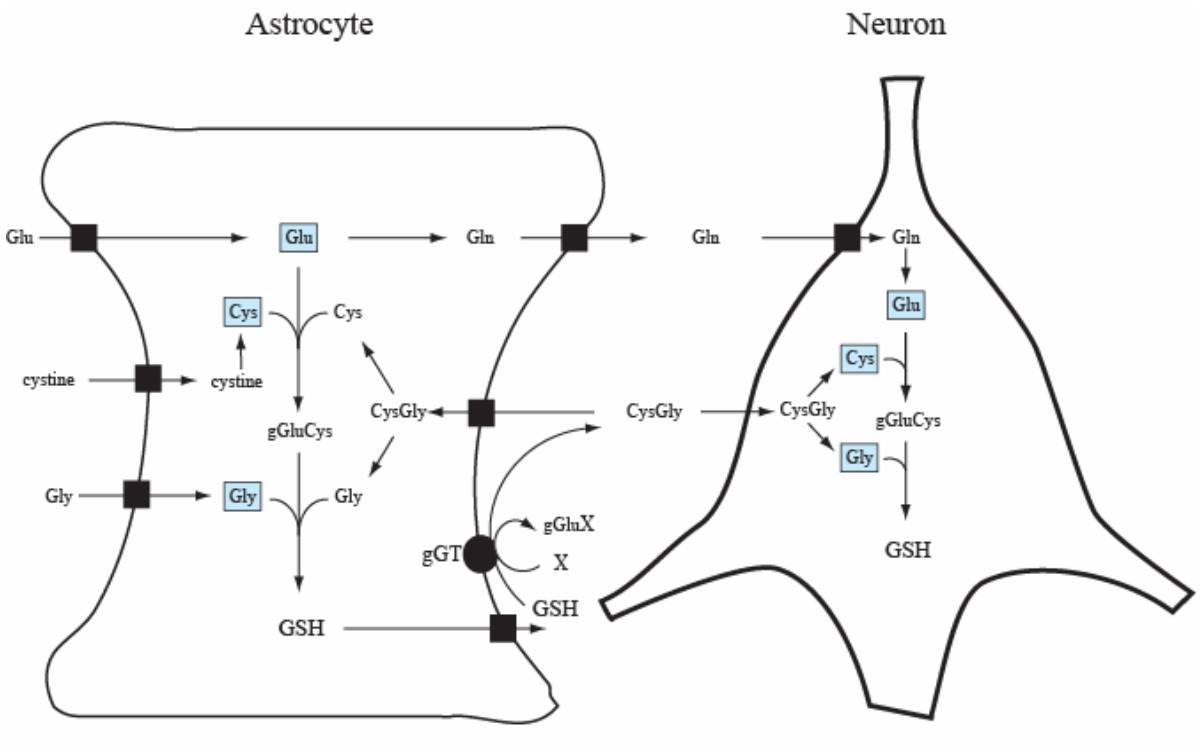
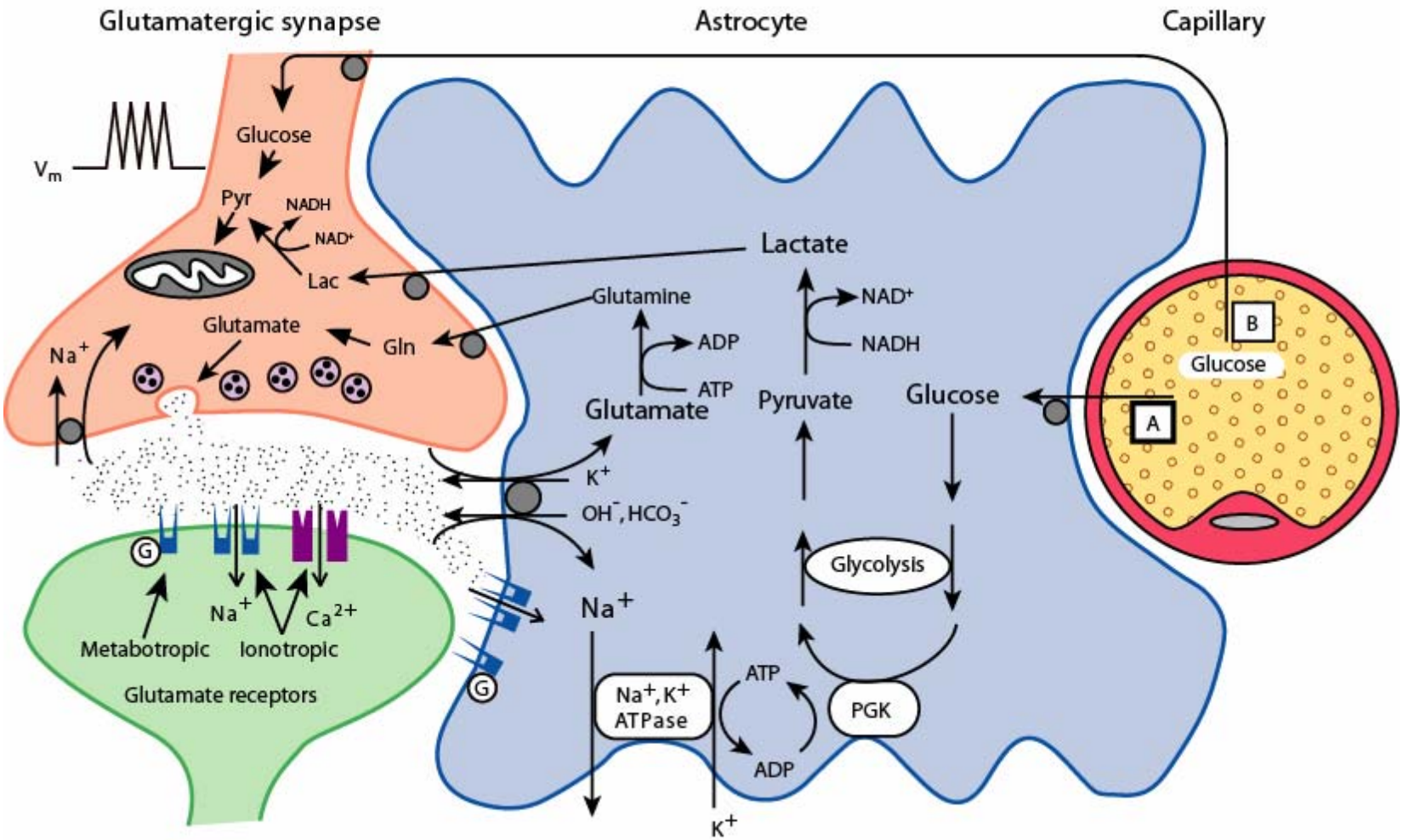
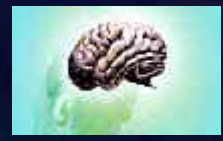
Couplage métabolique neurone-glie dans la synthèse du glutathion




Glutamatergic synapse
Astrocyte
Capillary
V_m
Glucose
Pyr
NADH
NAD+
Lac
Lactate
Glutamine
ADP
ATP
Glutamate
Pyruvate
NAD+
NADH
Glucose
B
Glucose
A
Na+
Glutamate
Gln
K+
OH-, HCO3-
G
Na+
Ca2+
Metabotropic
Ionotropic
Glutamate receptors
Glycolysis
Na+
Na+, K+ ATPase
ATP
ADP
PGK
K+

Main Metabolic Pathways of Glucose



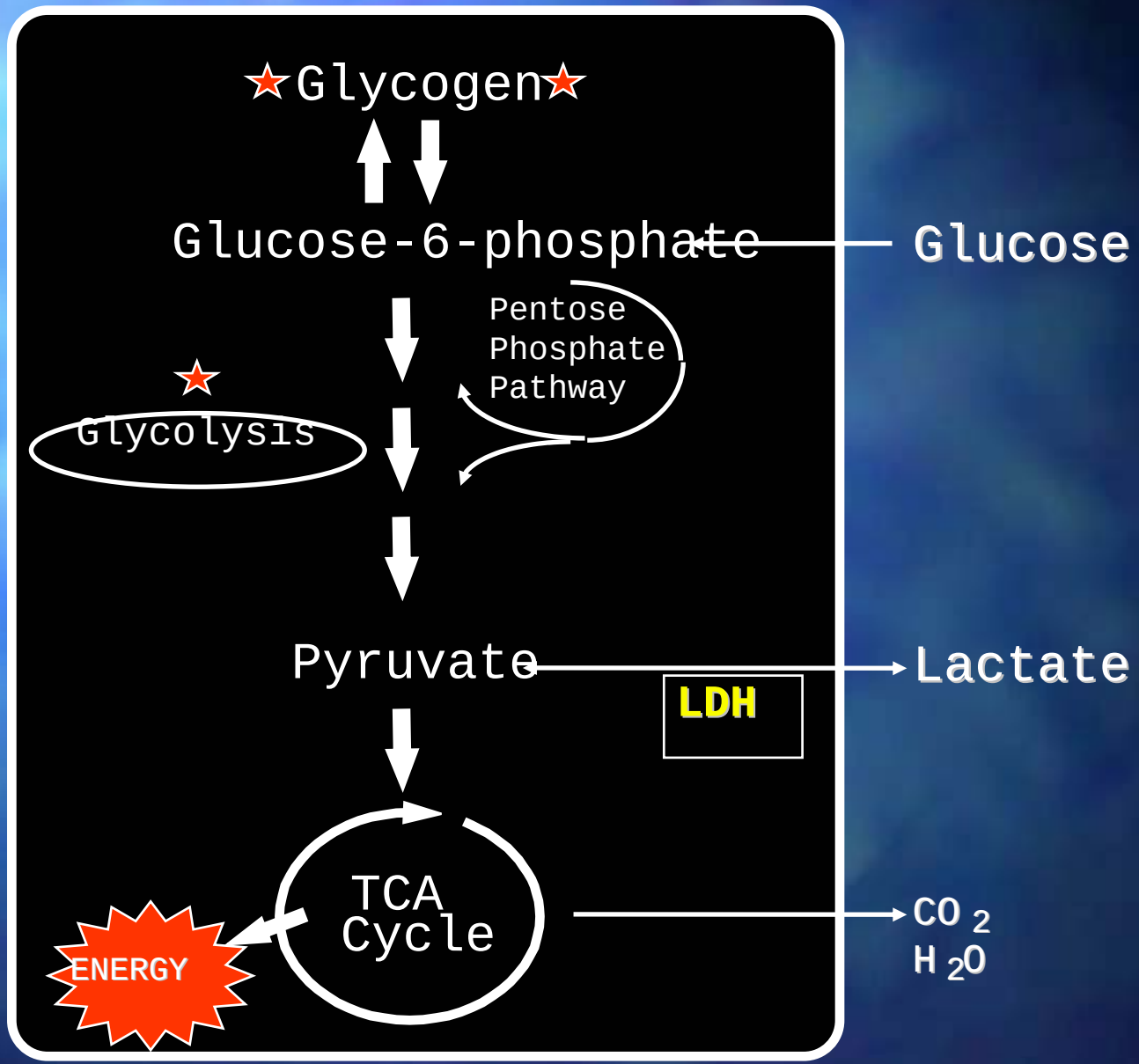
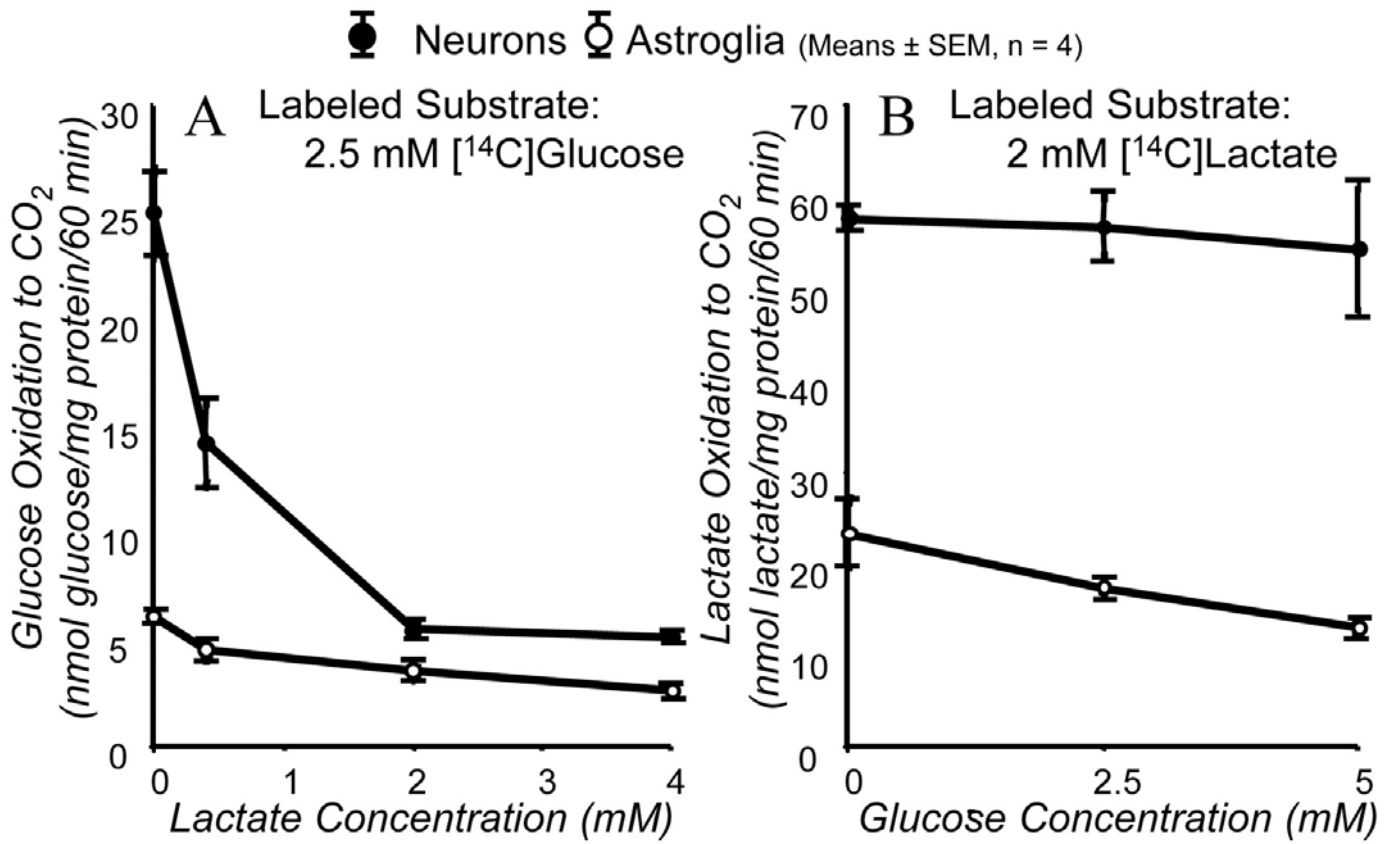


TABLE I. Apparent Kinetic Constants of Glucose and Lactate Consumption in Primary Cultures of Cortical Neurons in the Absence and Presence of the Corresponding Competitive Substrate

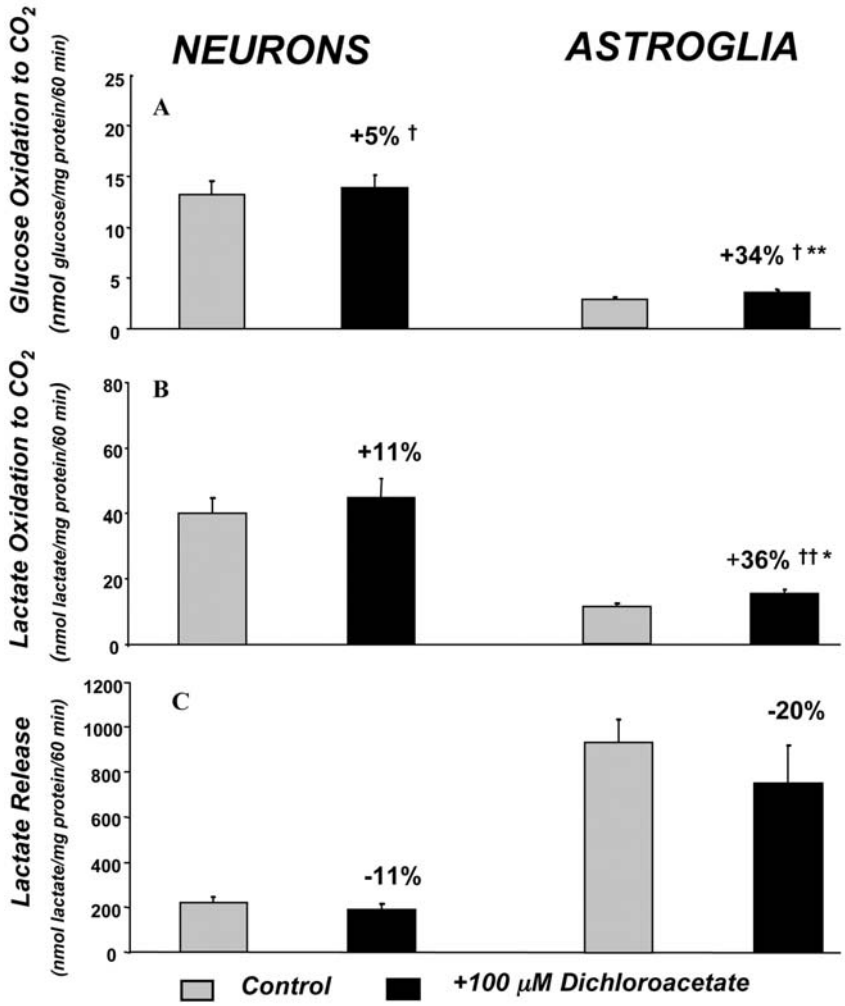
Process	Incubation condition	K_m (mM)[a]	V_{max} (nmol/mg/hr)[a]	K_i (mM)[b]
Glucose consumption	Glucose 0.25–5 mM	2.2 ± 0.2	600 ± 65	na
Glucose consumption in the presence of lactate	Glucose 0.25–5 mM and 5 mM lactate	3.6 ± 0.1	674 ± 54	3.6
Lactate consumption	Lactate 1–15 mM	7.8 ± 0.1	440 ± 3	na
Lactate consumption in the presence of glucose	Lactate 1–15 mM and 1 mM glucose	8.5 ± 0.1	451 ± 3	11.1

Ramirez et al, 2007



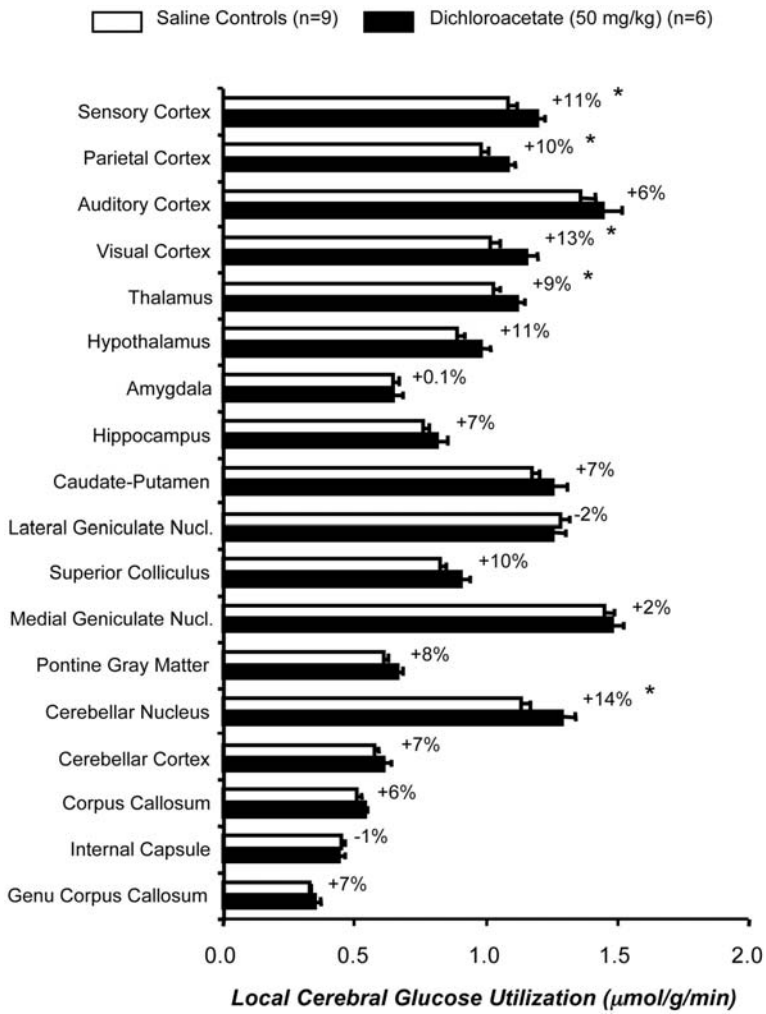
Itoh, Yoshiaki et al. (2003)

Effet du dichloroacétate sur l'oxydation du glucose



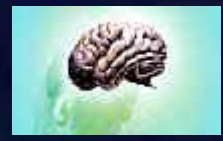
Itoh, Yoshiaki et al. (2003) Proc. Natl. Acad. Sci. USA 100, 4879-4884

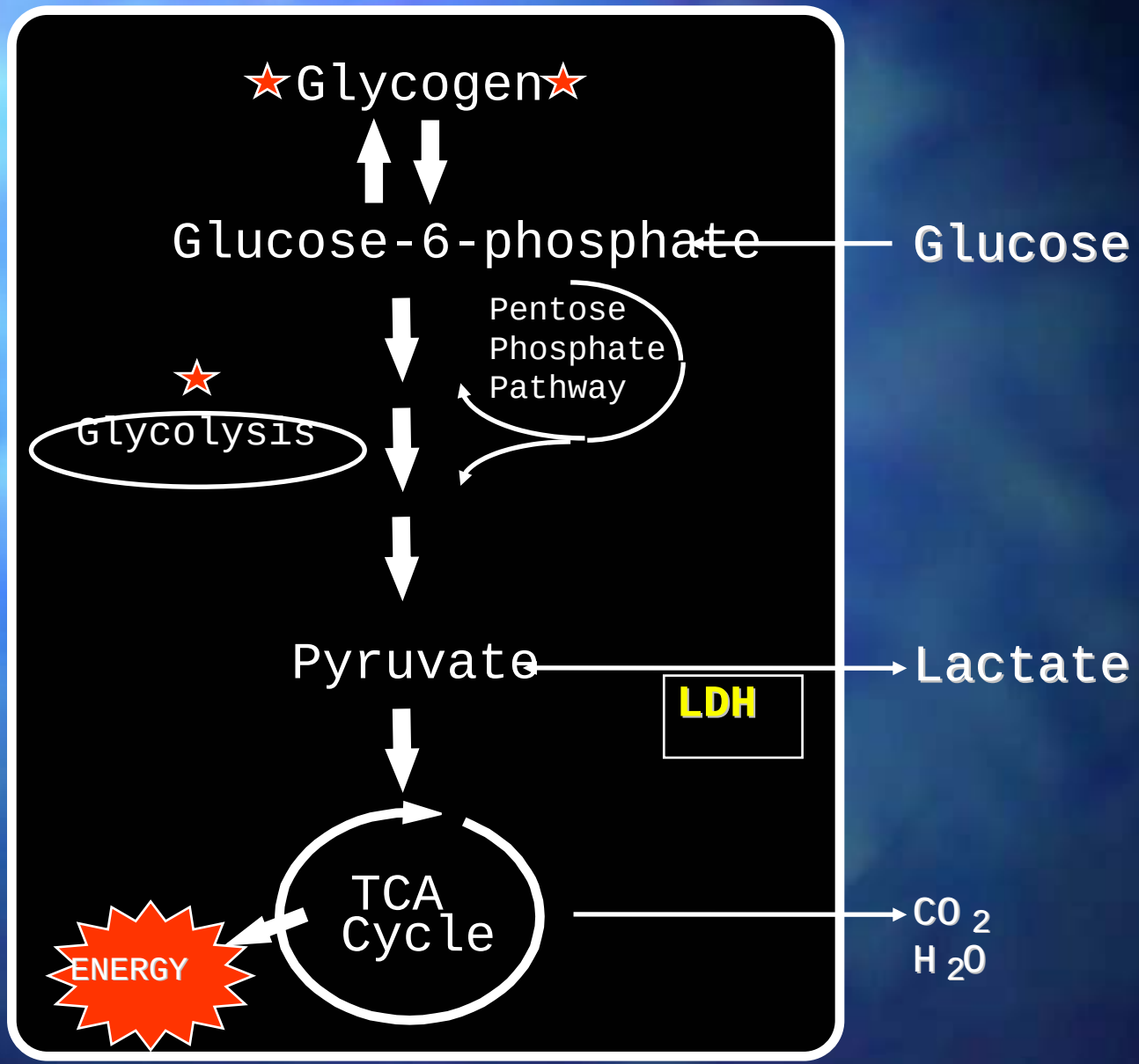
Effet du dichloroacétate sur la consommation locale de glucose



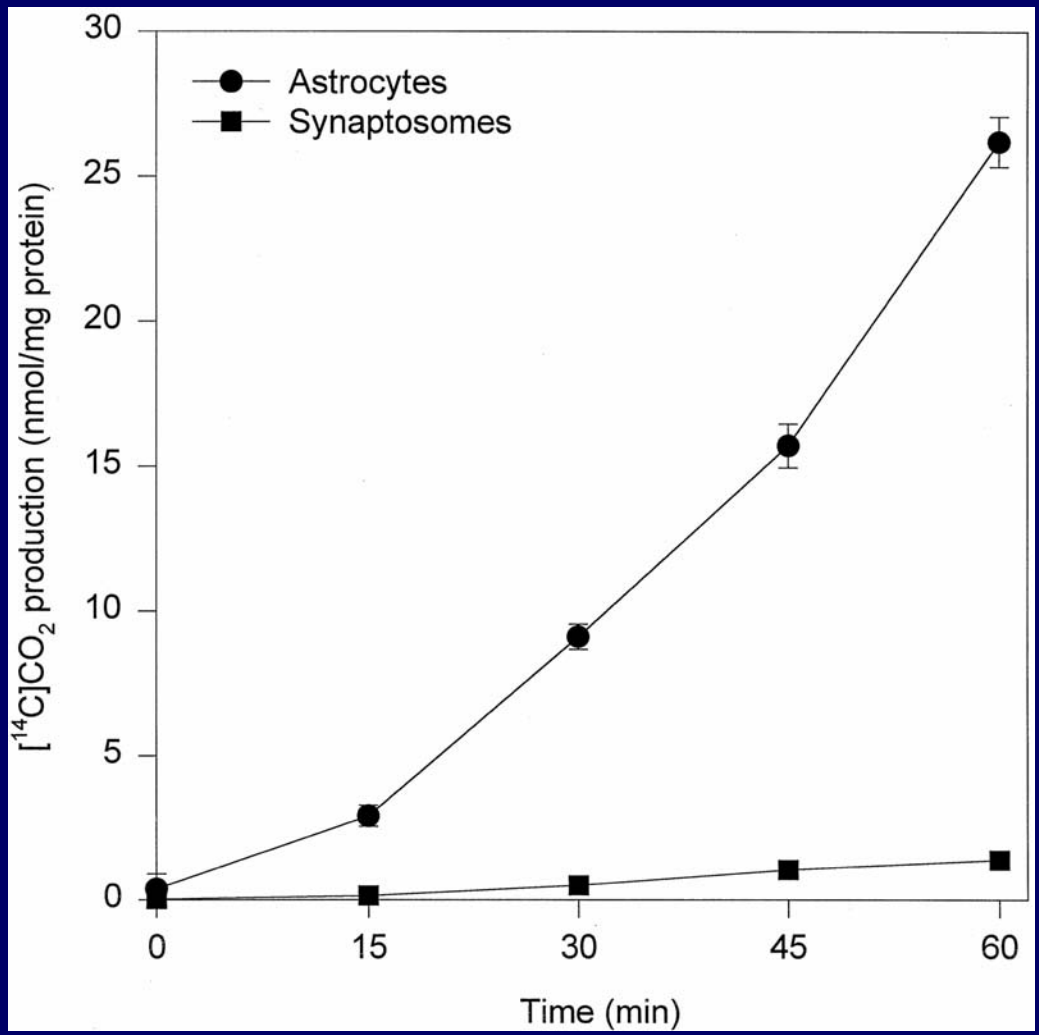
Itoh, Yoshiaki et al. (2003) Proc. Natl. Acad. Sci. USA 100, 4879-4884

Main Metabolic Pathways of Glucose





Capture préférentielle d'acétate dans les astrocytes



Waniewski, R. A. et al. J. Neurosci. 1998;18:5225-5233

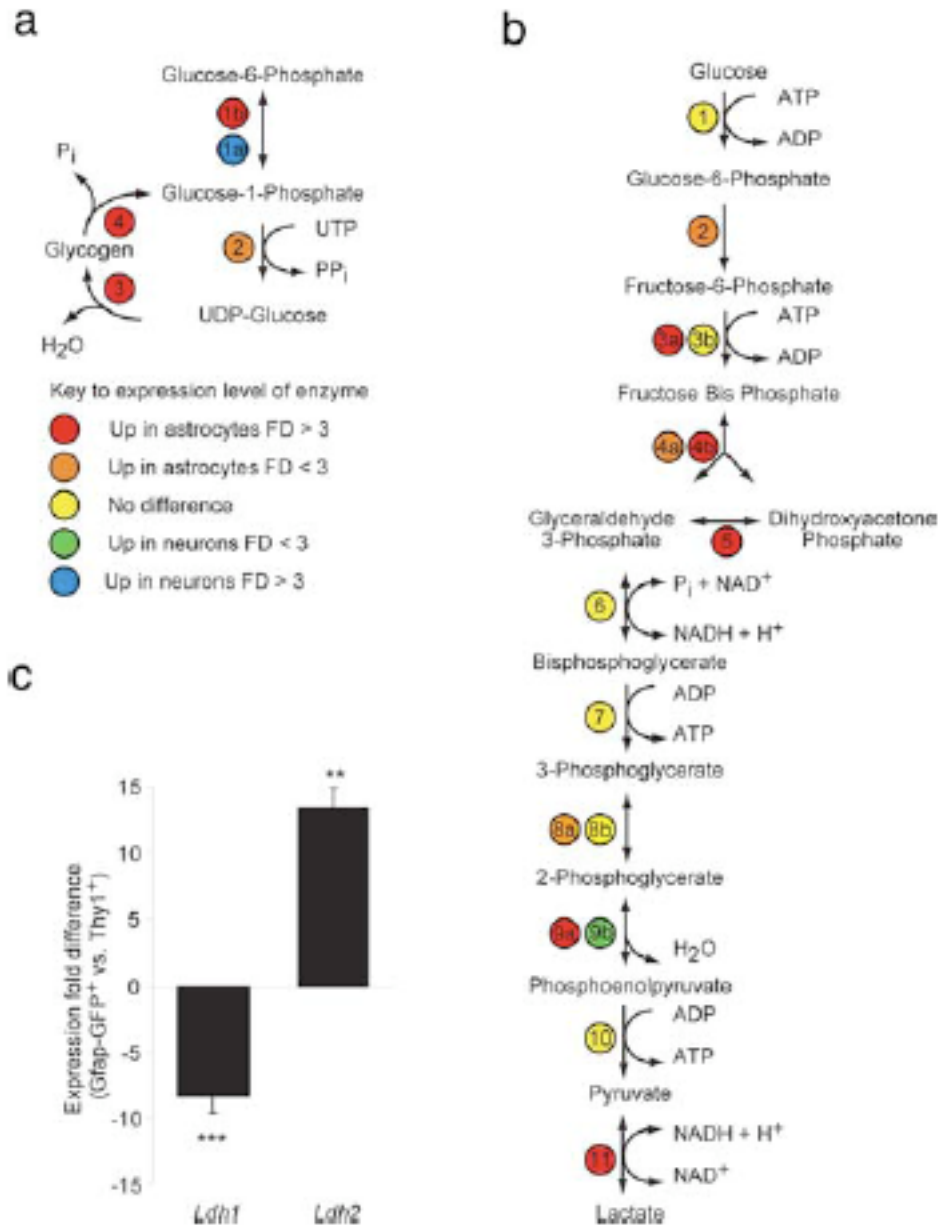
SOCIETY FOR NEUROSCIENCE The Journal of Neuroscience

The Journal of Neuroscience, March 1, 2002, 22(5):1523-

Astroglial Contribution to Brain Energy Metabolism in Humans Revealed by ^{13}C Nuclear Magnetic Resonance Spectroscopy: Elucidation of the Dominant Pathway for Neurotransmitter Glutamate Repletion and Measurement of Astrocytic Oxidative Metabolism

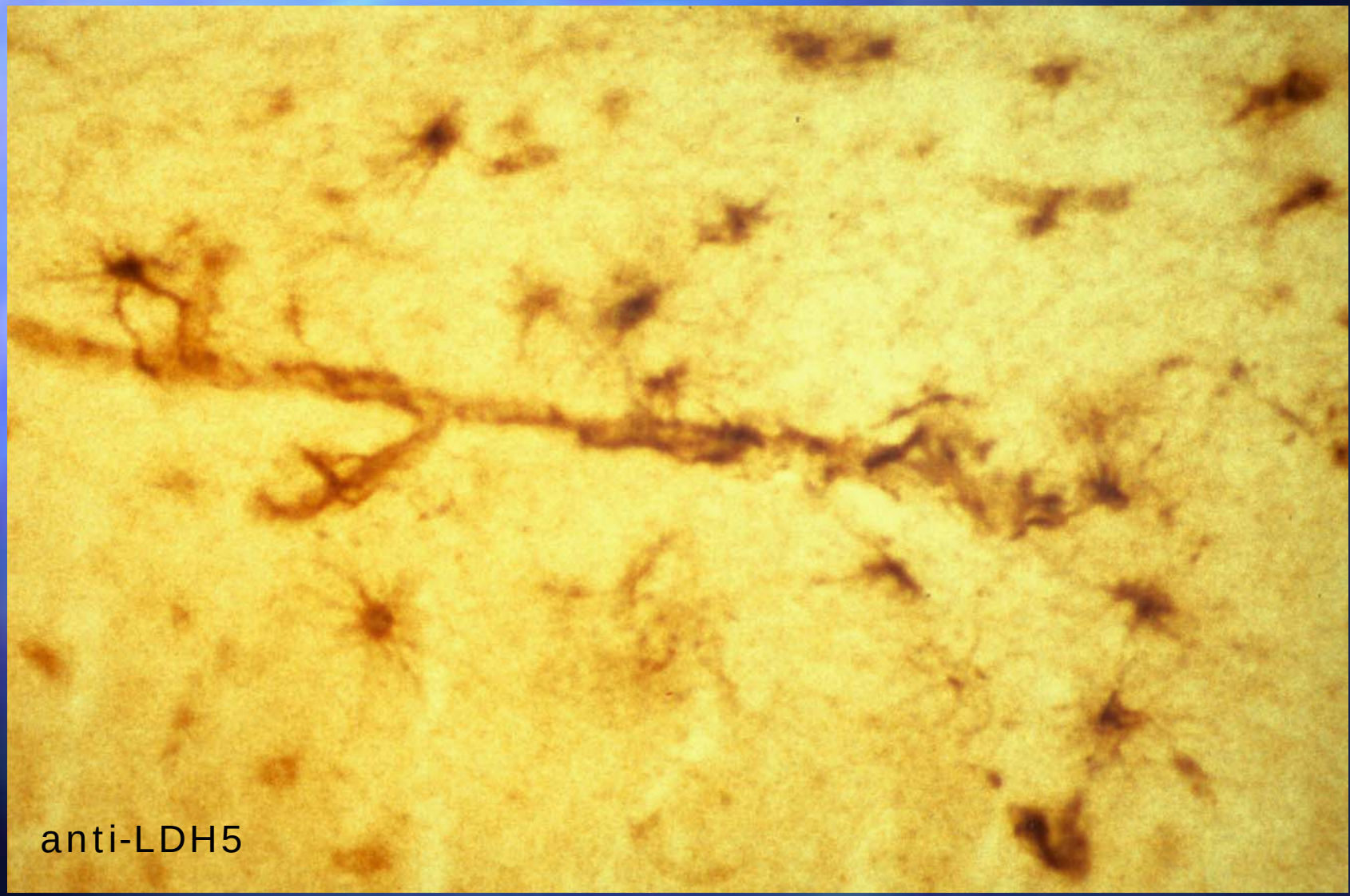
Vincent Lebon,[1,2] Kitt F. Petersen,[2] Gary W. Cline,[2] Jun Shen,[6] Graeme F. Mason,[3] Sylvie Dufour,[1,2] Kevin L. Behar,[3] Gerald I. Shulman,[1,2,4] and Douglas L. Rothman[5]

[1]Howard Hughes Medical Institute, Departments of [2]Internal Medicine, [3]Psychiatry, [4]Cellular and Molecular Physiology and [5]Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut 06510, and [6]Division of Medi Physics, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York 10962


a
Glucose-6-Phosphate
1a
1b
Pi
Glucose-1-Phosphate
4
Glycogen
2
UTP
PPi
3
UDP-Glucose
H2O
Key to expression level of enzyme
Up in astrocytes FD > 3
Up in astrocytes FD < 3
No difference
Up in neurons FD < 3
Up in neurons FD > 3
b
Glucose
1
ATP
ADP
Glucose-6-Phosphate
2
Fructose-6-Phosphate
3a
3b
ATP
ADP
Fructose Bis Phosphate
4a
4b
Glyceraldehyde 3-Phosphate
5
Dihydroxyacetone Phosphate
6
Pi + NAD+
NADH + H+
Bisphosphoglycerate
7
ADP
ATP
3-Phosphoglycerate
8a
8b
2-Phosphoglycerate
9a
9b
H2O
Phosphoenolpyruvate
10
ADP
ATP
Pyruvate
11
NADH + H+
NAD+
Lactate
c
Expression fold difference (Gfap-GFP+ vs. Thy1+)
15
10
5
0
-5
-10
-15
**
***
Ldh1
Ldh2

LDH 1 : Neurones

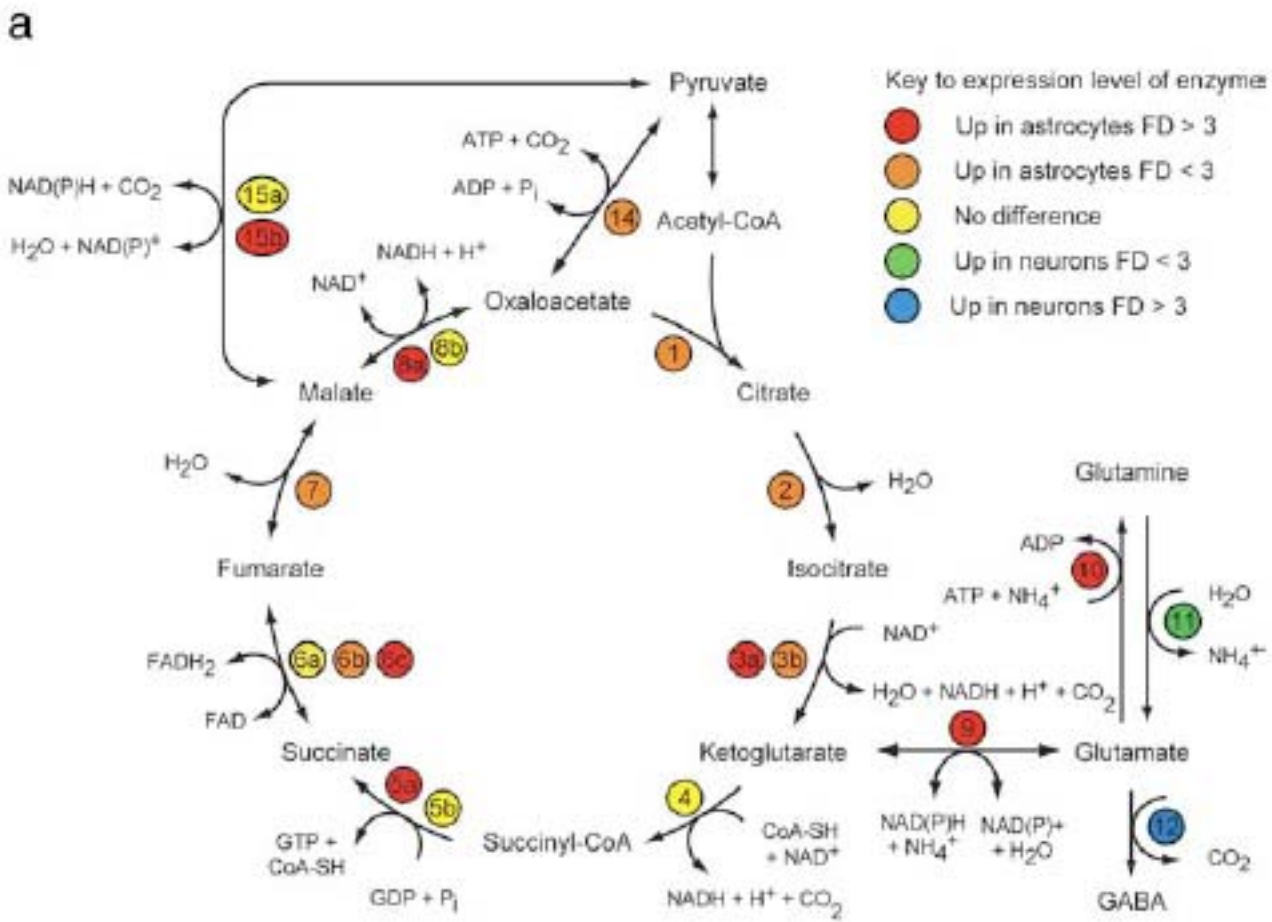
LDH 5 Astrocytes

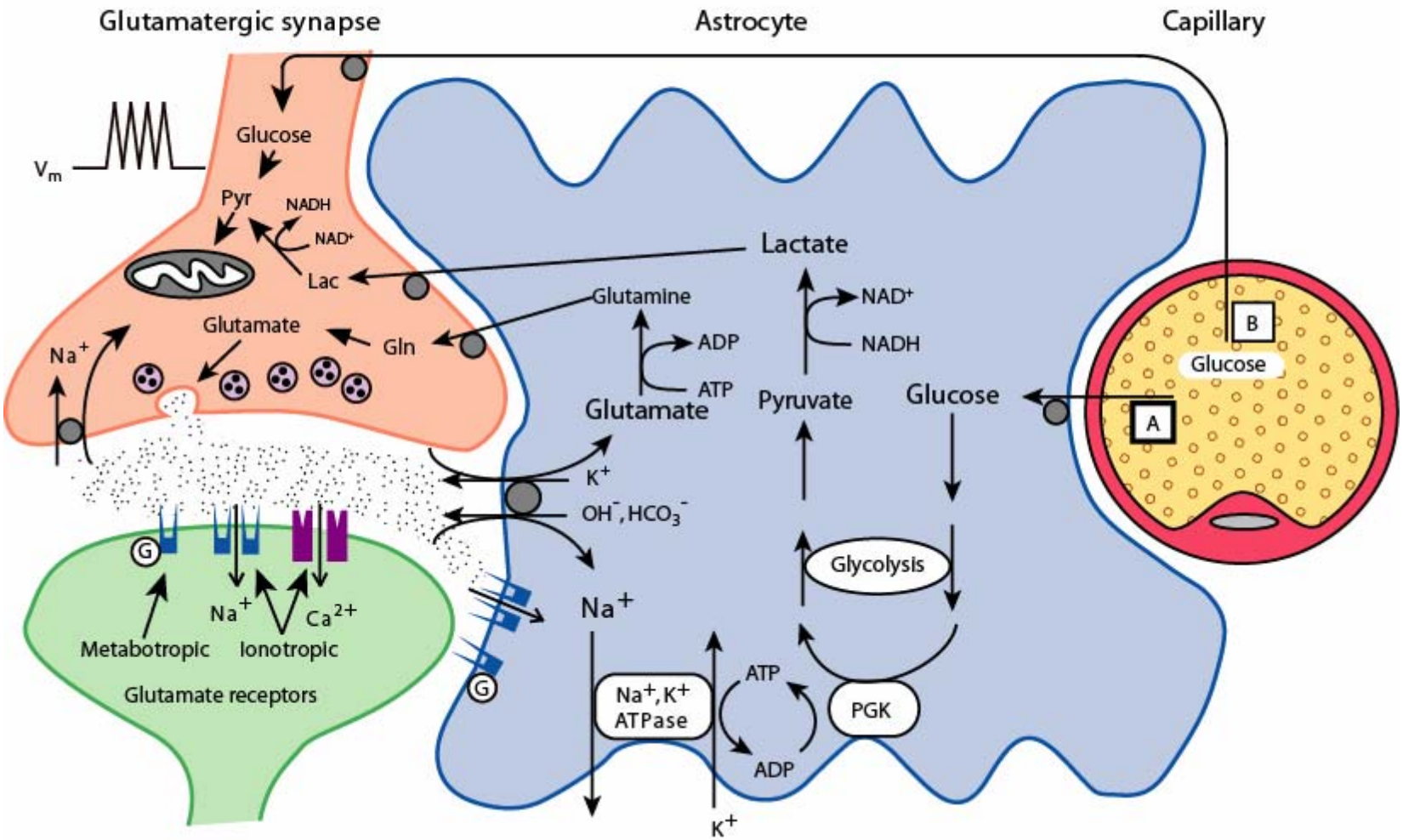


Enrichissement à partir de ^{13}C-glucose (Lovatt et al , 2007)

Table 3. Percentage enrichment in cell extracts and medium from MACS purified GLT1$^+$ astrocytes incubated with D-[U-^{13}C]glucose

	M+1	M+2	M+3
Medium			
Lactate	0.3 ± 0.15	2.7 ± 0.3	61.1 ± 3.4[a]
Cell extract			
Glutamate	8.8 ± 1.0	5.1 ± 1.6	6.5 ± 0.5
Aspartate	16 ± 4	1.1 ± 0.5	NE
Malate	NE	2.5 ± 0.8	1.3 ± 0.8
Citrate	NE	NE	2.4 ± 1.1


a
Pyruvate
Key to expression level of enzyme
Up in astrocytes FD > 3
Up in astrocytes FD < 3
No difference
Up in neurons FD > 3
ATP + CO2
ADP + Pi
14
Acetyl-CoA
NAD(P)H + CO2
H2O + NAD(P)+
15a
15b
NADH + H+
NAD+
Oxaloacetate
8a
8b
Malate
1
Citrate
H2O
7
2
H2O
Glutamine
Fumarate
Isocitrate
ADP
ATP + NH4+
10
11
H2O
NH4+
NAD+
3a
3b
FADH2
6a
6b
6c
H2O + NADH + H+ + CO2
FAD
Succinate
Ketoglutarate
9
Glutamate
5a
5b
4
GTP +
CoA-SH
Succinyl-CoA
CoA-SH
+ NAD+
NAD(P)H
+ NH4+
NAD(P)+
+ H2O
12
CO2
GDP + Pi
NADH + H+ + CO2
GABA


Glutamatergic synapse
Astrocyte
Capillary
V_m
Glucose
Pyr
NADH
NAD+
Lac
Lactate
Glutamine
ADP
ATP
Glutamate
Pyruvate
NAD+
NADH
Glucose
B
Glucose
A
Na+
Glutamate
Gln
K+
OH-, HCO3-
G
Na+
Ca2+
Metabotropic
Ionotropic
Glutamate receptors
Glycolysis
Na+
Na+, K+ ATPase
ATP
ADP
PGK
K+

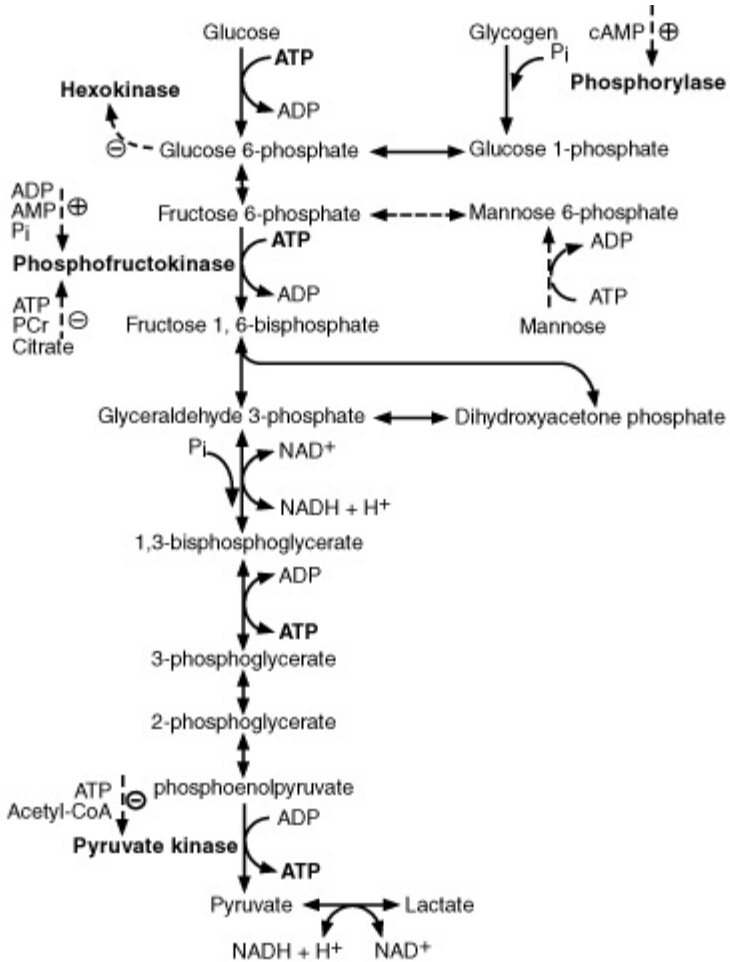
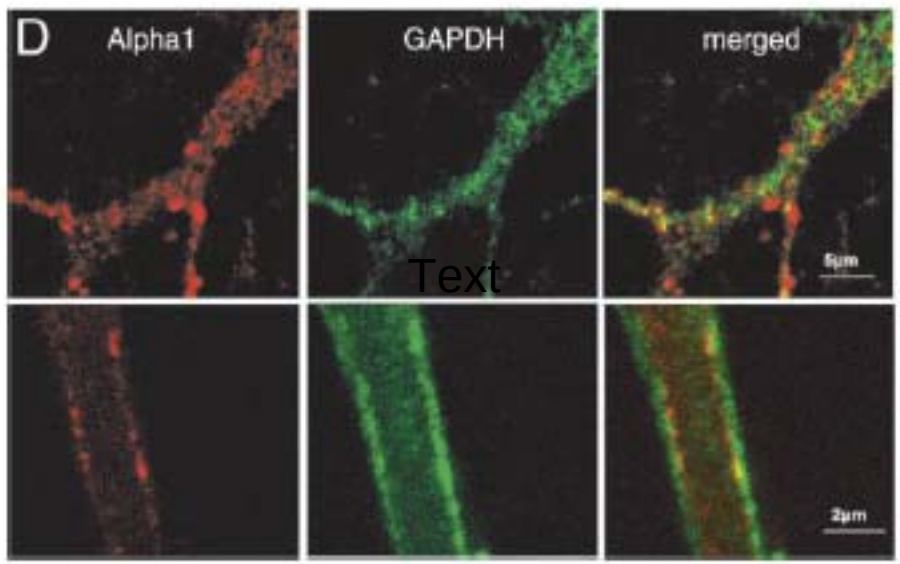


FIGURE 3.1 Glycolysis (Embden–Meyerhof pathway). Glucose phosphorylation is regulated by hexokinase, an enzyme inhibited by glucose 6-phosphate. Glucose must be phosphorylated to glucose 6-phosphate to enter glycolysis or to be stored as glycogen. Two other important steps in the regulation of glycolysis are catalyzed by phosphofructokinase and pyruvate kinase. Their activity is controlled by the levels of high-energy phosphates as well as of citrate and acetyl-CoA. Pyruvate, through lactate dehydrogenase, is in dynamic equilibrium with lactate. This reaction is essential to regenerate NAD^+ residues necessary to sustain glycolysis downstream of glyceraldehyde 3-phosphate. PCr, phosphocreatine.

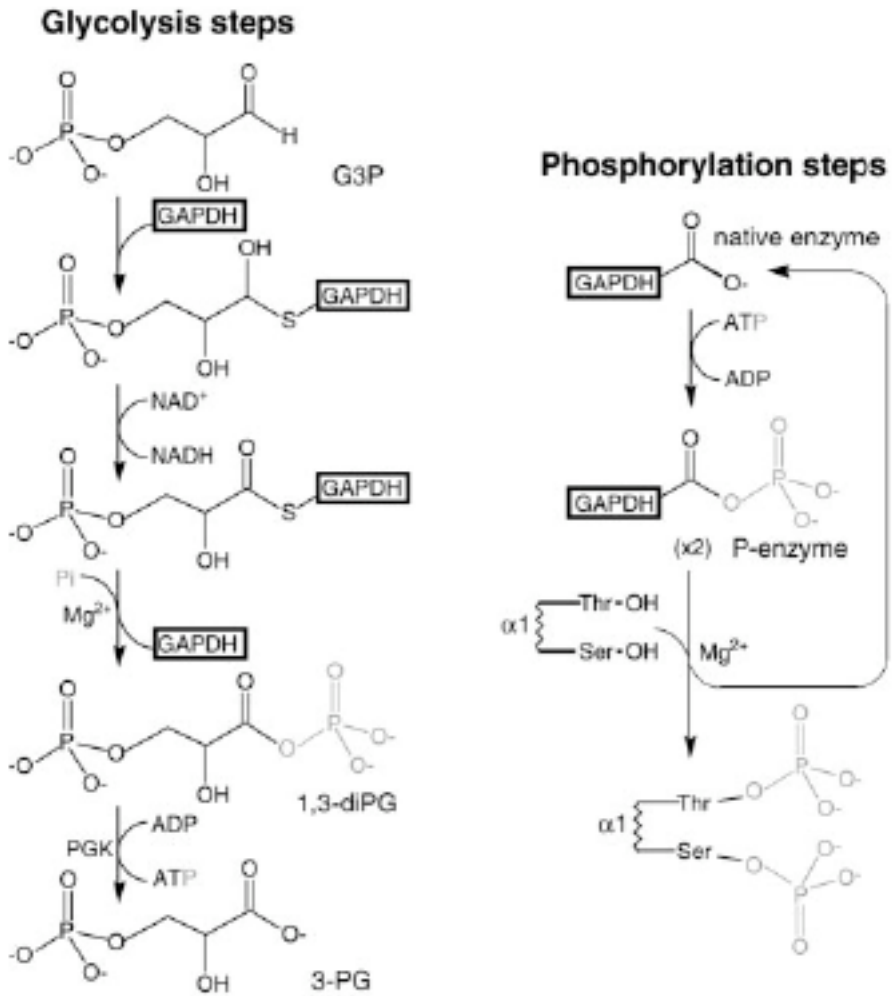
FROM MOLECULES TO NETWORKS John H. Byrne, James L. Roberts

Co-localization entre GAPDH et sous-unité alpaha 1 du récepteur GABA A



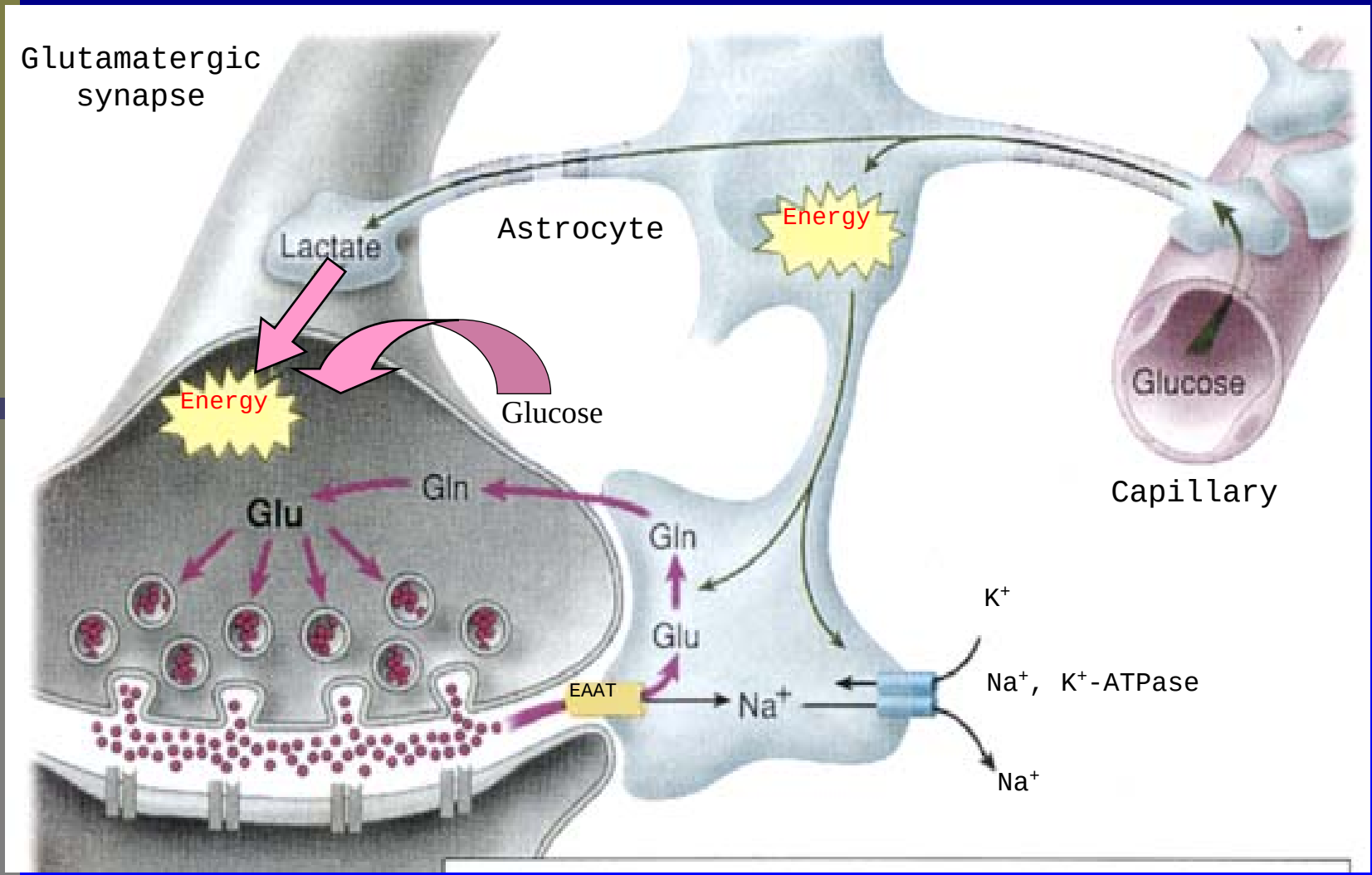
Laschet et al. 2004

Interaction métabolique entre GAPDH et récepteur GABA A

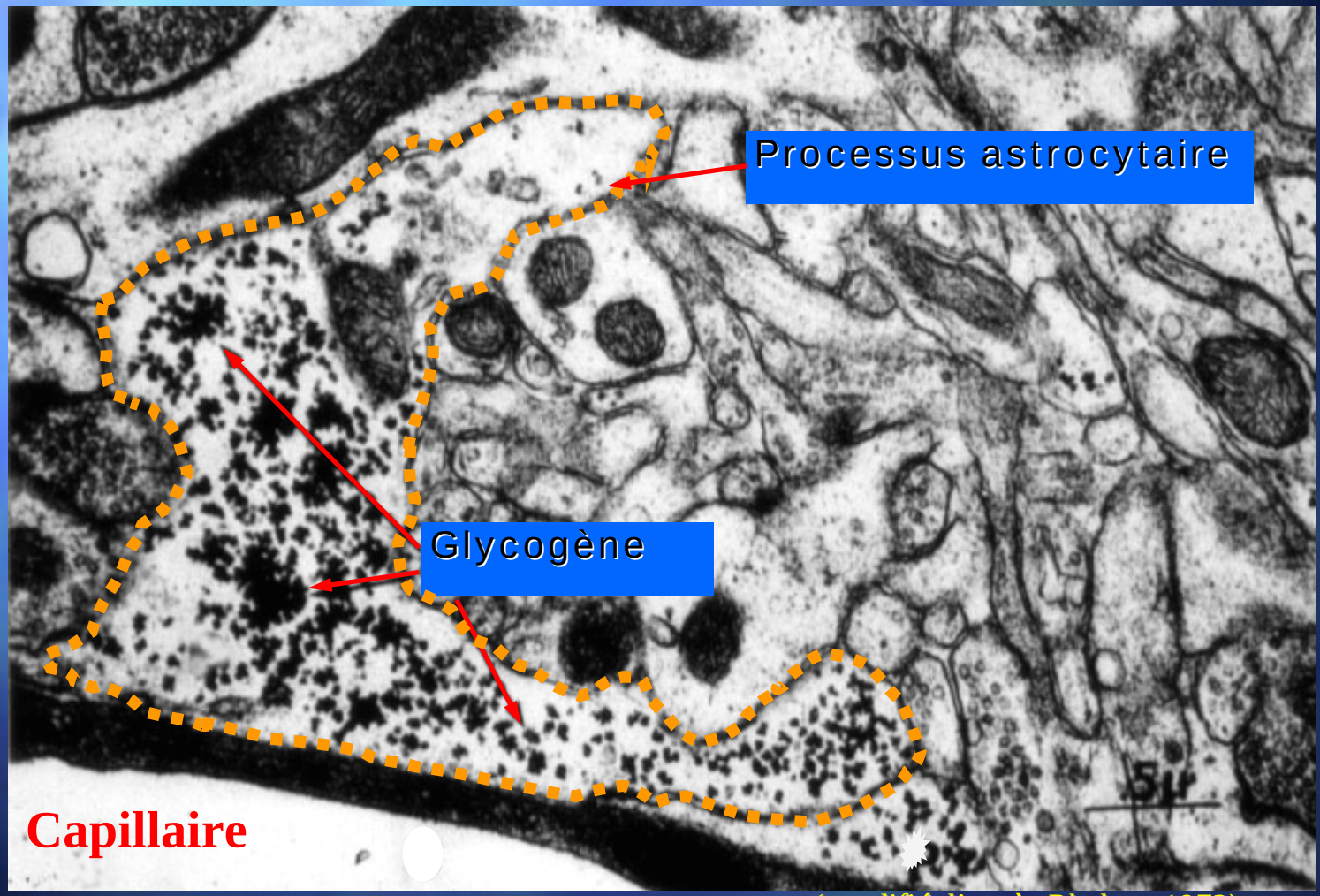


Laschet et al. 2004

Role of Astrocytes in Neuroenergetics



Le glycogène est presque exclusivement localisé dans les astrocytes



(modifié d'après Phelps., 1972)

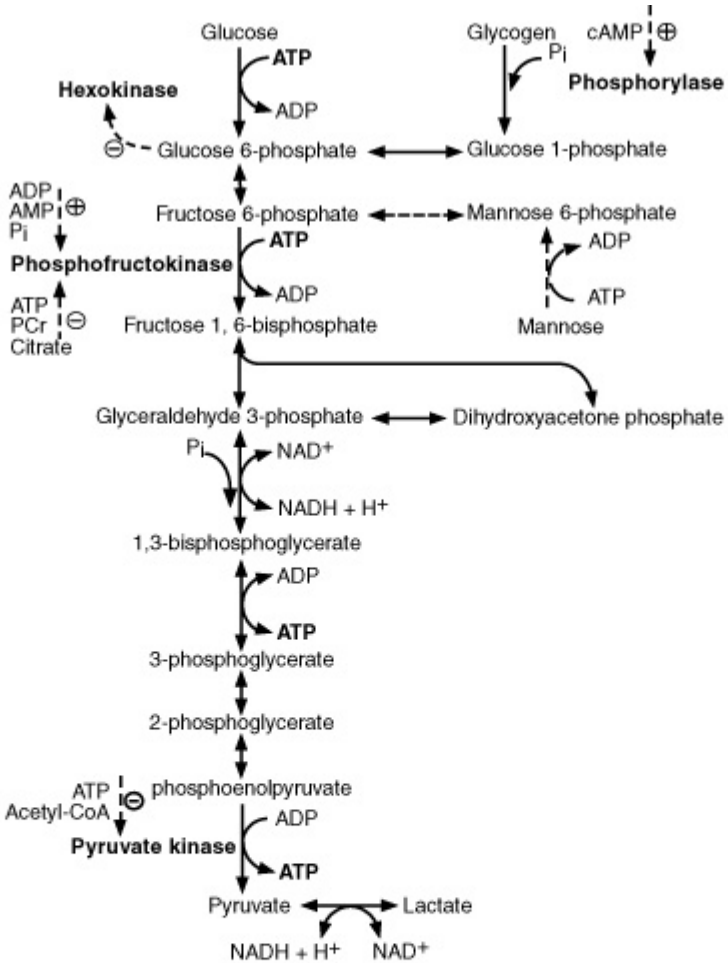
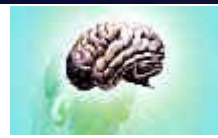


FIGURE 3.1 Glycolysis (Embden–Meyerhof pathway). Glucose phosphorylation is regulated by hexokinase, an enzyme inhibited by glucose 6-phosphate. Glucose must be phosphorylated to glucose 6-phosphate to enter glycolysis or to be stored as glycogen. Two other important steps in the regulation of glycolysis are catalyzed by phosphofructokinase and pyruvate kinase. Their activity is controlled by the levels of high-energy phosphates as well as of citrate and acetyl-CoA. Pyruvate, through lactate dehydrogenase, is in dynamic equilibrium with lactate. This reaction is essential to regenerate NAD^+ residues necessary to sustain glycolysis downstream of glyceraldehyde 3-phosphate. PCr, phosphocreatine.

FROM MOLECULES TO NETWORKS John H. Byrne, James L. Roberts

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)

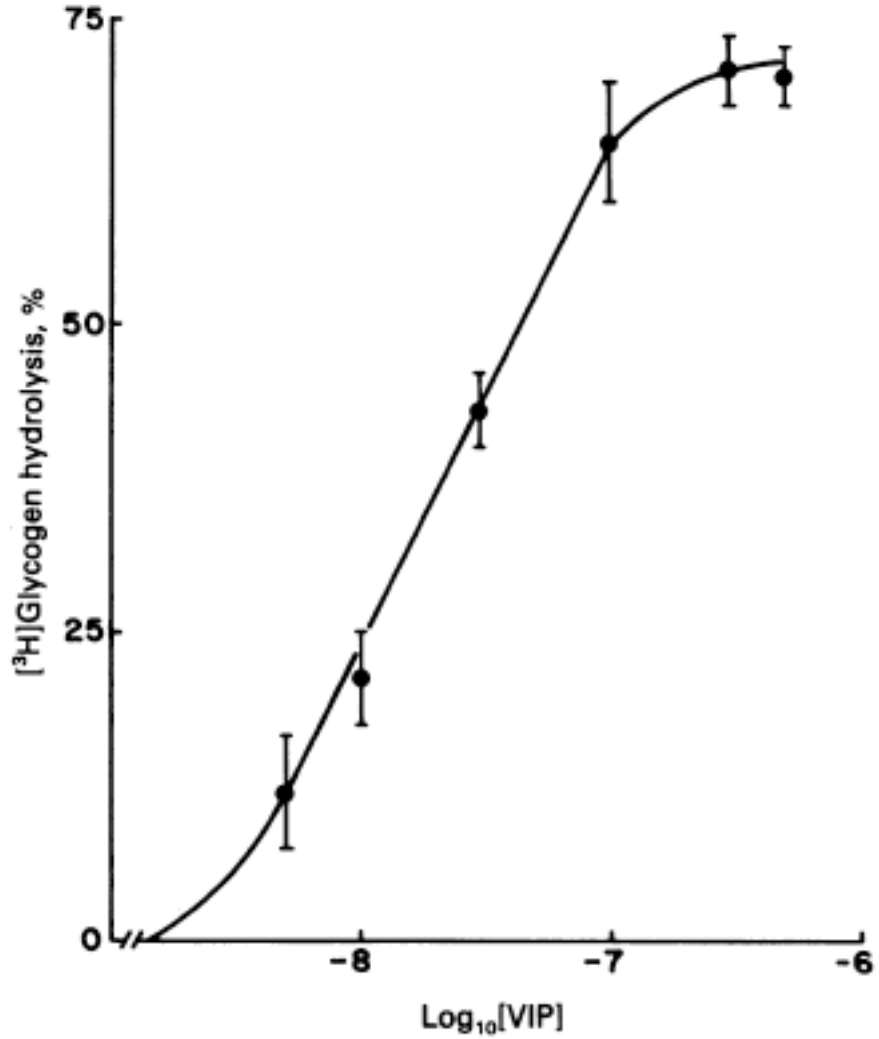
PIERRE J. MAGISTRETTI, JOHN H. MORRISON, WILLIAM J. SHOEMAKER, VIVECA SAPIN, AND FLOYD E. BLOOM

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

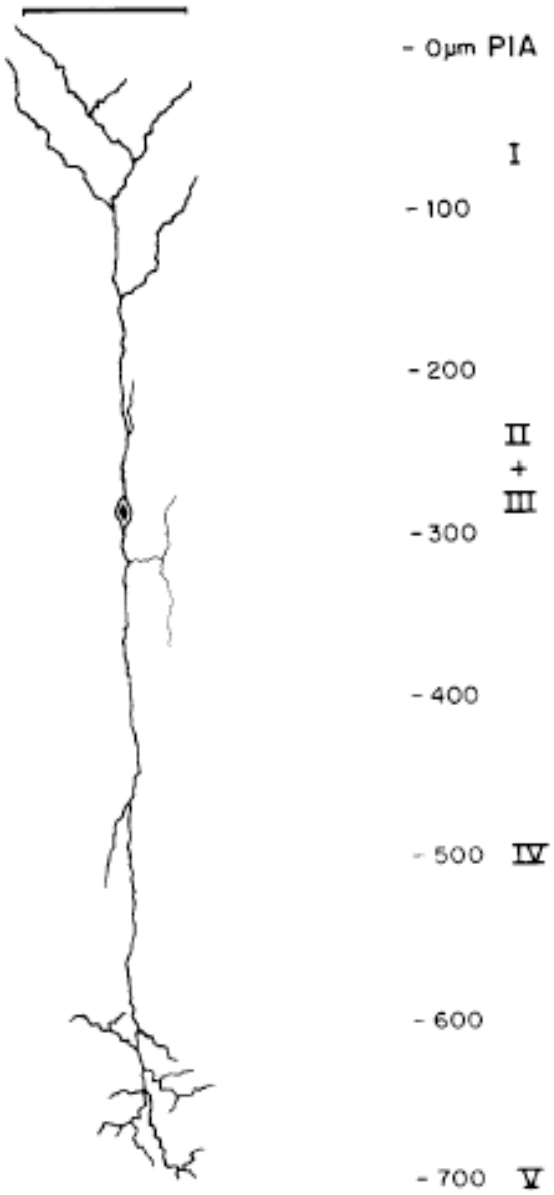
A final observation can be made: VIP and norepinephrine display similar glycogenolytic actions in peripheral tissues. This action may indicate that certain substances with specific hormonal roles in several cell systems may exert similar homeostatic functions at the cellular level within the central nervous system, which are constrained by the spatiotemporal functional precision inherent to neural transmission.

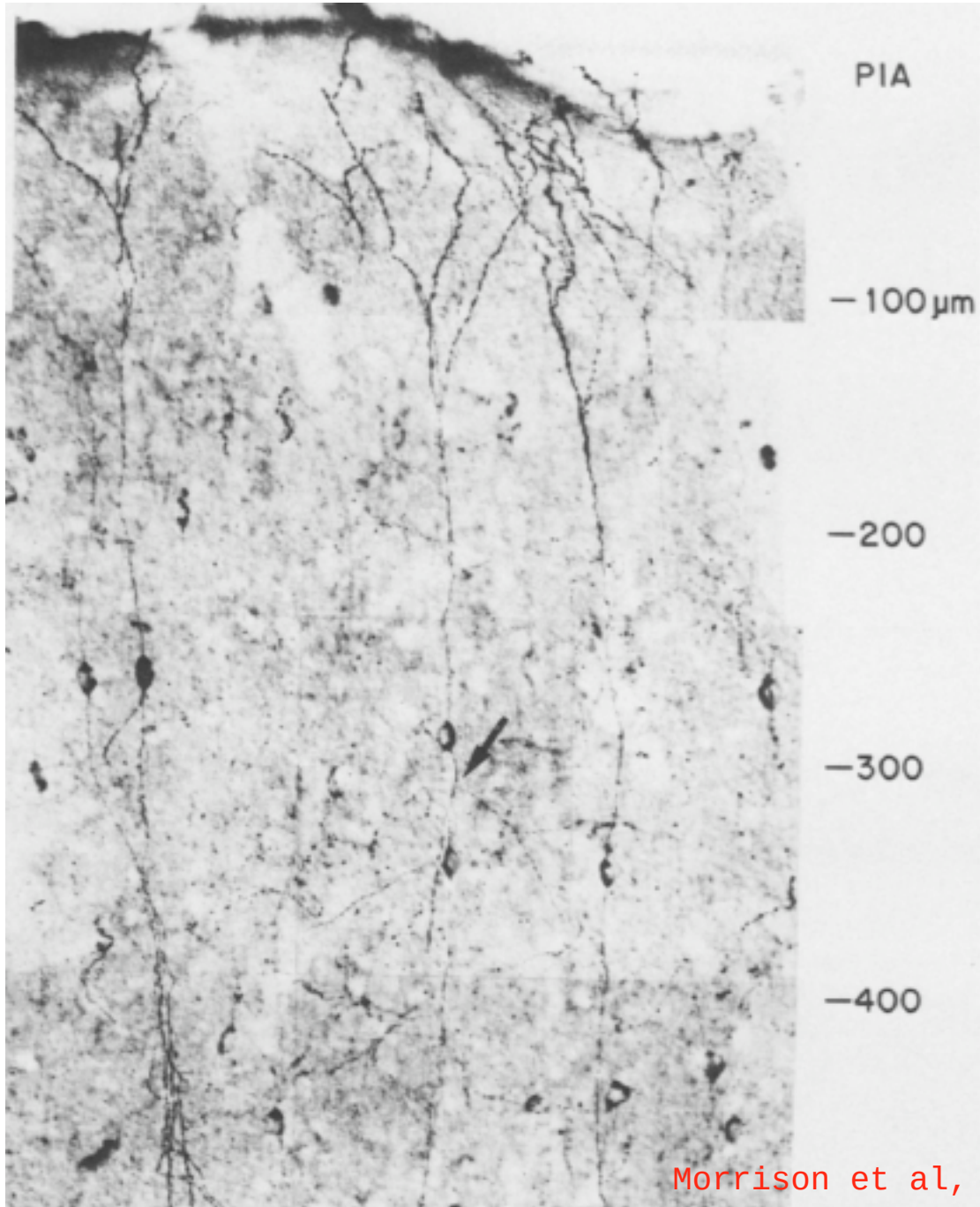
t glycogénolytique du VIP



Magistretti et al, 198

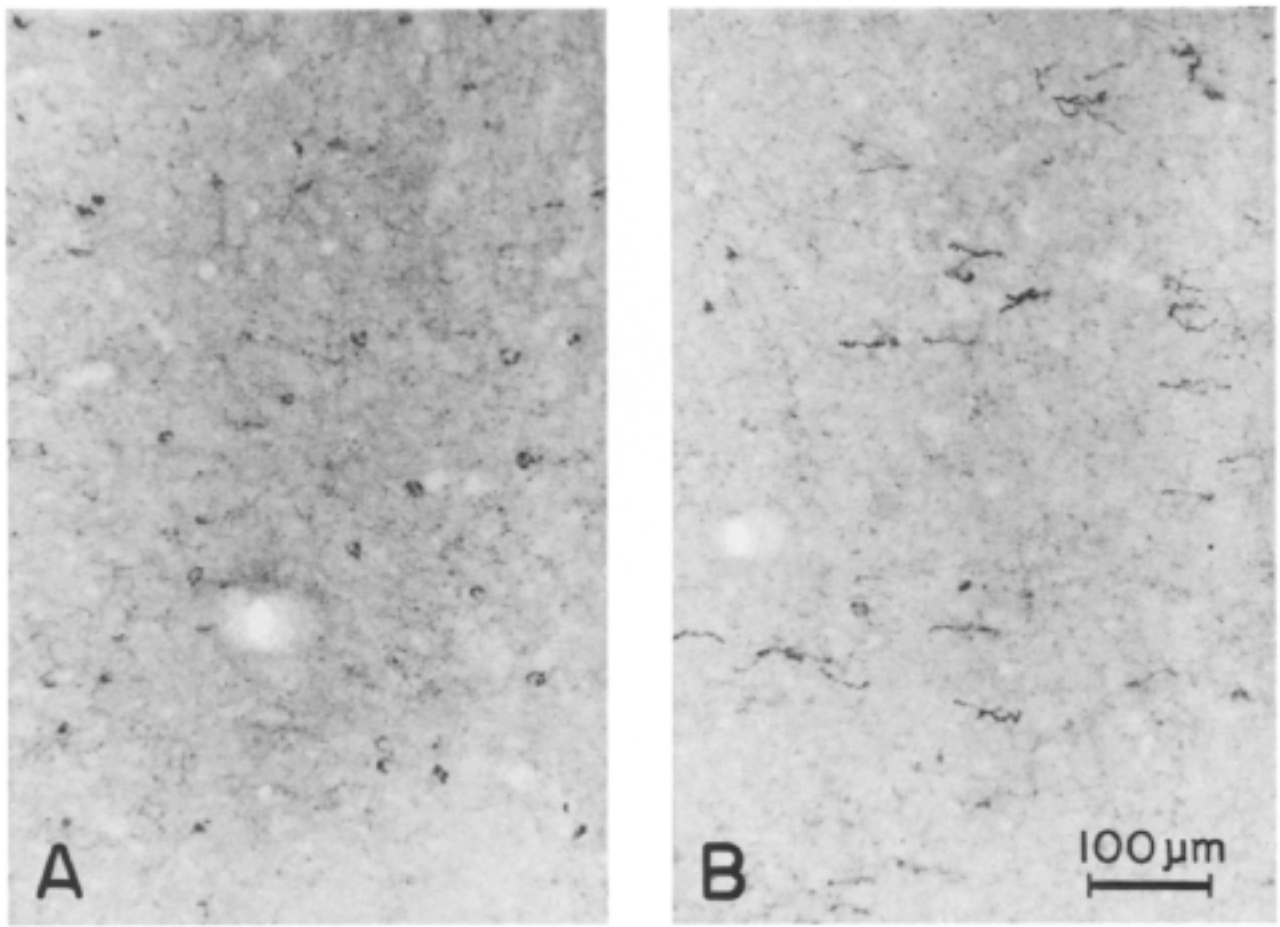
Neurones à VIP





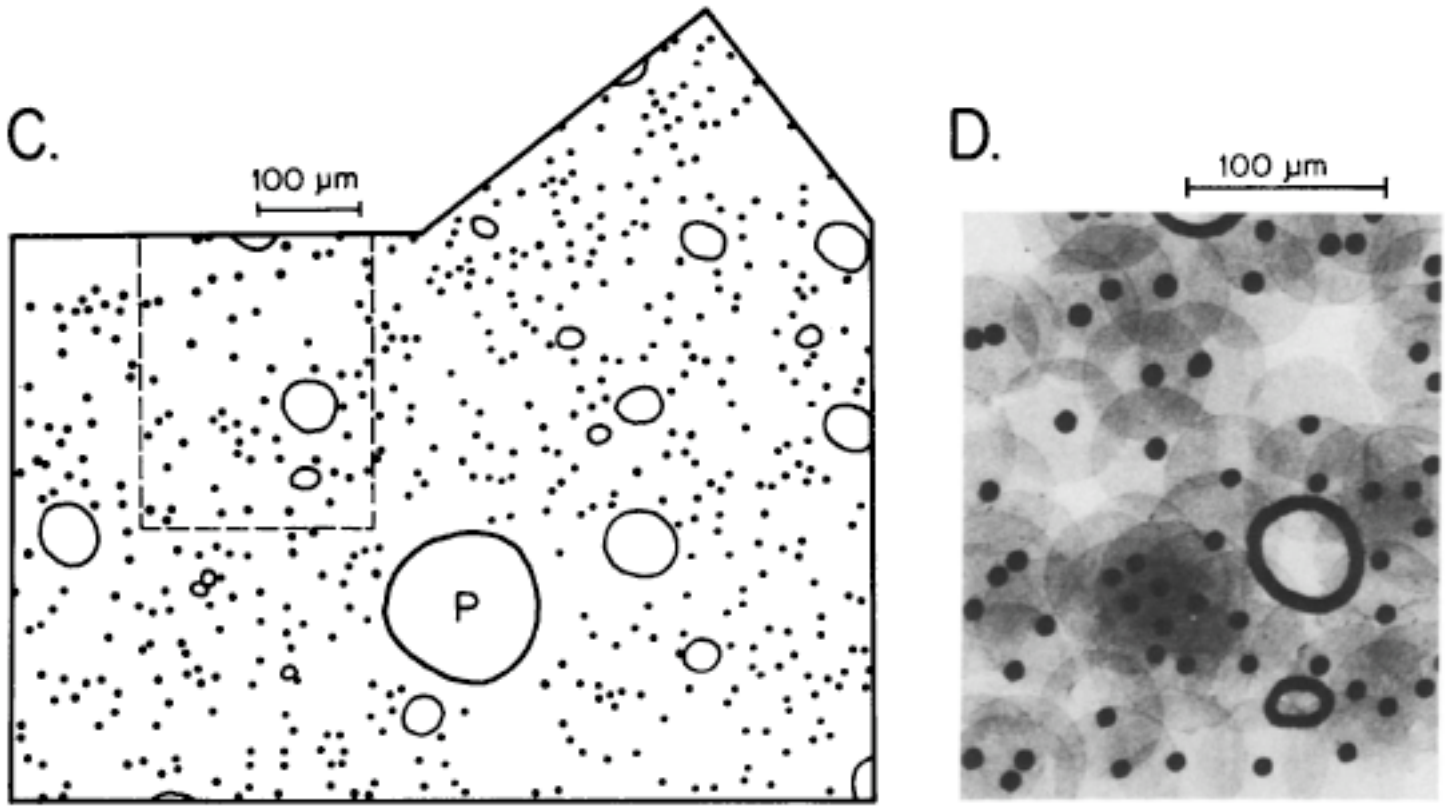
Morrison et al, 19

Vue tangentielle des neurones à VIP dans les couches III (A) et I (B)



Morrison et al, 19

Analyse de la distribution tangentielle des corps cellulaires des neurones à VIP dans le 600 premier microns de l’épaisseur corticale



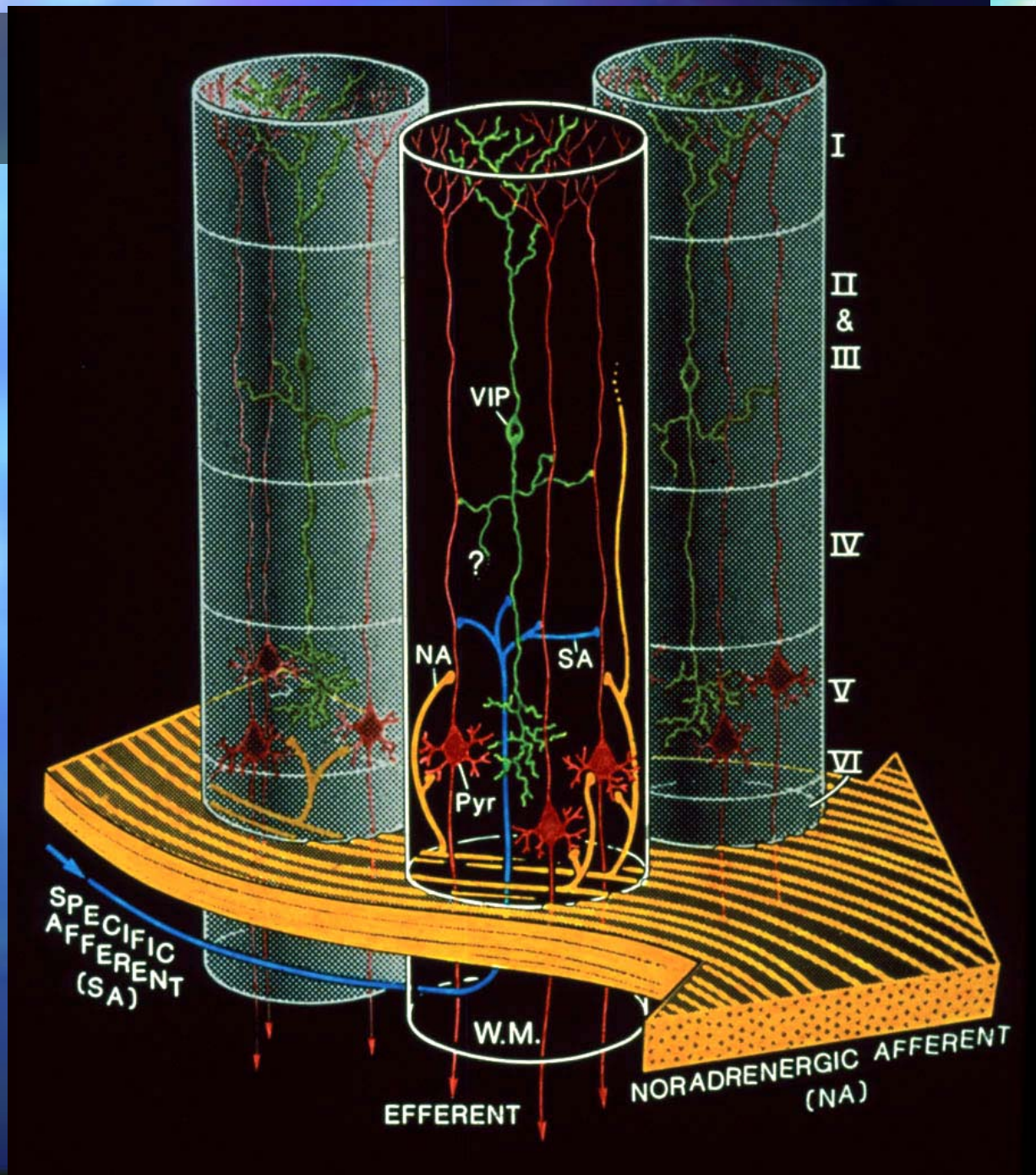
Morrison et al, 1984

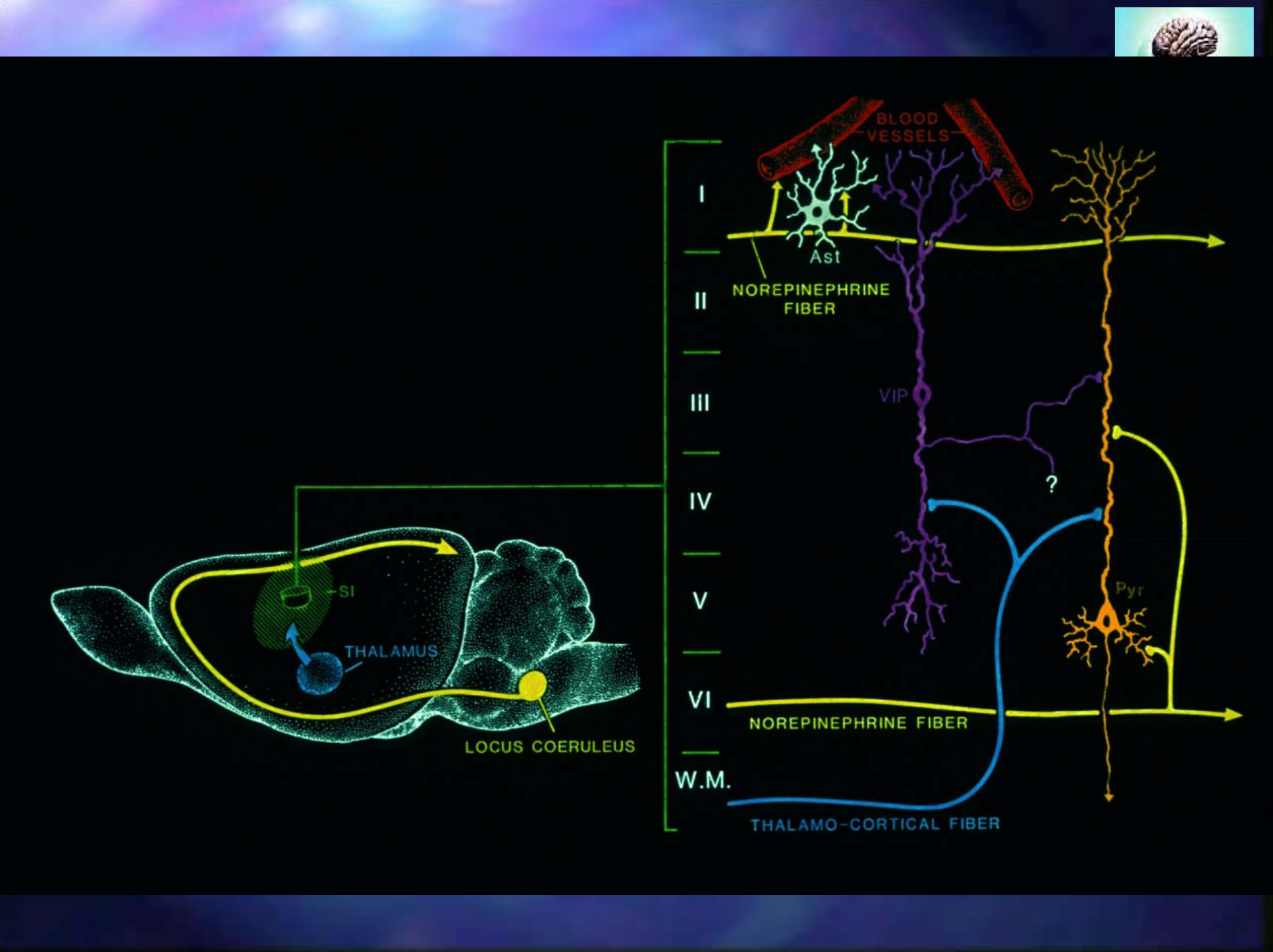
Distribution des neurones à VIP dans le cortex visuel primaire de rat

Mean density (n = 567)	1 VIP cell/737 μm^2 1 VIP cell/30.6 μm diameter
Largest surface area without a VIP cell	60–90 μm diameter
Mean nearest neighbor (n = 350)	14.8 ± 0.61 μm
Dendritic spread in layers I and IV–V	60–100 μm

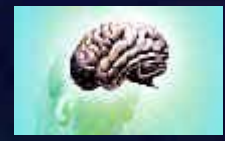
Morrison et al, 1984

Circuits à NA et à VIP



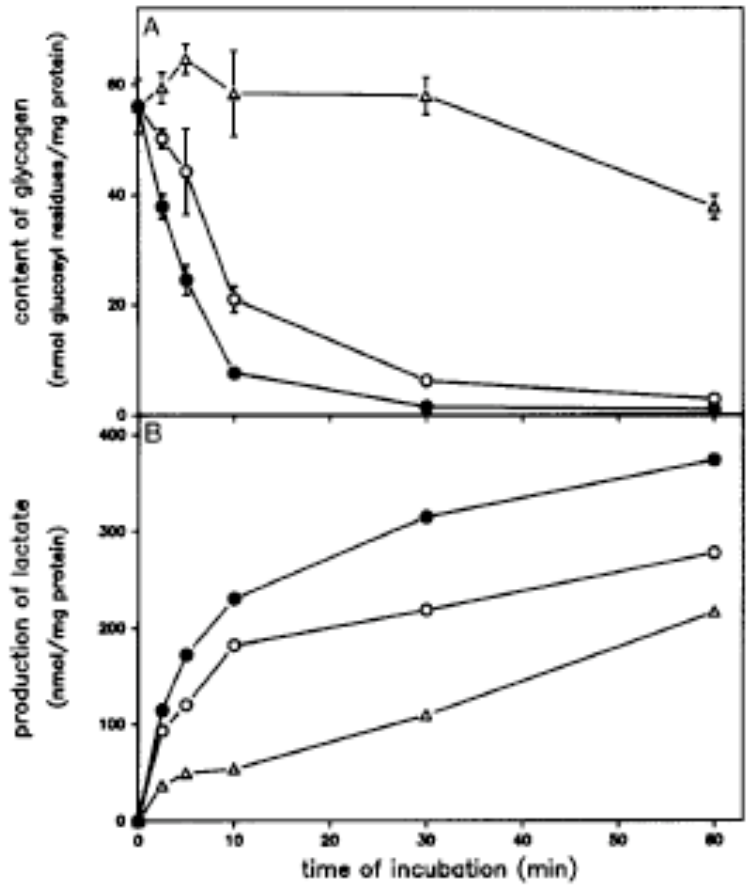

BLOOD VESSELS
Ast
NOREPINEPHRINE FIBER
VIP
?
Pyr
I
II
III
IV
V
VI
W.M.
NOREPINEPHRINE FIBER
THALAMO-CORTICAL FIBER
SI
THALAMUS
LOCUS COERULEUS

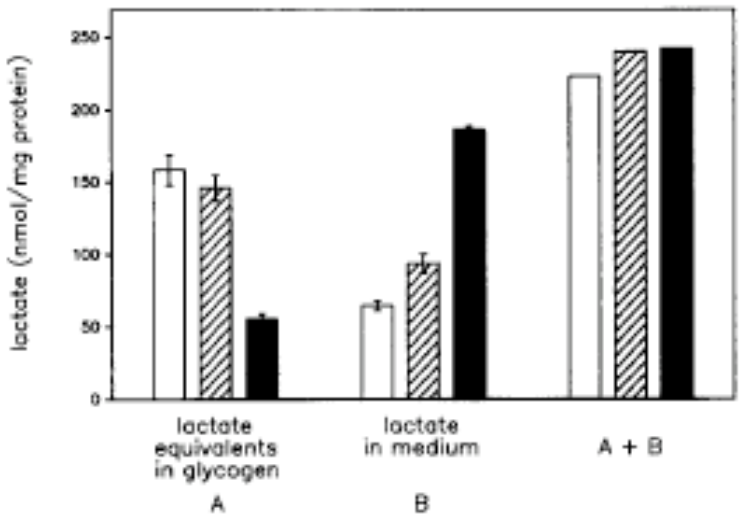
Neurotransmetteurs à action glycogenolytique au niveau des astrocytes



Neurotransmitter	EC_{50} (nM)	Receptor subtype	Transduction pathway
VIP	3	PACAP Type II	cAMP / PKA
PACAP	0.08	PACAP Type I or II ?	cAMP / PKA
Noradrenaline	20		
Isoproterenol	20	β	cAMP / PKA
Methoxamine	600	α 1	PKC ?
Adenosine	800	A_2 ?	cAMP / PKA ?
ATP	1300	P_{2y}	Arachidonate ?

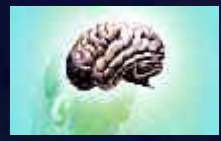
Relation entre contenu en glycogène et libération de lactate

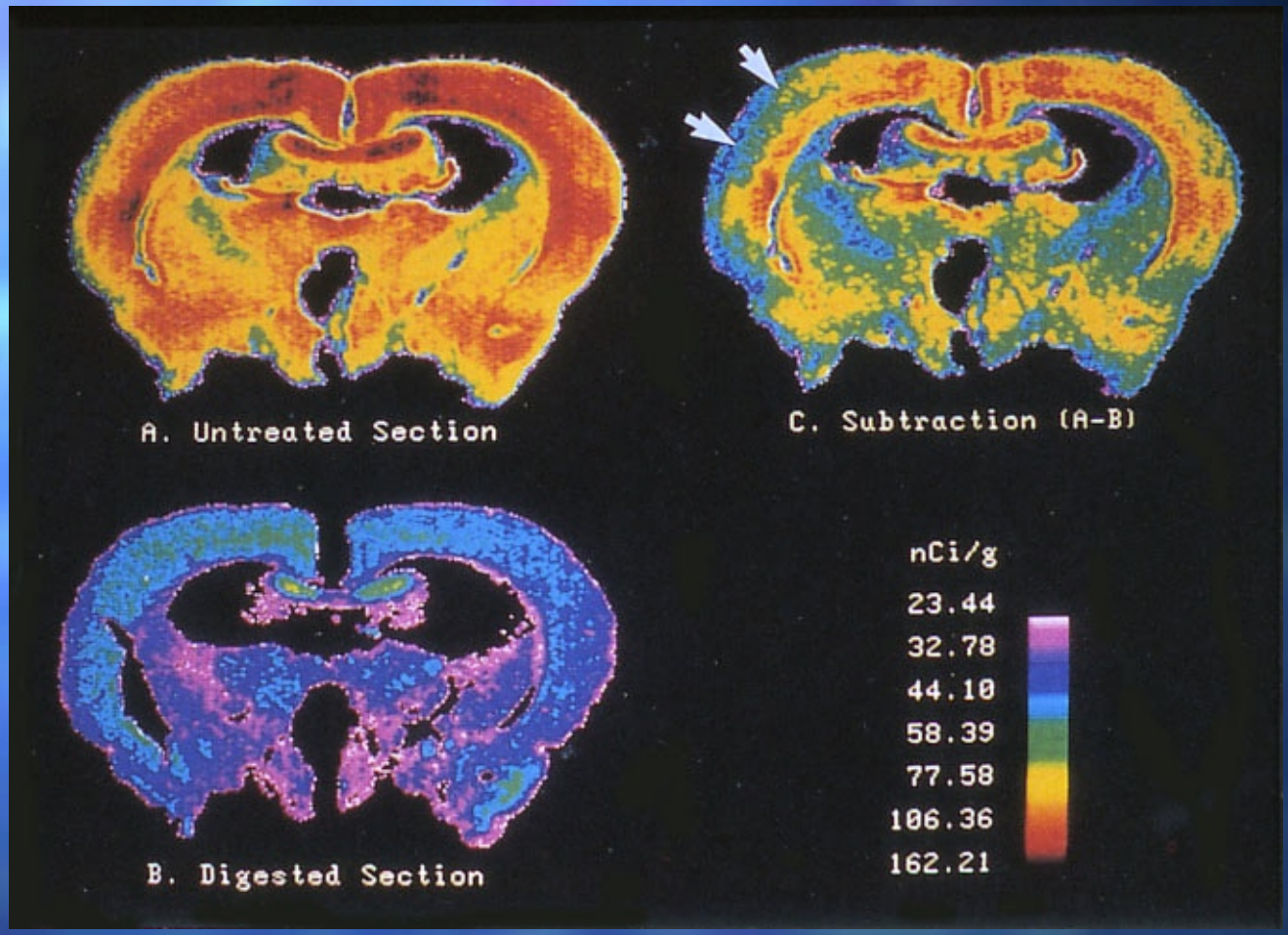




Dringen et al, 1993

Glycogenolyse suite à une stimulation sensorielle





Glycogen levels decrease in somato-sensory cortex following vibrissae stimulation in the rat (from Swanson et al., 1992).