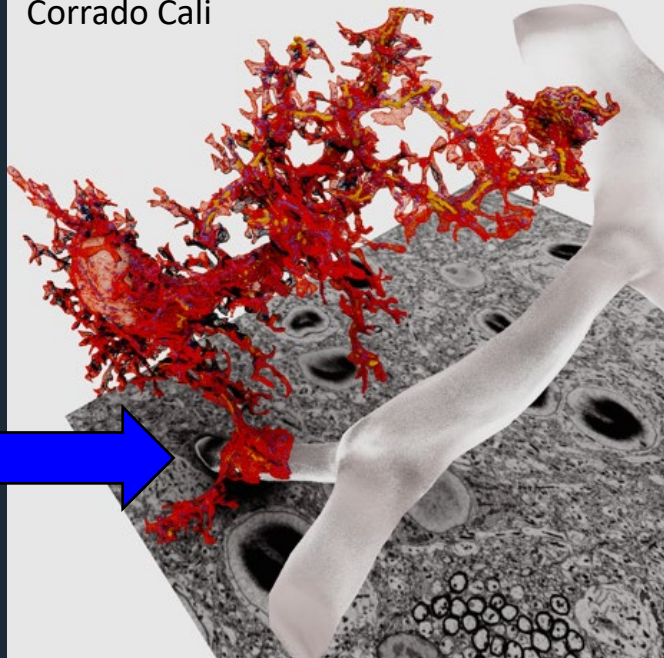
Graham Knott



Gilles Bonvento, URA CEA CNRS 2210, Orsay, France

*Lamellar profiles around  
synapse*

Corrado Cali

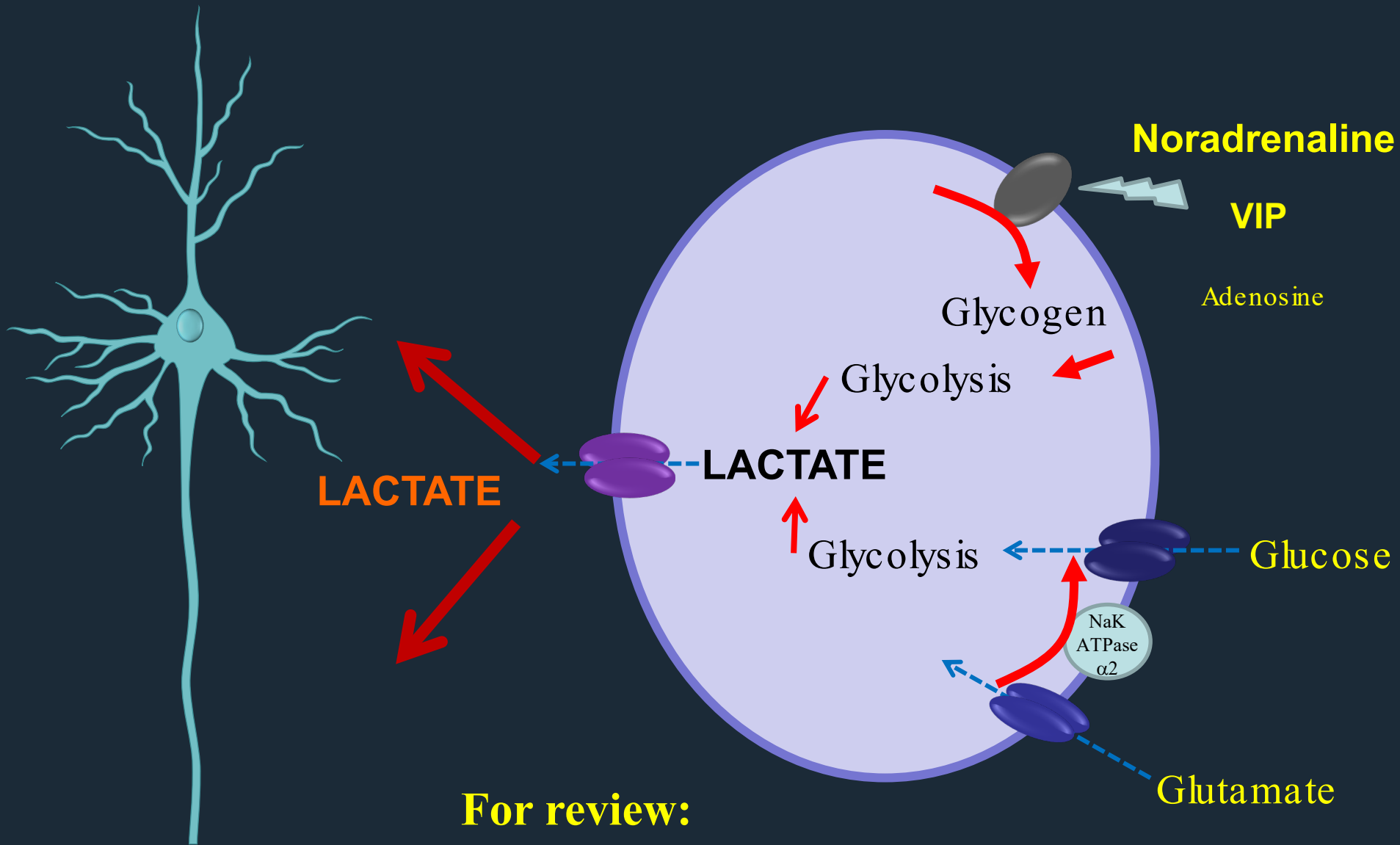


*Astrocyte end-foot on capillary*

*End-feet around capillaries*

**Neuron**

**Astrocyte**



**For review:**

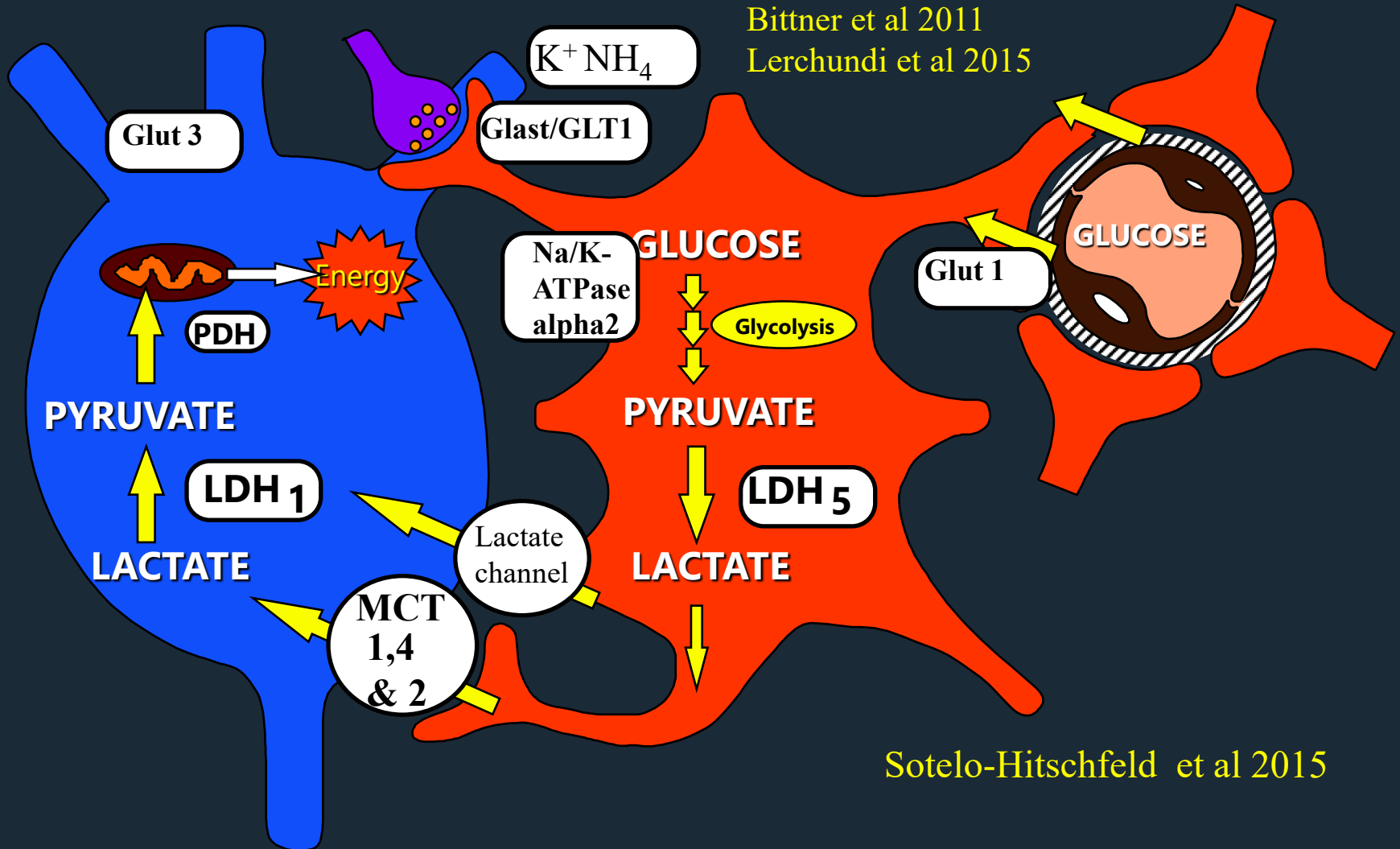
**Magistretti and Allaman, Neuron, 2015**

**Magistretti and Allaman, Nature Rev Neurosci, 2018**



# Astrocyte-Neuron Lactate Shuttle (ANLS)

Bittner et al 2011  
Lerchundi et al 2015



Sotelo-Hitschfeld et al 2015

Neurons are mainly oxidative

Astrocytes are mainly glycolytic

# Which are the cellular and molecular mechanisms that underlie the coupling of synaptic activity with metabolic responses?

.....

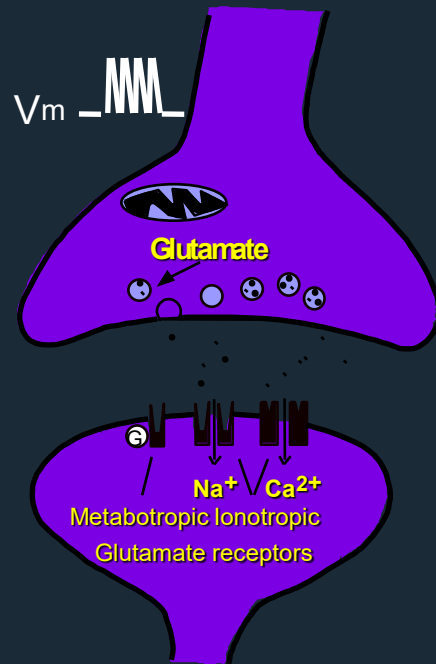
Neuronal  
Activity



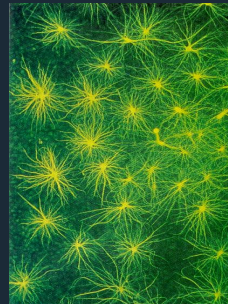
Metabolic  
Responses



- Functional Imaging
- Synaptic function



Coupling



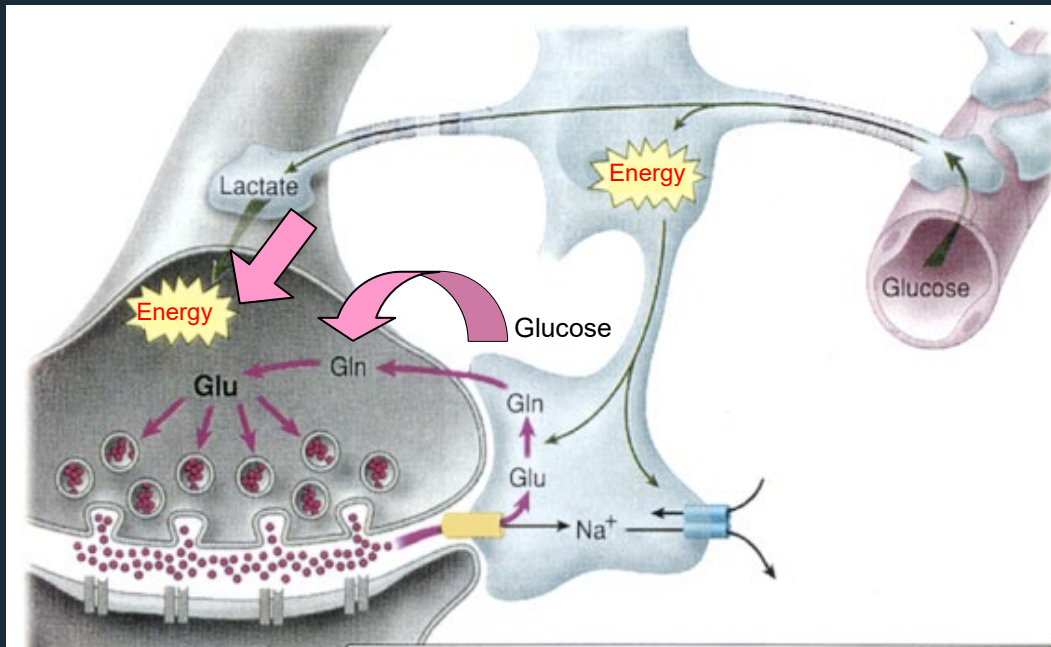
Astrocytes



- Neuroenergetics
- Neuronal plasticity
- Disease

# Metabolic Plasticity

Is the metabolic coupling between astrocytes and neurons subject to plasticity ?



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

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



**Cristina Alberini**



# Summary

---

1. Lactate is released with IA training in the hippocampus
2. Blocking glycogenolysis blocks both memory retention and lactate release, as well as molecular changes known to underlie long-term plasticity and memory formation and LTP.
3. Transport of lactate from astrocytes to neurons is required for memory consolidation.



**Glycogenolysis and astrocyte-neuron  
lactate shuttling are required  
for long-term memory formation.**

Question:

Is lactate necessary for extra  
energetic demands linked  
to plasticity or is it also  
**a regulatory signal for plasticity ?**

---

“However, glucose is much less efficient in rescuing the amnesia caused by DAB and its effect is transient, indicating that the end mechanisms of lactate or glucose might be different or at least have different kinetics.”

(Suzuki et al, Cell 2011)

# A role of lactate in neuronal plasticity processes

---

- L-lactate stimulates in a time and concentration-dependent manner the expression of the plasticity-related genes Arc, Zif268 and c-Fos (mRNA and protein) in primary cultures of cortical neurons.
- Intracortical injections of L-lactate similarly induce Arc, Zif268 and c-Fos expression
- This effect is mediated by NMDA receptors activation (MK 801, Glycine site) and it involves the Erk 1/2 signalling pathway
- L-lactate potentiates glutamate-evoked currents and increases in intracellular calcium
- Increases NADH/NAD ratio are involved in the effect of L-lactate
- **Lactate acts a signalling molecule and not only as an energy substrate**

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

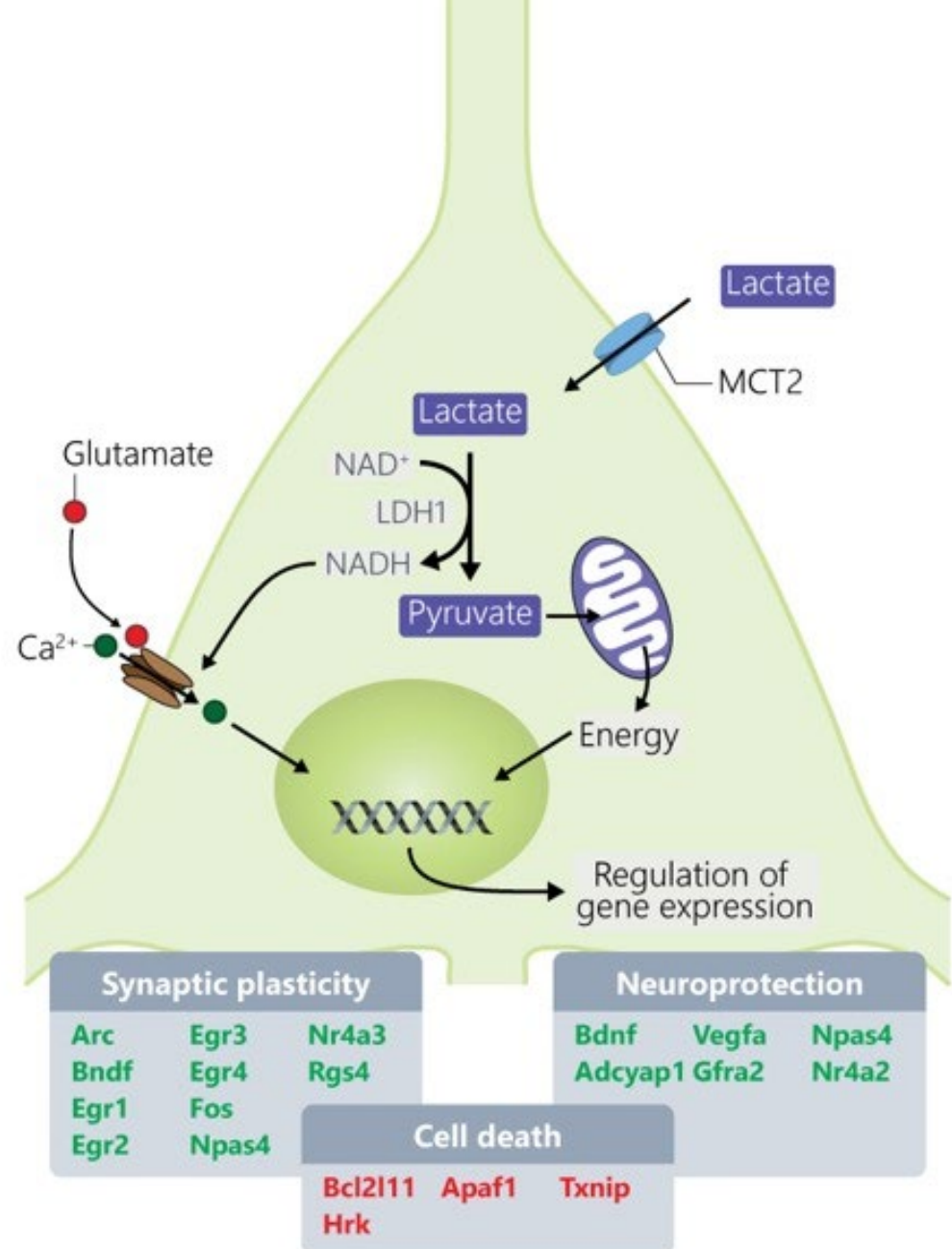


Michael Margineanu



Hubert Fiumelli

Margineanu et al, *Front in Neurosci*, 2018





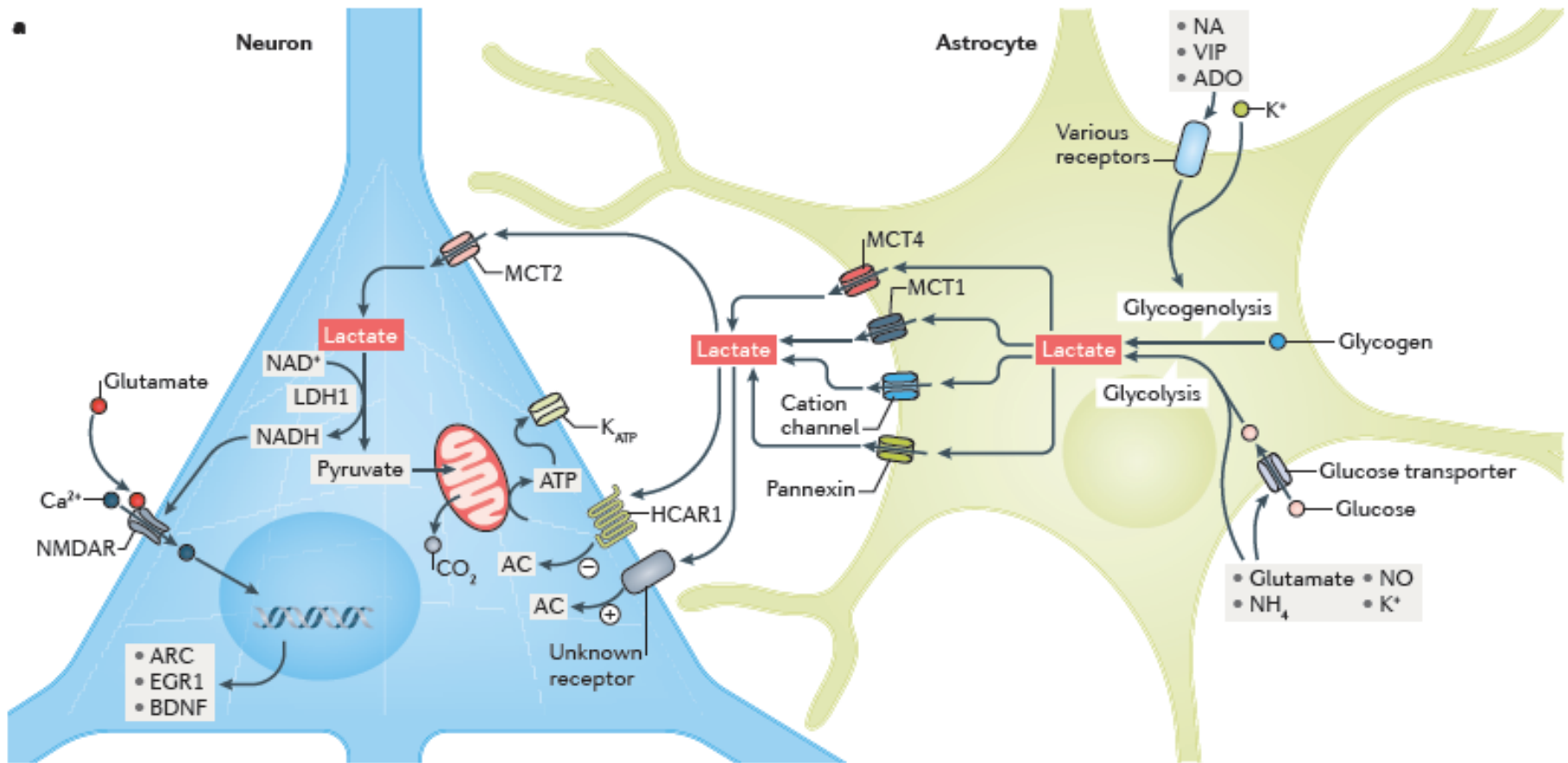
# REVIEWS

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

*Pierre J. Magistretti<sup>1,2,3\*</sup> and Igor Allaman<sup>2</sup>*

**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.

# Lactate-mediated metabolic coupling and signaling between astrocytes and neurons



# Which are the cellular and molecular mechanisms that underlie the coupling of synaptic activity with metabolic responses?

.....

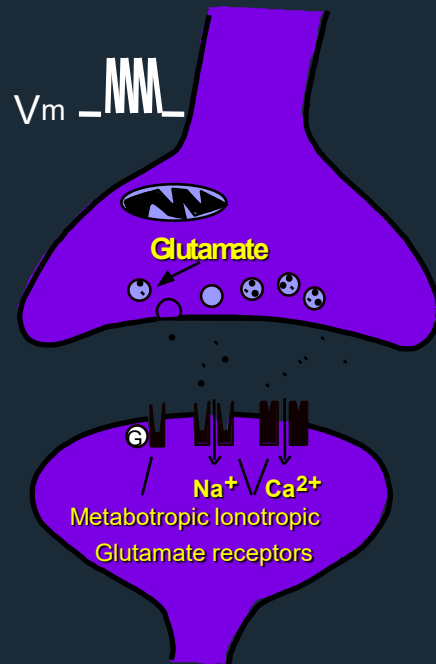
Neuronal  
Activity



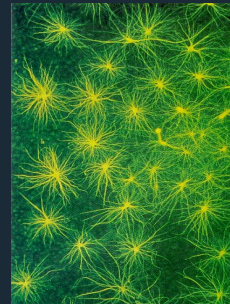
Metabolic  
Responses



- Functional Imaging
- Synaptic function



Coupling



Astrocytes



- Neuroenergetics
- Neuronal plasticity
- Disease

OPEN

Molecular Psychiatry (2016) 00, 1–8

[www.nature.com/mp](http://www.nature.com/mp)

## ORIGINAL ARTICLE

# Peripheral administration of lactate produces antidepressant-like effects

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



Jean-Luc Martin



Anthony Carrard



Peripheral administration of L-lactate produces antidepressant-like effects in different animal models of depression that respond to acute and chronic antidepressant treatment (AFST, OSFST, chronic corticosterone).

The antidepressant-like effects of L-lactate are associated with increases in hippocampal lactate levels and with changes in the expression of target genes involved in :

- serotonin receptor trafficking (p11)
- astrocyte functions (S 100 $\beta$ )
- neurogenesis (Hes 5)
- NO synthesis (NOS 1)
- cAMP signaling ( PDE4D)



Molecular Psychiatry

<https://doi.org/10.1038/s41380-021-01122-0>

ARTICLE



# Role of adult hippocampal neurogenesis in the antidepressant actions of lactate

Anthony Carrard<sup>1</sup> • Frédéric Cassé <sup>1</sup> • Charline Carron<sup>1</sup> • Sophie Burlet-Godinot<sup>1</sup> • Nicolas Toni<sup>1</sup> • Pierre J. Magistretti<sup>1,2</sup> • Jean-Luc Martin <sup>1,3</sup>

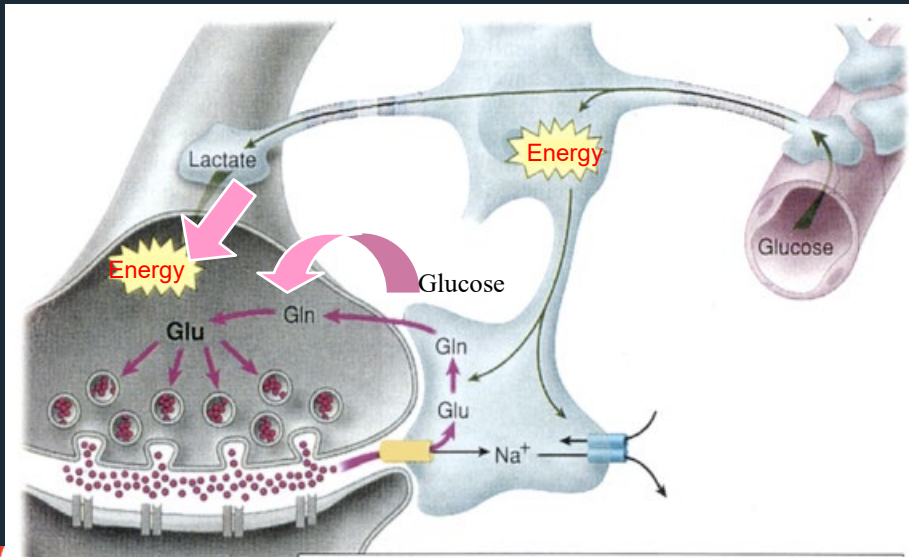
Received: 13 May 2020 / Revised: 1 April 2021 / Accepted: 13 April 2021

© The Author(s) 2021. This article is published with open access

# METABOLIC PLASTICITY

**Is the metabolic coupling between astrocytes and neurons subject to plasticity ?**

**→ Sleep/wake cycle**



# Genes Related to “Astrocyte-Neuron Lactate Shuttle” are Up-regulated in Astrocytes-enriched Cell Fraction Following Sleep Deprivation

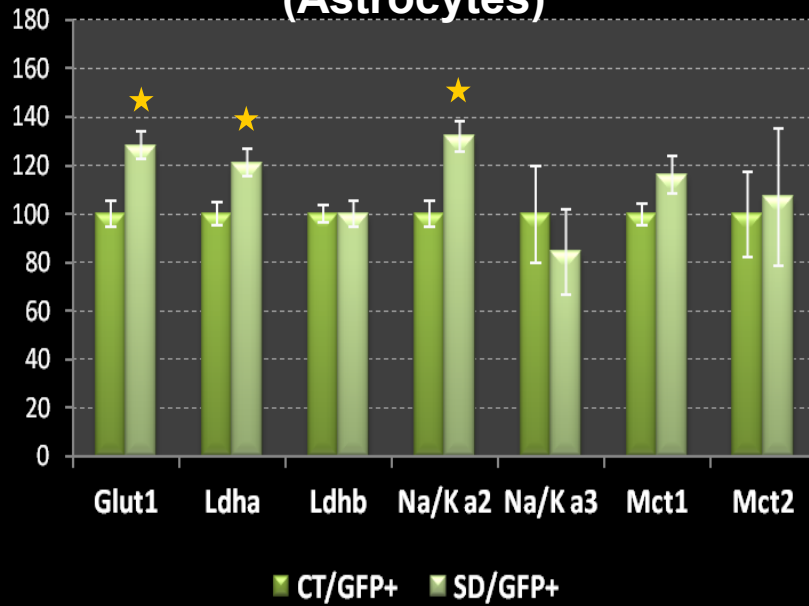
*FVB-Tg(GFAP-GFP)mice*  
*P25-P28*

Acute Sleep Deprivation

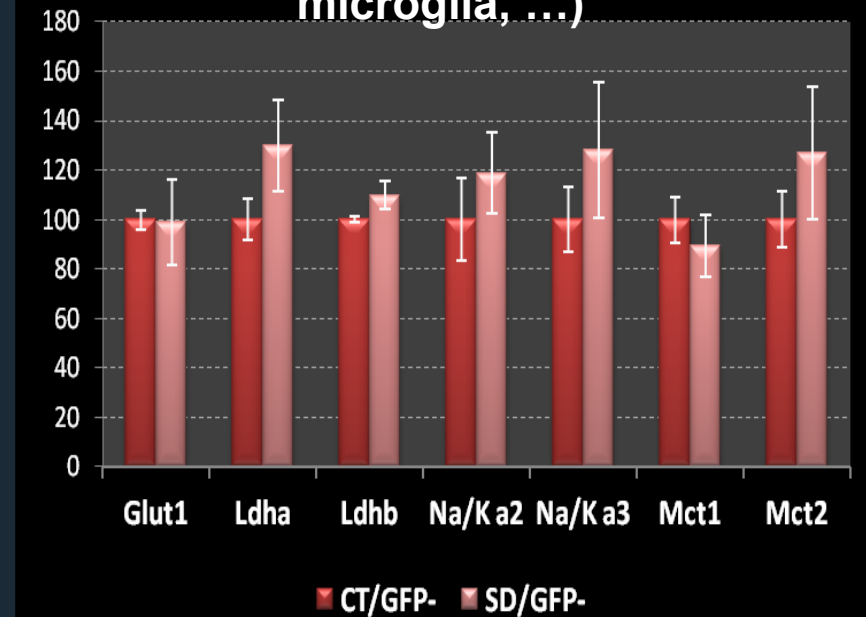
Cortical dissection  
and tissue  
disruption

Cell  
sorting

GFP-positive cells  
(Astrocytes)



GFP-negative cells  
(Neurons, oligodendrocytes,  
microglia, ...)





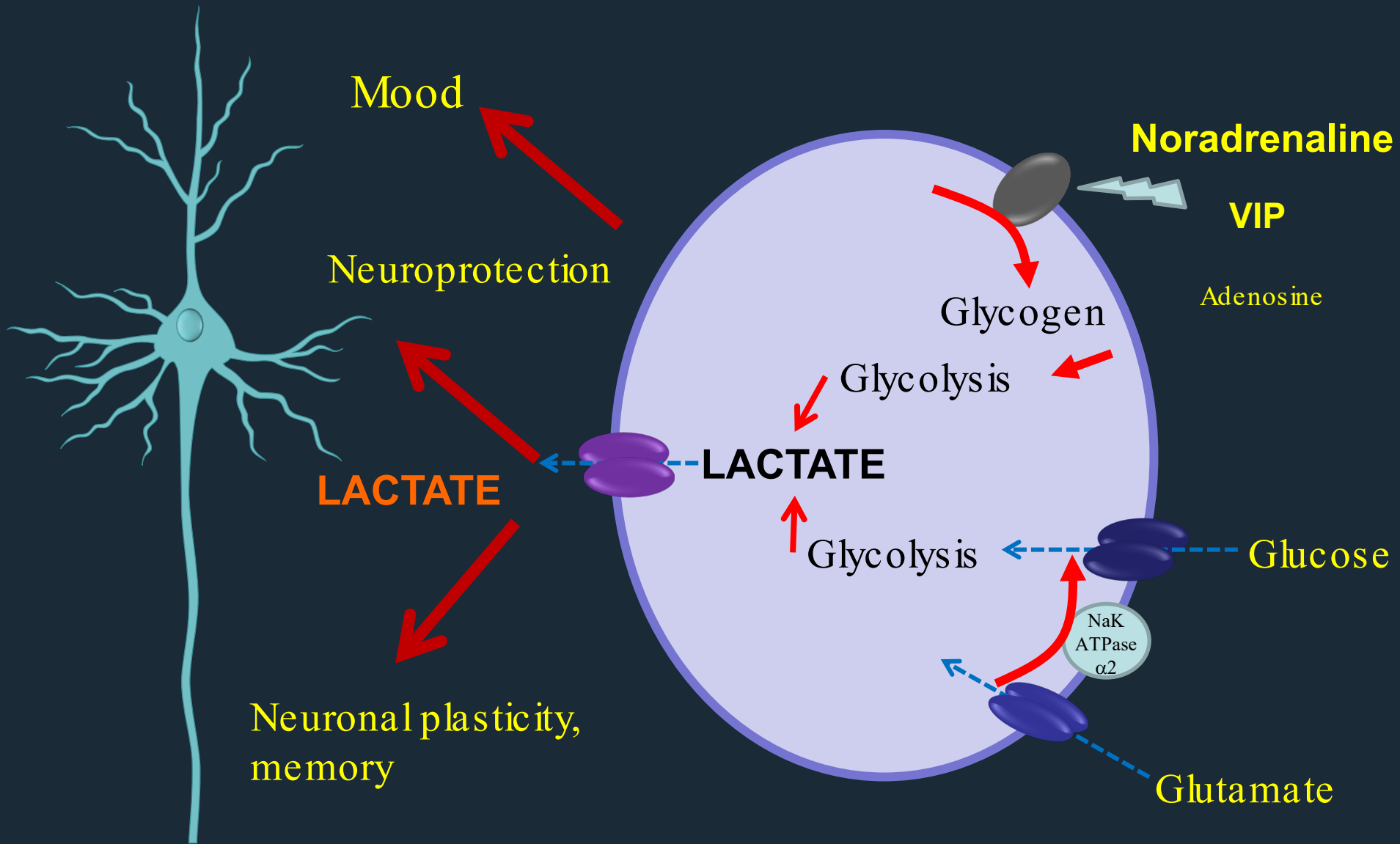
## *Conclusion (II)*

These results indicate that :

- ❖ The transcriptional phenotype induced by sleep deprivation observed for glycogen metabolism also involves genes related to the “Astrocyte-Neuron Lactate Shuttle”.
- ➔ *The astrocytes likely adapt their energy metabolism pathways to maintain the neuro-metabolic coupling challenged by the sleep deprivation.*

# Neuron

# Astrocyte



**EPFL**

Igor Allam

Jean-Marie Petit

Monika Tadi

Gabriele Grenningloh

Sylvain Lengacher

Jiangyan Yang

Charles Finsterwald

**CHUV - Psychiatry**

Jean-Luc Martin

Anthony Carrard

Benjamin Boutrel

Benjamin Boury-Jamot

Pascal Jourdain

Pierre Marquet

Kaspar Rothenfusser

**KAUST**

Hubert Fiumelli

Corrado Cali

Heikki Levashlaio

Michael Margineanu

Fouad Lemtiri

**NYU**

Cristina Alberini

Sarah Stern

Akinobu Suzuki

**CHUV – Neurology**

Lorenz Hirt

Carole Berthet

**University of Zurich**

Bruno Weber

**Centro de Estudios Cientificos, Valdivia**

Felipe Barros

**Blue Brain Project**

Henry Markram

Felix Schürmann

Jay Coggan

Daniel Keller

**CERN - UNIGE**

Renaud Jolivet