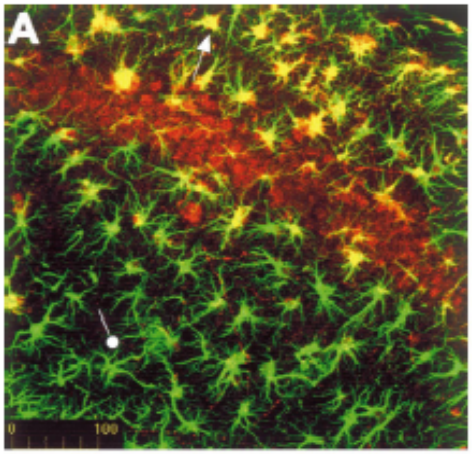
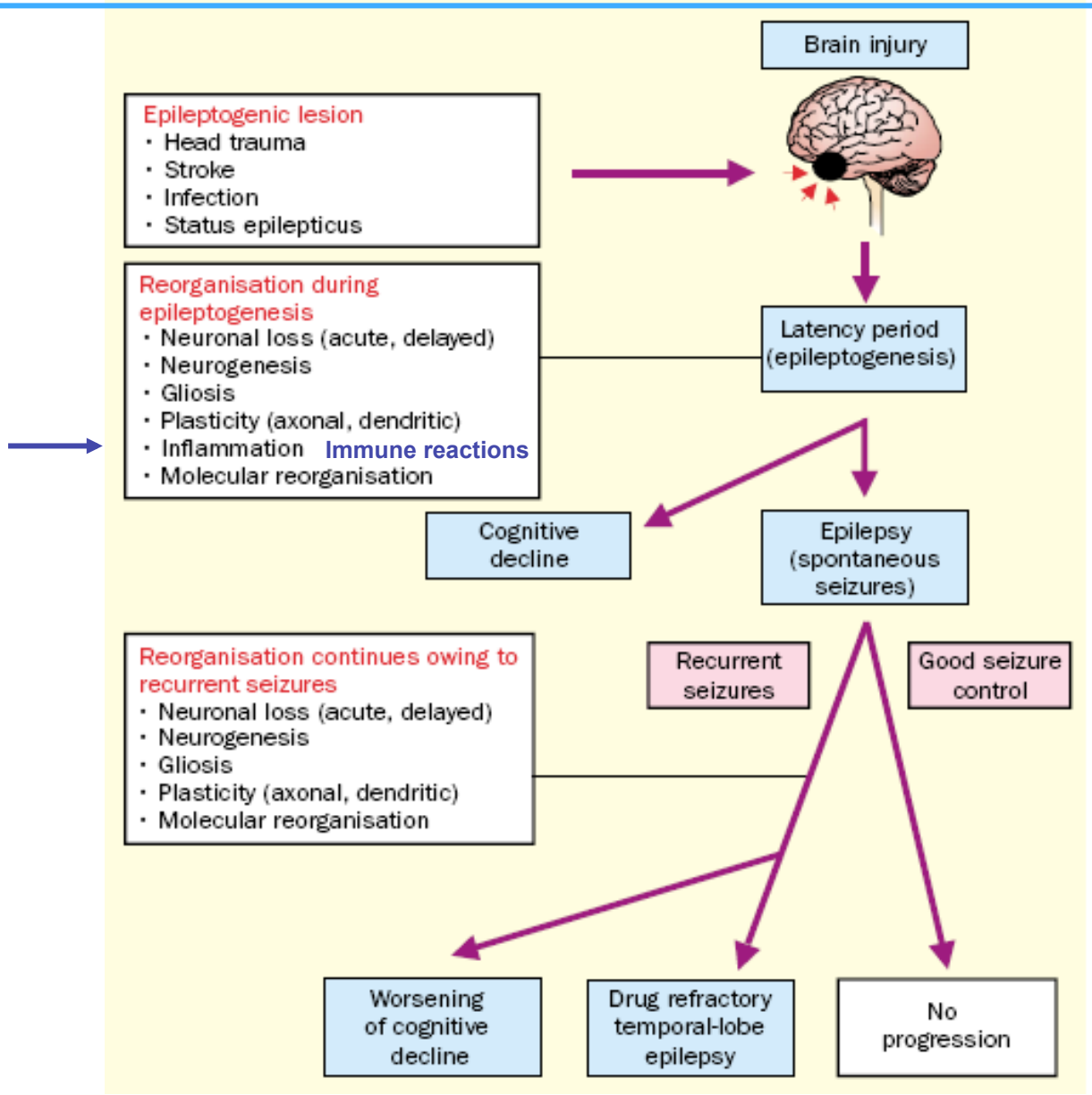


Inflammation et Epilepsies

Mireille Lerner-Natoli, PhD

Institut de Génomique Fonctionnelle
CNRS UMR5203 - INSERM U661 - Universités Montpellier I et II

Hypothèses sur la cinétique des évènements au cours de l'épileptogenèse

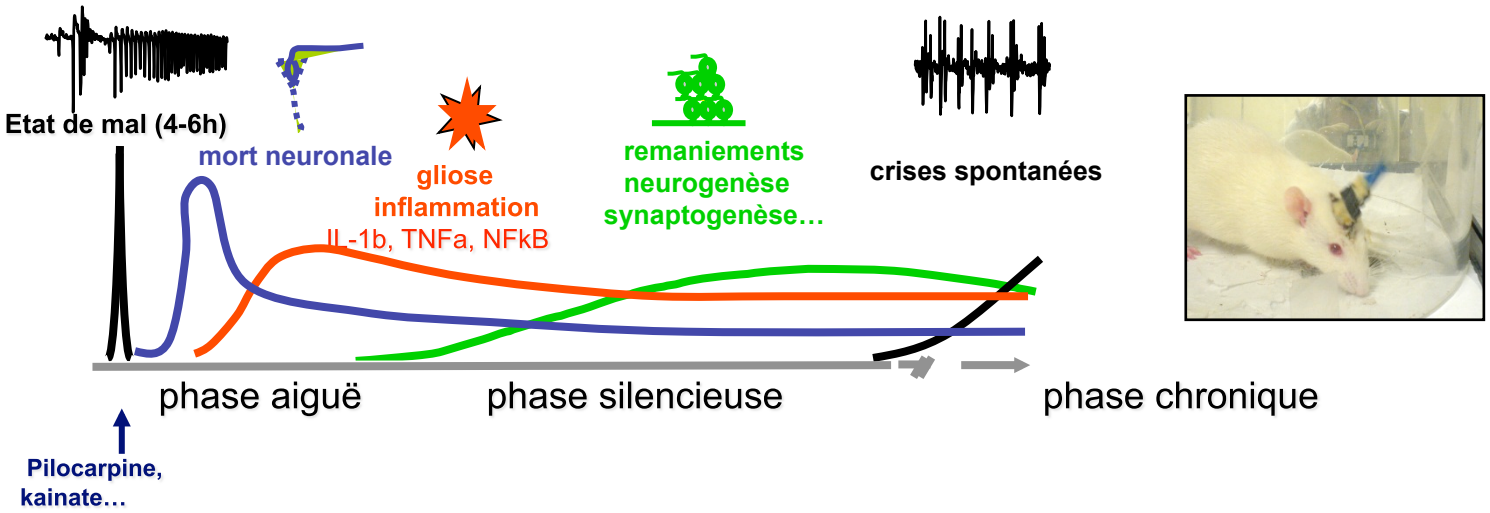


Is epilepsy a progressive disorder ?

Pitkanen & Sutula,
Lancet Neurol, 2002

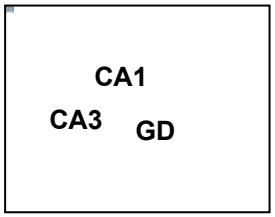
Cinétique et mécanismes de l'épileptogenèse abordés par les modèles animaux

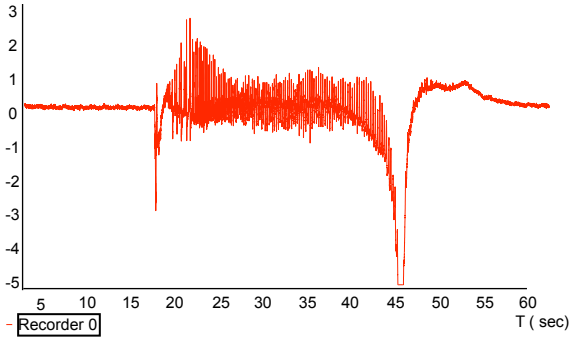
- in vivo (rats/souris):

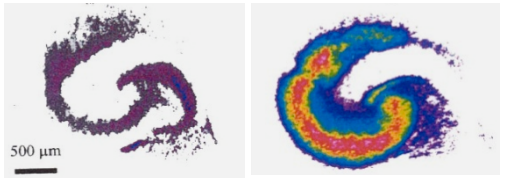


- in vitro (rats/souris):
  - modèle ***in vitro*** (rats) : cultures organotypiques d'hippocampe de rats

    Traitement kainate induit des **crises et des lésions comparable à l'*in vivo***







Incorporation de PI (zones lésées en rouge) *(De Bock et al, 1996)*

Contrôle *Kainate*

Epilepsie expérimentale: la crise induit la production gliale de cytokines

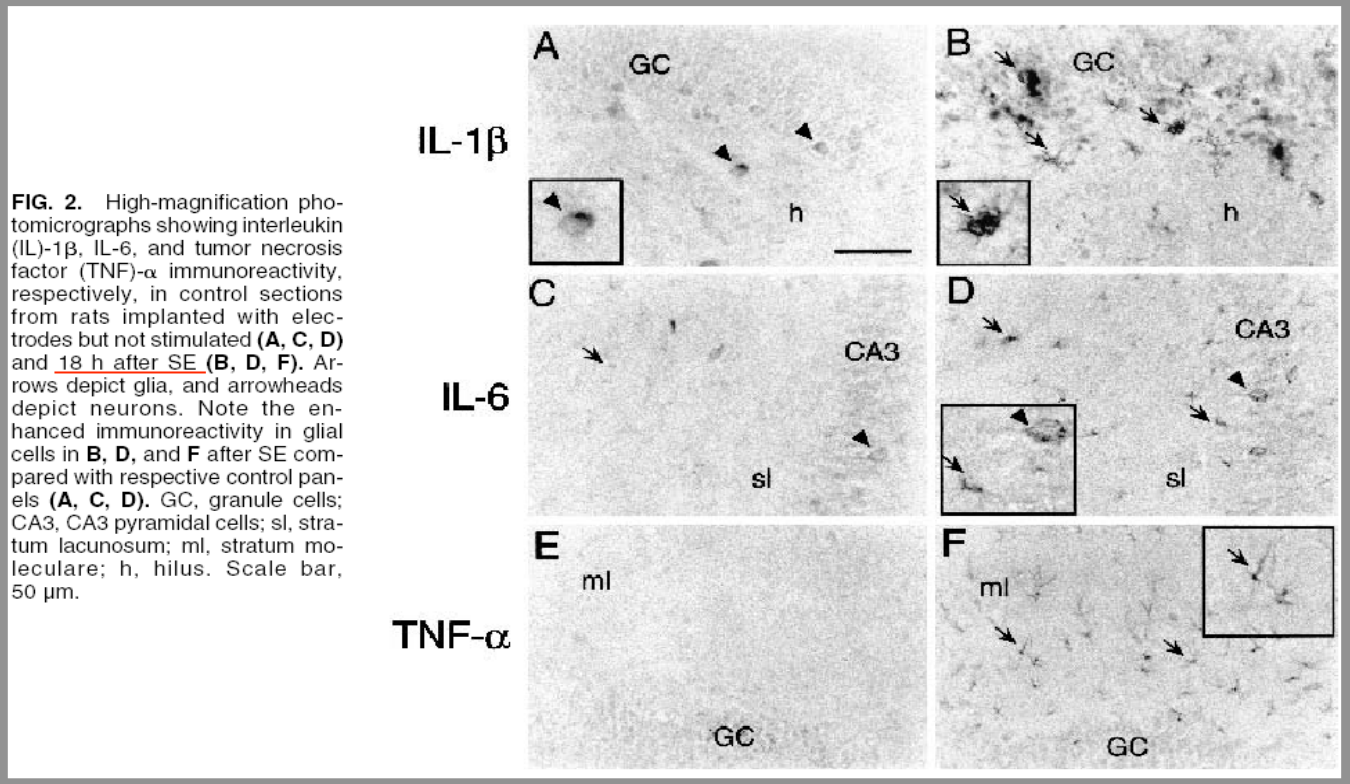
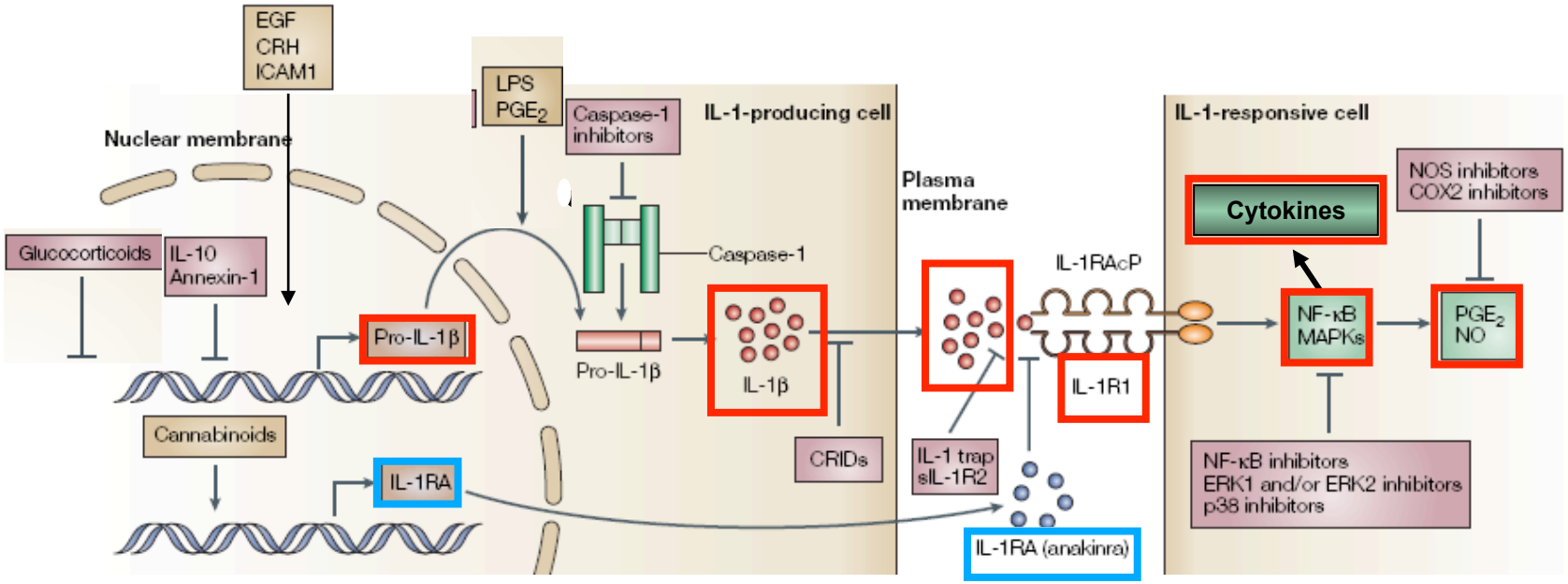


FIG. 2. High-magnification photomicrographs showing interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α immunoreactivity, respectively, in control sections from rats implanted with electrodes but not stimulated **(A, C, D)** and 18 h after SE **(B, D, F).** Arrows depict glia, and arrowheads depict neurons. Note the enhanced immunoreactivity in glial cells in **B, D,** and **F** after SE compared with respective control panels **(A, C, D).** GC, granule cells; CA3, CA3 pyramidal cells; sl, stratum lacunosum; ml, stratum moleculare; h, hilus. Scale bar, 50 μm.

Vezzani A, Moneta D, Richichi C, Aliprandi M, Burrows SJ, Ravizza T, Perego C, De Simoni MG ***Epilepsia 2002;43:30-5***

L'**interleukine-1β** et son antagoniste naturel **IL-1RA** : un rôle majeur dans la neuro-inflammation



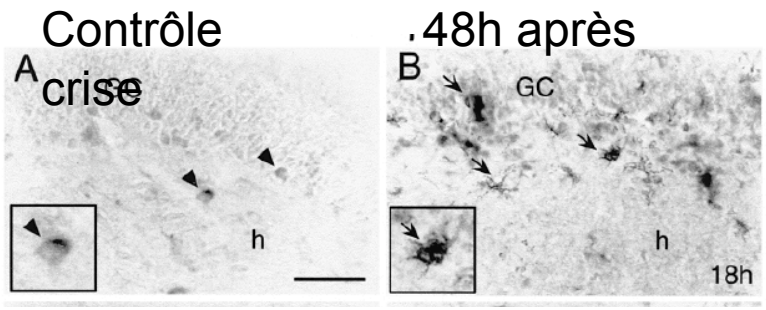
INTERLEUKIN-1 AND NEURONAL INJURY

NATURE REVIEWS | IMMUNOLOGY
VOLUME 5 | AUGUST 2005 | 631

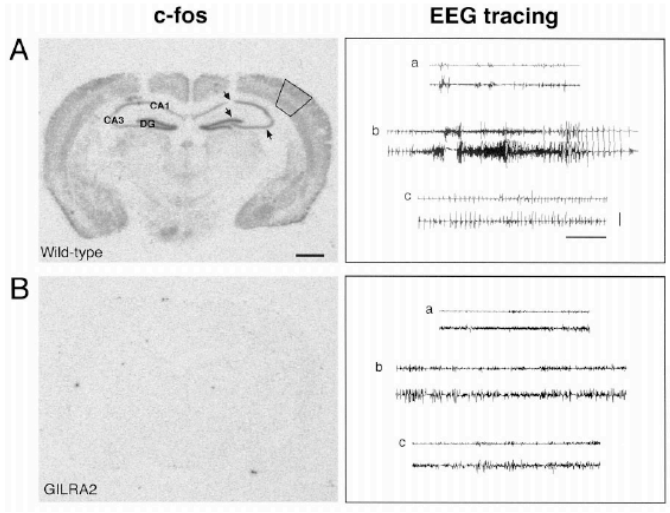
Stuart M. Allan, Pippa J. Tyrrell‡ and Nancy J. Rothwell**

Expression et rôle de l'IL-1-β et de son antagoniste naturel l'IL-1RA dans l'épilepsie expérimentale (Vezzani 1992-2007…)

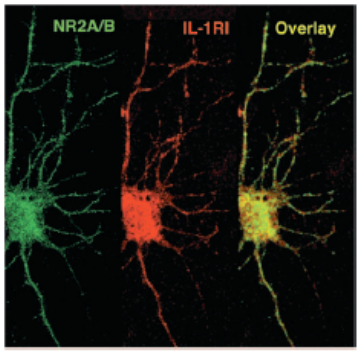
IL1-β

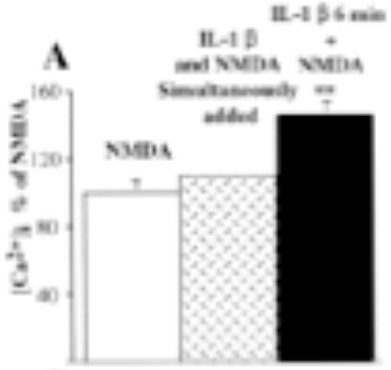


2h après une crise, l'IL-1b puis l'antagoniste IL-1RA sont sécrétés par la microglie (+ astrocytes et neurones)



L'expression constitutive de l'IL-1RA a un effet inhibiteur sur les crises expérimentales





L'IL-1β en se liant à son récepteur IL-1R facilite l'activation du récepteur au glutamate NMDA

=> IL-1b = « cytokine épileptogène »

IL-1β : la nouvelle cible thérapeutique

Epilepsy	Increased expression of IL-1 in brain parenchyma; polymorphisms in genes encoding IL-1 might influence susceptibility

Inactivation of Caspase-1 in Rodent Brain: A Novel Anticonvulsive Strategy

Ravizza, Lucas, Balosso, Bernardino, Ku, Noé, Malva, . Randle, Allan, Vezzani. Epilepsia 2006

Dans un modèle de SE au kainate chez le rat, le pralnacasan (inhibiteur de Caspase-1) bloque la production d'IL-1β, retarde les crises et réduit leur durée.

Les souris mutantes pour la caspase-1 ont des crises moins sévères (-70%) que les souris sauvages

Interleukin 1 in the brain: biology, pathology and therapeutic target

Nancy J. Rothwell and Giamal N. Luheshi

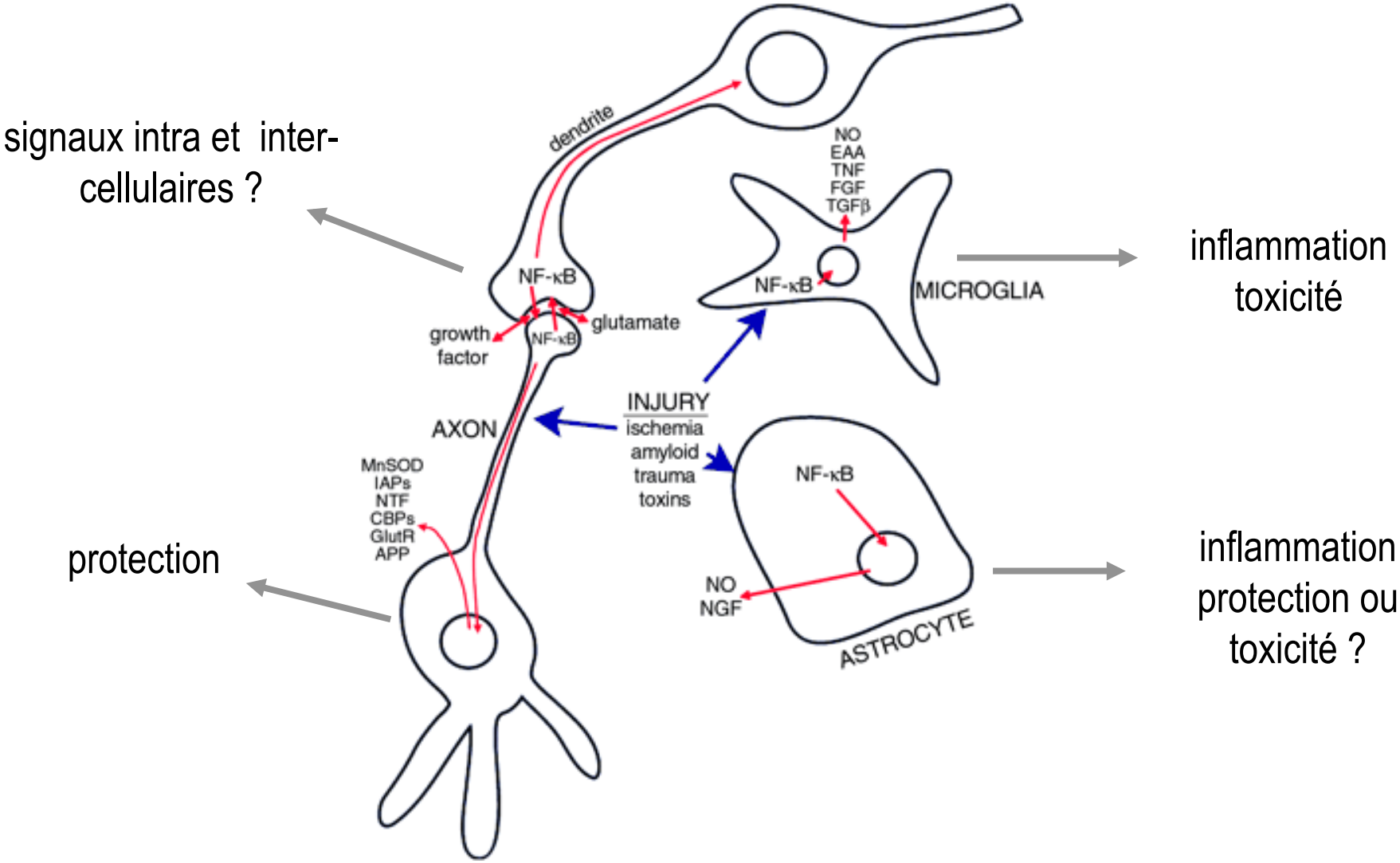
Trends Neurosci. (2000) 23, 618–625

TABLE 1. Regulation of IL-1 activity

Regulator	Effect	Refs
	Stimulatory	
IL-1	Induction of IL-1	79
	IL-1ra expression	80
Bacterial products e.g. LPS, muramyl dipeptide	Increased IL-1 expression	81
	Caspase 1 activity	82–84
	Common signalling with IL-1	85
Hypoxia	Increased IL-1 expression	86,87
	Caspase-1 activity	88,89
	Induction of IL-1ra	90
Extracellular ATP	Increased IL-1 expression and release	91
	Caspase 1 activity	10,11,92
	Induction of IL-1ra	12
Leptin	Induction of hypothalamic IL-1	41
	Inhibitory	
Glucocorticoids	Inhibition of IL-1 expression	50,93
	Induction of IL-1RII	50,93
	Inhibition of IL-1 actions	50,93
Lipocortin-1	Inhibition of IL-1 expression and release	94
IL-4, IL-10	Inhibition of IL-1 expression	95,96
	Inhibition of IL-1 actions	97
Cannabinoids	Inhibition of IL-1 expression	[a]
	Inhibition of IL-1 actions	
	Induction of IL-1ra	

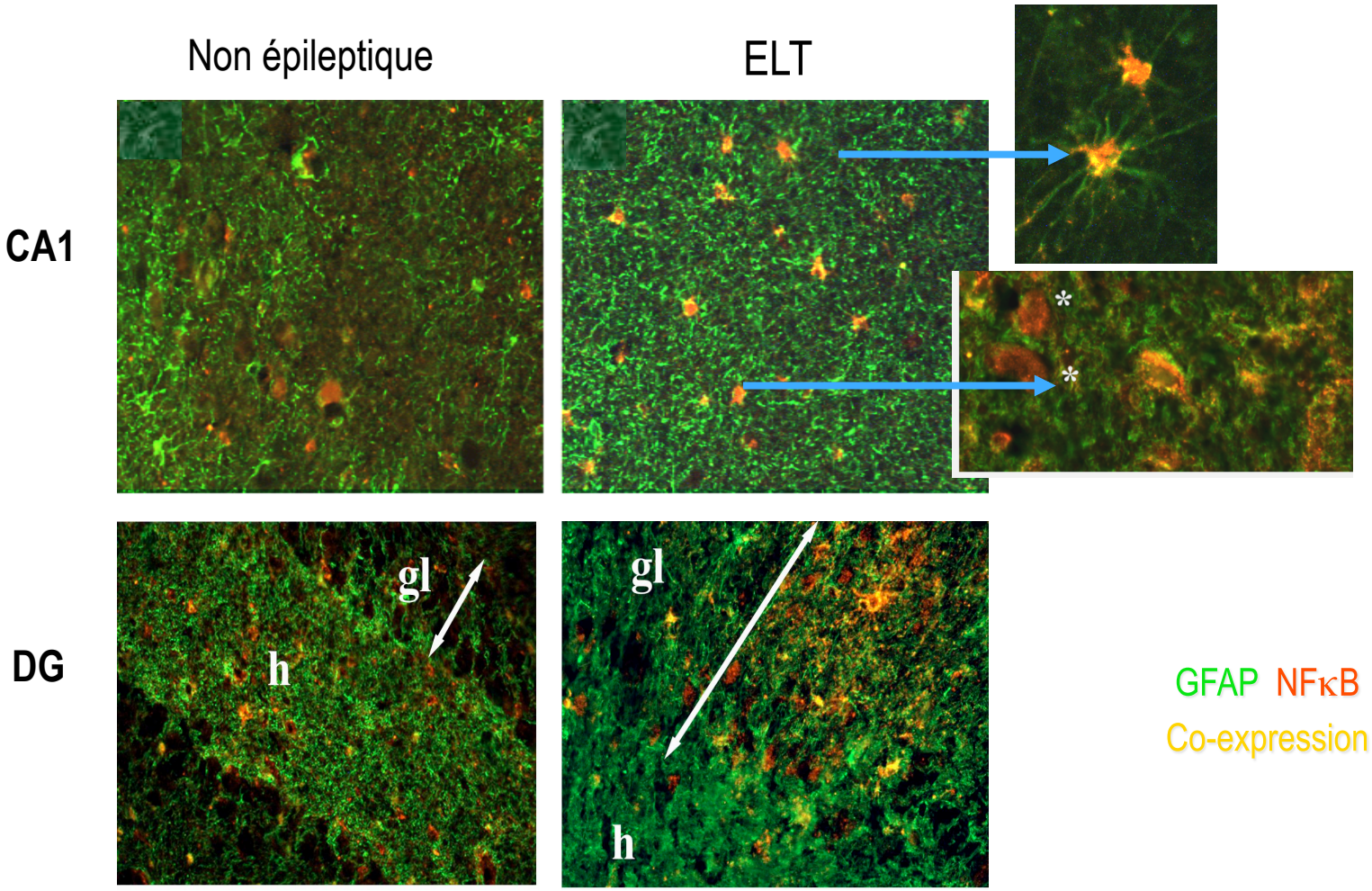
[a]F. Molina-Holgado and N.J. Rothwell, unpublished observations.
Abbreviations: IL-1, interleukin 1; IL-4, interleukin 4; IL-10, interleukin 10; IL-RII, IL-1 receptor II; IL-1ra, IL-1 receptor antagonist; LPS, lipopolysaccharide.

NFκB, chef d'orchestre de la neuro-inflammation ?



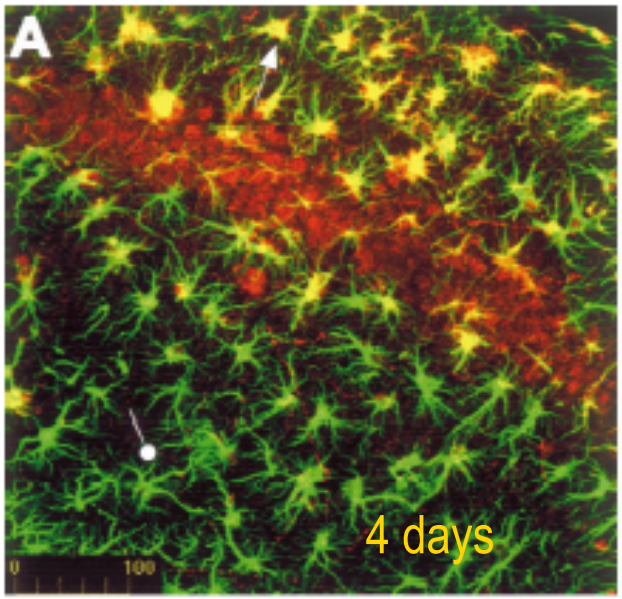
MATTSON & CAMADOLA 2001

Expression de NFkB par les astrocytes et les neurones dans l'ELT avec SH

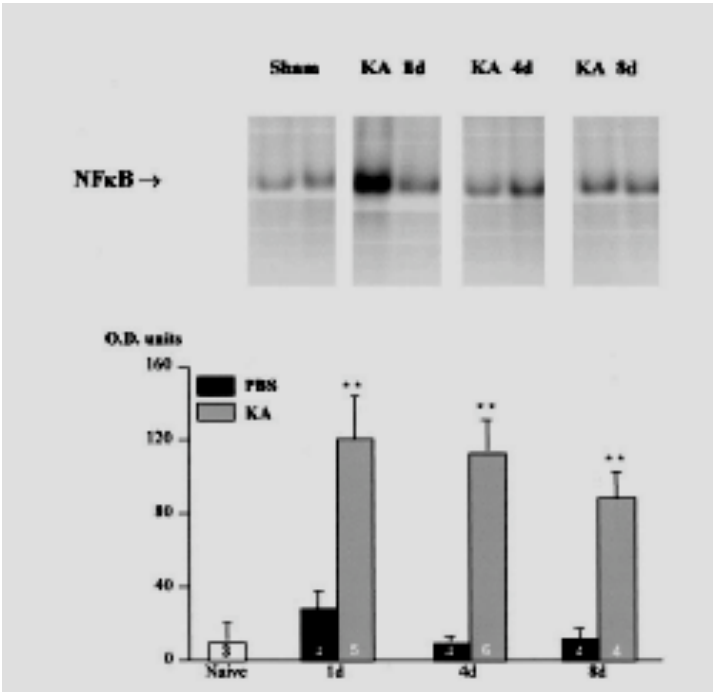


CRESPEL et al. 2002

Expression de NFkB par les astrocytes et les neurones dans l'épilepsie expérimentale chez le rat



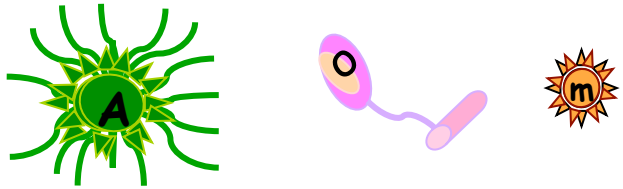
GFAP NFκB co-expression



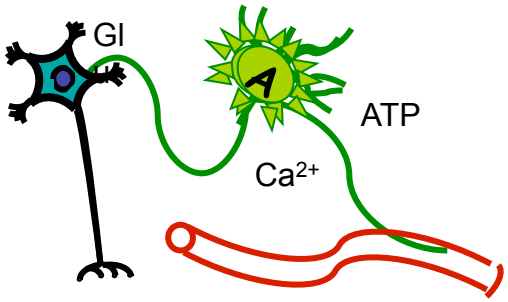
La surexpression de NFκB est associée à une augmentation de sa liaison à l'ADN => activité transcriptionnelle

LERNER-NATOLI et al. 2000

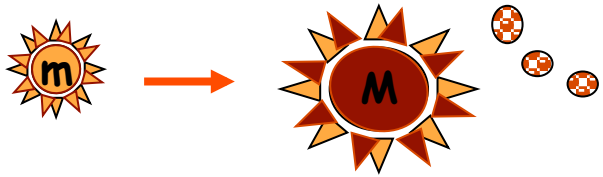
Gliose réactionnelle et épilepsies symptomatiques



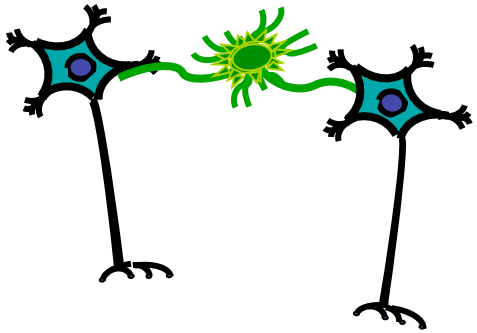
Glio-transmission



Inflammation



Synchronisation neuronale



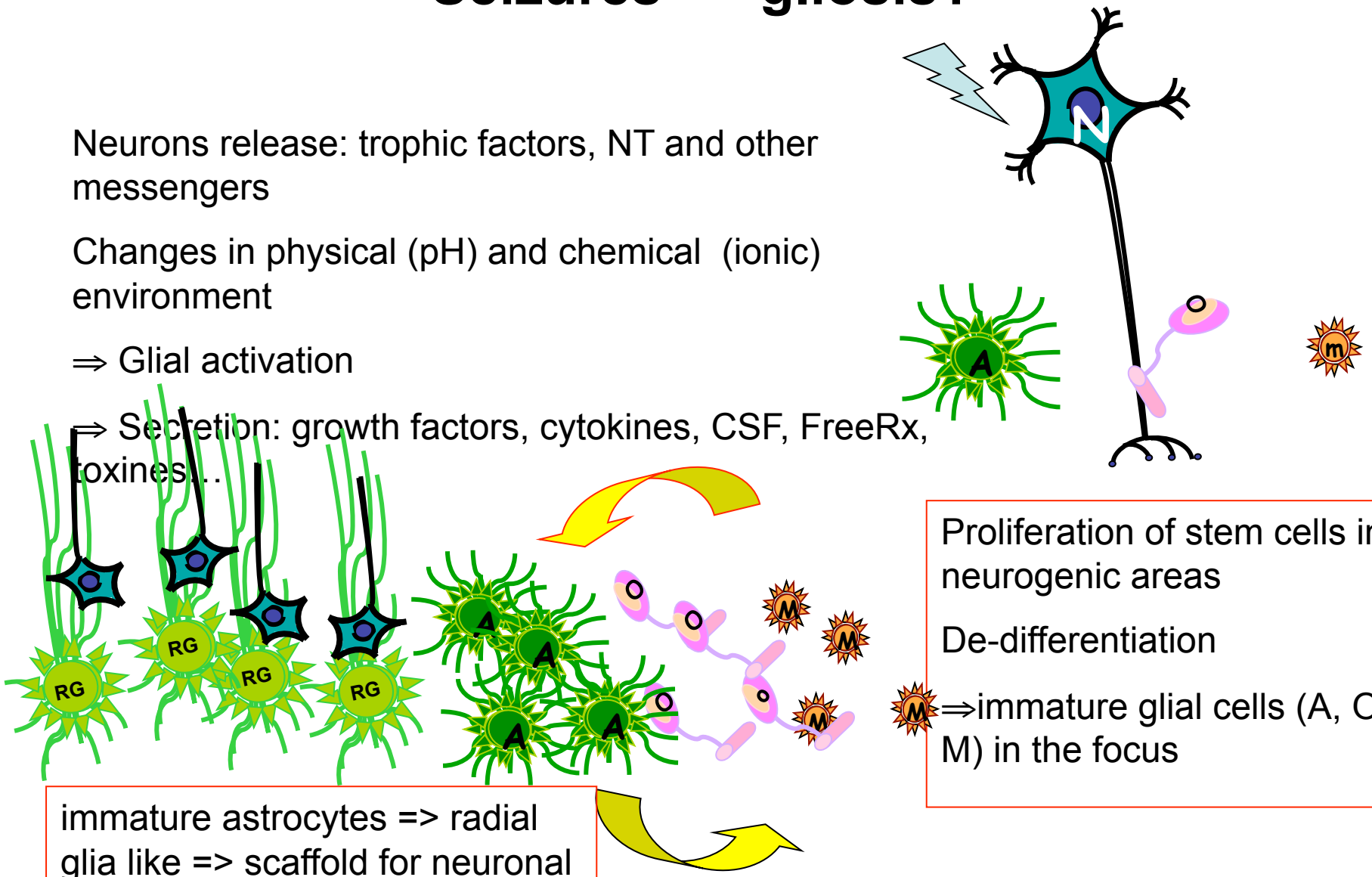
Seizures => gliosis?

Neurons release: trophic factors, NT and other messengers

Changes in physical (pH) and chemical (ionic) environment

⇒ Glial activation

⇒ Secretion: growth factors, cytokines, CSF, FreeRx, toxines…



immature astrocytes => radial glia like => scaffold for neuronal ectopic migration => DGD

Proliferation of stem cells in neurogenic areas

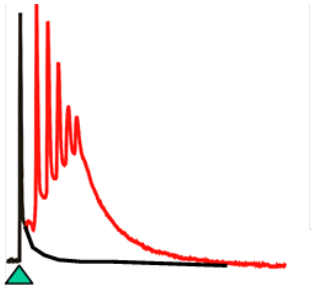
De-differentiation

⇒immature glial cells (A, O, M) in the focus

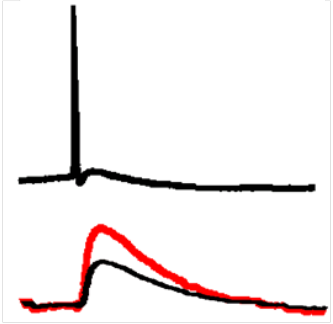
Reactive glia => epileptogenesis ?

Hypothesis about pathophysiology of epilepsies

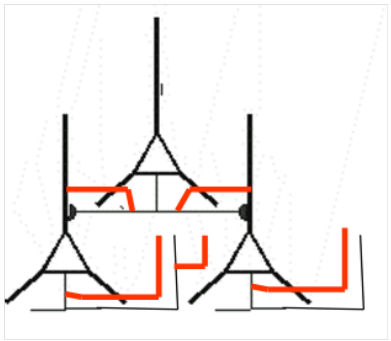
intrinsic properties



synaptic efficacy

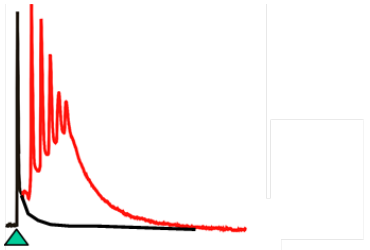


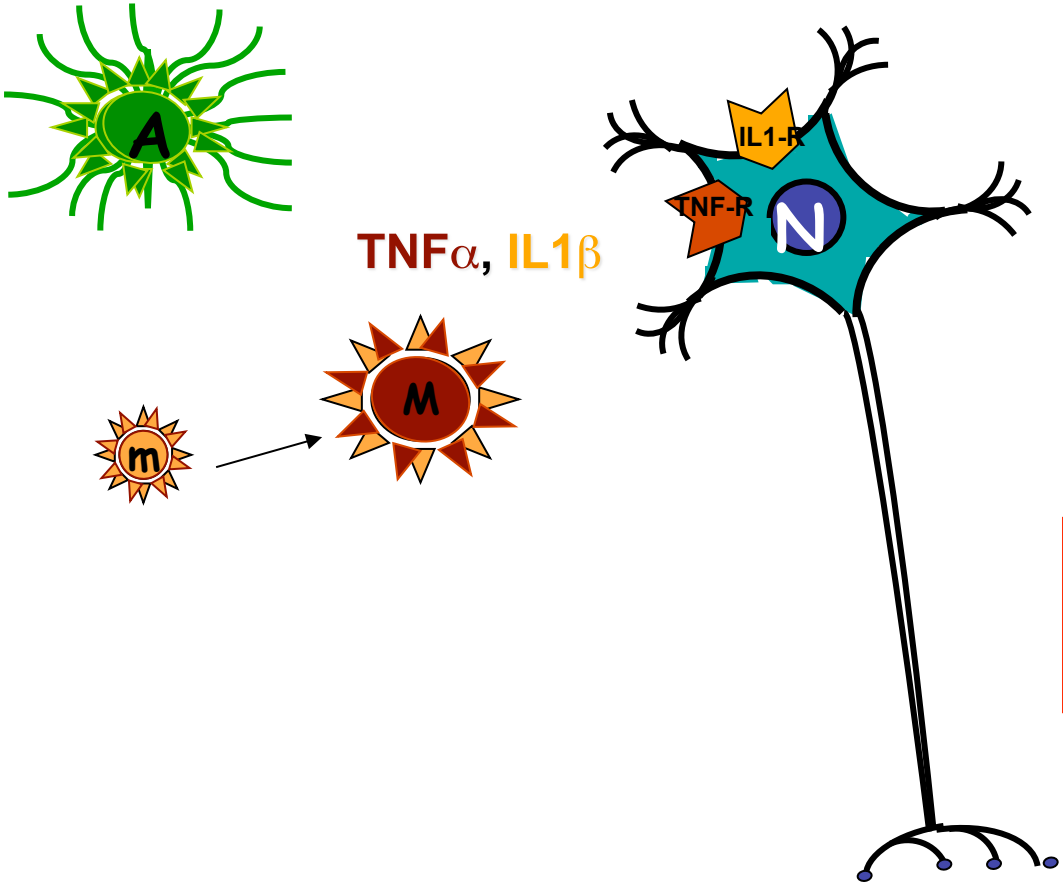
synaptic connectivity



Impact of reactive glia on epileptogenesis at each level?

1- Changes in intrinsic properties
=>
prolong action potentials



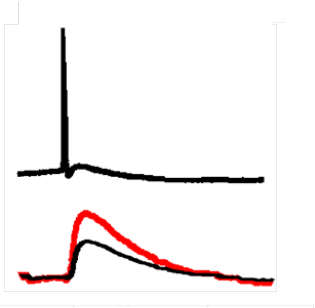


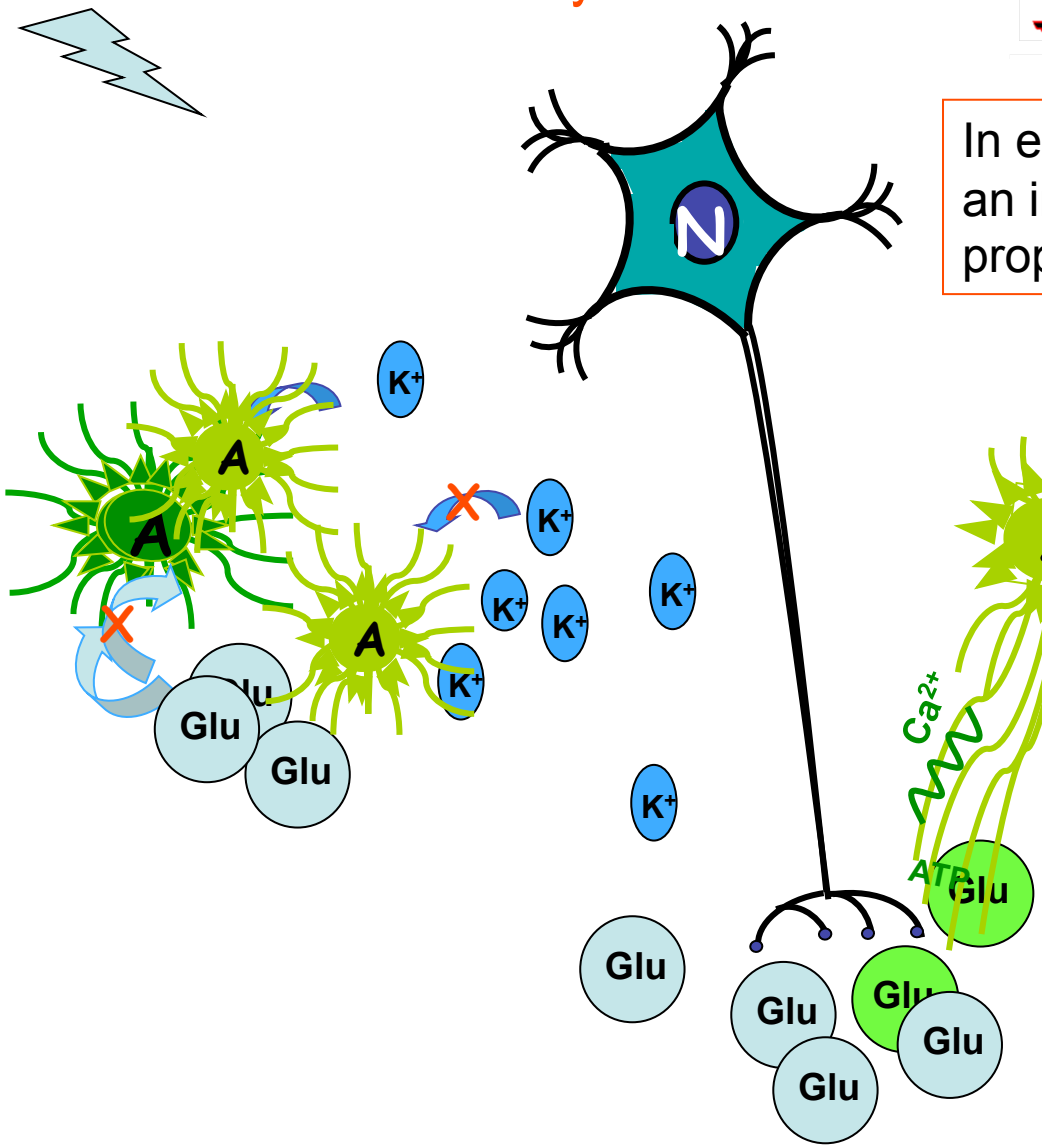
TNF-R =>
AMPA-R exocytosis
$GABA_A$-R endocytosis

IL1β-R => NMDA activation

=> Cytokines secreted by activated glia increase neuron excitability by activation of kinases

2- Synaptic transmission changes => increase excitatory transmission





In epileptic focus, astrocytes display an immature phenotype: their buffering properties for K^+ and Glu decrease.

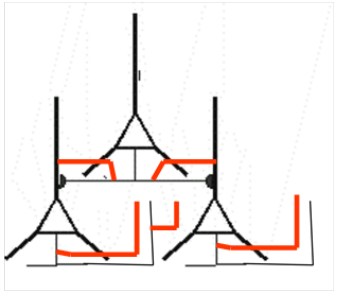
Immature astrocytes with long processes signal to adjacent neurons by releasing glutamate in a calcium-dependent manner.

Therefore astrocytes prevent neuronal repolarisation and increase glutamate concentration in synaptic cleft.

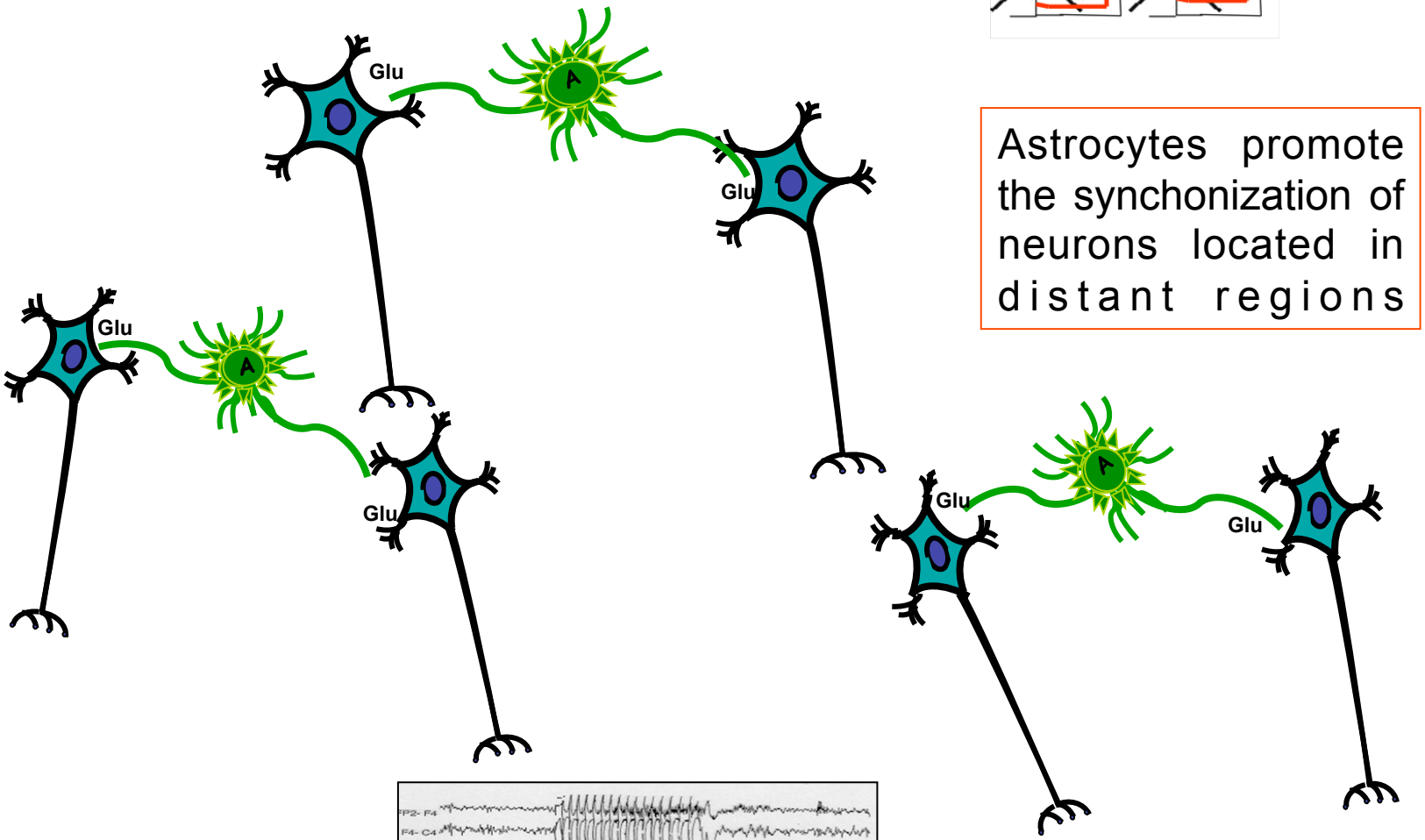
=> EXCITABILITY, TOXICITY

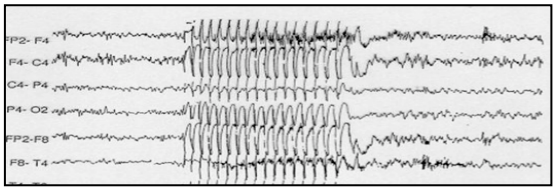
3- recurrent excitation

synaptic connectivity

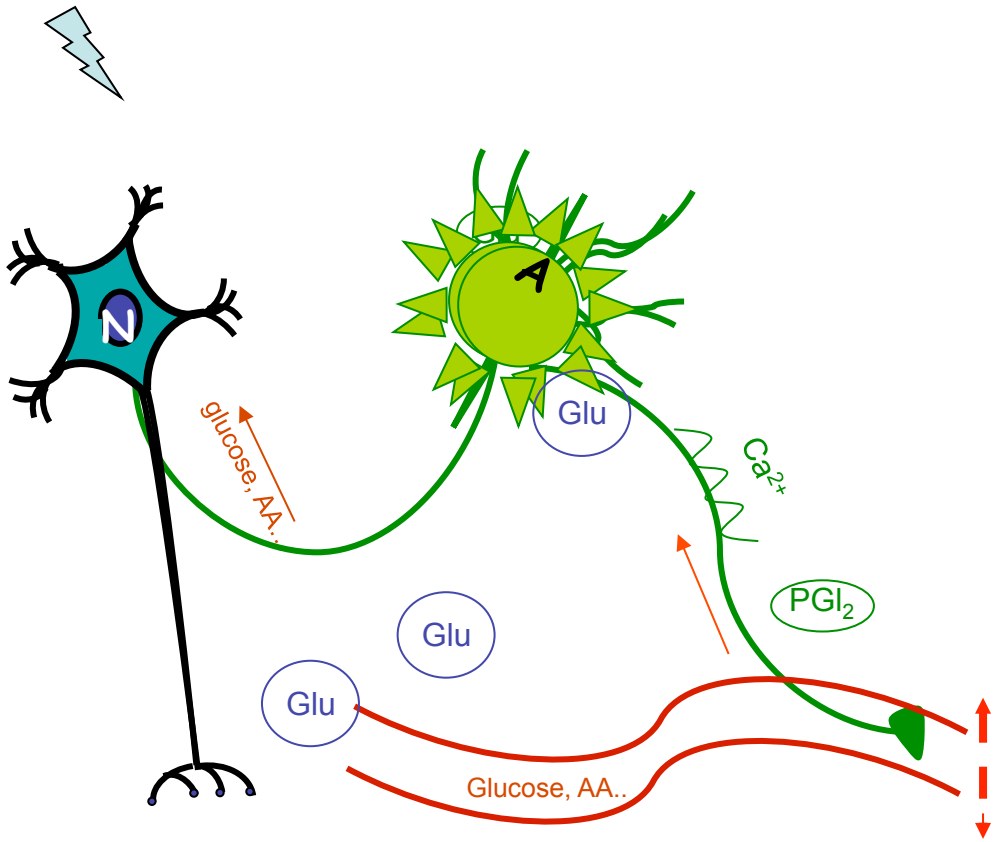


Astrocytes promote the synchonization of neurons located in distant regions





4- Other effects : neuro-vascular coupling

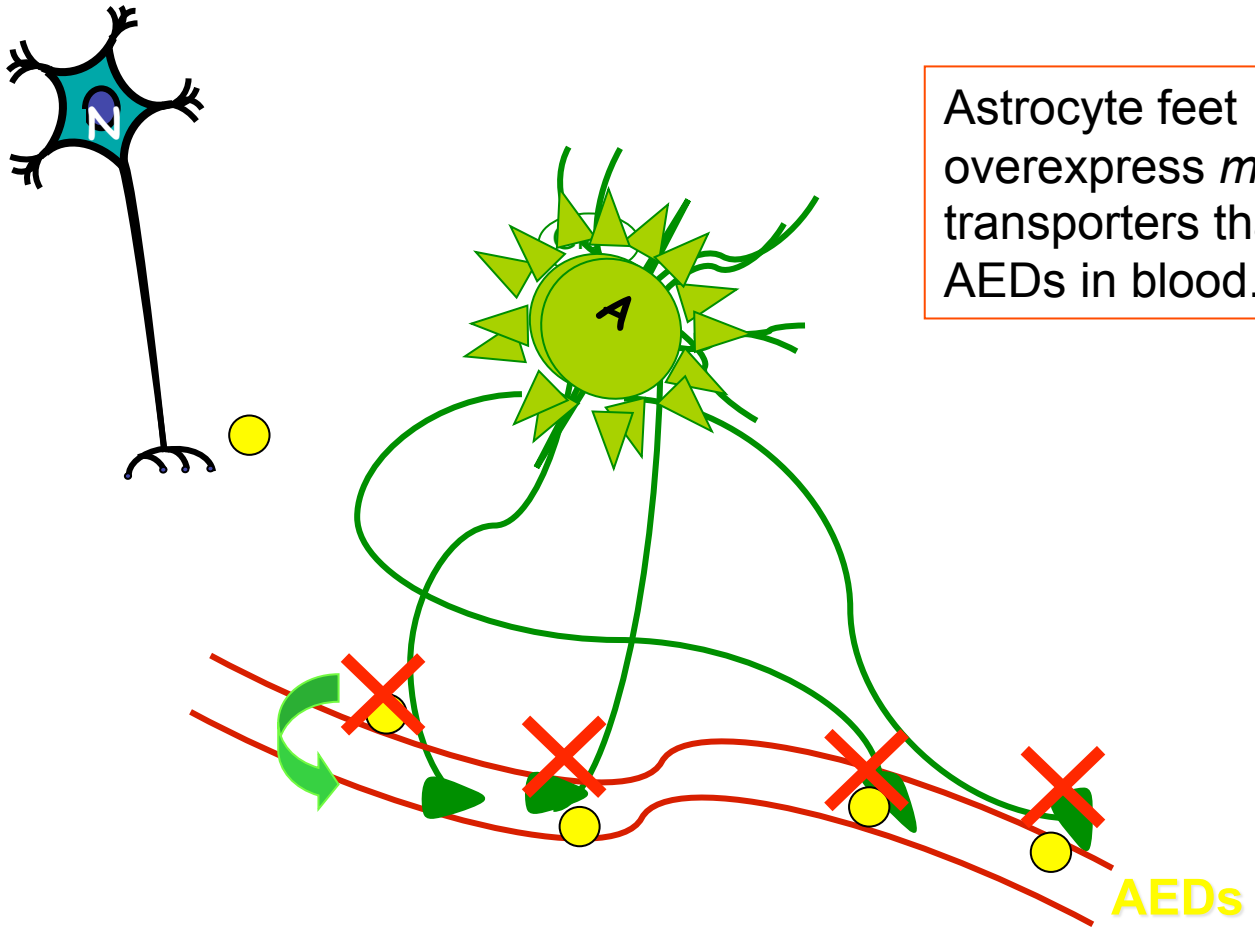


During seizures, neurons release glutamate =>

Astrocytes adapt blood flow to the neuronal energetic demand.

DSC adaptation

5- Other (putative) effects : pharmaco-resistance?



Astrocyte feet overexpress *mdr* transporters that reject AEDs in blood.

Perspectives ?

Complex cross talk between neurons and glial cells during seizures and in the chronic focus…

Further investigations should focus on microglial cells and oligodendrocytes and their participation in excitability...

The FASEB Journal article fj.07-090985. Published online May 8, 2008.
The FASEB Journal • Research Communication

Glial cells are born with synapses

Maria Kukley,*,[1] Maia Kiladze,* Reshmi Tognatta,* Michael Hans,[†] Dieter Swandulla,[†] Johannes Schramm,* and Dirk Dietrich*,[1]

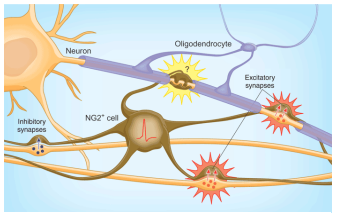
Glia get excited

Thomas S Otis & Michael V Sofroniew

nature neuroscience
NEWS AND VIEWS

Spiking and nonspiking classes of oligodendrocyte precursor glia in CNS white matter

Ragnhildur Káradóttir[1,2], Nicola B Hamilton[1], Yamina Bakiri[1] & David Attwell[1]

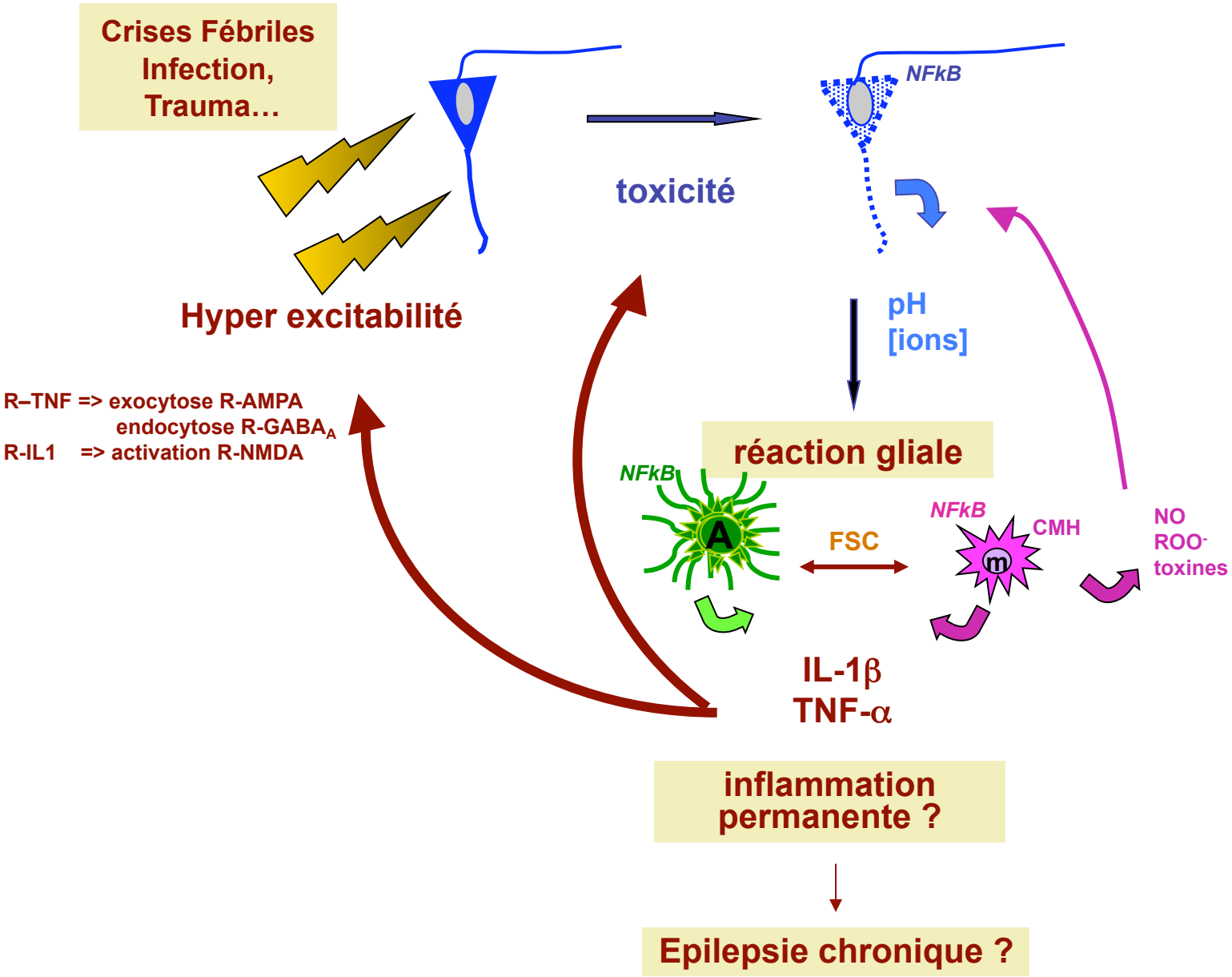


VOLUME 11 | NUMBER 4 | APRIL 200

Review TRENDS in Neurosciences Vol.30 No.10

Neurotransmitter receptors on microglia

Jennifer M Pocock[1] and Helmut Kettenmann[2]


Crises Fébriles
Infection,
Trauma…
Hyper excitabilité
toxicité
NFkB
pH
[ions]
R–TNF => exocytose R-AMPA
endocytose R-GABA$_A$
R-IL1 => activation R-NMDA
réaction gliale
NFkB
A
FSC
NFkB
CMH
m
NO
ROO-
toxines
IL-1β
TNF-α
inflammation
permanente ?
Epilepsie chronique ?

Autre source d’inflammation dans le foyer épileptique:

inflammation vasculaire

=> fuites de leucocytes et protéines sériques

?

…

Epileptogenicité de l'inflammation vasculaire

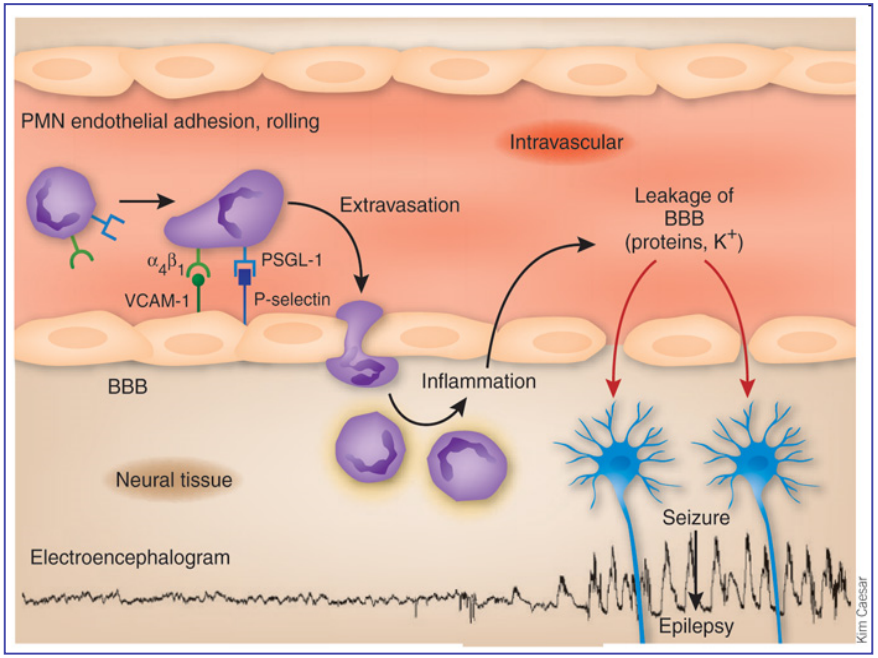
nature medicine 2008

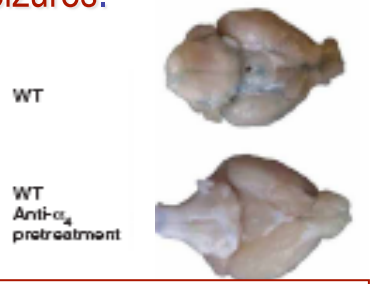
A role for leukocyte-endothelial adhesion mechanisms in epilepsy

Paolo F Fabene[1], Graciela Navarro Mora[1], Marianna Martinello[2], Barbara Rossi[2], Flavia Merigo[1], Linda Ottoboni[2], Simona Bach[2], Stefano Angiari[2], Donatella Benati[1], Asmaa Chakir[1], Lara Zanetti[1], Federica Schio[1], Antonio Osculati[3], Pasquina Marzola[4], Elena Nicolato[1], Jonathon W Homeister[5], Lijun Xia[6], John B Lowe[7], Rodger P McEver[6], Francesco Osculati[1,8], Andrea Sbarbati[1], Eugene C Butcher[9,10] & Gabriela Constantin[2]

Seizures activate vascular CAM => ↑ leukocyte extravasation

Inhibiting leukocyte-endothelial interactions or P-selectin interactions reduces seizures.





NATURE|Vol 457|8 January 2009

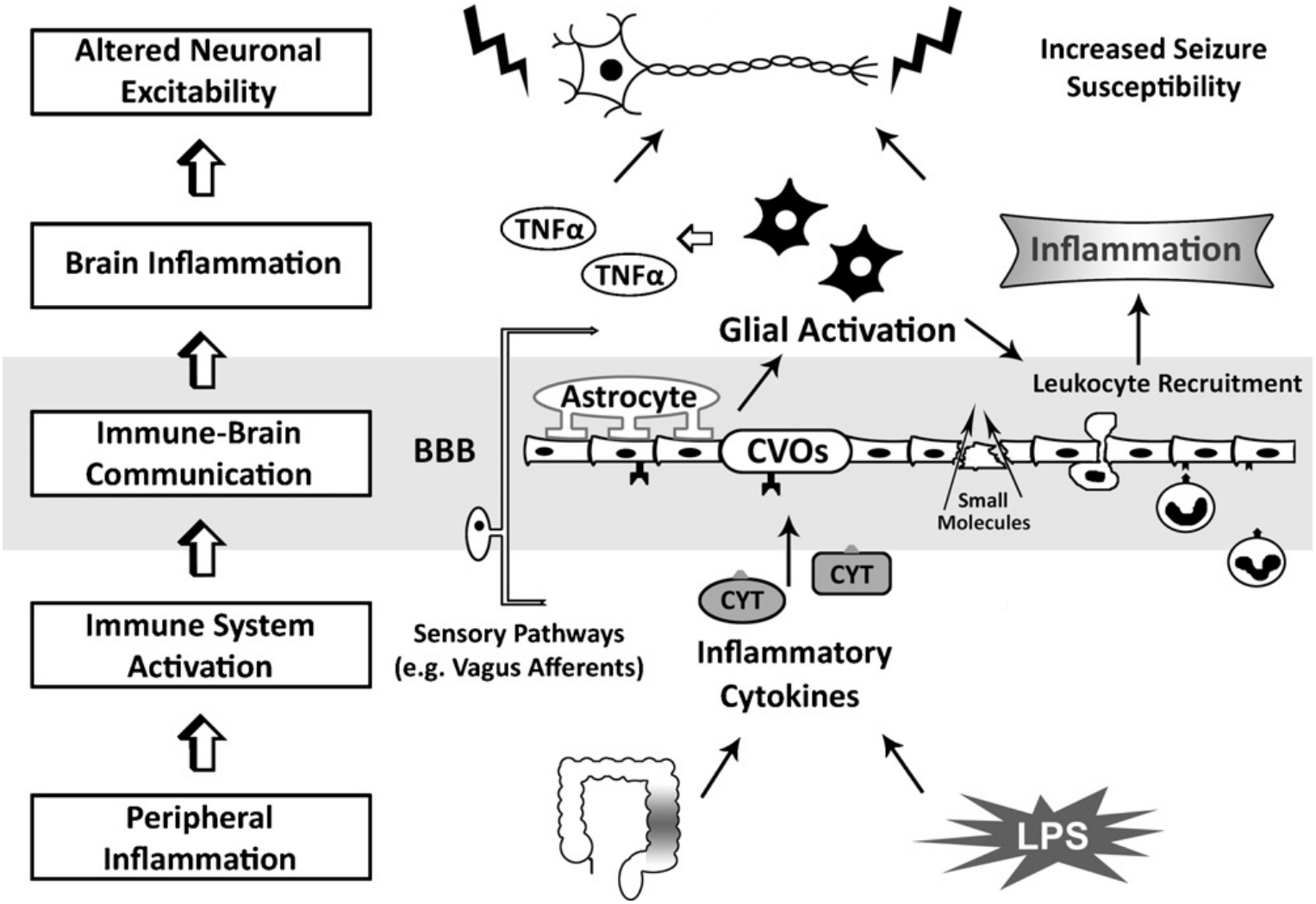
IMMUNOLOGY

Barrier to electrical storms

Richard M. Ransohoff

Epilepsy is characterized by repetitive seizures due to abnormal electrical activity in the brain. Immune cells promote development of this disorder by mediating the breakdown of the blood–brain barrier.

Inflammation périphérique : épileptogène ?



Contributions of peripheral inflammation to seizure susceptibility: Cytokines and brain excitability
Kiarash Riazi , Michael A. Galic, Quentin J. Pittman

Toutes les pathologies aiguës