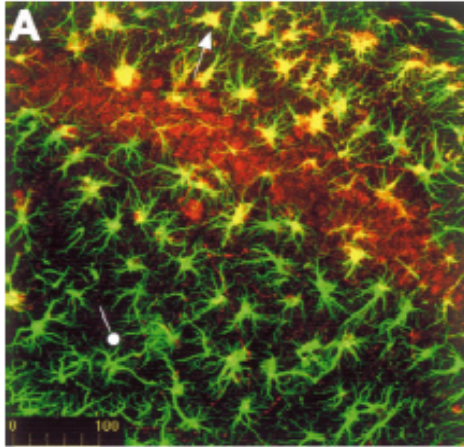




Inflammation et Epilepsies

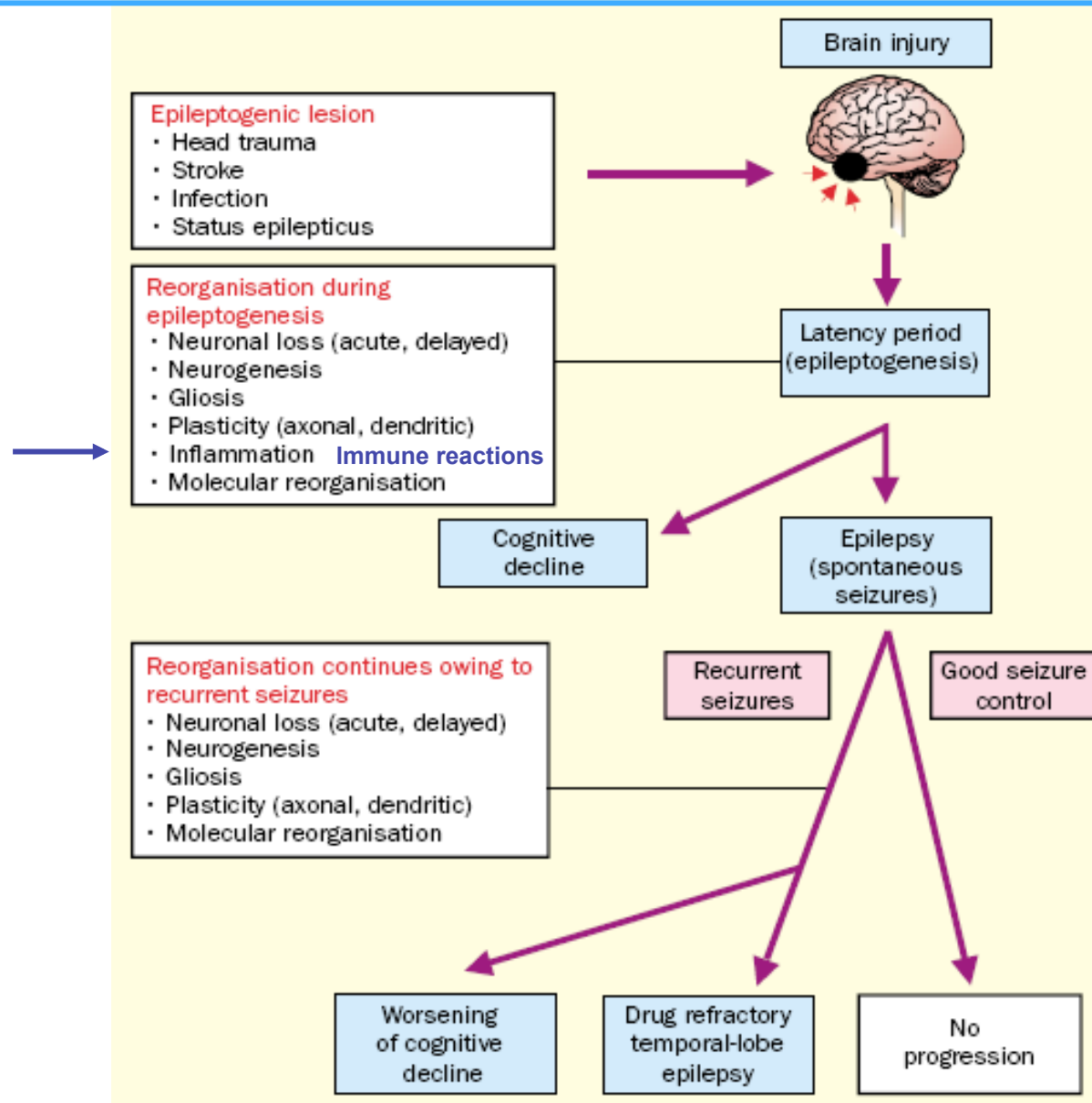
Mireille Lerner-Natoli, PhD



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



Hypothèses sur la cinétique des événements au cours de l'épileptogénèse

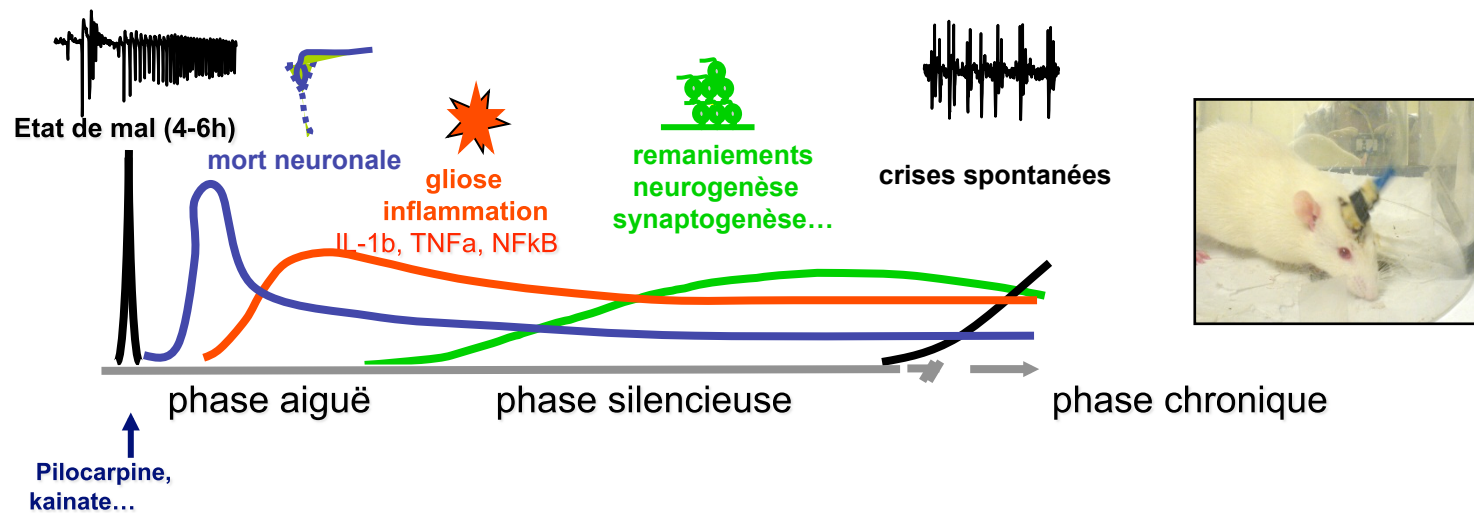


Is epilepsy a progressive disorder ?

Pitkanen & Sutula,
Lancet Neurol, 2002

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

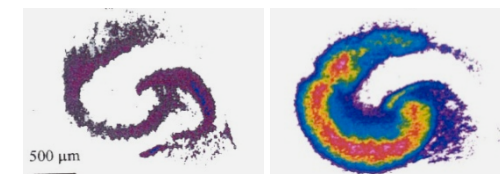
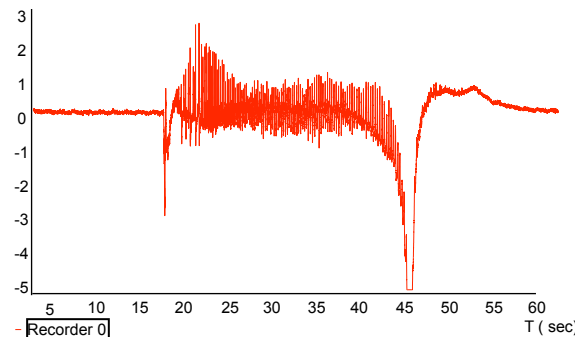
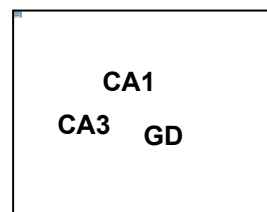
- in vivo (rats/souris):



- 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***

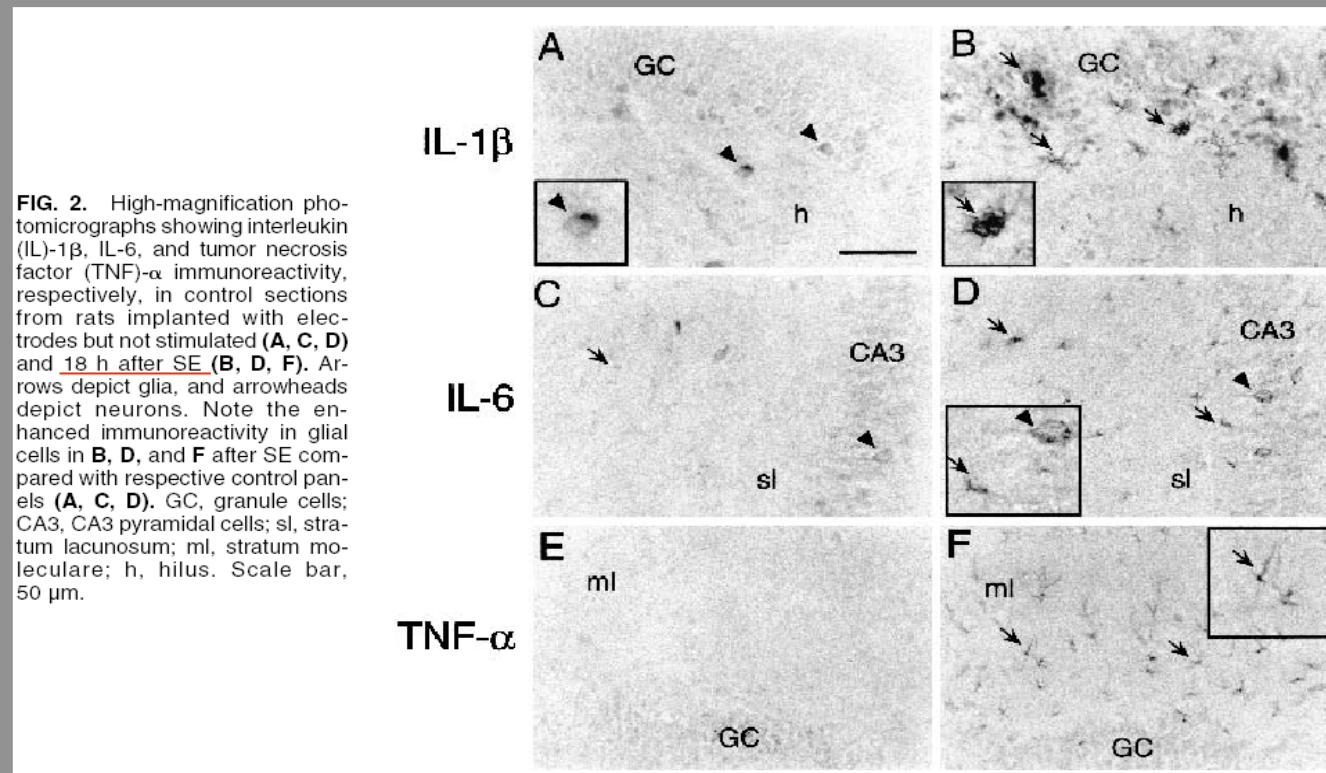


Incorporation de PI (zones lésées en rouge) (De Bock et al, 1996)

Contrôle

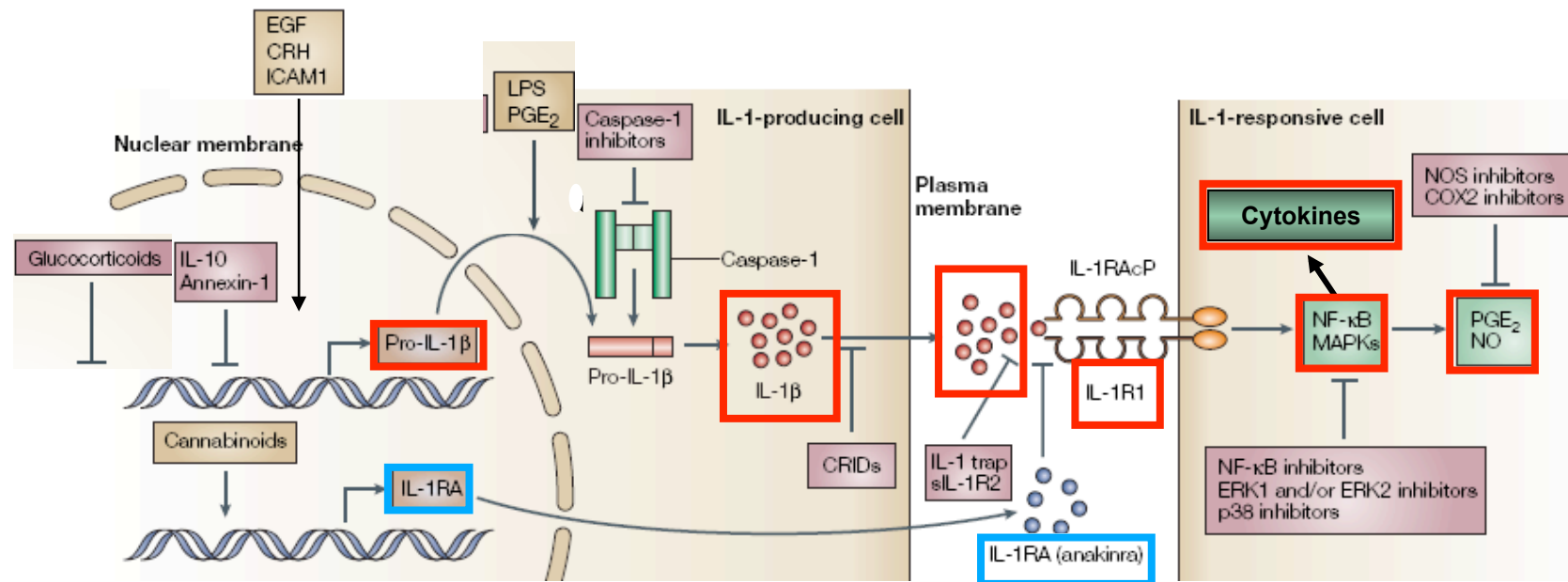
Kainate

Epilepsie expérimentale: la crise induit la production gliale de cytokines



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

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

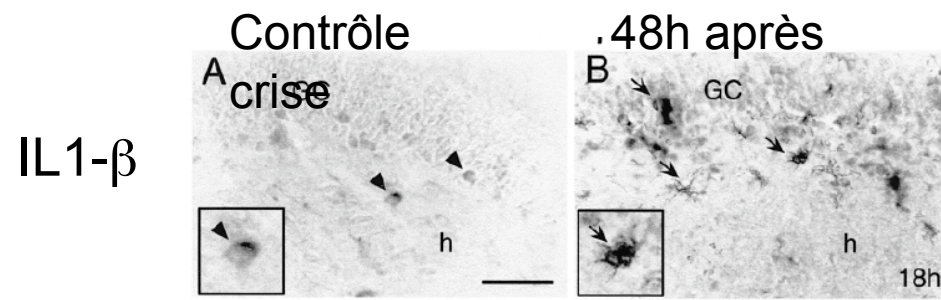


INTERLEUKIN-1 AND NEURONAL
INJURY

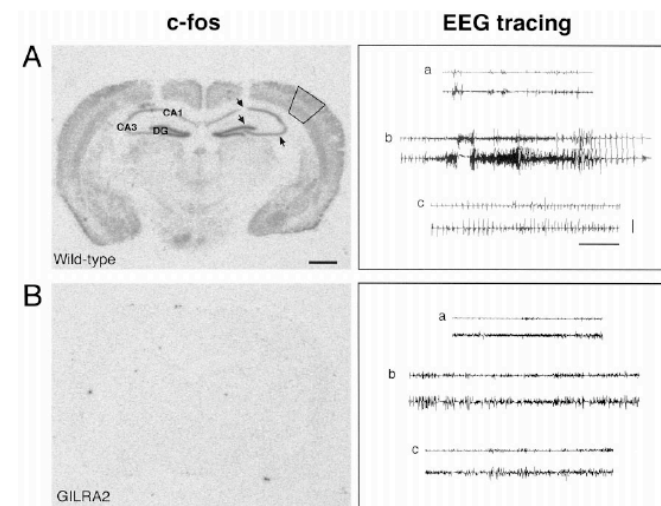
NATURE REVIEWS | IMMUNOLOGY
VOLUME 5 | AUGUST 2005 | 631

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

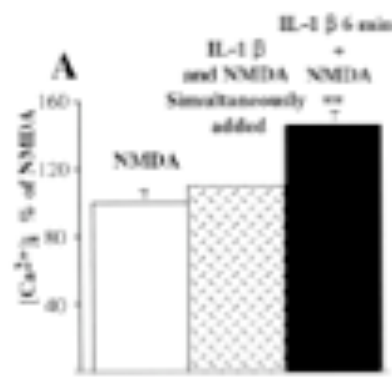
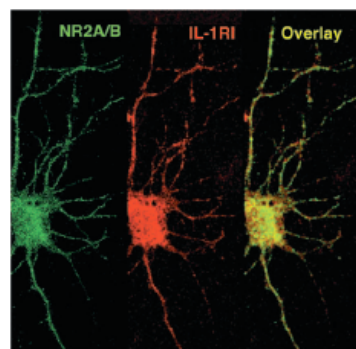
Expression et rôle de l'IL-1 β et de son antagoniste naturel l'IL-1RA dans l'épilepsie expérimentale (Vezzani 1992-2007...)



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



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



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

=> IL-1 β = « cytokine épileptogène »

IL-1 β : 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-1 β , 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

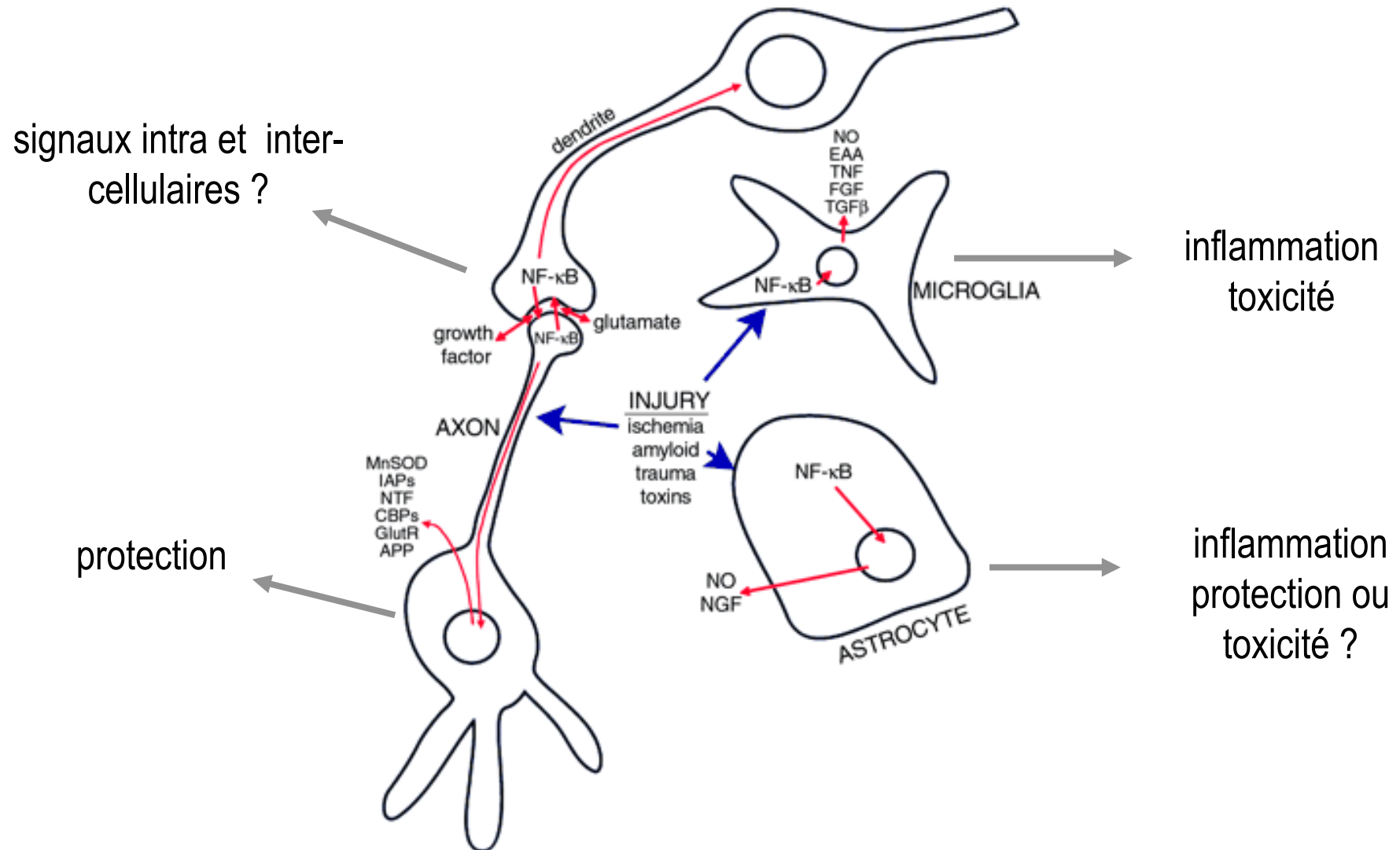
TABLE 1. Regulation of IL-1 activity

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

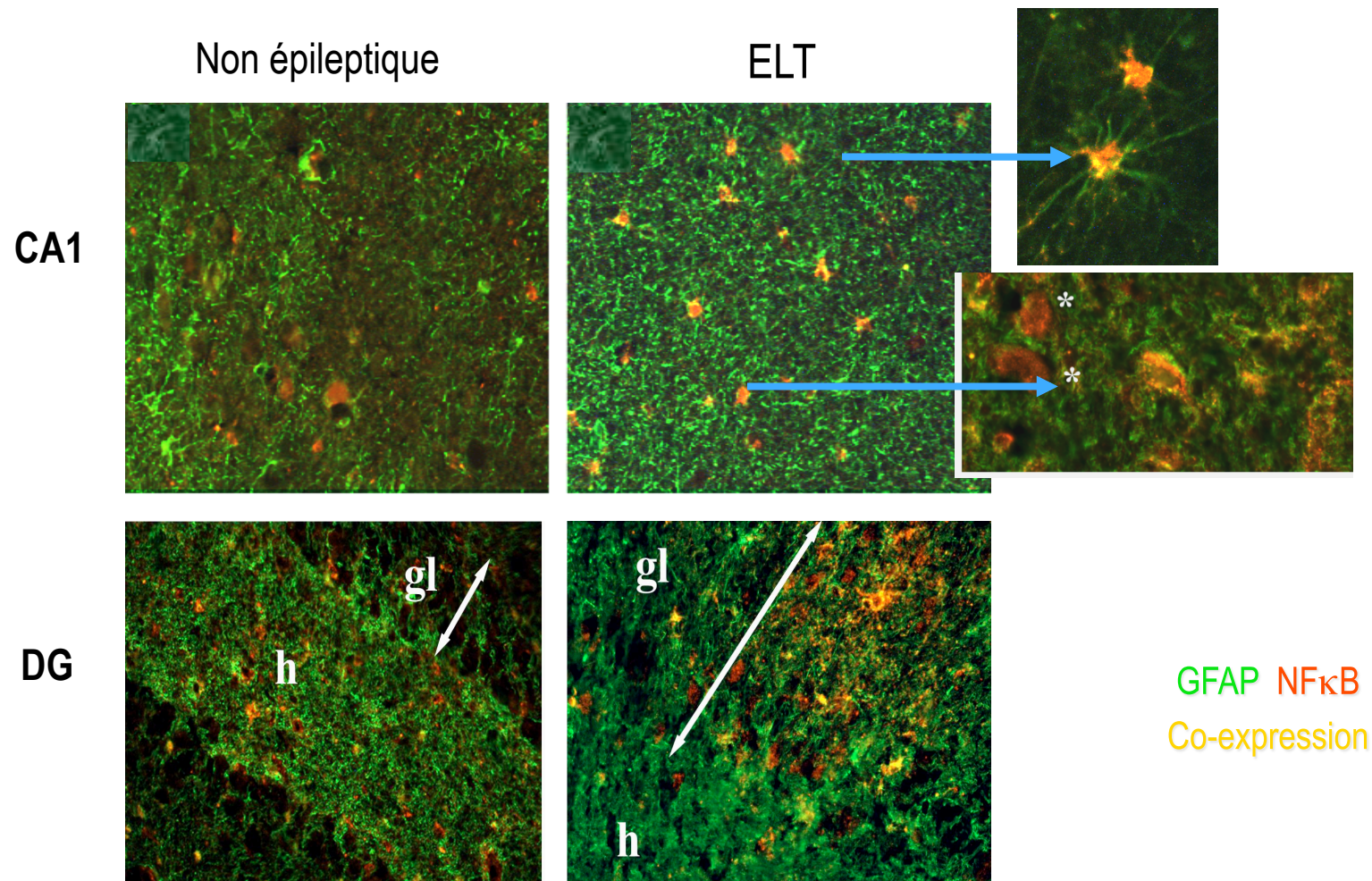
^aF. Molina-Holgado and N.J. Rothwell, unpublished observations.

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.

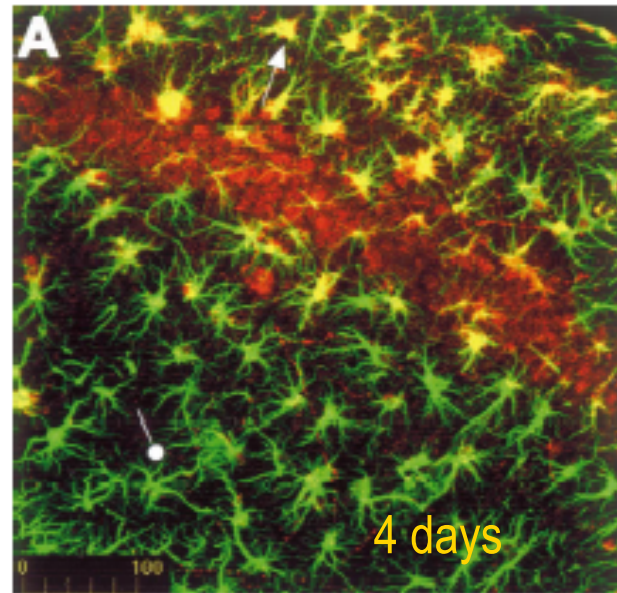
NF κ B, chef d'orchestre de la neuro-inflammation ?



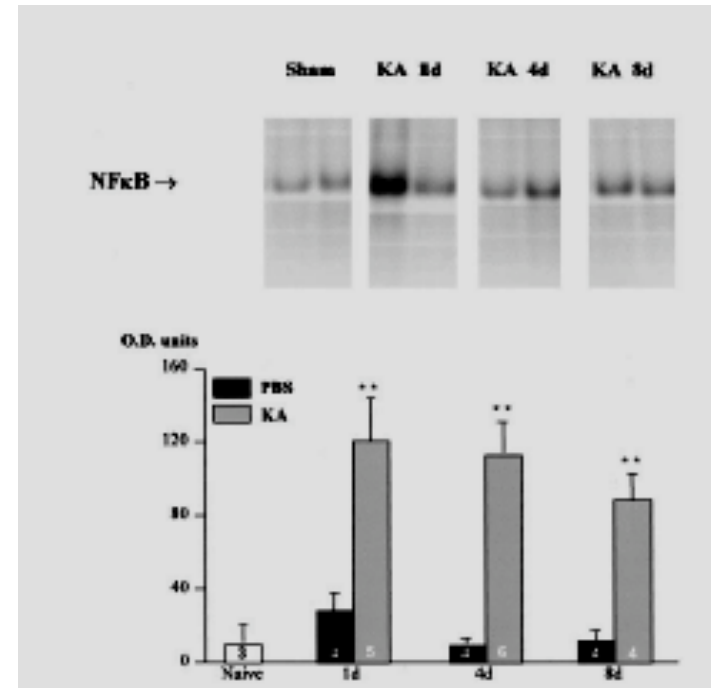
Expression de NF κ B par les astrocytes et les neurones dans l'ELT avec SH



Expression de NF κ B par les astrocytes et les neurones dans l'épilepsie expérimentale chez le rat

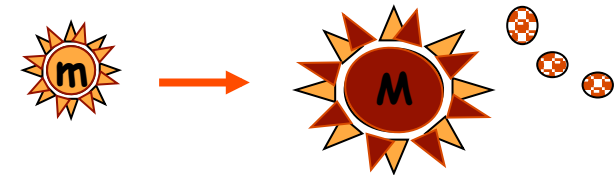
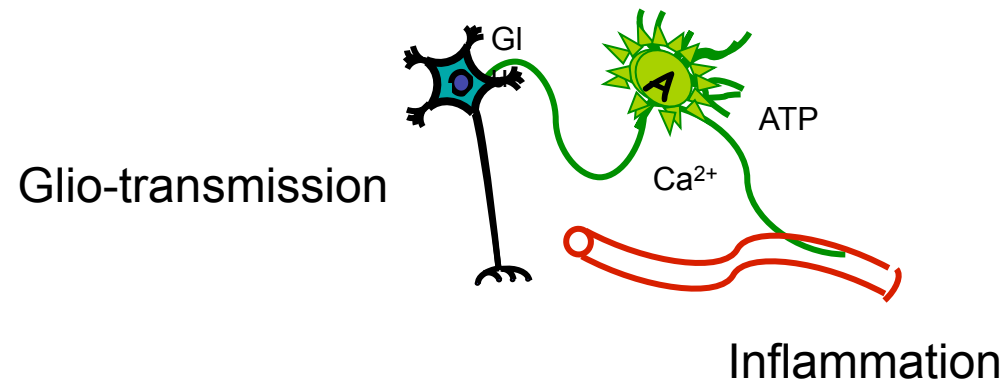
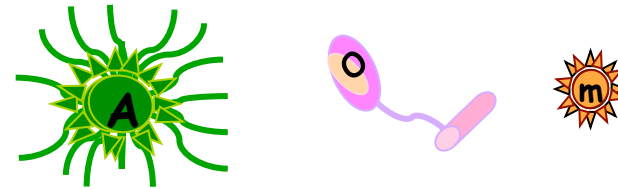


GFAP NF κ B co-expression

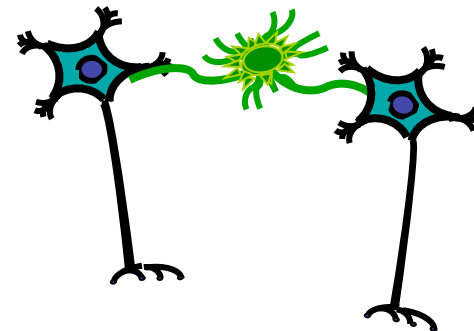


La surexpression de NF κ B est associée à une augmentation de sa liaison à l'ADN => activité transcriptionnelle

Gliose réactionnelle et épilepsies symptomatiques



Synchronisation neuronale



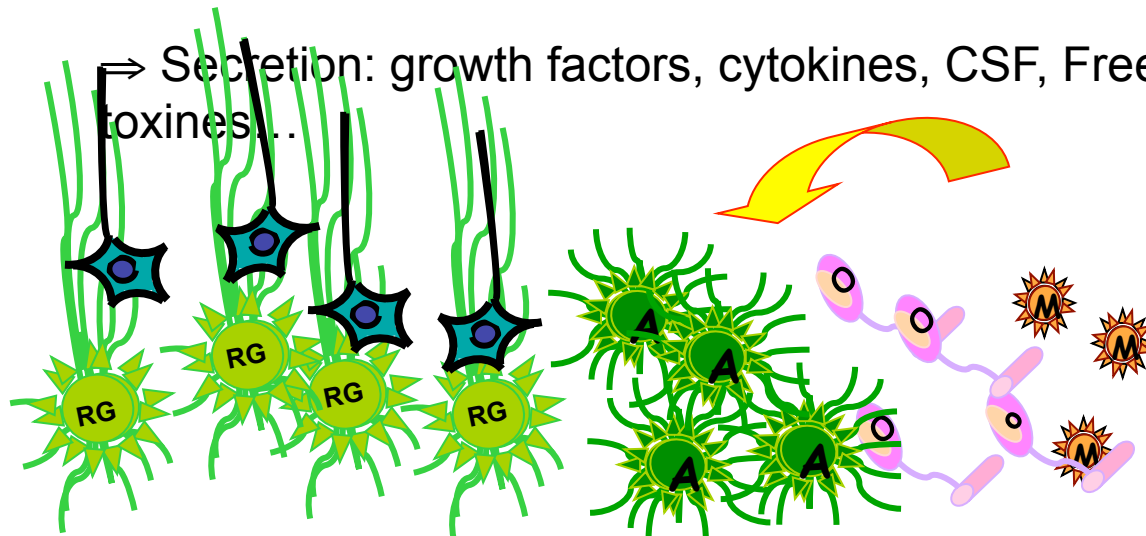
Seizures => gliosis?

Neurons release: trophic factors, NT and other messengers

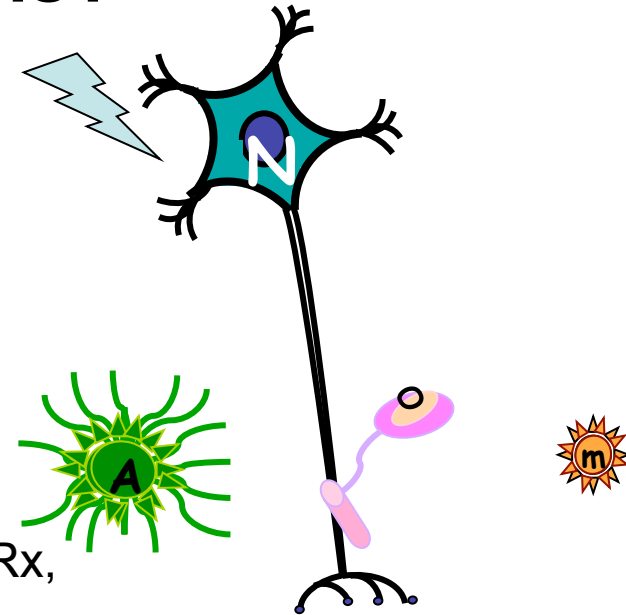
Changes in physical (pH) and chemical (ionic) environment

=> Glial activation

=> Secretion: growth factors, cytokines, CSF, FreeRx, toxins...



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



Proliferation of stem cells in neurogenic areas

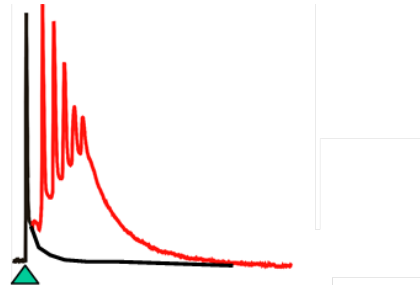
De-differentiation

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

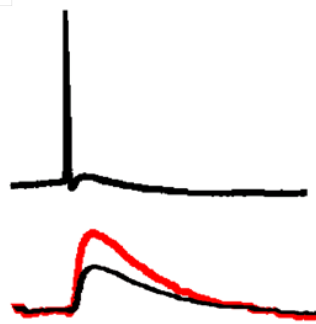
Reactive glia => epileptogenesis ?

Hypothesis about pathophysiology of epilepsies

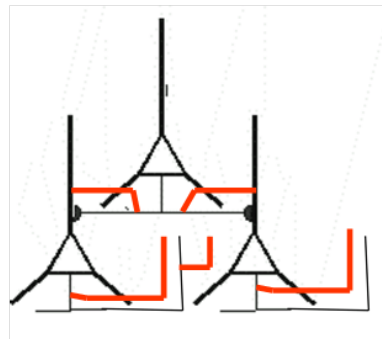
intrinsic
properties



synaptic
efficacy

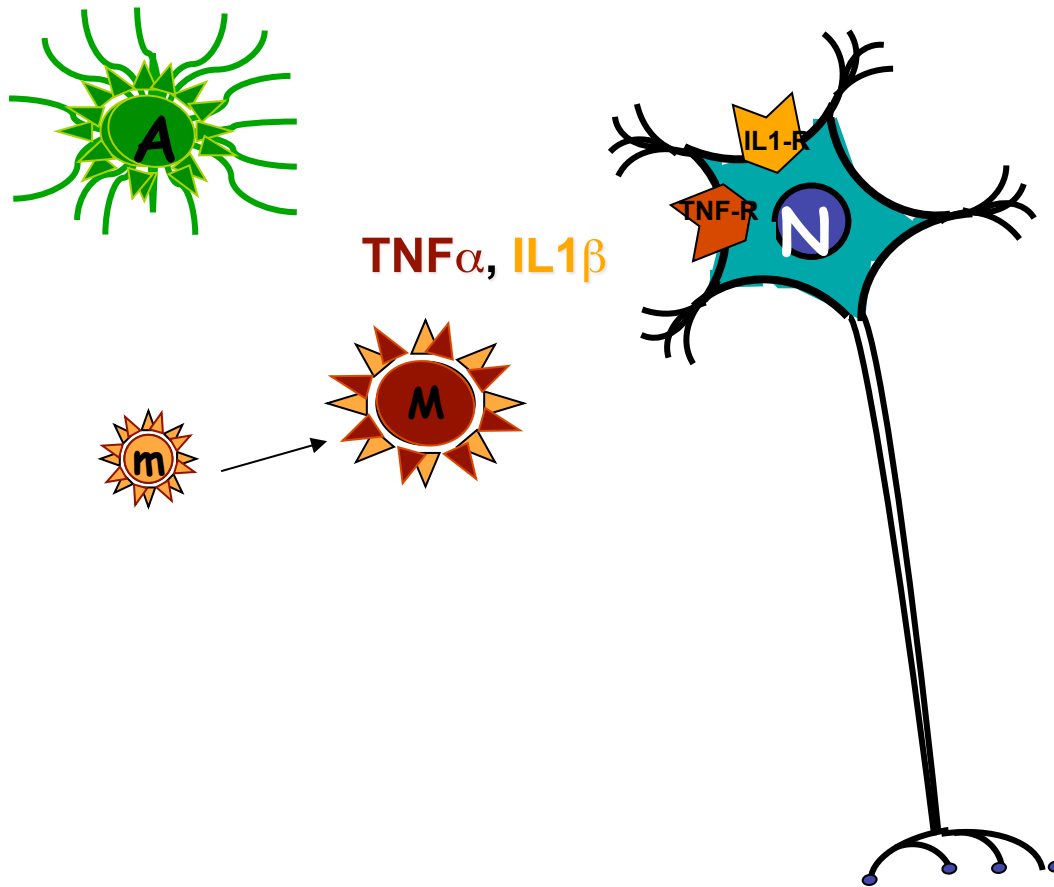
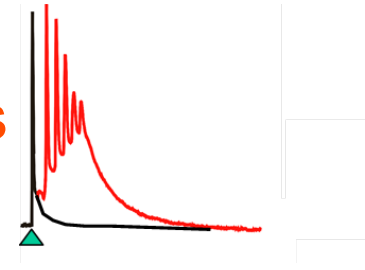


synaptic
connectivity



**Impact of reactive
glia on
epileptogenesis
at each level?**

1- Changes in intrinsic properties => prolong action potentials

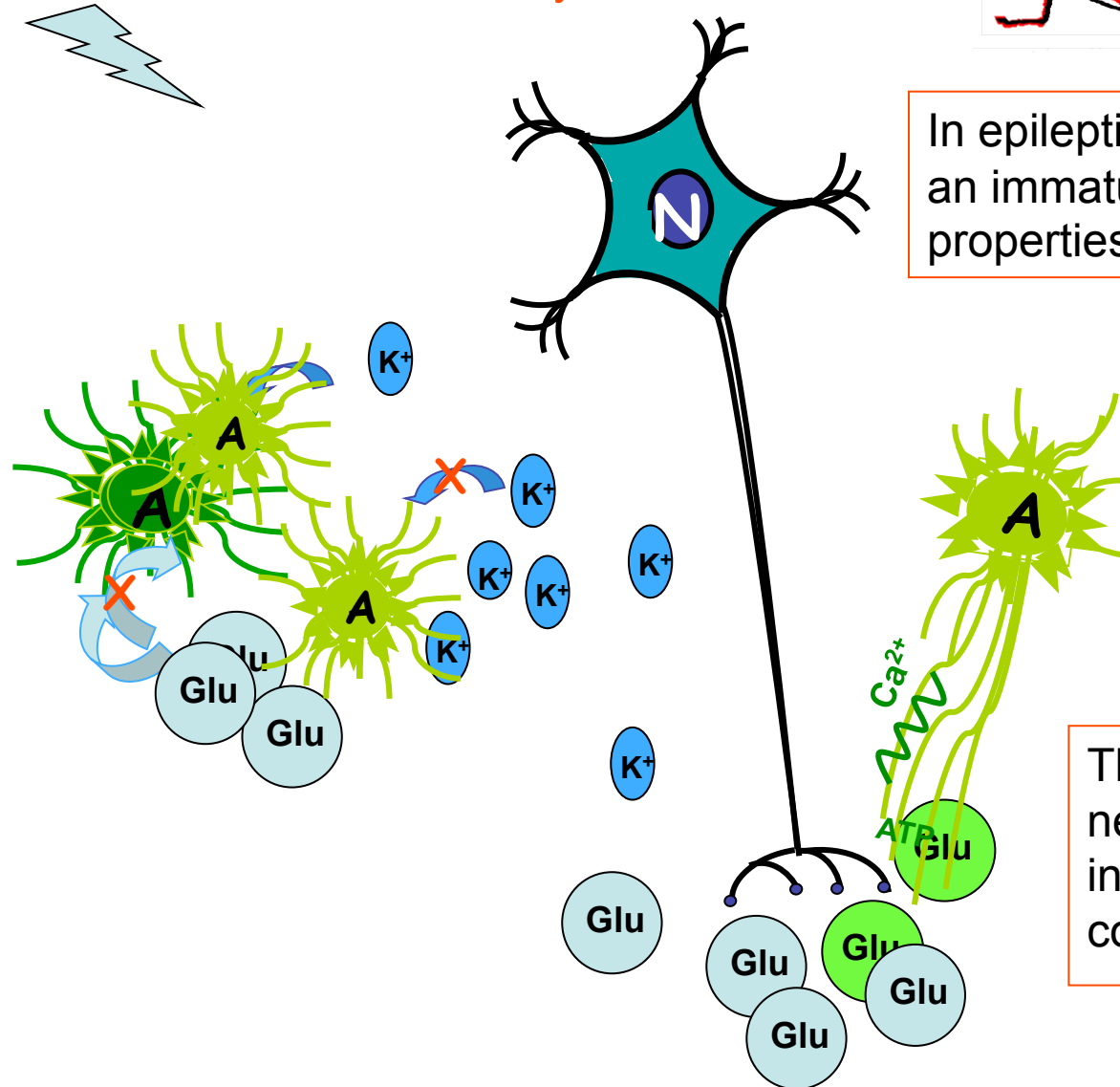
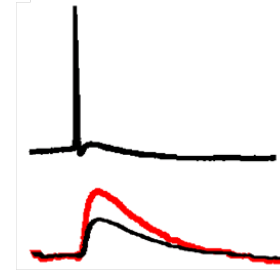


**$TNF-R \Rightarrow$
AMPA-R exocytosis
 $GABA_A-R$ endocytosis**

**$IL1\beta-R \Rightarrow$ 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.

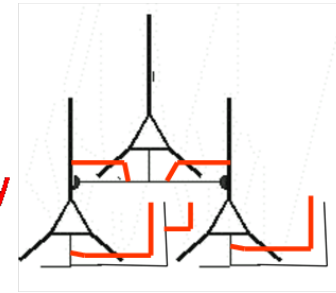
Immature astrocytes with long processes signal to adjacent neurons by releasing glutamate in a calcium-dependent manner.

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

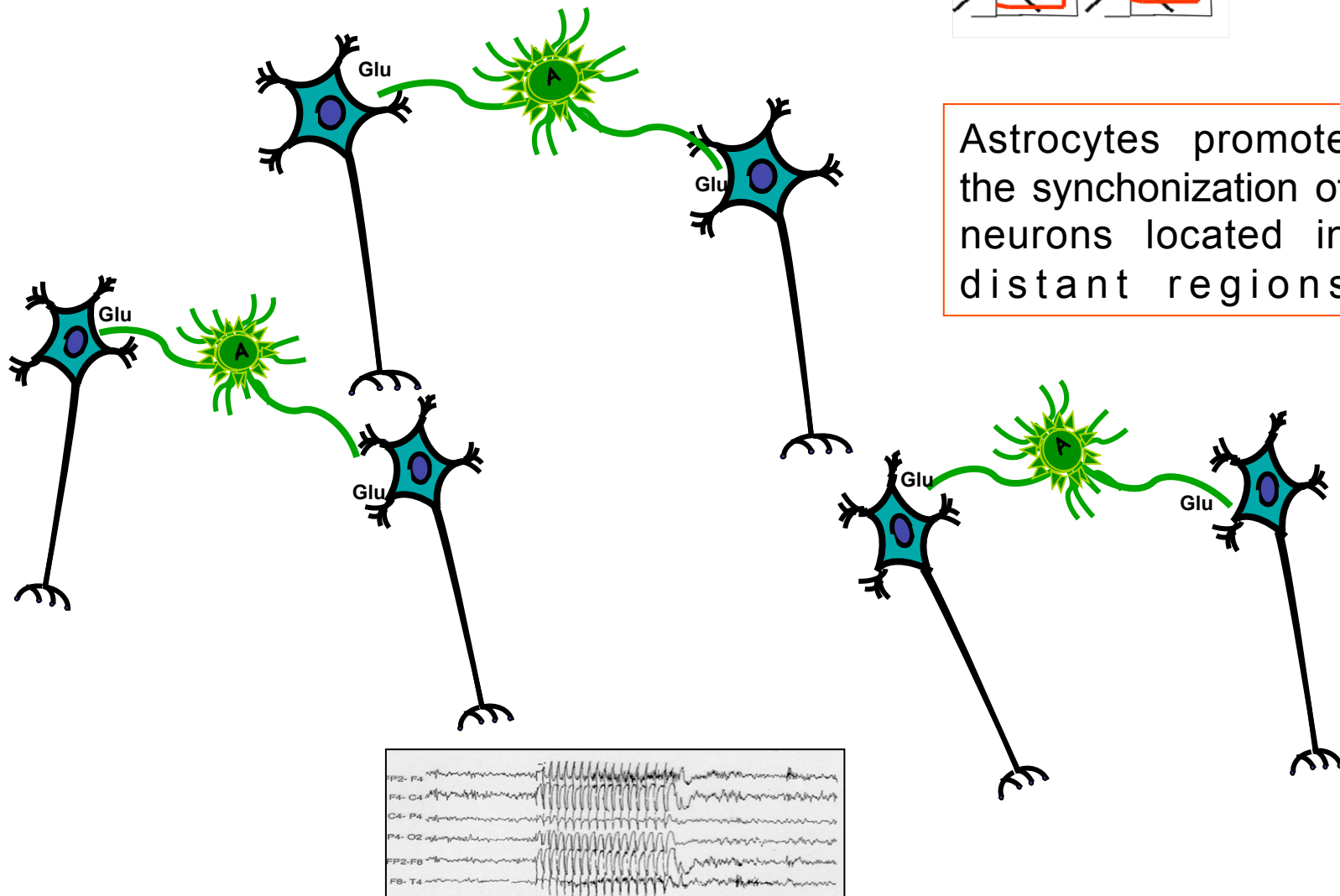
=> EXCITABILITY, TOXICITY

3- recurrent excitation

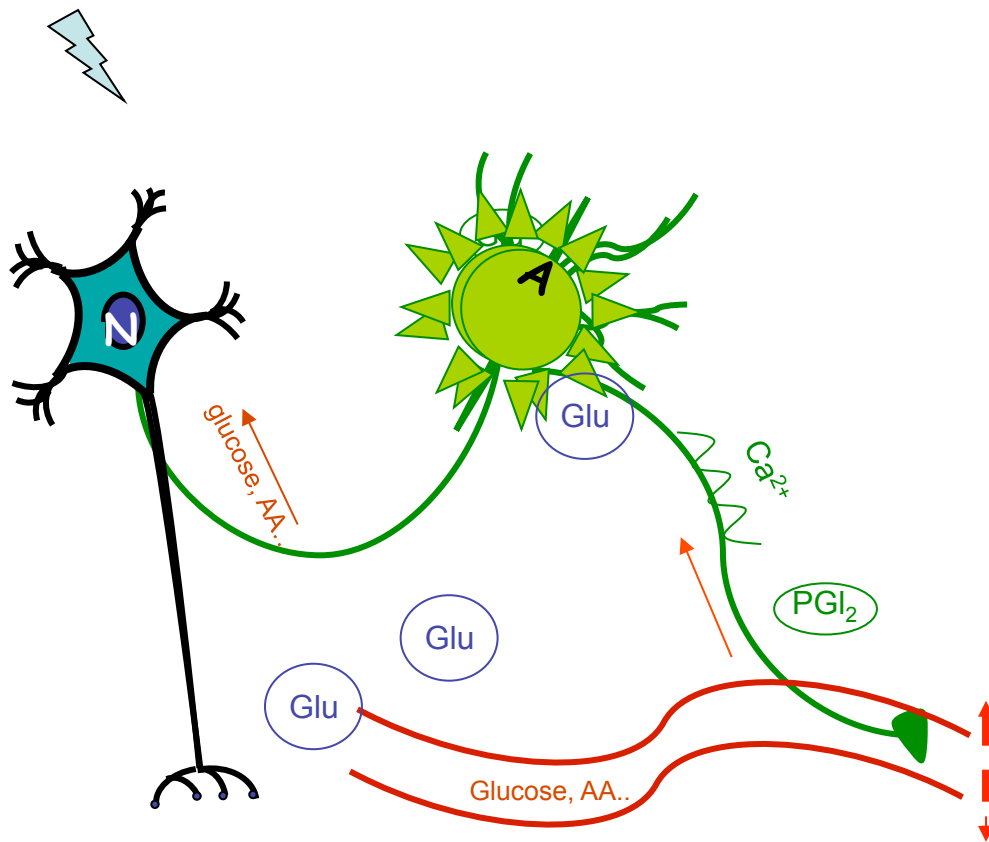
synaptic
connectivity



Astrocytes promote
the synchronization of
neurons located in
distant regions



4- Other effects : neuro-vascular coupling

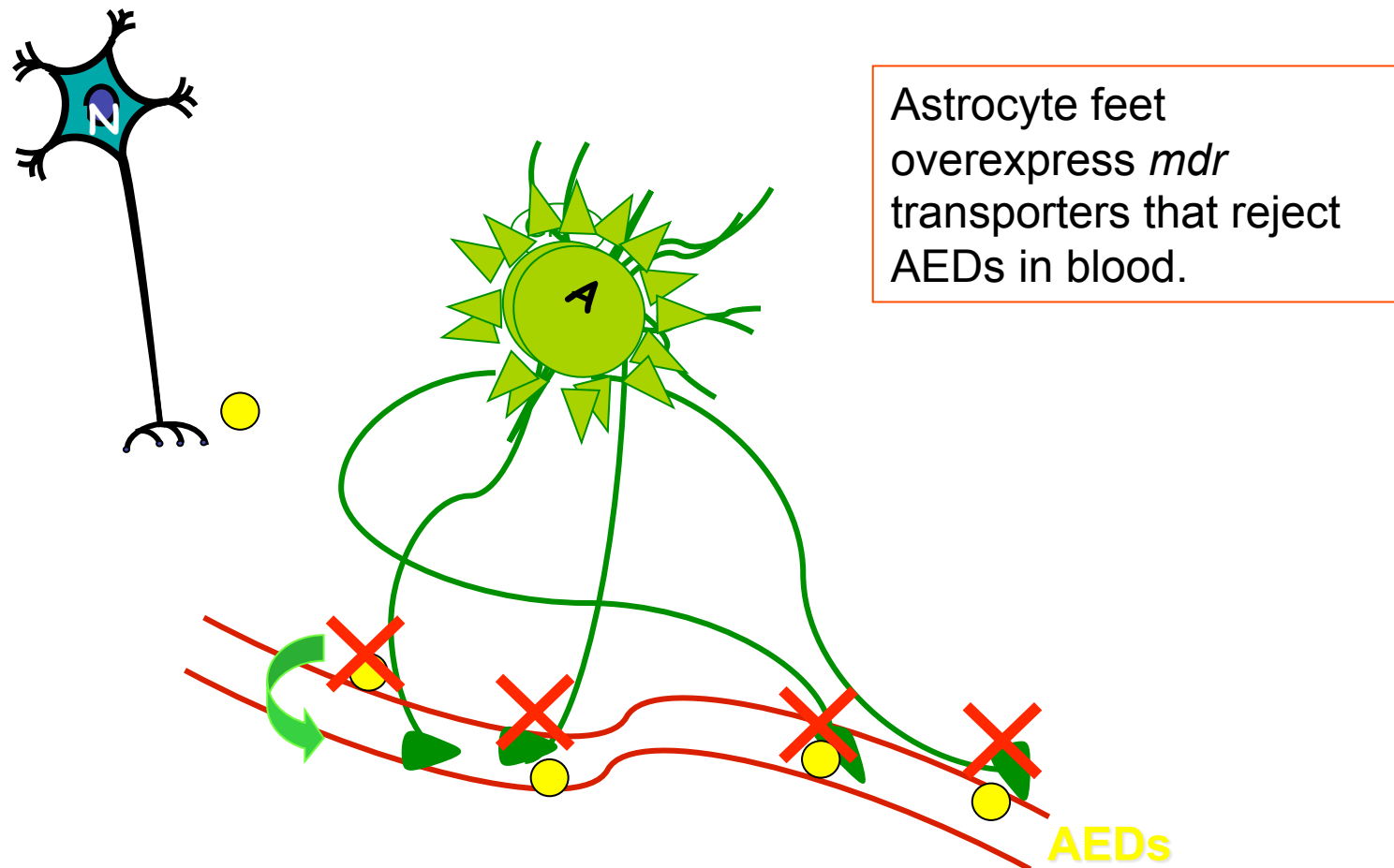


During seizures, neurons release glutamate =>

Astrocytes adapt blood flow to the neuronal energetic demand.

DSC
adaptation

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



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}

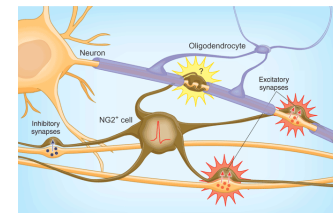
Glia get excited

Thomas S Otis & Michael V Sofroniew

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

Ragnhildur Káradóttir^{1,2}, Nicola B Hamilton¹, Yamina Bakiri¹ & David Attwell¹

**nature
neuroscience**
NEWS AND VIEWS



VOLUME 11 | NUMBER 4 | APRIL 2008

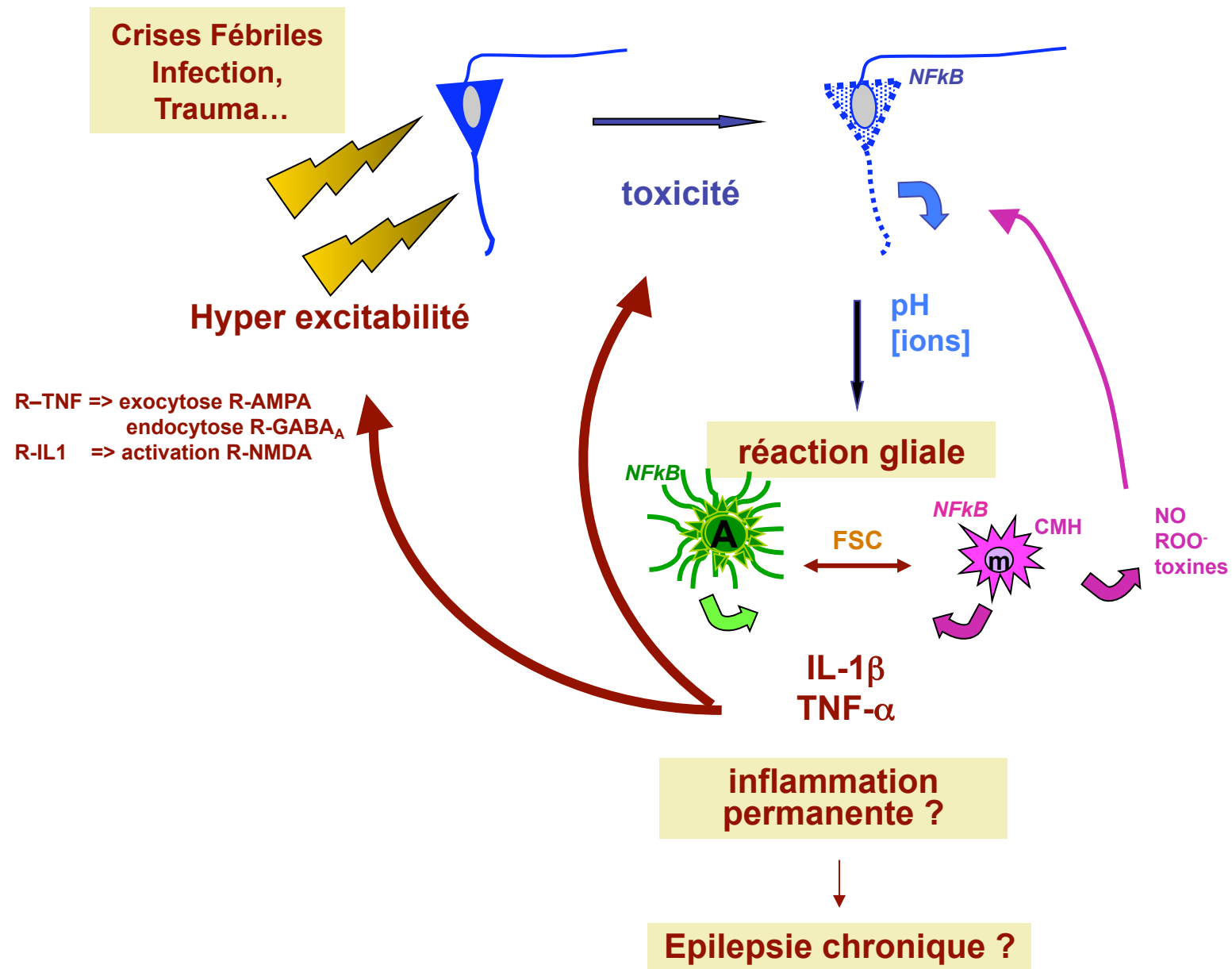


Review

TRENDS in Neurosciences Vol. 30 No. 10

Neurotransmitter receptors on microglia

Jennifer M Pocock¹ and Helmut Kettenmann²



Autre source d'inflammation dans le foyer épileptique:

inflammation vasculaire

=> fuites de leucocytes et protéines sériques

?

...

Epileptogenicité de l'inflammation vasculaire

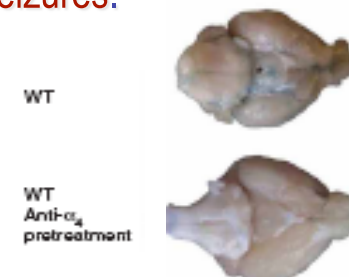
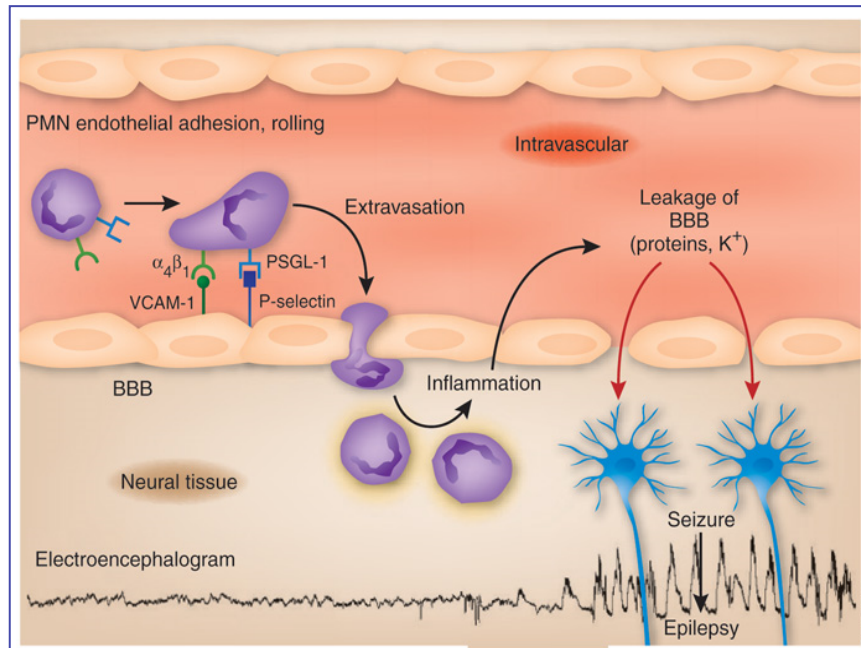
**nature
medicine 2008**

A role for leukocyte-endothelial adhesion mechanisms in epilepsy

Paolo F Fabene¹, Graciela Navarro Mora¹, Marianna Martinello², Barbara Rossi², Flavia Merigo¹, Linda Ottoboni², Simona Bach², Stefano Angiari², Donatella Benati¹, Asmaa Chakir¹, Lara Zanetti¹, Federica Schio¹, Antonio Osculati³, Pasquina Marzola⁴, Elena Nicolato¹, Jonathon W Homeister⁵, Lijun Xia⁶, John B Lowe⁷, Rodger P McEver⁶, Francesco Osculati^{1,8}, Andrea Sbarbati¹, Eugene C Butcher^{9,10} & Gabriela Constantin²

Seizures activate vascular CAM => ↑ leukocyte extravasation

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



NATURE|Vol 457|8 January 2009

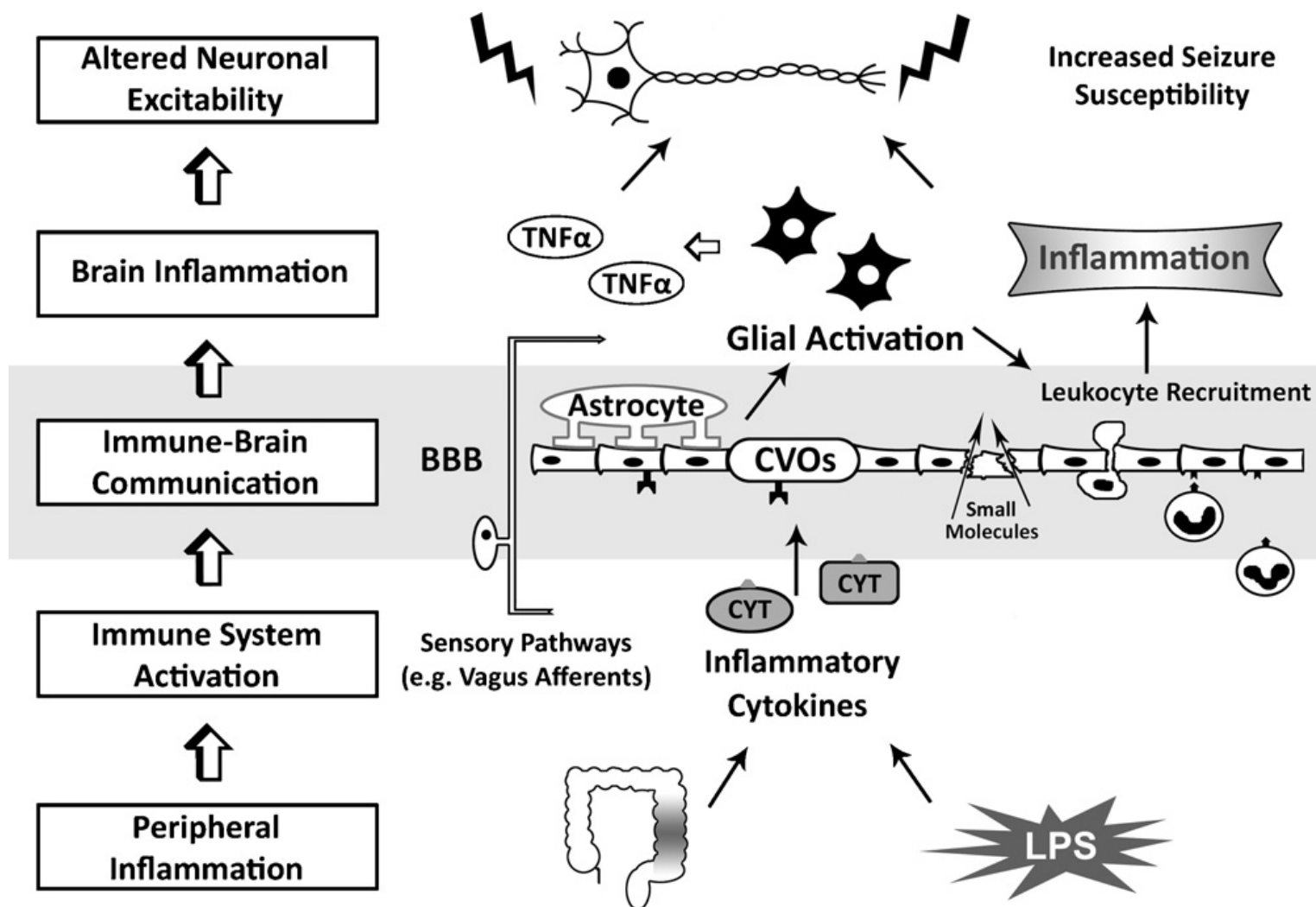
IMMUNOLOGY

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

