

## INTERACTIONS NEUROHUMORALES

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## CONNEXIONS NEUROHUMORALES

### ANATOMIQUES

Câblage (*Hardwiring*) sympathique : Innervation des organes hématopoïétiques et lymphoïdes  
Câblage parasympathique : innervation du système réticuloendothéliale

### MOLECULAIRES

Neurotransmetteurs: E/NE, Ach, VIP, Histamine, Substance P...  
Neurohormones: CRF,  $\alpha$ -MSH, Leptine...

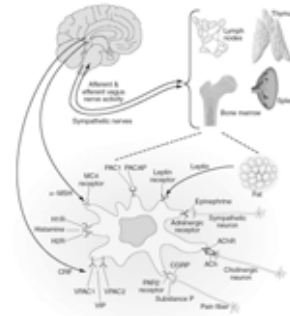
## HEMISPHERES D/G

### Réponse immunitaire différente

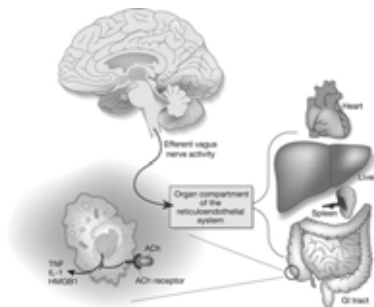
« Cerebral lateralization may be important in neural control of immune function. Animal studies have demonstrated differential effects of left and right brain lesions on immune function, but human studies are inconclusive. Here, we show that resections in the language dominant hemisphere of patients with epilepsy reduce lymphocytes, total T cells, and helper T cells. In contrast, resections in the language nondominant hemisphere increased the same cellular elements. T-cell responses to mitogens and microbial antigens were not differentially affected. Left/right arm histamine skin response ratios were altered in patients with left cerebral epileptic focus, and flare skin responses were reduced by left cerebral resections in contrast with an increase after right cerebral resections. The findings demonstrate a differential role of the left and right cerebral hemispheres on immune functions in humans. »

*Meador et al Ann Neurol 2004*

## CONNEXIONS NEUROHUMORALES



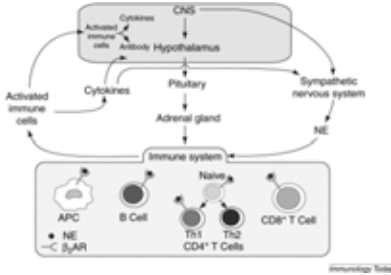
## CONNEXIONS NEUROHUMORALES



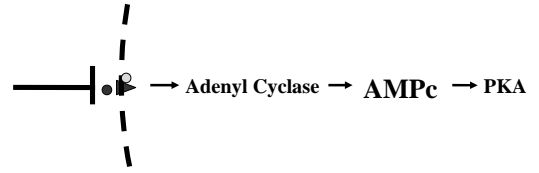
## CONNEXIONS ADRENERGIQUES

Le récepteur adrénergique  $\beta_2$  ( $\beta_2AR$ ) est exprimé à la surface des thymocytes, des lymphocytes T et B ainsi que des cellules présentatrices de l'antigène (APC) et des macrophages.

## CONNEXIONS ADRENERGIQUES

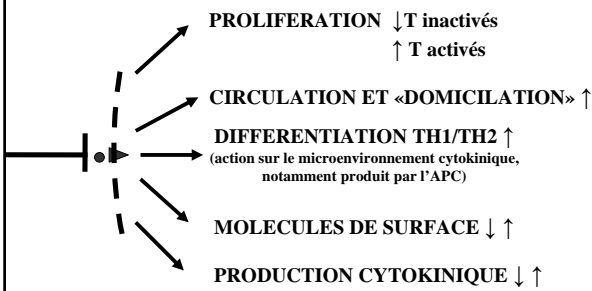


## TRANSDUCTION DU SIGNAL - LT

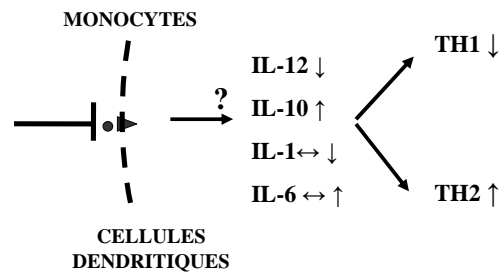


Le récepteur  $\beta 2AR$  est fonctionnel

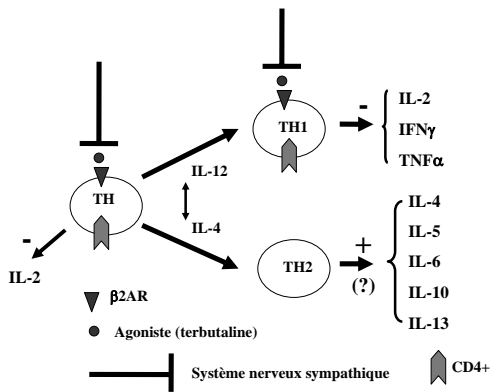
## EFFETS ADRENERGIQUES SUR LT



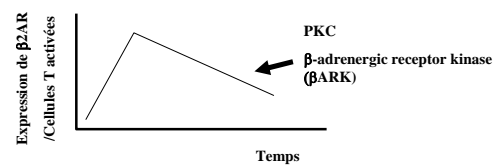
## EFFETS ADRENERGIQUES SUR L'APC



## TH1/TH2 INACTIVES ET ACTIVÉS



## RESTING AND ACTIVATED TH1/TH2



L'absence d'expression de  $\beta 2AR$  dans les TH2 dépendrait de :  
Acétylation des histones  
PKC

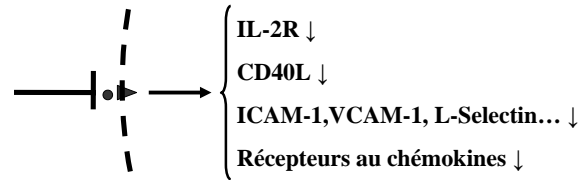
### TH1/TH2 INACTIVES ET ACTIVES

La réponse TH1 à la Norépinéphrine est influencée par la stimulation préalable des  $\beta$ 2AR des cellules T naïves;

La Norépinéphrine peut modifier la production cytokinique des TH2, qui n'expriment pas  $\beta$ 2AR, par l'intermédiaire d'autres cellules exprimant ce récepteur

Les souris déficientes en  $\beta$ -Hydroxylase ont une réponse TH1-/TH2- en cas d'infection à *L. Monocytogenes* et TH1-/TH2+ en cas d'infection à *M. Tuberculosis*.

### EFFETS ADRENERGIQUES SUR L'EXPRESSION DES MOLECULES DE SURFACES DES LT



### EFFETS ADRENERGIQUES SUR LES NK

Augmentation du nombre de cellules NK

Suppression de l'activité des cellules NK

Cette inhibition est soit directe, étant alors expliquée par la densité membranaire des récepteurs  $\beta$ 2AR, soit indirecte par l'effet anti-TH1

Ceci rend compte de la diminution de l'activité NK au cours des situations de stress

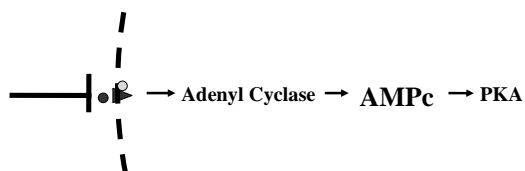
### EFFETS ADRENERGIQUES SUR TC

Diminution de l'activité des LT CD8+

Cette inhibition est soit directe, étant alors expliqué par la densité membranaire des récepteurs  $\beta$ 2AR, soit indirecte par l'effet anti-TH1

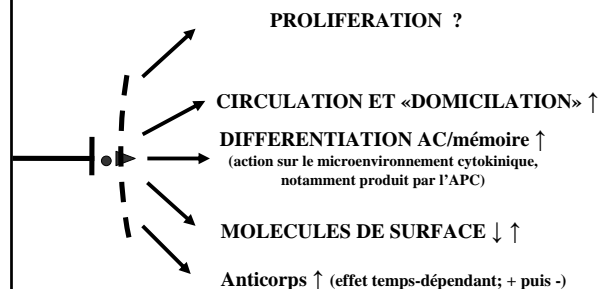
Ceci rend compte de la diminution de l'activité NK au cours des situations de stress

### TRANSDUCTION DU SIGNAL - LB

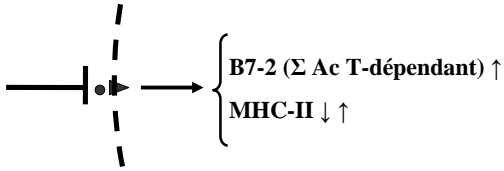


Le récepteur  $\beta$ 2AR est fonctionnel

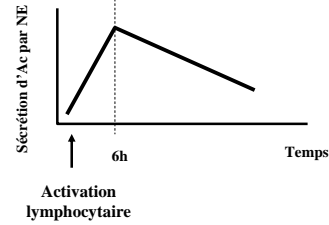
### EFFETS ADRENERGIQUES SUR LB



### EFFETS ADRENERGIQUES SUR L'EXPRESSION DES MOLECULES DE SURFACES DES LT



### SECRETION DES ANTICORPS



Augmentation du taux d'anticorps, chez l'adulte, après stimulation précoce des  $\beta$ 2AR  
Synthèse préférentielle d'IgG1 et d'IgE (signal B7-2 ou IL-4R)

### EFFETS ADRENERGIQUES SUR LES MACROPHAGES

Expression de  $\beta$ 2AR et  $\alpha$ 2AR à la surface des macrophages

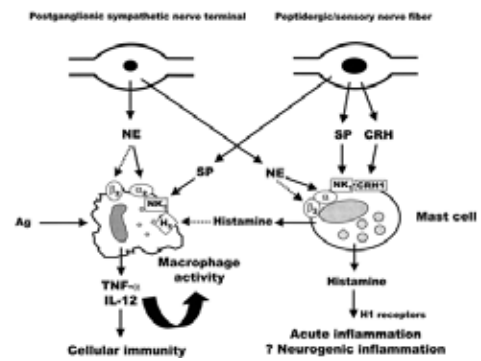
Action contradictoire de la NE sur les macrophages

$\alpha$ 2AR : effet pro-inflammatoire (naïfs)

$\beta$ 2AR: effet anti-inflammatoire (activées)

Cette action dépend d'autres facteurs (SP, Histamine, Ag, cytokines, CRH...)

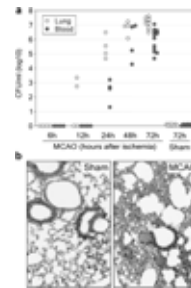
### EFFETS ADRENERGIQUES SUR LES MACROPHAGES



### APPLICATIONS CLINIQUES

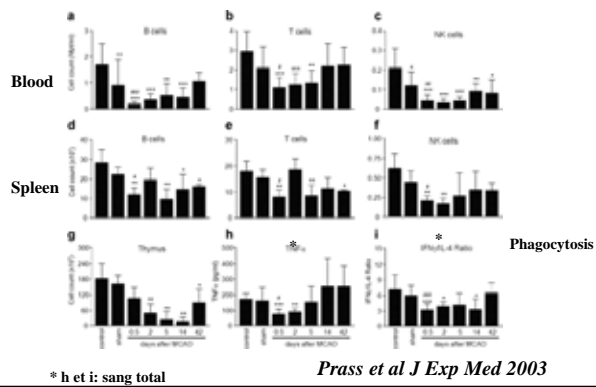
Conditions	Réponse de l'hôte	Réponse pathogénique	Rôles des E/NE et du stress
Infections M. Tuberculosis H. Pylori HIV/Virus hiver.	TH1 protecteur	Immunité C. ↓ IL-2 et IFN- $\gamma$ ↓ TH2 avec évolution de l'infection	Stress=>E/NE=> TH2
Traumatisme	TH2 protecteur?	Immunité C. ↓ IL-2 et IFN- $\gamma$ ↓ IL-10 et TH2 ↑	Stress=>E/NE=> Immunité C. ↓ => Infection
Auto-immunité	Réponse TH1 excessive	TH1 ↑, IL-12, TNE, IFN- $\gamma$ ↑ IL-10 ↓	E/NE ↓ => TH1 ↑
Tumeur	TH1 protecteur	Immunité C. ↓ IL-2 et IFN- $\gamma$ ↓ IL-10 et TGF- $\beta$ ↑	E/NE ↑ => TH2 => progression Ca

### CONNEXIONS ADRENERGIQUES AIC

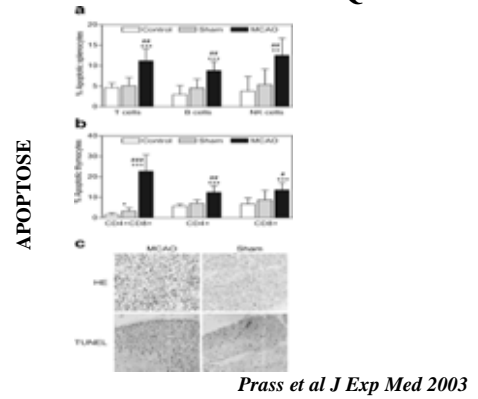


Prass et al J Exp Med 2003

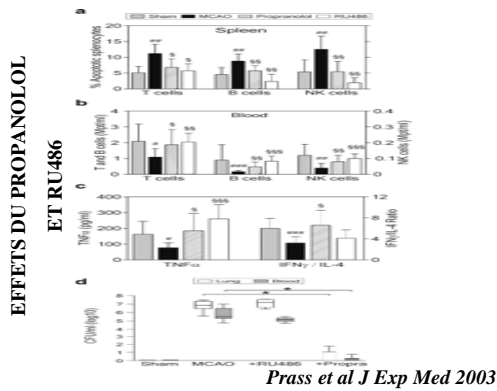
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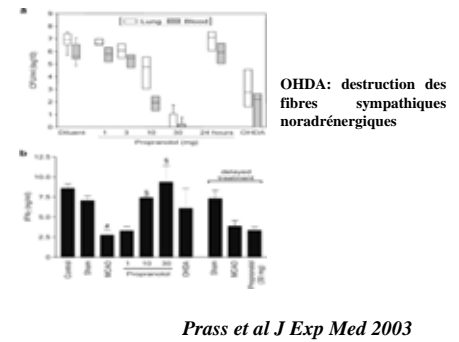
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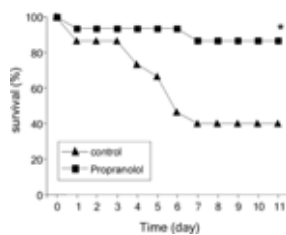
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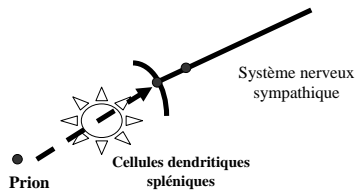


### CONNEXIONS ADRENERGIQUES AIC

L'hyperactivité sympathique au cours de l'AIC favoriserait la survenue d'un sepsis par la diminution de la réponse TH1 et de la sécrétion d'IFN- $\gamma$ .

Prass et al J Exp Med 2003

## ENCEPHALOPATHIE SPONGIFORME



*Prinz et al Nature 2003*

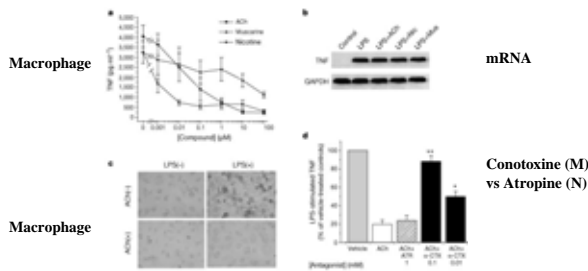
## CONNEXIONS CHOLINERGIQUES

ou « *l'aventure de Kevin J Tracey* »

La sécrétion macrophagique de TNF- $\alpha$  est

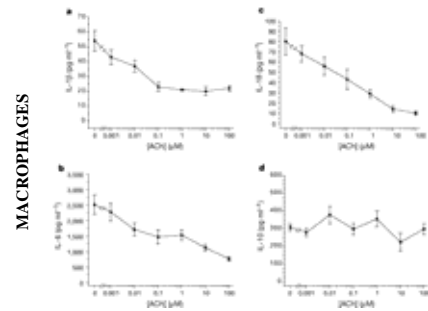
1. diminuée par a stimulation du nerf vague
2. Diminuée par l'injection ICV de CNI-1493 (*guanlylhydrazone qui stimule le nerf vague*)
3. augmentée par la vagotomie
4. régulée à un niveau post-transcriptionnel par des récepteurs nicotinique à l'acétylcholine

## CONNEXIONS CHOLINERGIQUES



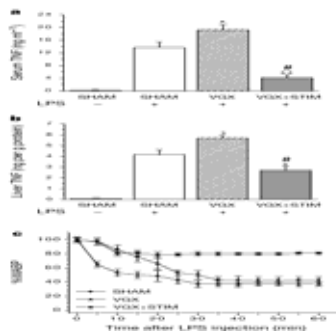
*Borovikova et al Nature 2000*

## CONNEXIONS CHOLINERGIQUES



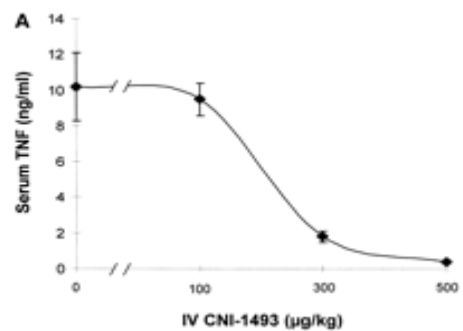
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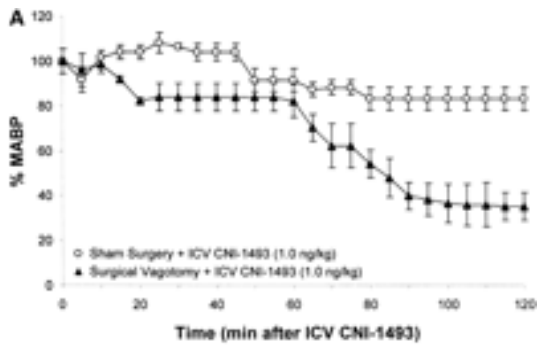
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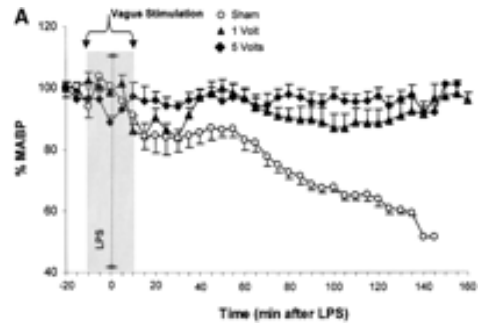
*Bernik et al J Exp Med 2002*

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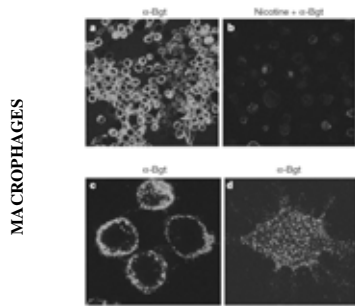
Bernik et al J Exp Med 2002

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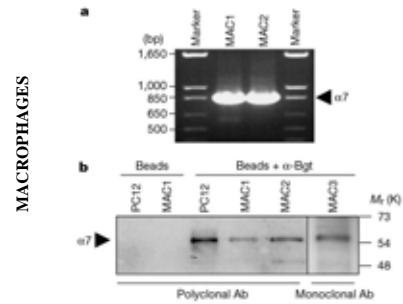
Bernik et al J Exp Med 2002

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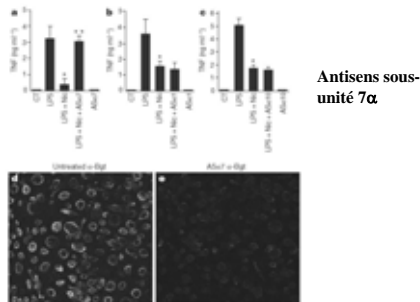
Wang et al Nature 2003

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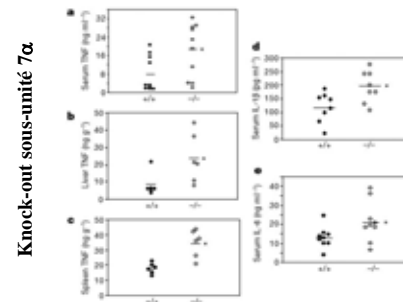
Wang et al Nature 2003

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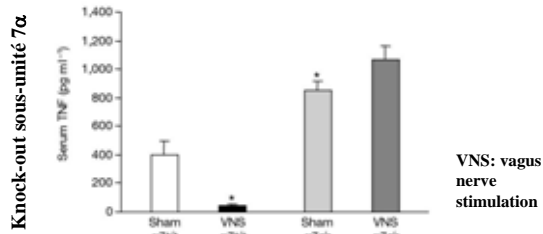
Wang et al Nature 2003

### CONNEXIONS CHOLINERGIQUES



Wang et al Nature 2003

## CONNEXIONS CHOLINERGIQUES



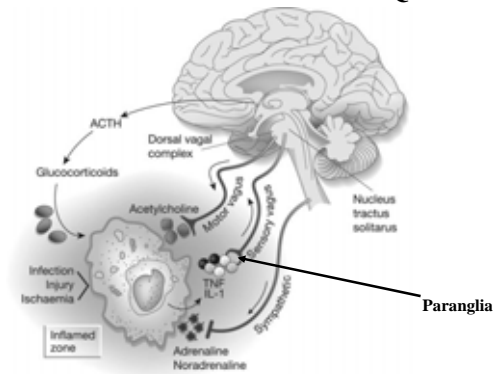
Wang et al Nature 2003

## CONNEXIONS CHOLINERGIQUES ou « l'aventure de Kevin J Tracey »

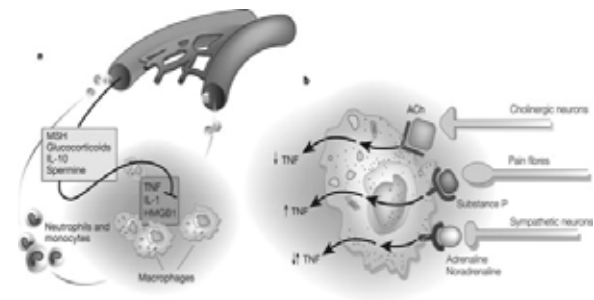
### Concepts

1. Réflexe inflammatoire (Tracey Nature 2002)
  1. Afférence « motrice » cholinergique
  2. Efférence sensitive (Watkins et al PNAS 1999)
  3. Synergie entre les système sympathique parasympathique
2. Sixième sens (Blalock J Immunol 1984)

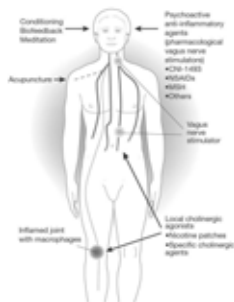
## CONNEXIONS CHOLINERGIQUES



## CONNEXIONS CHOLINERGIQUES



## CONNEXIONS CHOLINERGIQUES



## CONNEXIONS HUMORONEURONALES



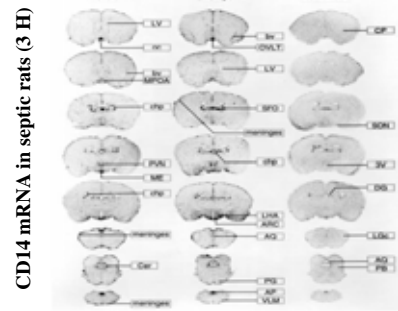
## C.B.F. AUTOREGULATION

### CONTROVERSY

- Reduction or preservation of cerebral blood flow, oxygen consumption and vasomotor reactivity in human septic shock and experimental endotoxemic shock.
- It has been shown neuronal viability is not threatened by a 62% reduction of cerebral blood flow
- Severity of ischemic lesions did not correlate with duration of hypotension in patients who had died from septic shock

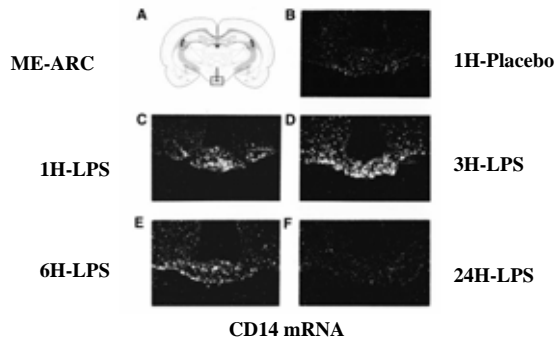
*Papadopoulos et al CCM 2000; Sharshar et al Lancet 2003*

## CD14-LPS



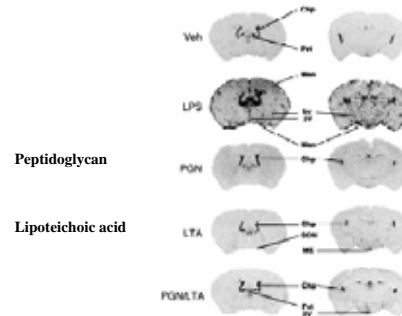
*Lacroix et al Brain Pathol 1998*

## CD14-LPS



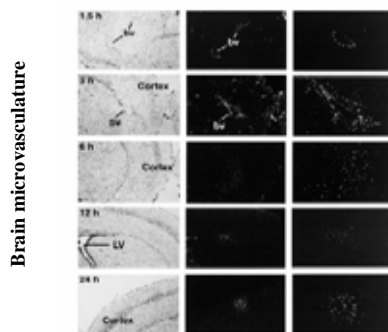
*Lacroix et al Brain Pathol 1998*

## TOLL-LIKE RECEPTOR 2



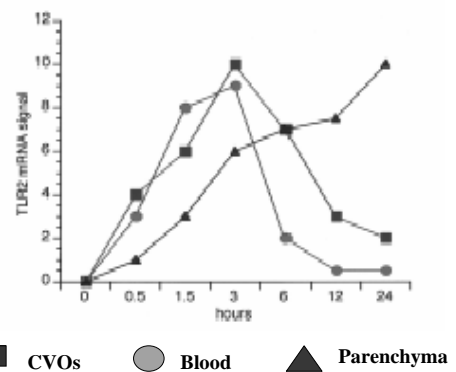
*Laflamme et al J Neurochem 2001*

## TOLL-LIKE RECEPTOR 2



*Laflamme et al J Neurochem 2001*

## TOLL-LIKE RECEPTOR 2



## TOLL-LIKE RECEPTOR 4

TABLE 3. Toll-like receptor 4 (TLR4) gene expression in the rat brain following a single injection of the endotoxin lipopolysaccharide (LPS)\*

	Vehicle (Distill)	LPS			
		15 min	30 min	60 min	3 hrs
<b>Circumventricular organs</b>					
Vascular organ of the lamina terminalis	+/+/+	-	-/+	-/+	-/+
Subfornical organ	+ +/+ + +	+/+ + +	+/+ + +	-	+/+ + +
Median eminence	-/+	+/+ + +	-	-/+	-/+
Area postrema	-	-/+	-/+	-	-/+
Meninges	+ +/+ + +	+/+ + +	+/+ + +	-	-/+
Choroid plexus	- +	+/+ + +	+/+ + +	-	-/+
<b>Diffused signal in parenchymal structures</b>					
Medial preoptic area	- +	+/+ + +	-/+	-/+	-/+
Paraventricular nucleus of the hypothalamus	- +	- +	-/+	-/+	-/+
Dorsomedial nucleus of the hypothalamus	-/+	- +	-/+	-/+	-/+
Arvane/Ventromedial nucleus of the hypothalamus	+ + +	+ +/+ + +	+ + +	-/+	-/+
Cerebral appendix (surrounding sinus)	-	-/+	-/+	-	-/+
Dorsal ganglion	+ + +	+/+ + +	+ + +	-	-/+
<b>Diffused signal in nuclei</b>					
Posterior hypothalamic nucleus	-	- +	-/+	-/+	-/+
Ventrolateral midline	+ + +	+/+ + +	- +	-	-/+
Cerebral nucleus	+ +/+ +	-	- +	-	+ +/+ +
Paraventricular and gigantocellular parvocellular nuclei	-/+	-/+	-/+	-	-
Supraoptic nucleus	- +	+ +/+ + +	+ + +	-	+ +/+ +
IL4 mRNA	-/+	-	+ + +	+ + +	+ +/+ + +

Laflamme et al FASEB 2001

## CD14-LPS

LPS i.v./i.p.	1H	3H	6H
CD14 mRNA	CVO (No B.B.B.)	MPOA-AHA (No B.B.B.)	PVN-SON-ARC NTS-PB
CELLS	Phagocytes Glial cells	Glial cells	Glial cells Neurons

Migratory-like pattern

Lacroix et al Brain Pathol 1998

## NF-κB

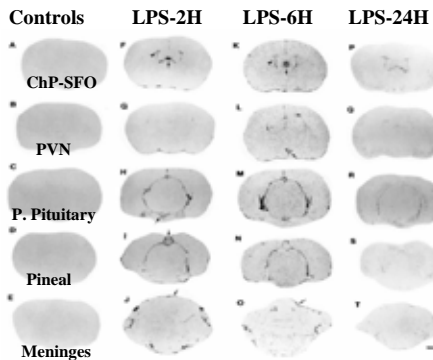
- Recognised to be essential for the release of pro-inflammatory cytokines
- Key Mediator of LPS effect on cellular response
- Dramatic increase in NF-κB activity in CVOs, choroid plexus and brain microvasculature 1 and 2Hours after i.p. LPS

Quan et al PNAS 1997

## NITRIC OXIDE AND CYTOKINES

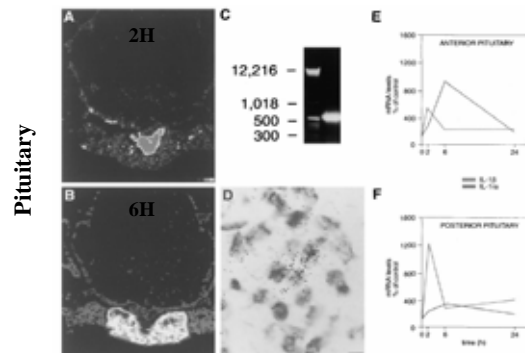
- In vivo stimulation of neurones and glial cells by endotoxin induced release of NO and TNF $\alpha$ , IL-1 $\beta$  and IL-6.
- Pro-inflammatory cytokines can penetrate into the brain through regions deprived of blood brain barrier (*lamina terminalis, area postrema ...*)
- Endotoxin shock induced a neuronal, glial and endothelial expression of iNOs, TNF $\alpha$ , IL-1 $\beta$  and IL-6 in various regions involved in the control of body temperature, neuroendocrine and autonomic functions.
- NO and pro-inflammatory cytokines influence the release of neurotransmitters, neuroendocrine hormones (CRH, ACTH, Vasopressin) and sympathetic activity.

## IL-1 $\beta$ mRNA

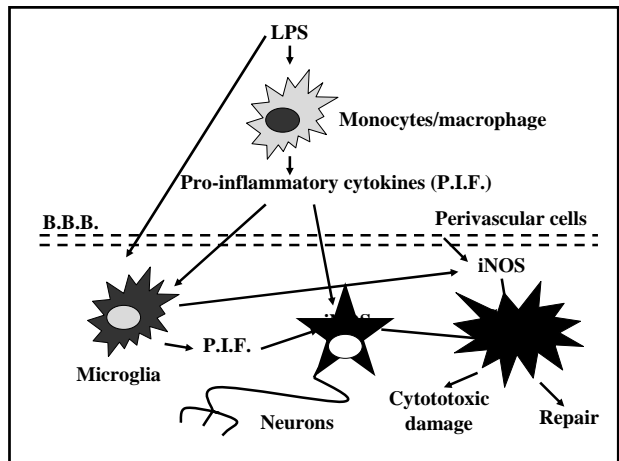
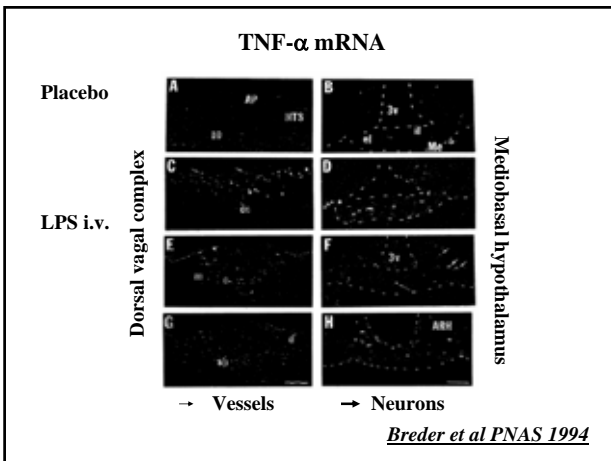
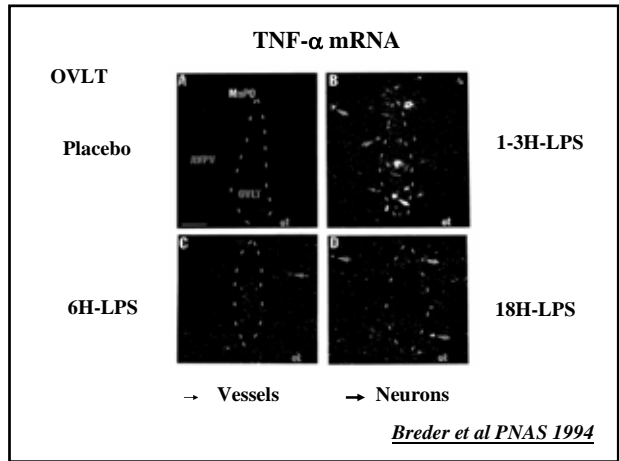
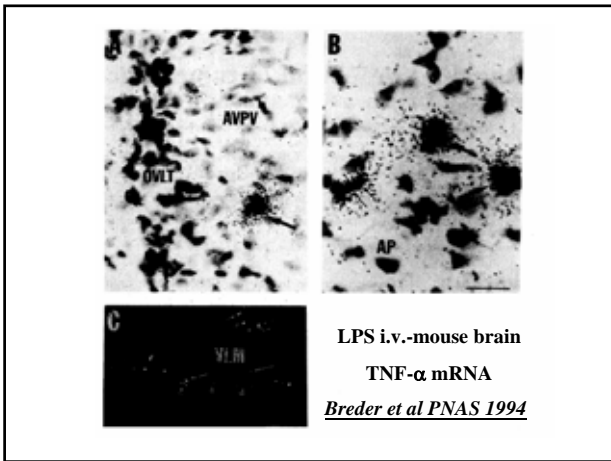
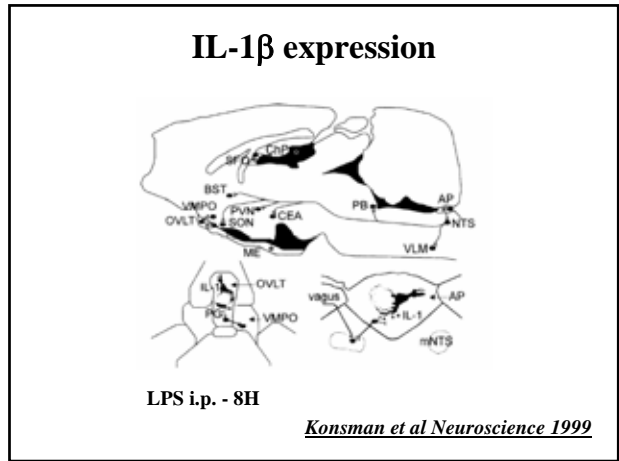
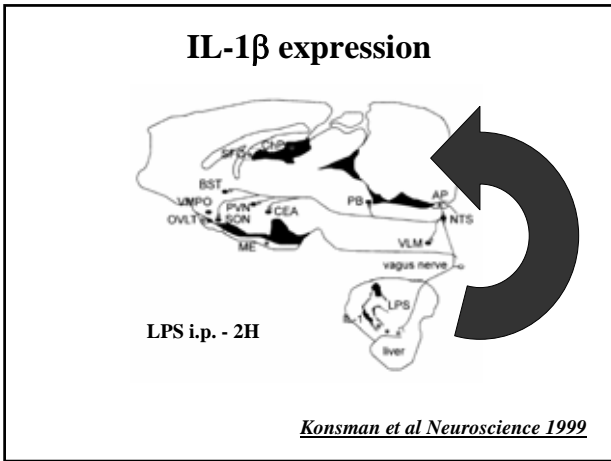


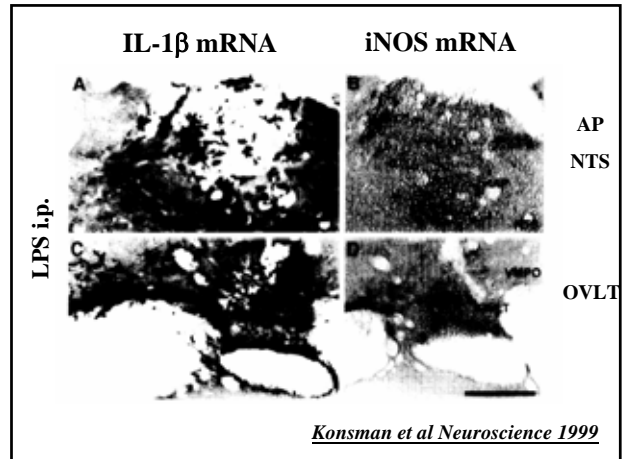
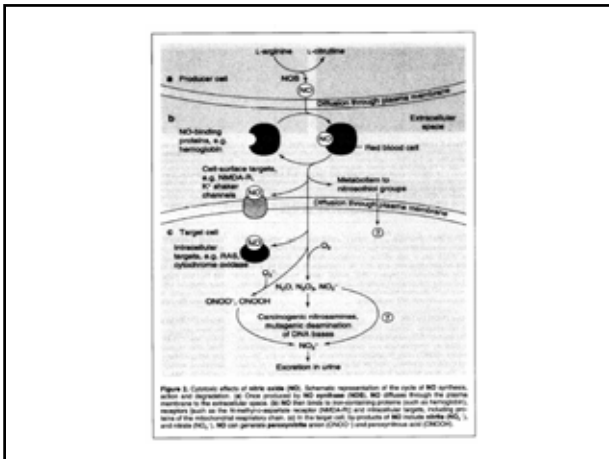
Wong et al PANS 1997

## IL-1 $\beta$ and IL-1ra mRNA



Wong et al PANS 1997



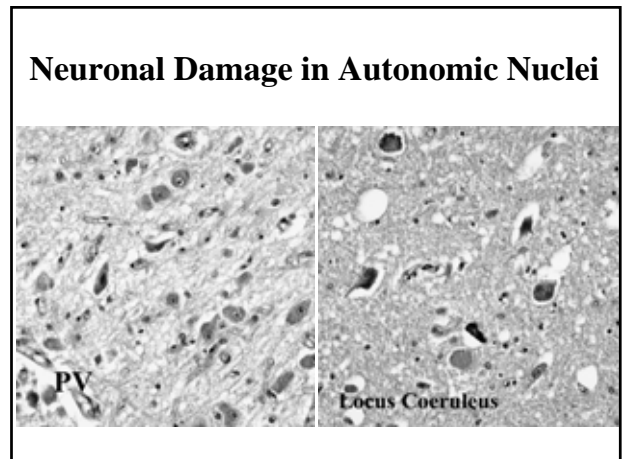
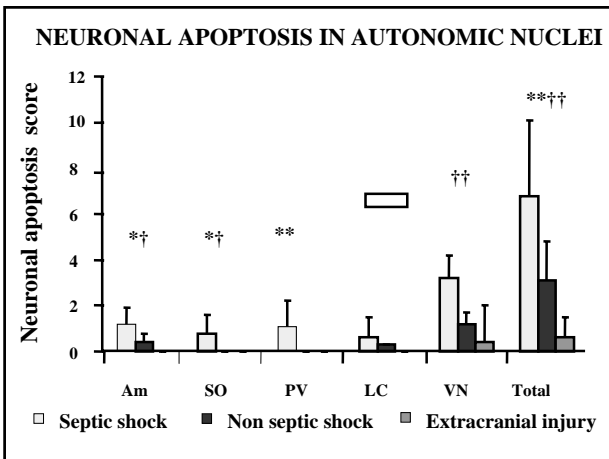
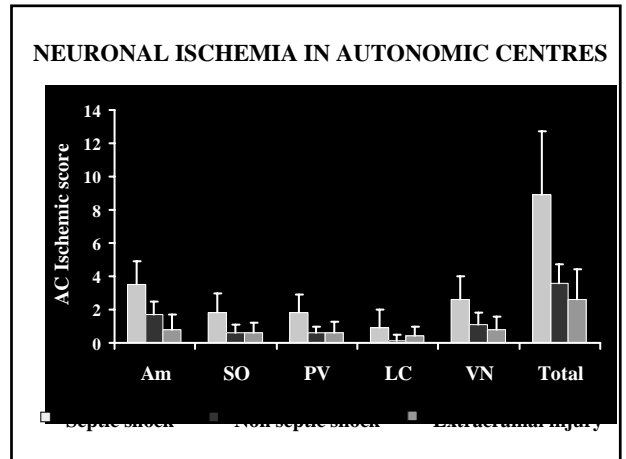


**Table 1. Temporal and spatial expression of interleukin-1 $\beta$ , inducible nitric oxide synthase messenger RNA and Fos in circumventricular organs and adjacent structures after i.p. injection of 250  $\mu$ g/kg lipopolysaccharide**

	2h			4h			8h		
	IL-1 $\beta$	iNOS	Fos	IL-1 $\beta$	iNOS	Fos	IL-1 $\beta$	iNOS	Fos
AP									
medial	*	-	-	*	-	-	**	-	*
ventrolateral border	*	-	-	*	-	-	***	**	*
NTS									
Median eminence			**			**			*
ventral	*	-	-	*	-	-	**	-	-
dorsolateral border	-	-	-	-	-	-	*	-	-
Arcuate nucleus	-	-	-	-	-	-	**	-	-
OVLT									
medial	+	-	-	+	-	-	**	-	**
lateral borders	-	-	-	-	-	-	***	**	*
Medial preoptic area	-	-	**	-	-	**	**	-	*
Subfornical organ	+	-	-	+	-	-	**	-	*
ventromedial	+	-	-	+	-	-	***	**	*
dorsolateral border	+	-	-	+	-	-	***	**	*
Hypocampal commissure	-	-	-	-	-	-	*	-	*
Choroid plexus	-	-	-	-	-	-	*	-	*

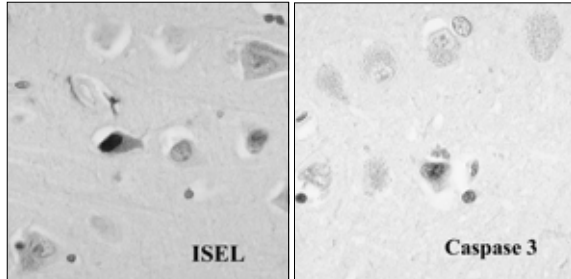
-, no or very few positive cells (<5%); +, few positive cells (5-25%); \*\*, high number of positive cells (25-67%); \*\*\*, very high number of positive cells (>75%); n, numbers of labelled cells in a representative section of a given structure.

*Konsman et al Neuroscience 1999*



## NEURONAL APOPTOSIS

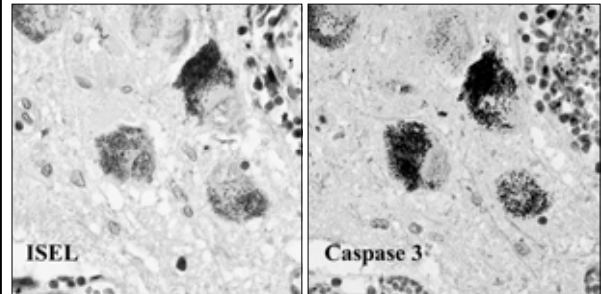
### Cerebral Amygdala



*Sharshar et al Lancet 2003*

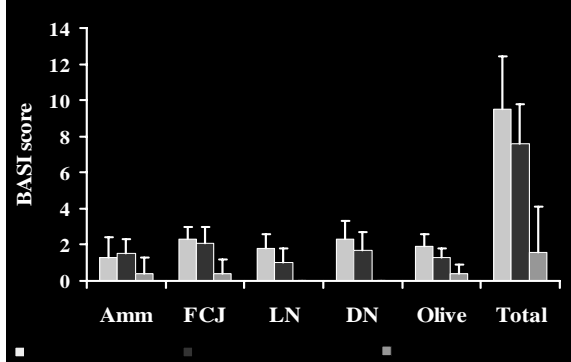
## NEURONAL APOPTOSIS

### Locus Coeruleus



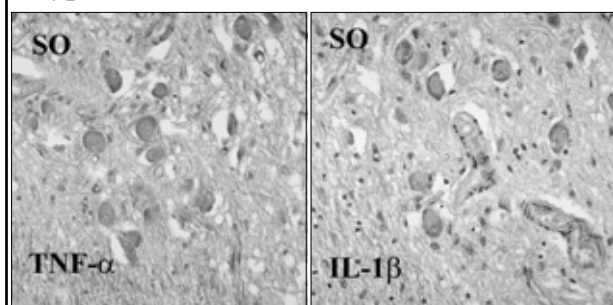
*Sharshar et al Lancet 2003*

## BRAIN AREAS SUSCEPTIBLE TO ISCHEMIA



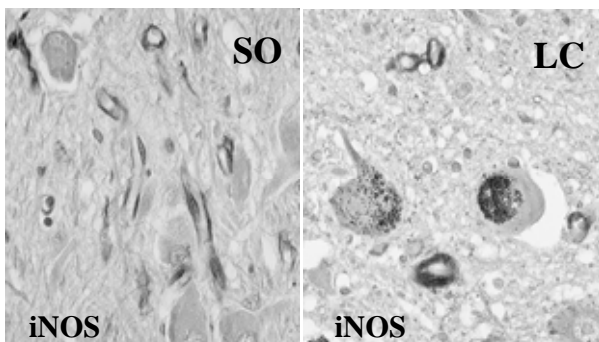
## EXPRESSION OF CYTOKINES

### Hypothalamus



*Sharshar et al Lancet 2003*

## VASCULAR iNOS EXPRESSION

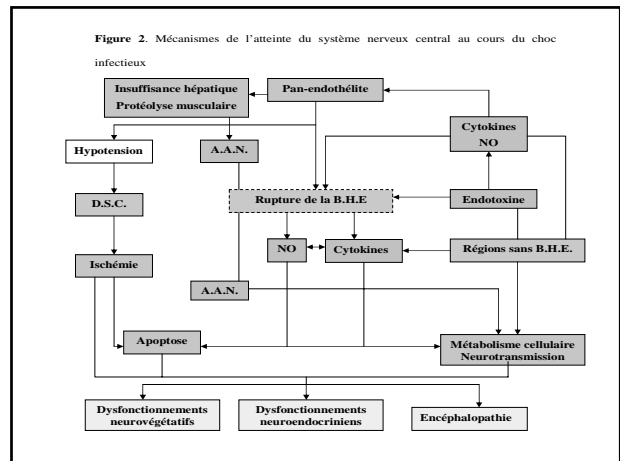
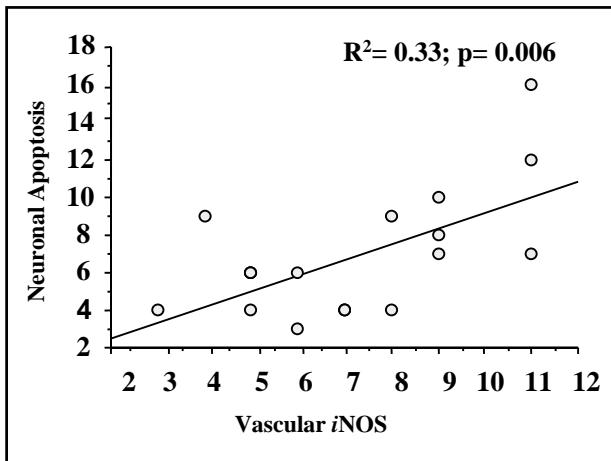


*Sharshar et al Lancet 2003*

## CORRELATION

AC DAMAGES	ISCHAEMIA	APOPTOSIS
Glial TNF $\alpha$	NS	NS
Endothelial iNOS	NS	p = 0.009
Dysautonomia	P = 0.014	-
MBP < 60 mm Hg (h)	P = 0.034	-

*Sharshar et al Lancet 2003*



### EFFET NEUROCHIMIQUES DES CYTOKINES

	CRF	ACTH	ADH	NE	Autres NT
LPS	↑	↑	↑	↓ NE	↑DA, Try, 5H
IL-1β	↑	↑	↑	↑ (turnover) NTS=>Hypo	DA, Try, 5H
IL-6	↑	↑	↑	↔ (?)	DA, Try, 5H
TNFα	↑	↑	↑	↓ NE release	Try
IL-4	↓	↓	↓		
IL-10	↓	↓	↓		

Expression intracérébrale de cytokines anti-inflammatoires: contre-régulation  
 Réponses différentes au cours de stimulations répétées cytokiniques ou LPS :  
 adaptation