



Metabolic encephalopathy

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General remarks

- Brain is not a privileged and protected organ
- Encephalopathy independently associated with increased ICU and hospital survival
- Linked to long-term cognitive dysfunction

Common clinical features

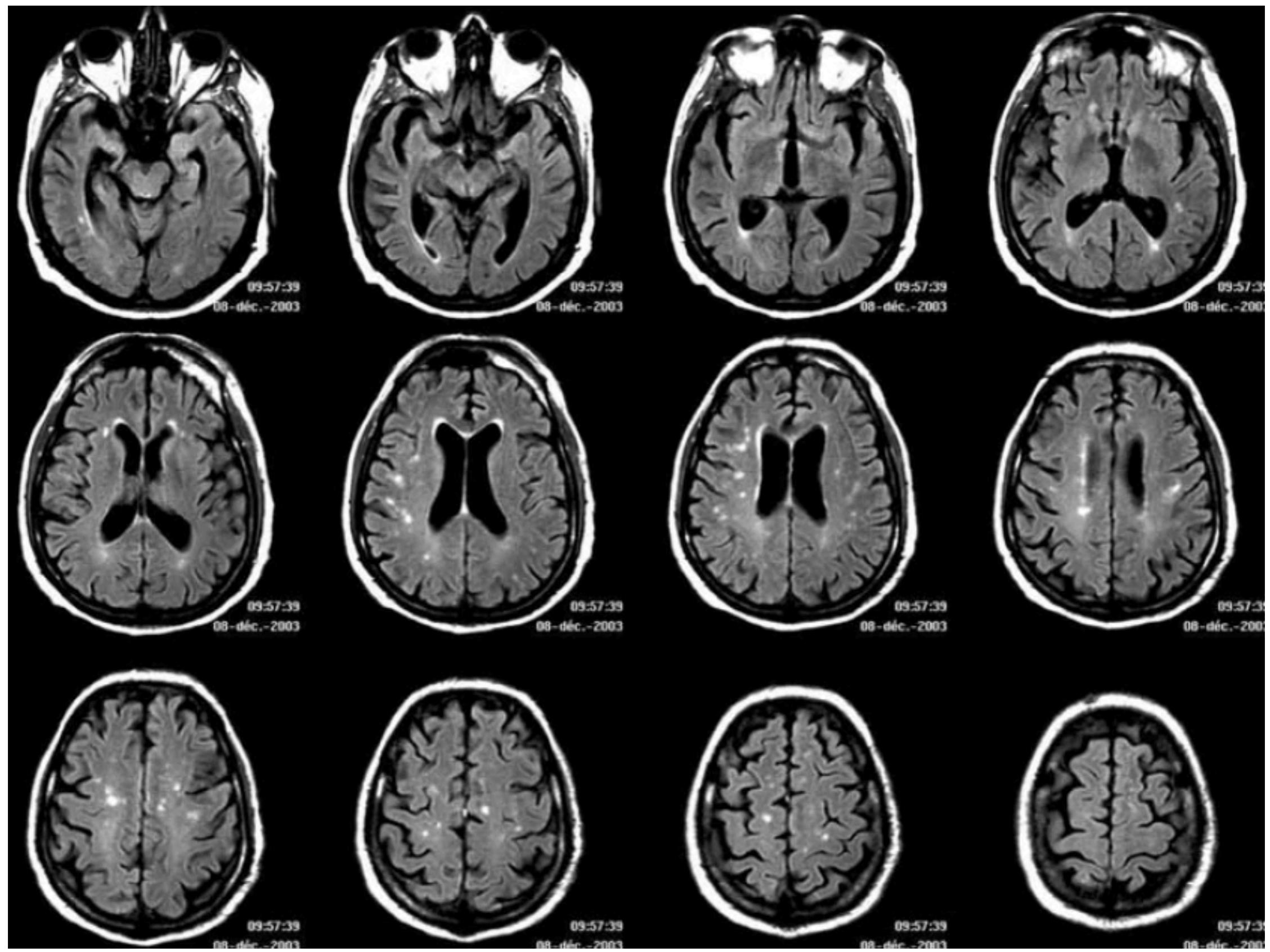
- Acute onset
- Global alteration in cognitive function
- Change in level of consciousness
- Underlying metabolic process - no structural damage

Specific etiologies in ICU

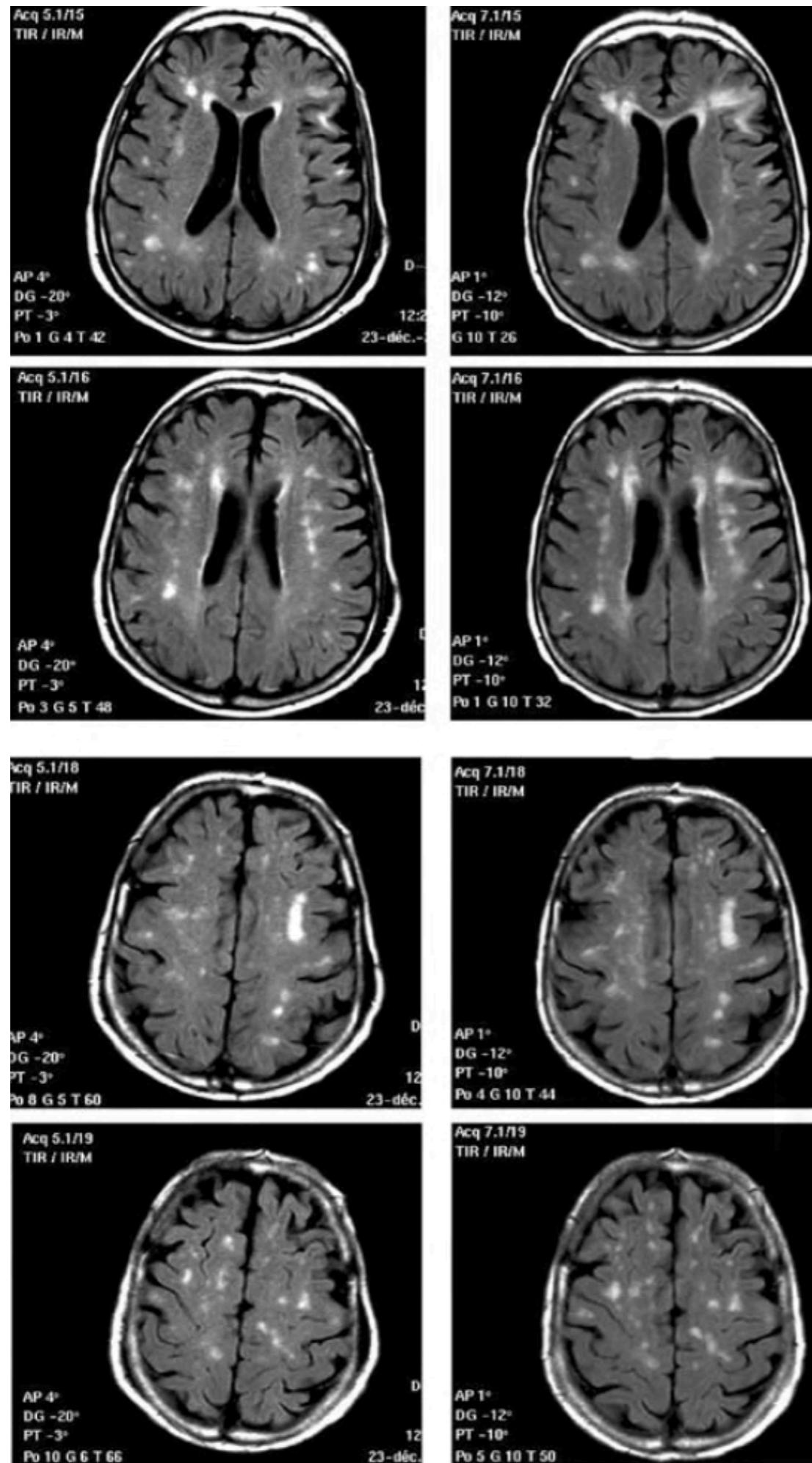
- Sepsis
- Hepatic encephalopathy
- Uremic encephalopathy
- Hypo- & hypernatremia / hypoglycemia
- Thiamine deficiency
- Post-transplantation

Sepsis-associated encephalopathy

- Changes in awareness/consciousness which ranges from alterations in sleep/wake cycle to deep coma
- Changes in cognition including symptoms of delirium
- Alterations in EEG (excessive theta, predominant delta, burst suppression) and SSEP

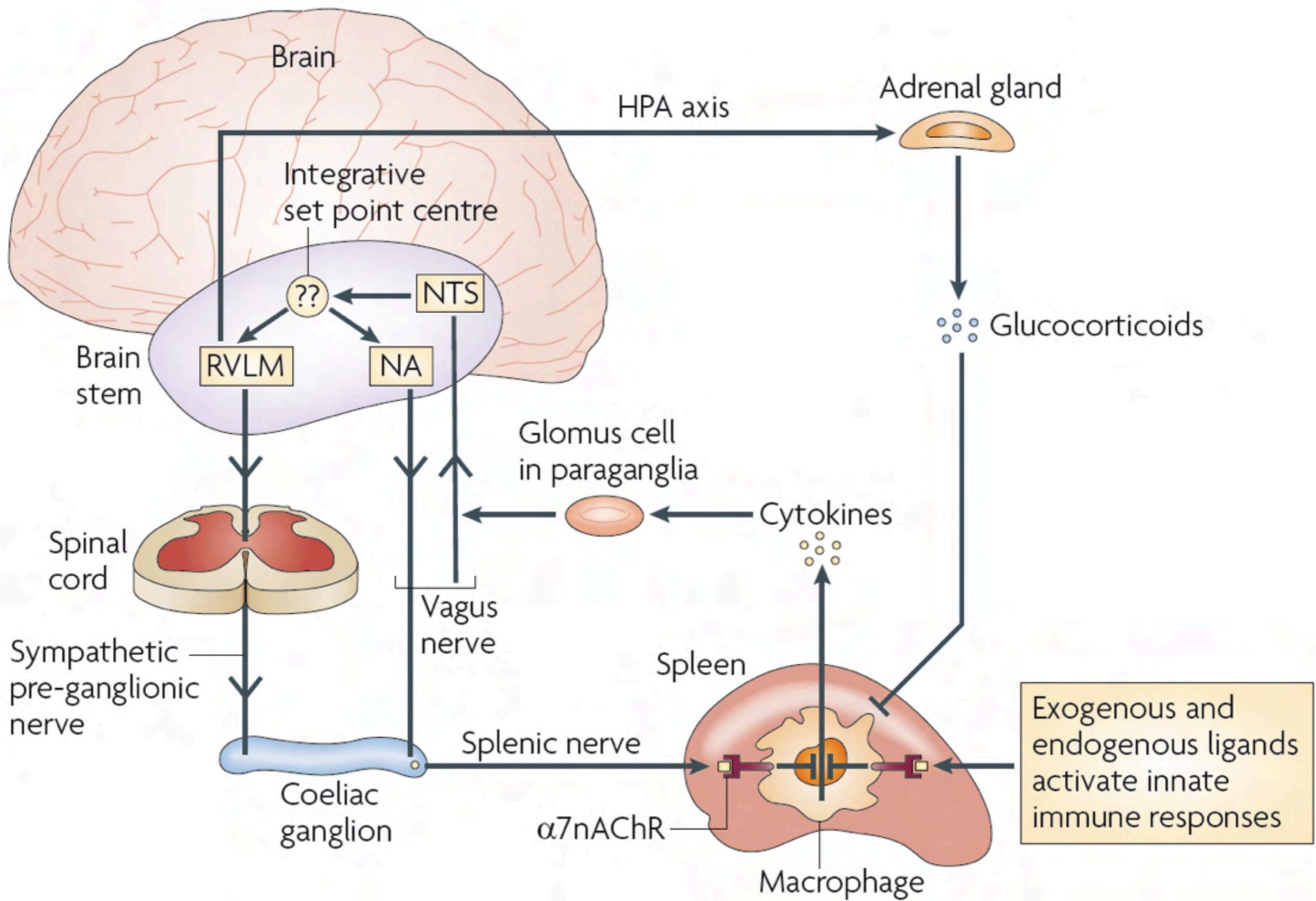


Axial FLAIR images



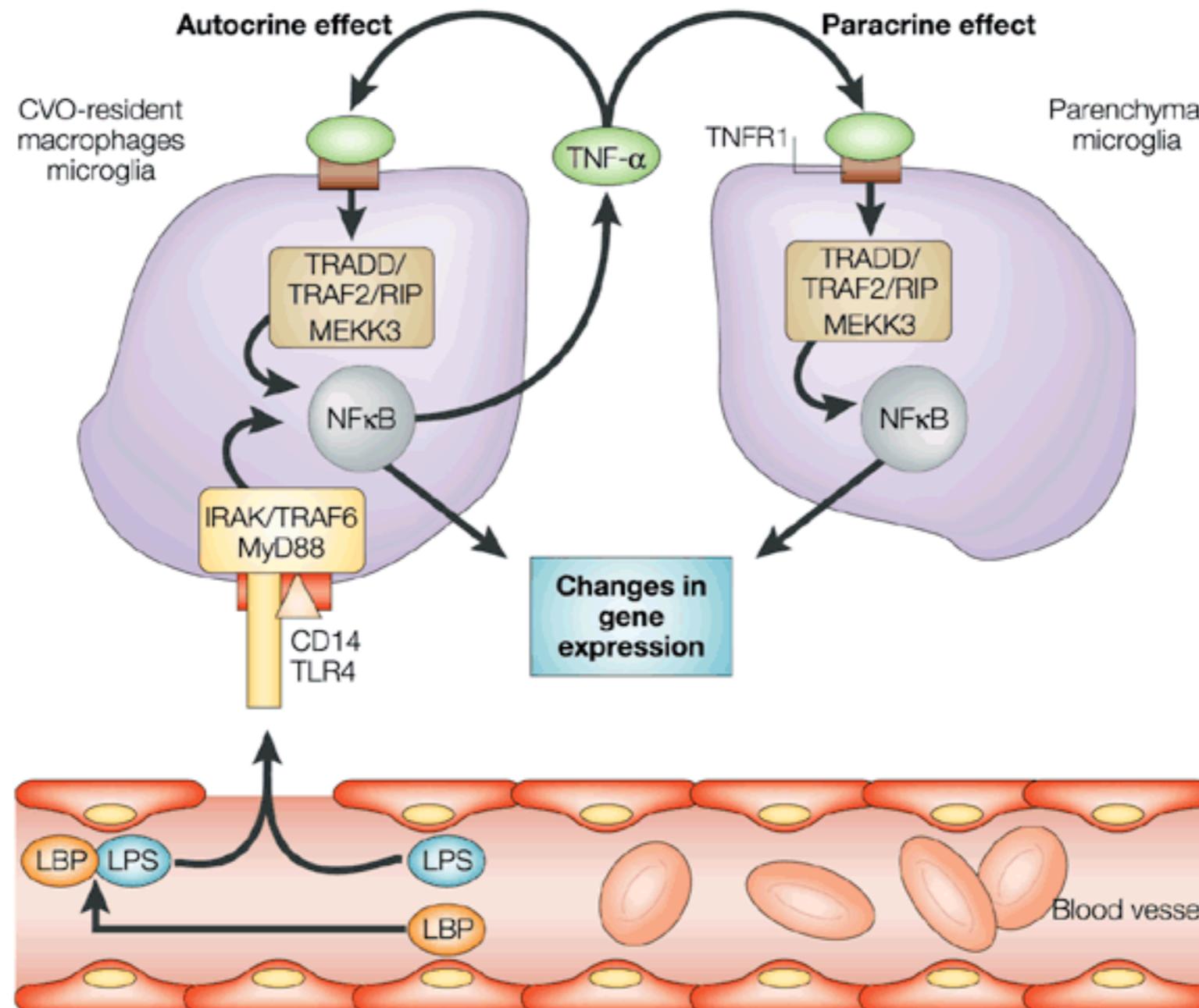
Diffuse leucoencephalopathy (Virchow-Robin spaces)
Cerebral infarctions
Posterior reversible encephalopathy syndrome

How the brain senses inflammation (I)



Tracey K. Nature Immunology 2009;9:418-428

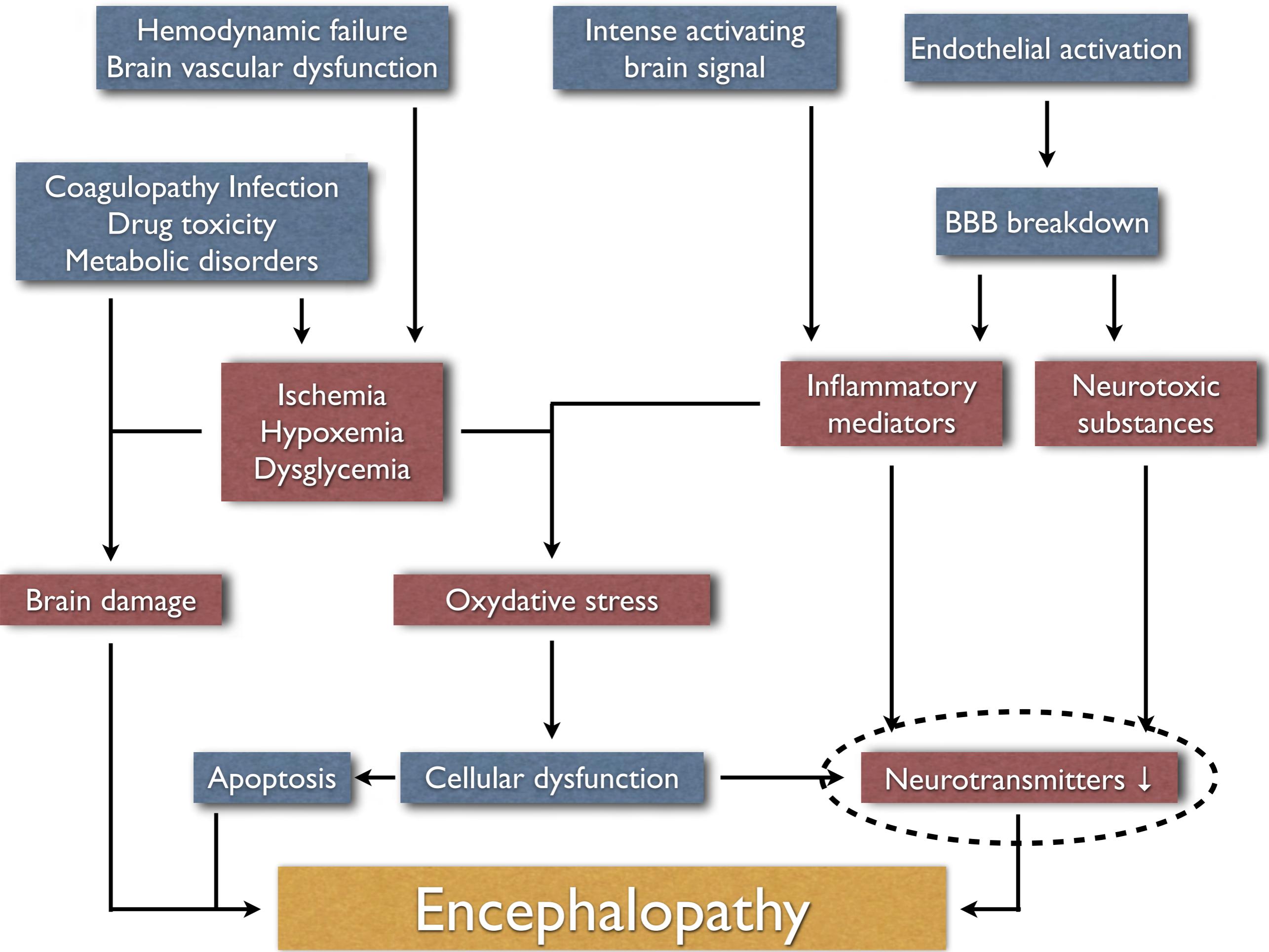
How the brain senses inflammation (2)



Nature reviews | Neuroscience

Circumventricular organs

(subfornical organ, area postrema, organum vasculosum laminae terminalis, posterior pituitary

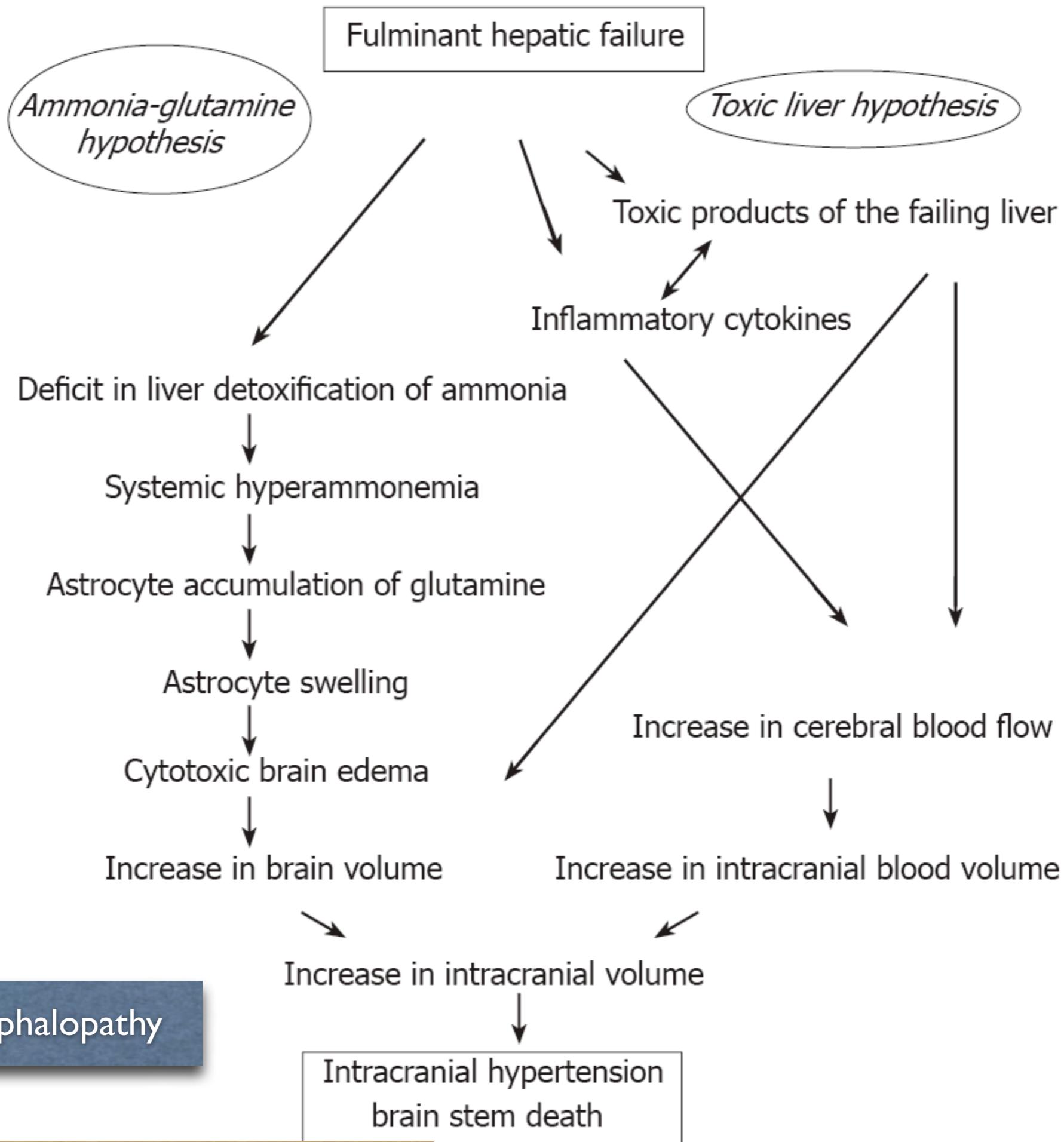


Diagnosis

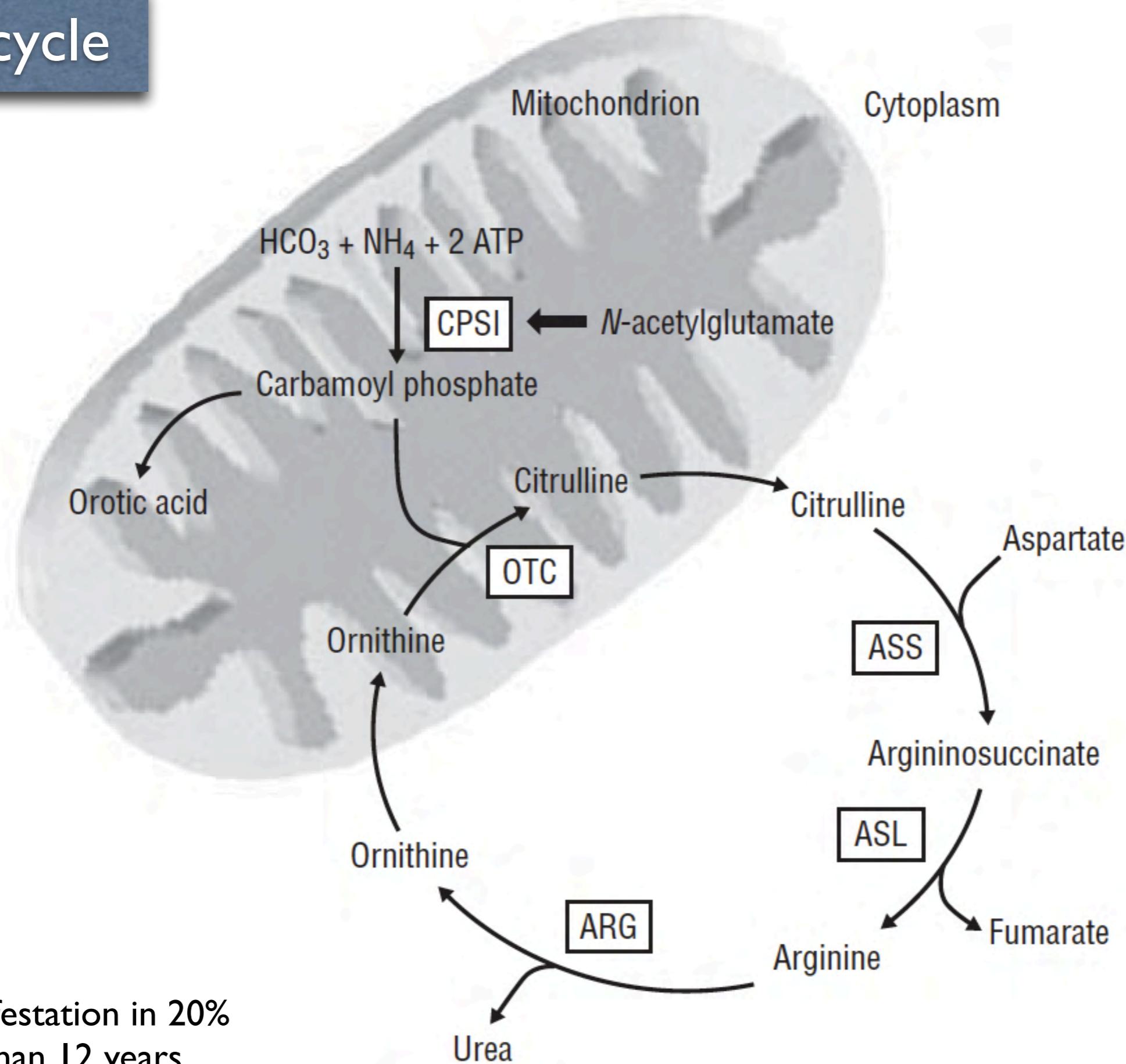
- Always remember the differential as encephalopathy is often multifactorial
- Lumbar puncture in case of suspected meningitis
- Brain imaging if focal signs are present
- EEG with myoclonus and persistent coma
- Exclude medication as underlying cause

Treatment

- No specific therapy - sepsis control
- No proven benefits from strict normoglycemia, corticosteroids or aPC.



Urea cycle

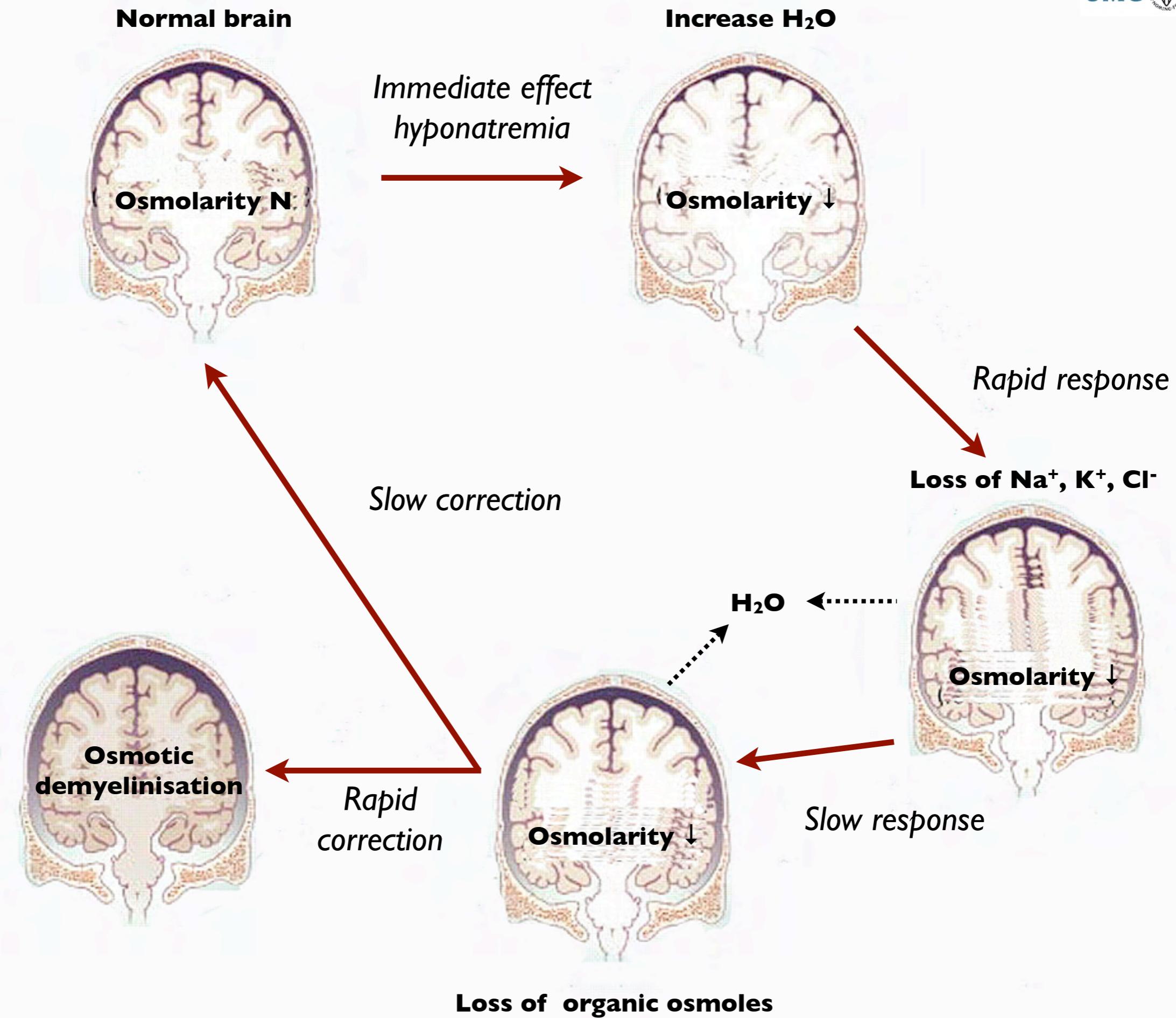


First manifestation in 20%
older than 12 years

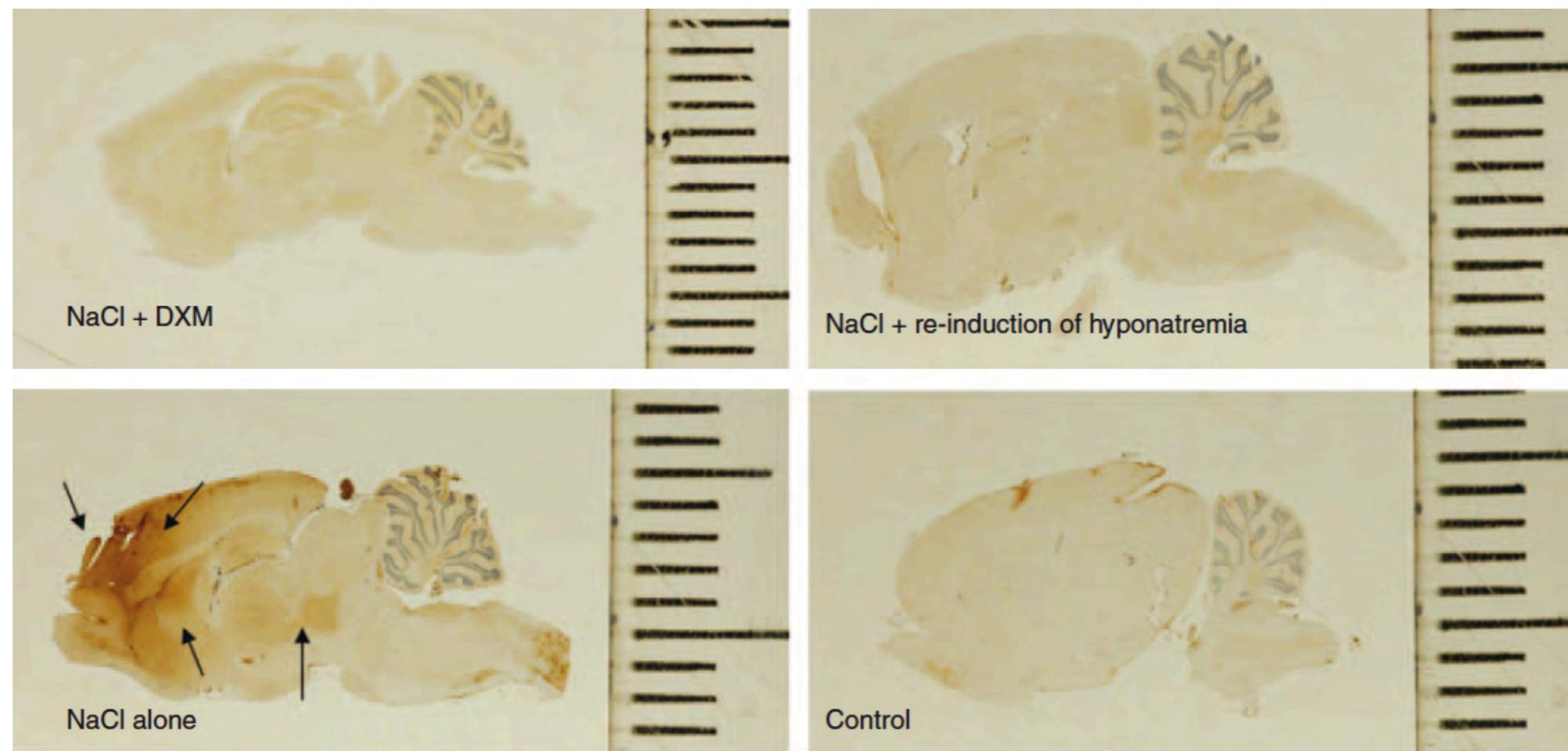
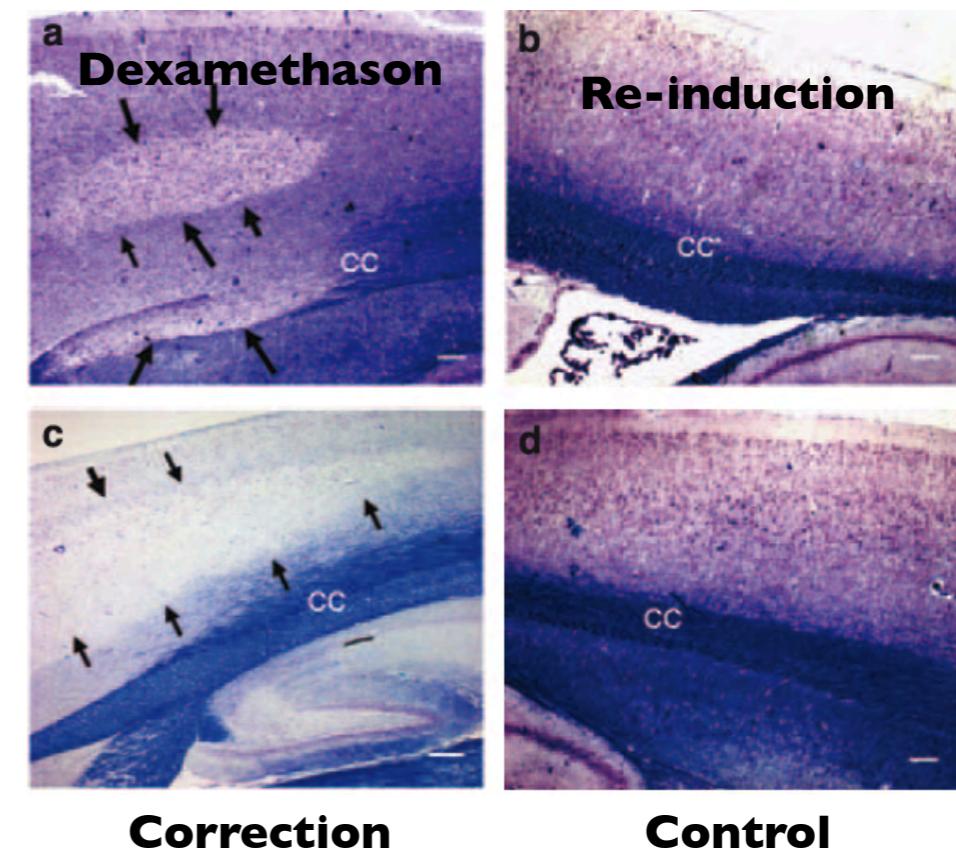
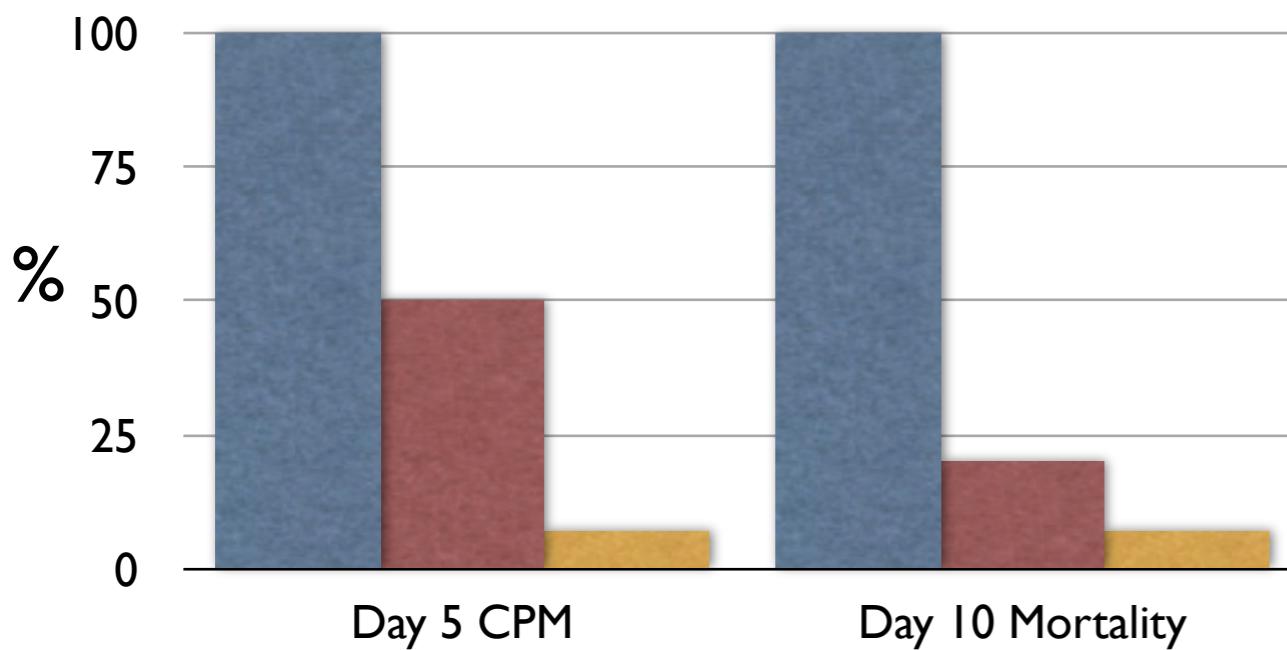
Urea cycle disorders

Table 2. Urea Cycle Disorders

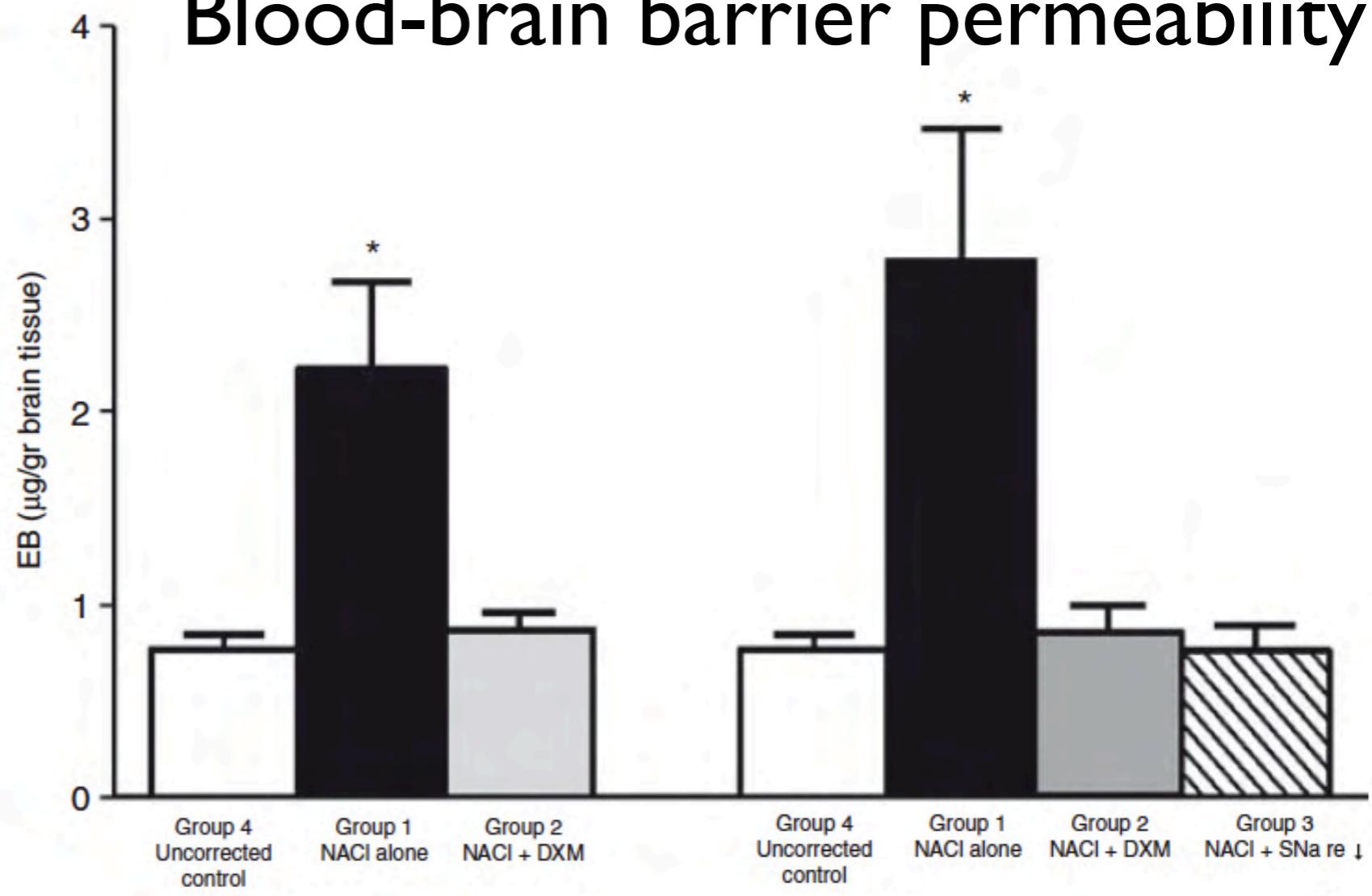
Subtype	Carbamoyl Phosphate Synthetase I Deficiency	Ornithine Transcarbamylase Deficiency	Citrullinemia	Argininosuccinic Aciduria	Argininemia
Enzyme deficiency	Carbamoyl phosphate synthetase I	Ornithine transcarbamylase	Argininosuccinic acid synthetase	Argininosuccinic acid lyase	Arginase
Inheritance	Autosomal recessive	X linked	Autosomal recessive	Autosomal recessive	Autosomal recessive
Chromosome	2	X	9	7	6
Prevalence	1:200 000 to 1:800 000	1:40 000 to 1:80 000	1:100 000	1:150 000	1:1 100 000
Metabolites	↑ Ammonia, ↑ glutamine and asparagine, ↓ citrulline, ↓ arginine	↑ Ammonia, ↑↑ orotic acid, ↑ glutamine and asparagine, ↓ citrulline, ↓ arginine, ↑ ornithine	↑ Ammonia, ↑ orotic acid, ↑↑ citrulline, ↑ or ↓ arginine	↑ Ammonia, ↑ orotic acid, ↑↑ argininosuccinate, ↑ citrulline	↔ Or ↑ ammonia, ↑ orotic acid, ↑ arginine



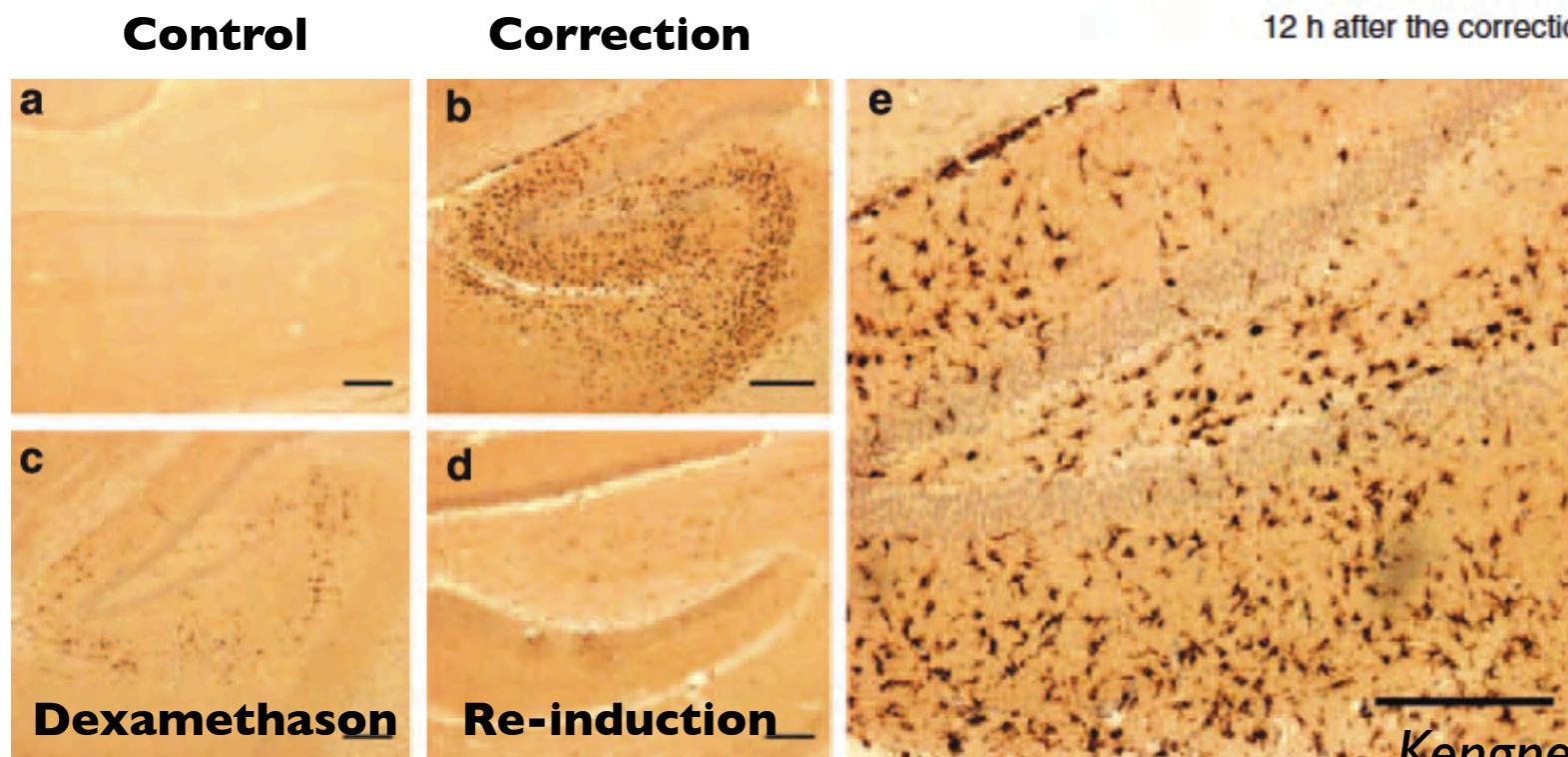
Correction Dexamethason Re-induction hyponatremia



Blood-brain barrier permeability

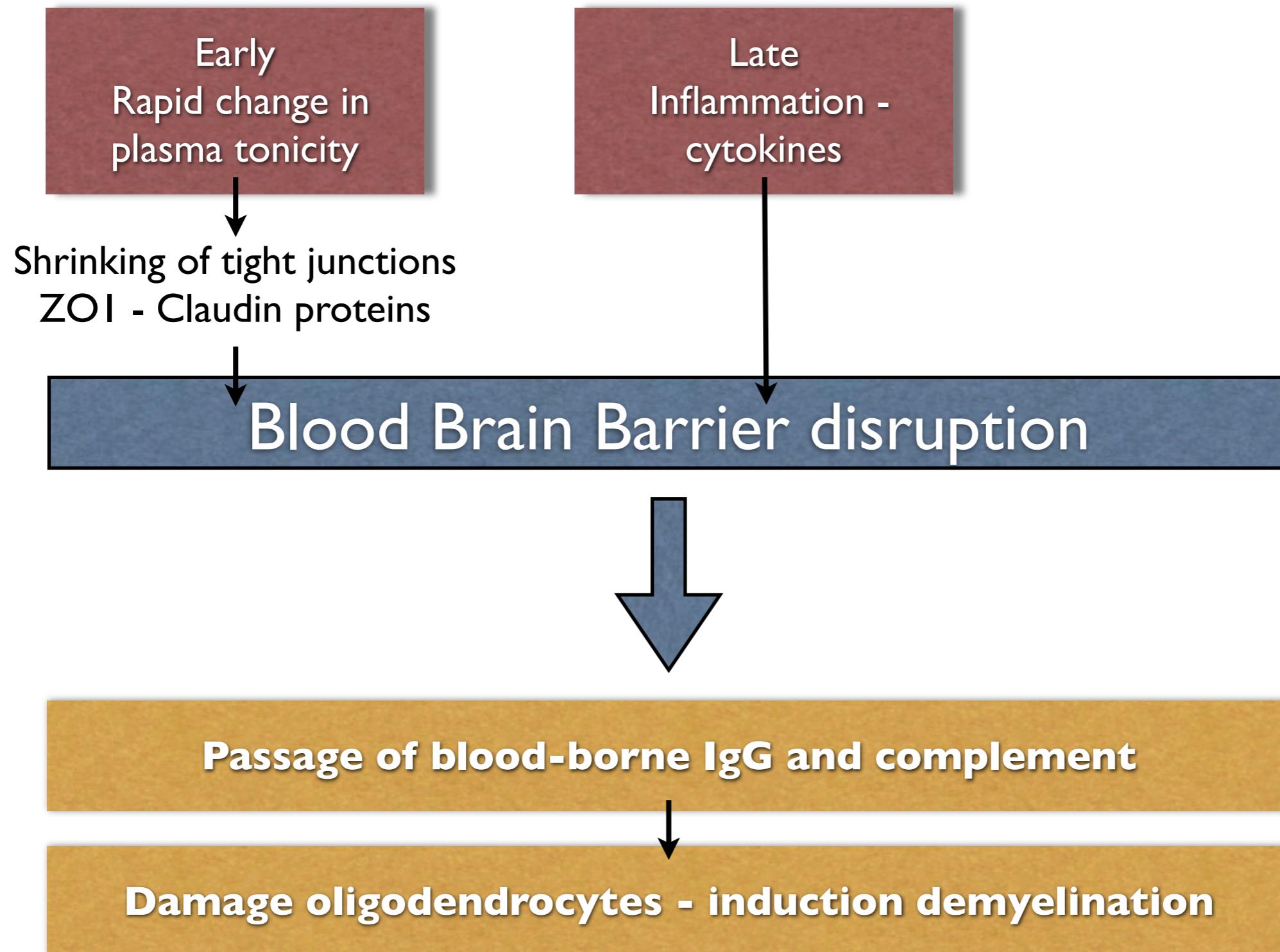


Microglial activation



Kengne FG. Kidney International 2009;76:614-621

Pathophysiology



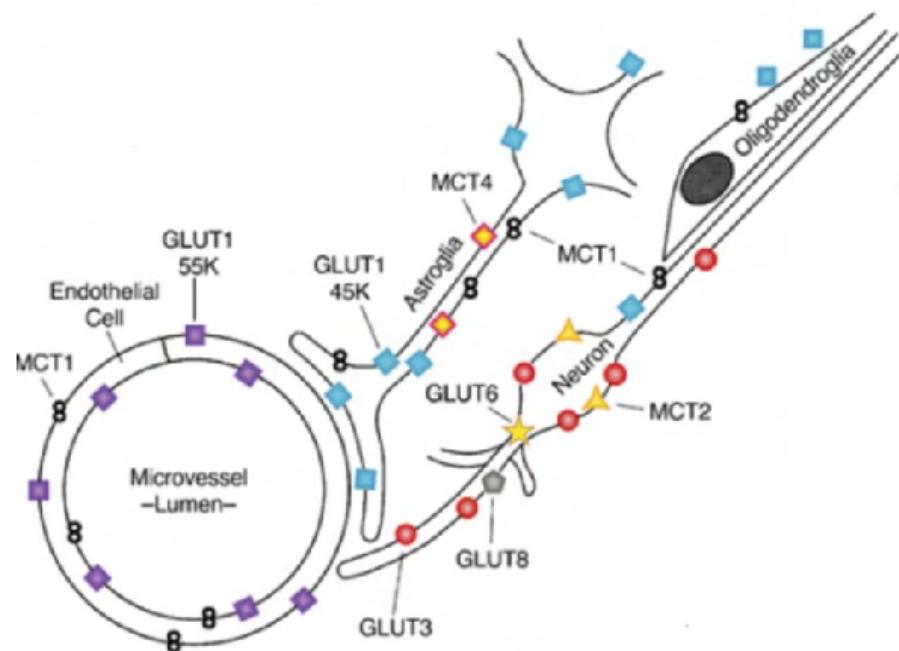
Post-transplantation encephalopathy

- Complication of the underlying disease
- Immunosuppressive medication (cyclosporine, tacrolimus, corticosteroids, OKT3)
- Rejection (especially acute renal allograft)
- Infection

General conclusion

- Metabolic encephalopathy often multi-factorial
- Requires meticulous diagnostic plan
- Associated with increased mortality and long-term cognitive defects
- May have structural abnormalities on MRI

Glucose regulatie bij neuro-IC patiënten

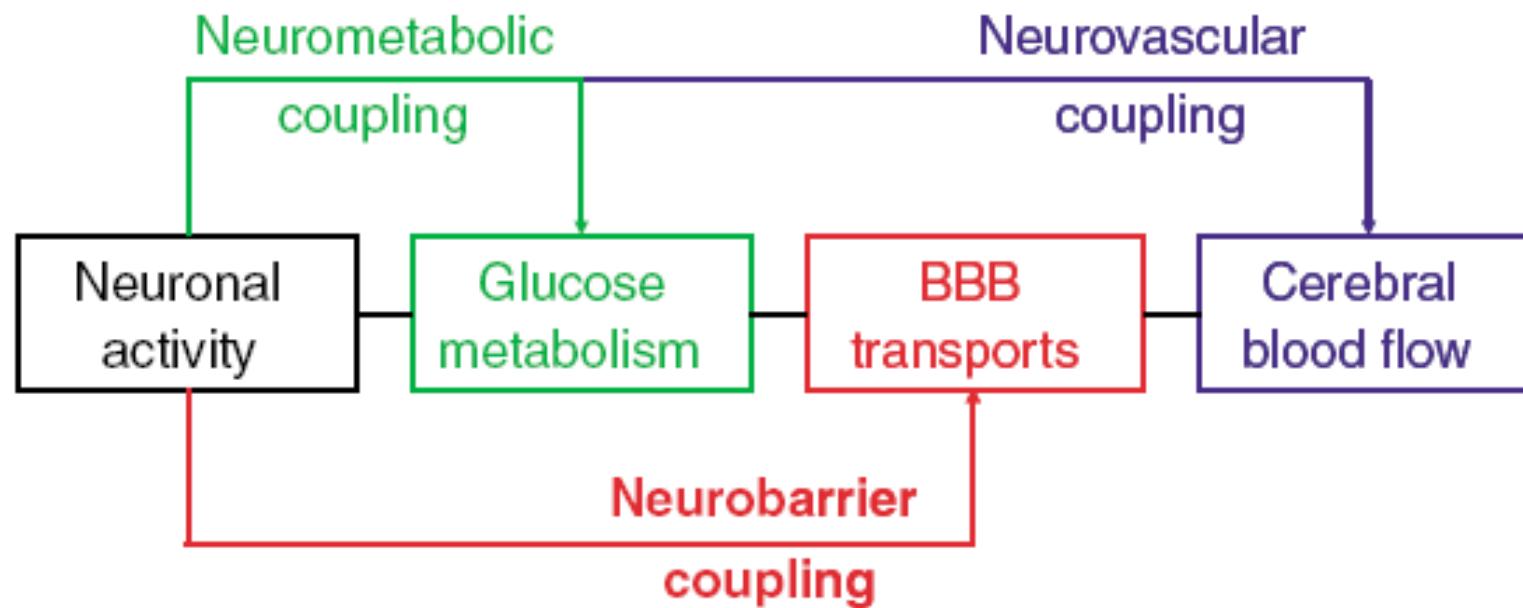


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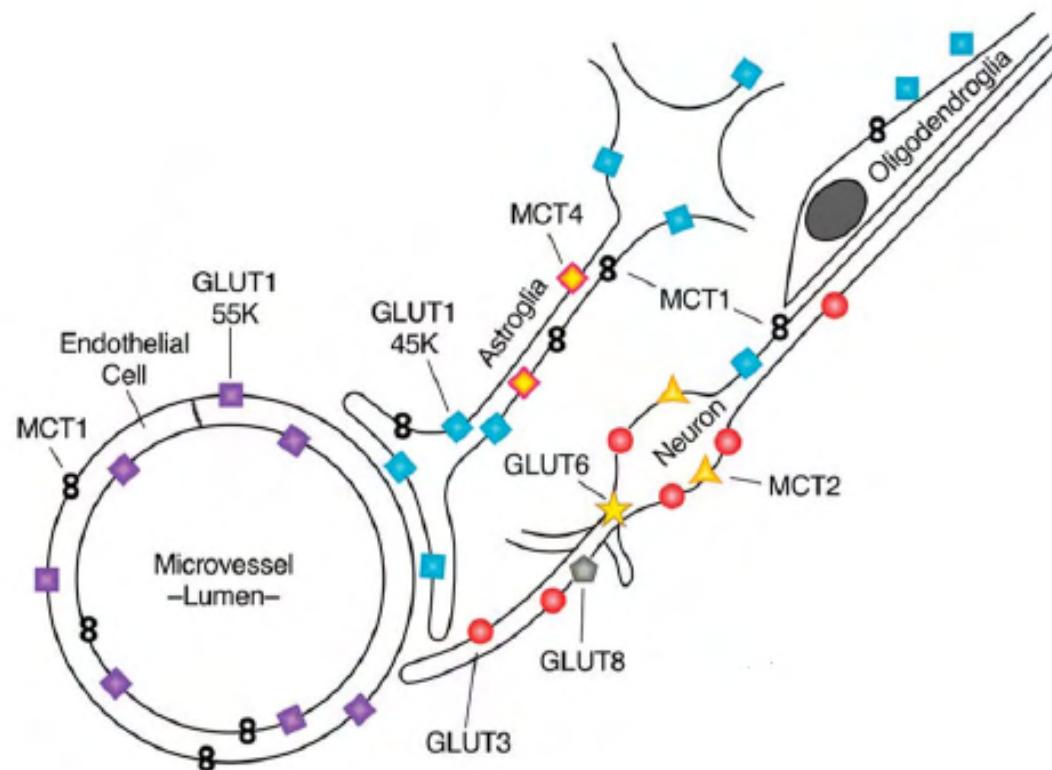
Glucose regulatie bij neuro-IC patiënten

- Glucose als brandstof
- Glucose als vijand
- Glucose regulatie op de IC
 - Stricte regulatie?
 - Rol van glucose variabiliteit

Wat maakt de hersenen bijzonder?

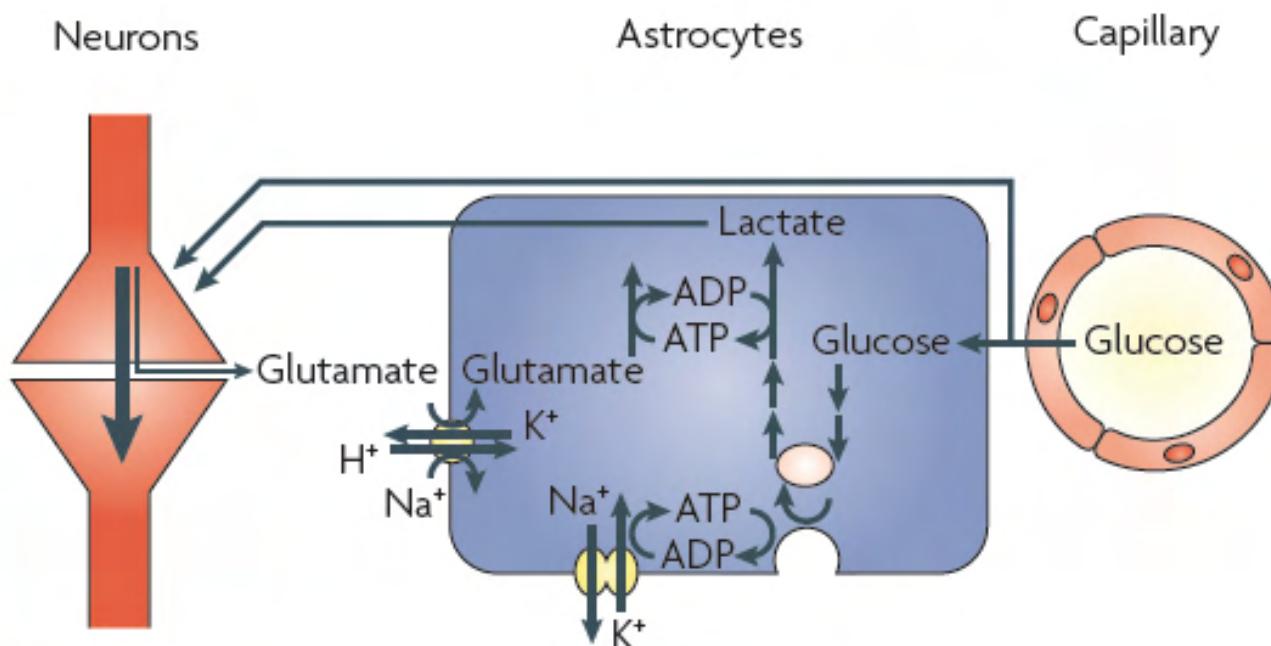


Transport van glucose en monocarboxylaat



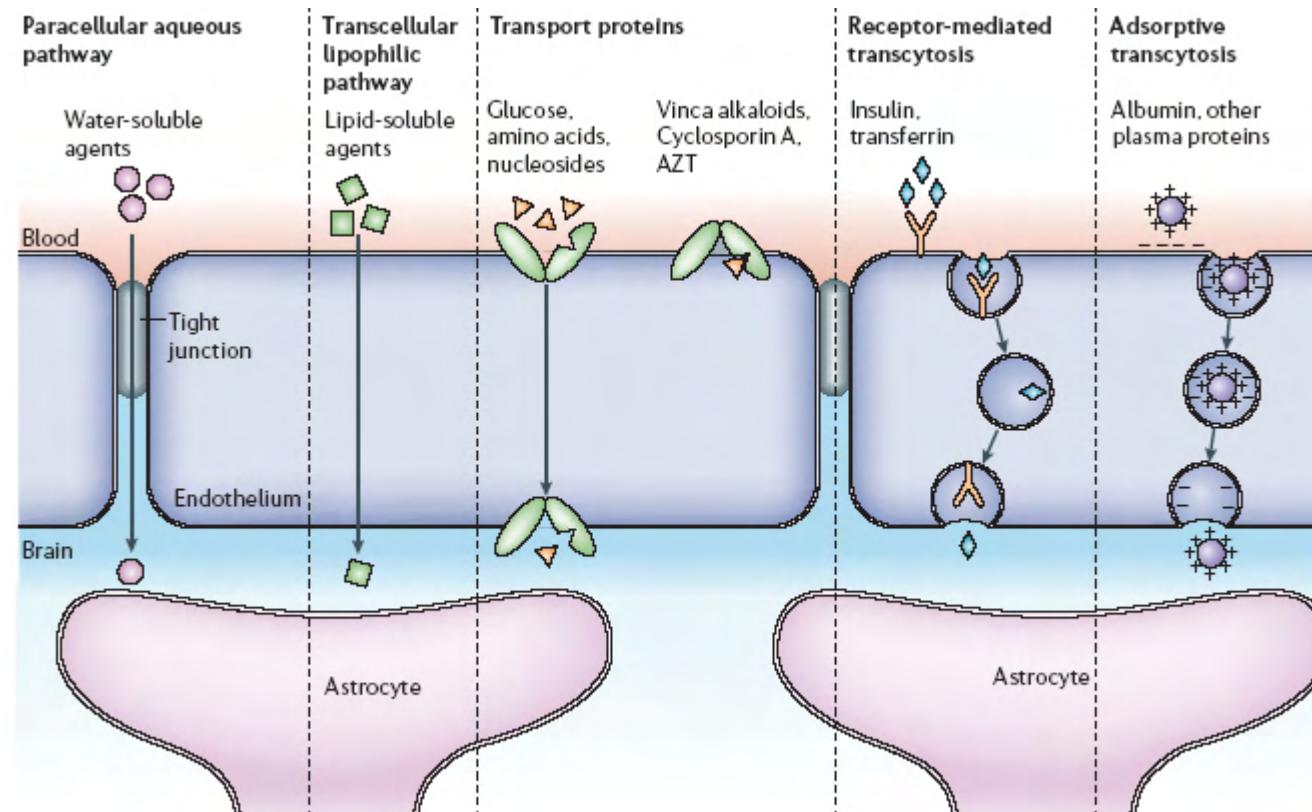
Simpson et al, JCBFM 2007

Astrocyt-neuron lactaat shuttle



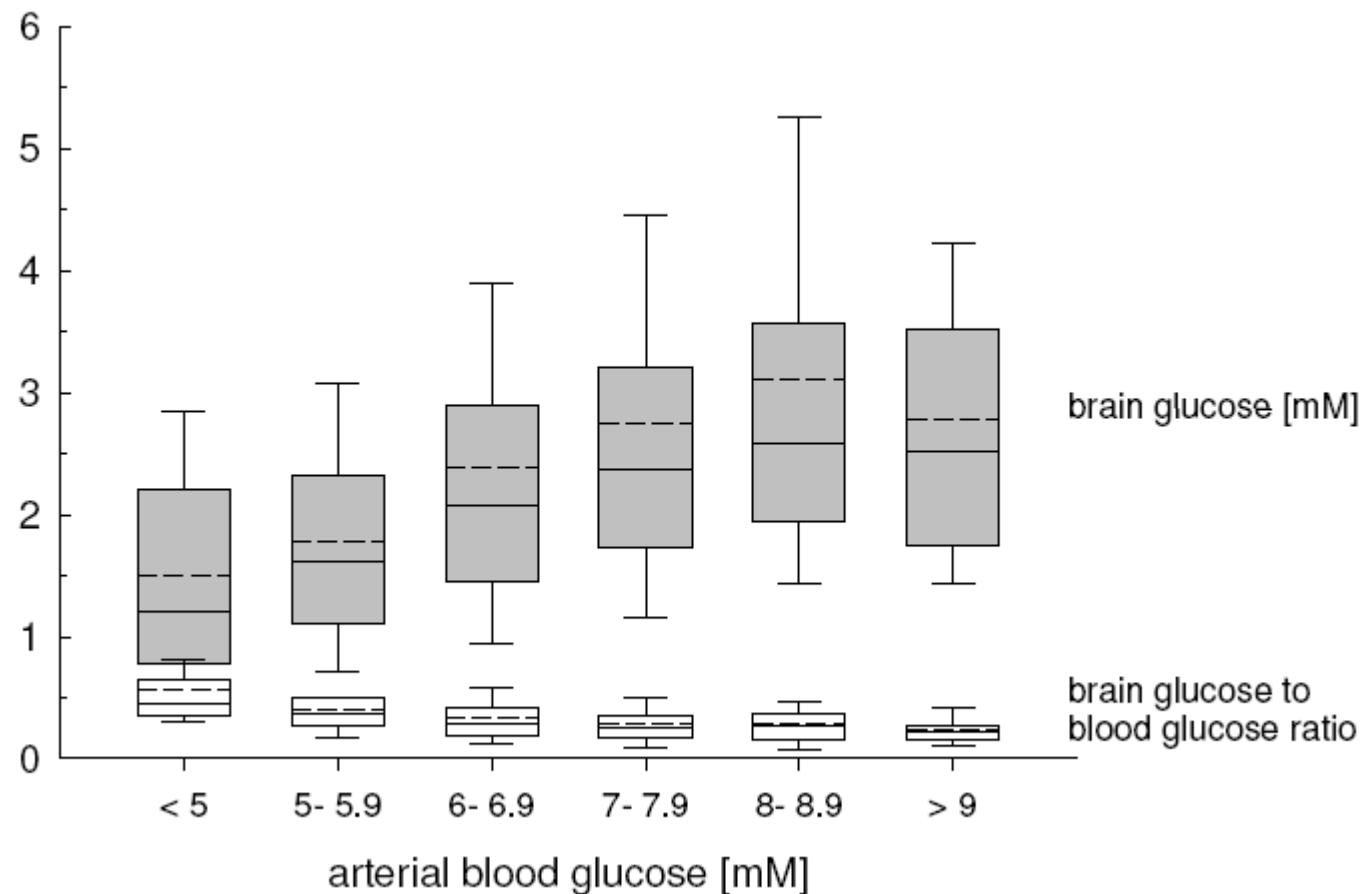
Giaume et al, Nature reviews 2010

Neurobarrieref koppeling



Abbott et al, Nature reviews 2006

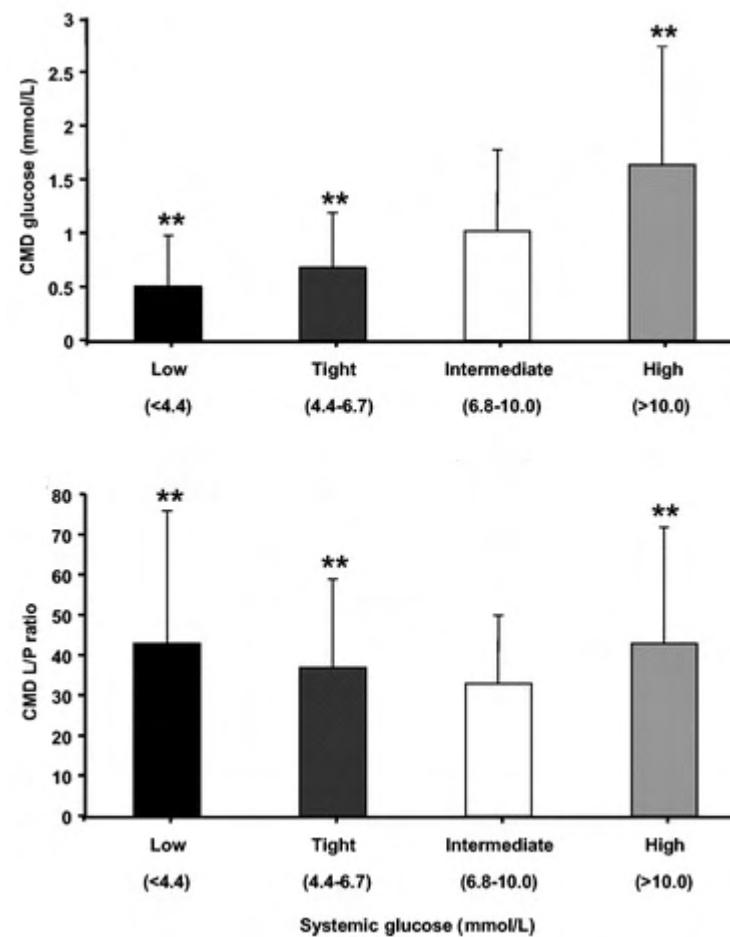
Glucose concentratie in hersenen is lager



Meierhans et al, Crit Care 2010

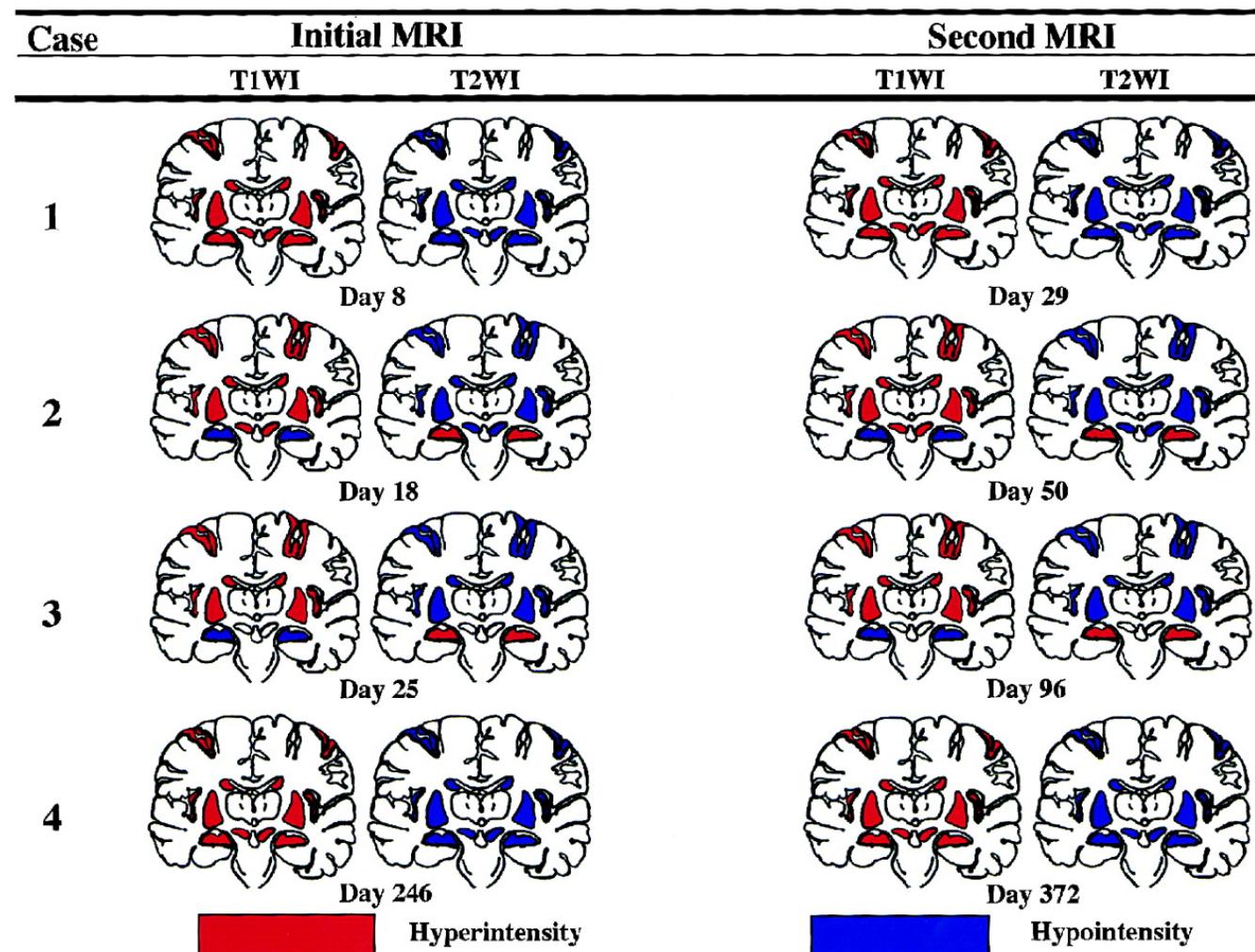
Hypoglycemie

- Stress respons
- Metabole ontregeling
- Toename cerebrale bloed flow
- Verlies van autoregulatie



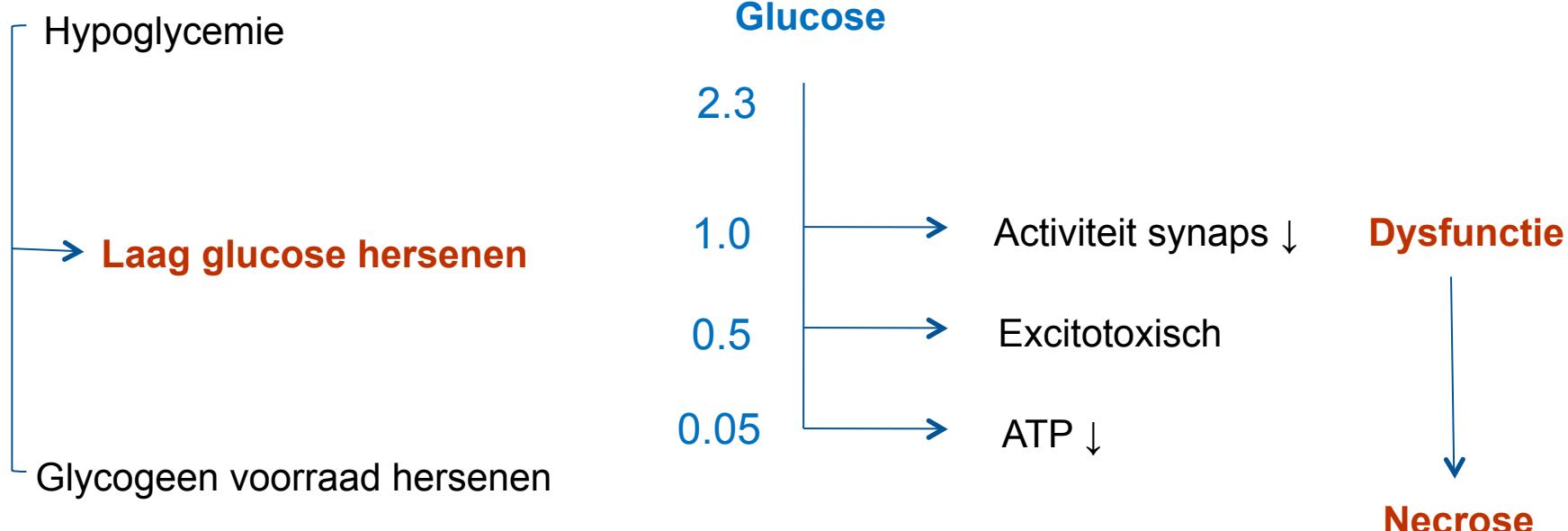
Ondo et al, CCM 2008

Effect van hypoglycemie

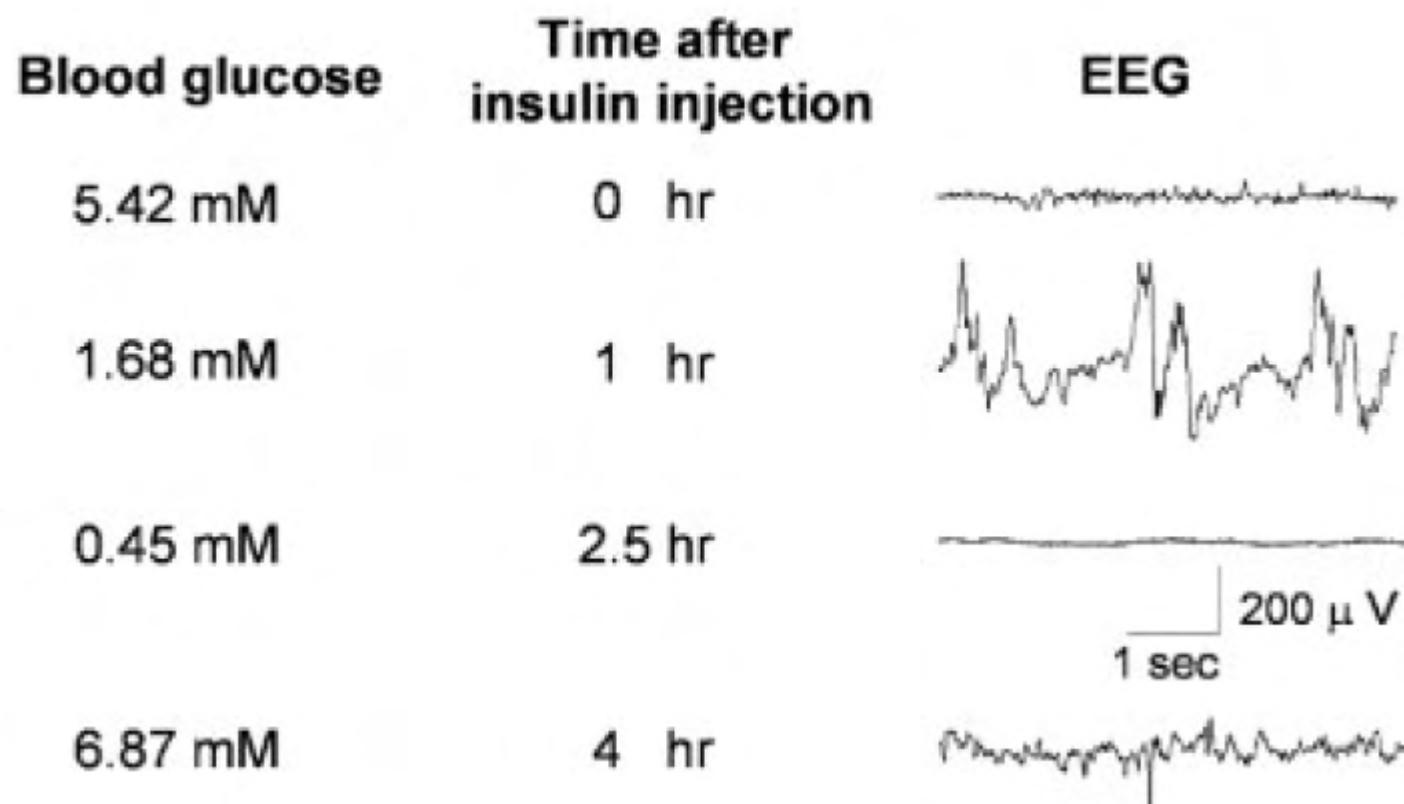


Fujioka et al, Stroke 2007

Effect van hypoglycemie

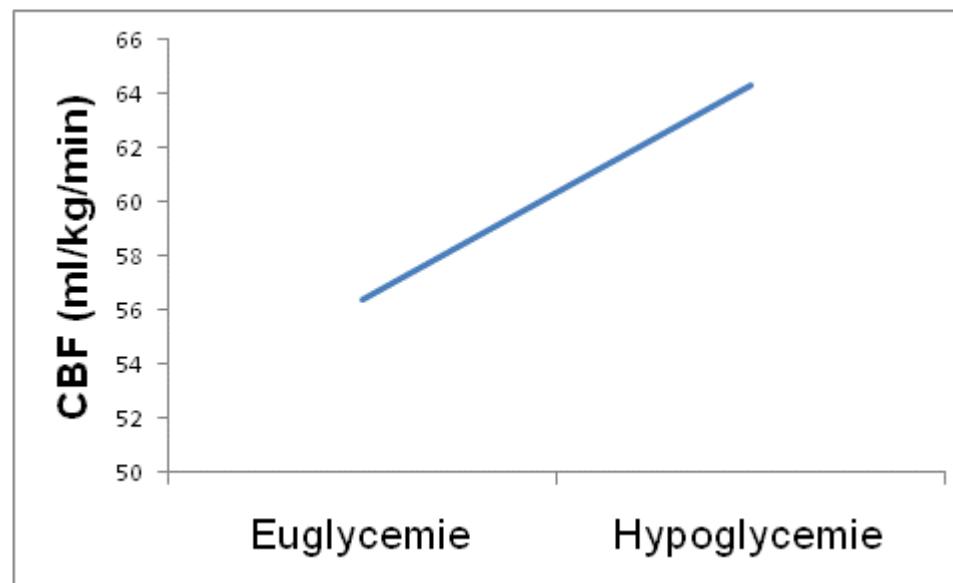


Hypoglycemia EEG



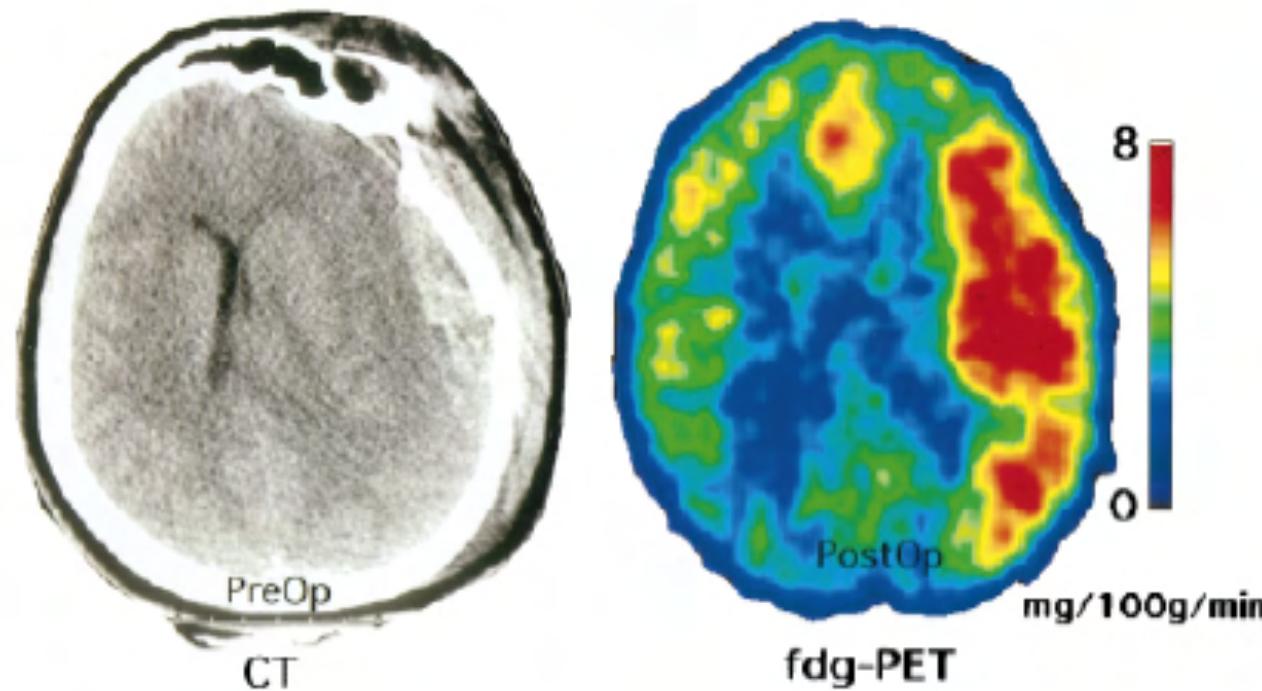
Suh et al, Glia 2007

Hypoglycemie verhoogt de CBF



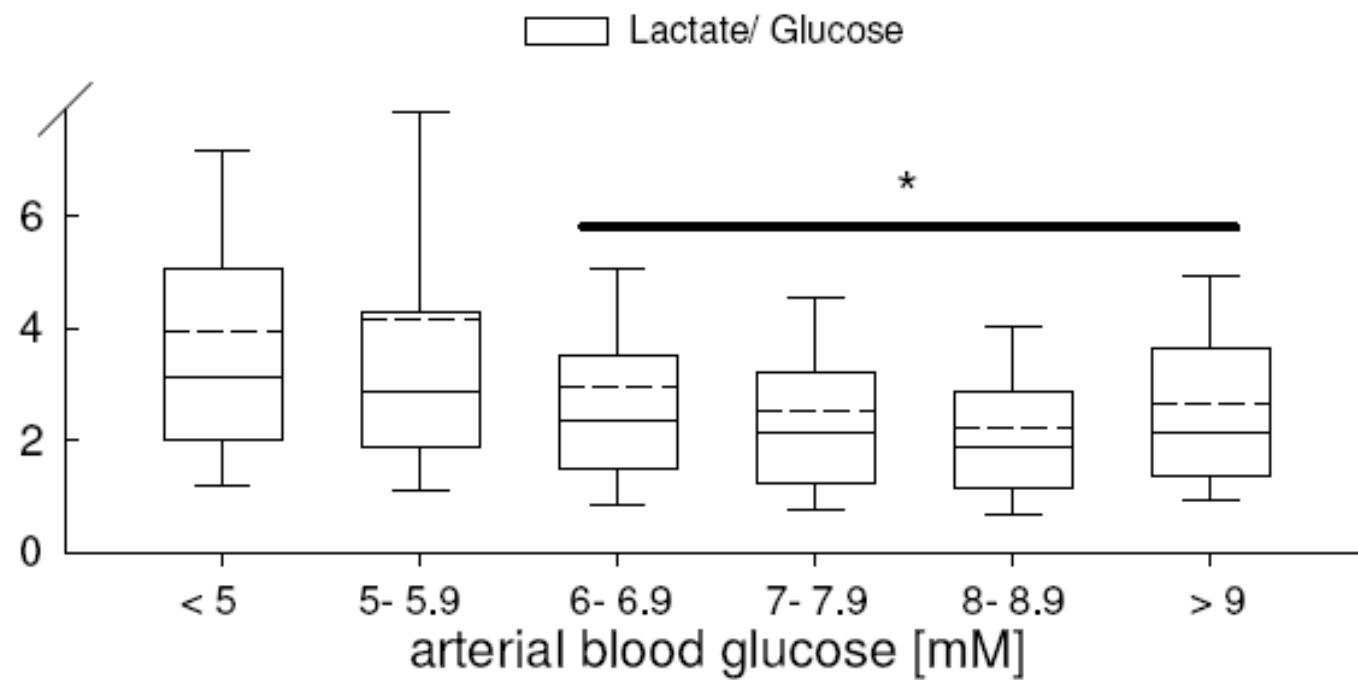
Kennan et al, JCBFM 2005

Hyperglycolysis na neurotrauma



Bergschneider et al, JNS 1997

Anaerobe verbranding bij glucose < 6 mmol/l



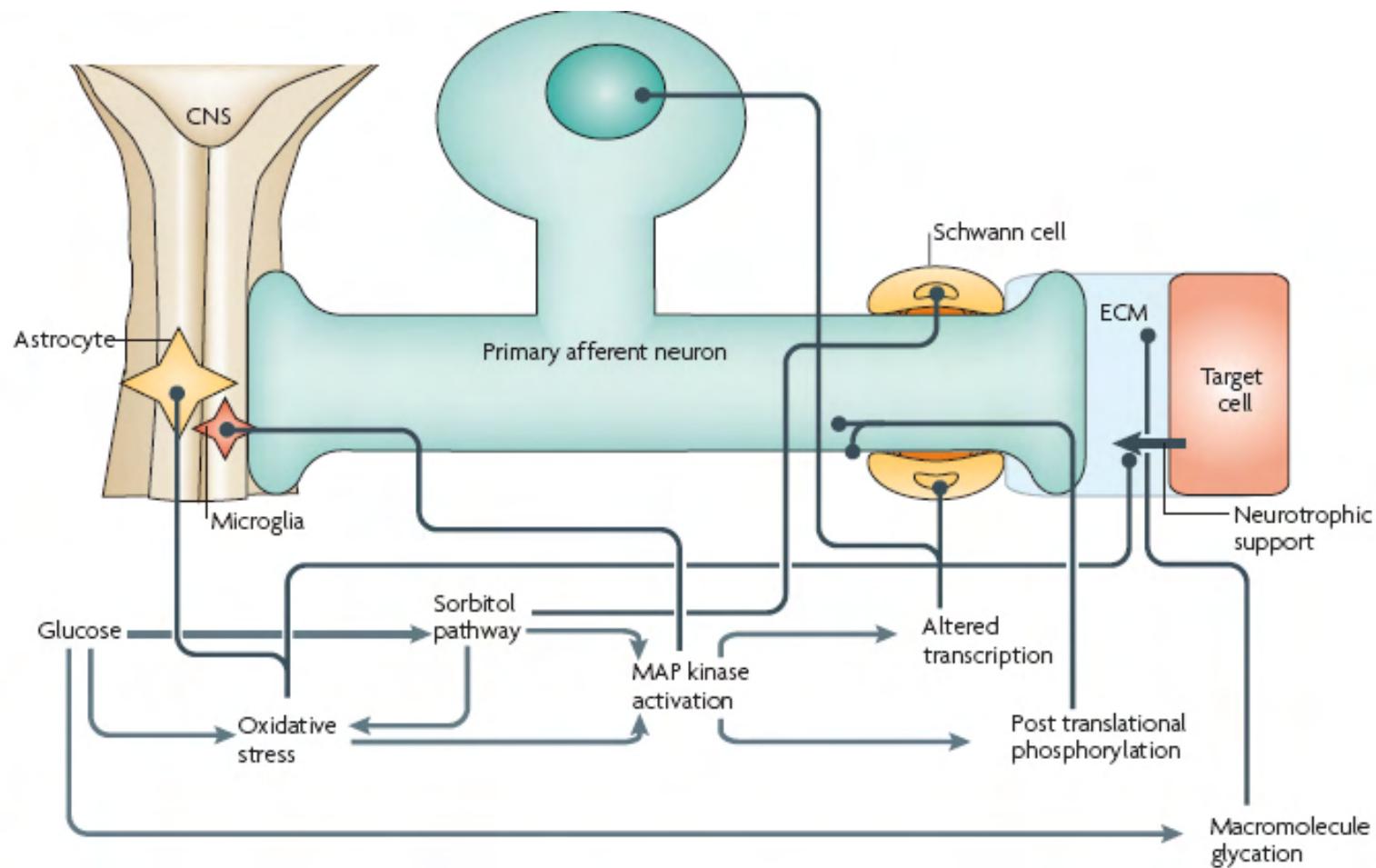
Meierhans et al, Crit Care 2010

Hogere suikers beter?

	All patients (n = 178)	Normoglycemic (≤7.8 mmol/l [1]) (n = 110)	Hyperglycemic (>7.8 mmol/l) (n = 68)	P
Clinical group: asymptomatic/AFND/DIND	71/65/42	55/23/32	16/42/10	0.04
Glasgow Outcome Score at 12 months				0.001
GOS 1–2 n (%)	27 (19%)	8 (9%)	19 (32%)	
GOS 3 n (%)	22 (15%)	11 (13%)	11 (19%)	
GOS 4–5 n (%)	97 (66%)	68 (78%)	29 (49%)	
Mortality at 12 months	19.3%	10.5%	32.8%	0.001

bloed glucose >7.8 mmol/l onafhankelijke risicofactor mortaliteit

Glucose als vijand



Tomlinson et al, Nat Rev 2008

Glucose als vijand

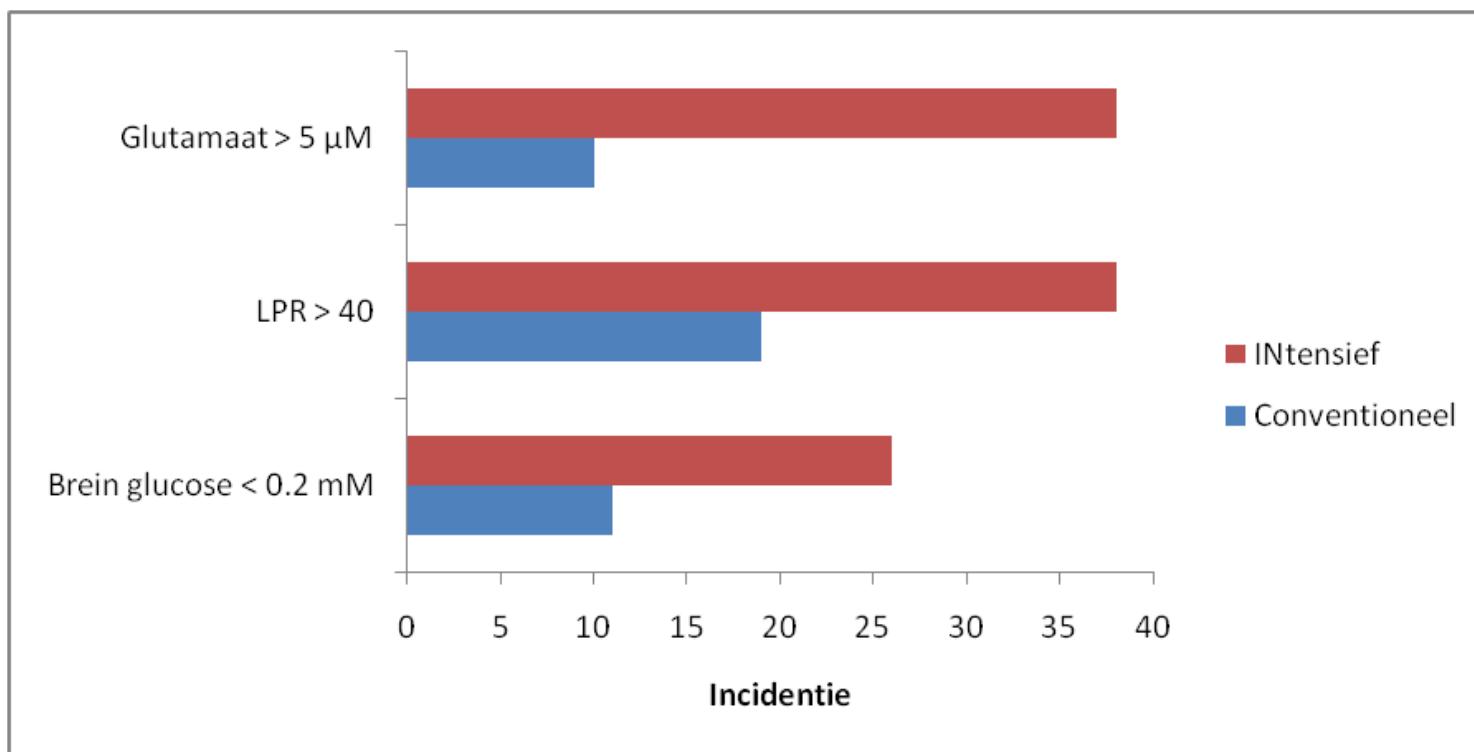
- Toename van hersenschade tgv
 - Inflammatie
 - Afname CBF
 - Toename lactaat en vrije radicalen
 - Toename excitatoire aminozuren
 - Mitochondriale dysfunctie
 - Endotheel dysfunctie

Strakke glucose regulatie op de neuro-IC?

Auteur	Jaar	N	Aandoening	Uitkomst
Bilotta	2007	78	SAB	Negatief
Gray	2007	933	CVA	Negatief
Oksanen	2007	90	Postanoxisch	Negatief
Bilotta	2008	97	TBI	Negatief
Bilotta	2008	483	Neurochirurgie	Negatief
Bruno	2008	46	CVA	Negatief
Green	2010	81	NeuroIC	Negatief
Coester	2010	88	TBI	Negatief

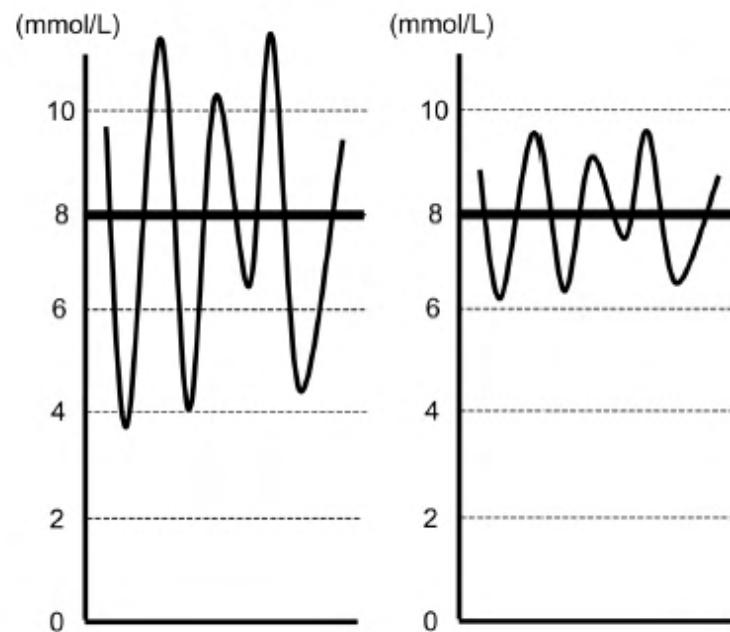
Frequenter hypoglycemieen
(afname infecties)

Intensieve insuline therapie tijdens microdialyse

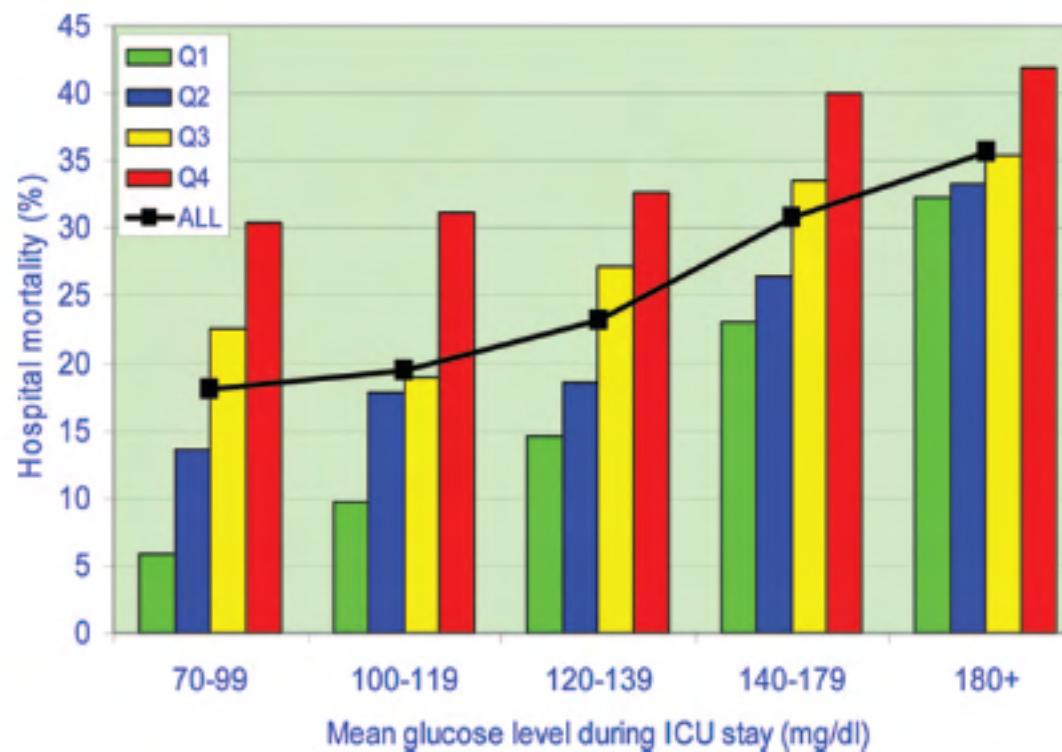


Vespa et al, CCM 2006

Rol van variabiliteit



Variabiliteit is ongunstig

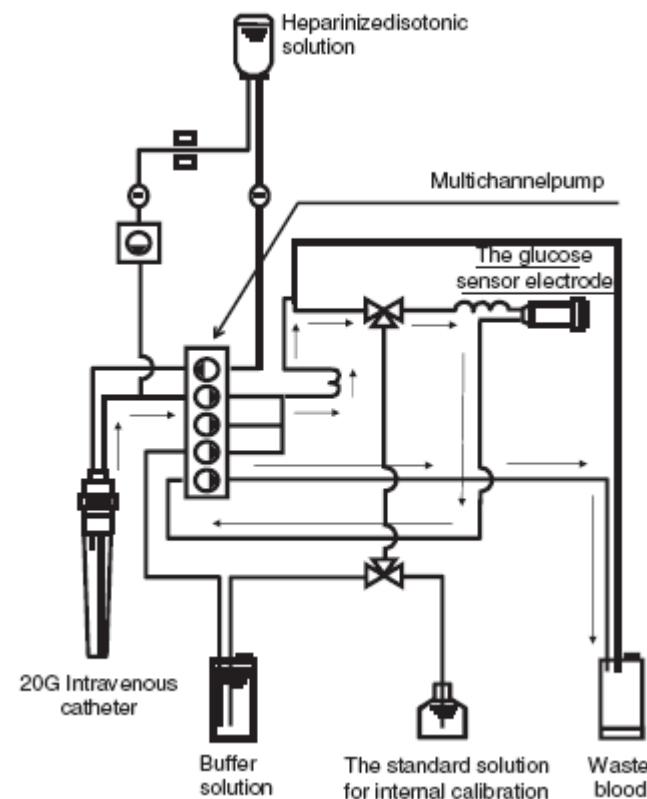
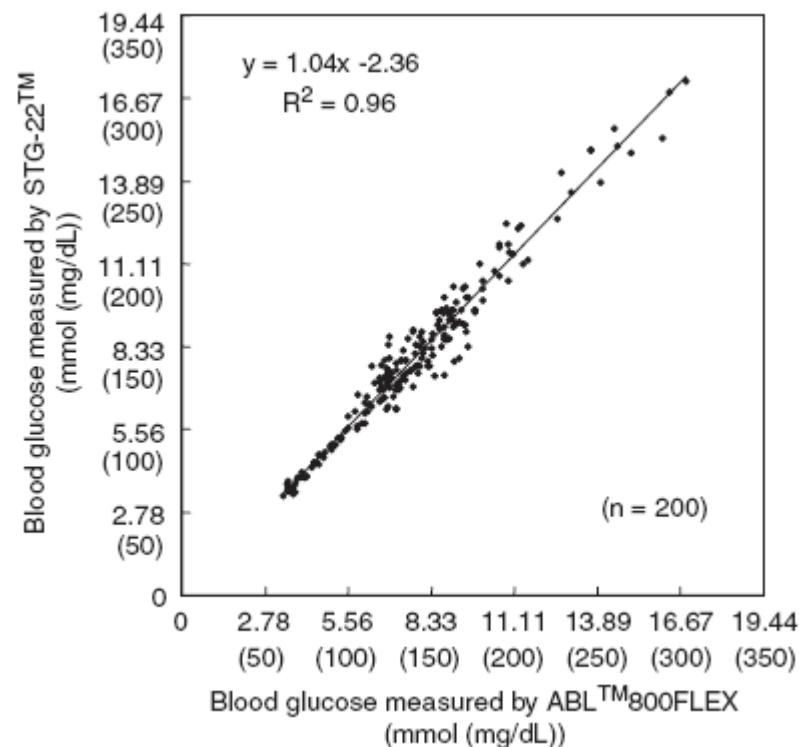


Krinsley et al, CCM 2008

Variabiliteit en mortaliteit

- Nauwkeurige zorg
- Minder zieke patienten
- Biologische factoren
- Combinatie

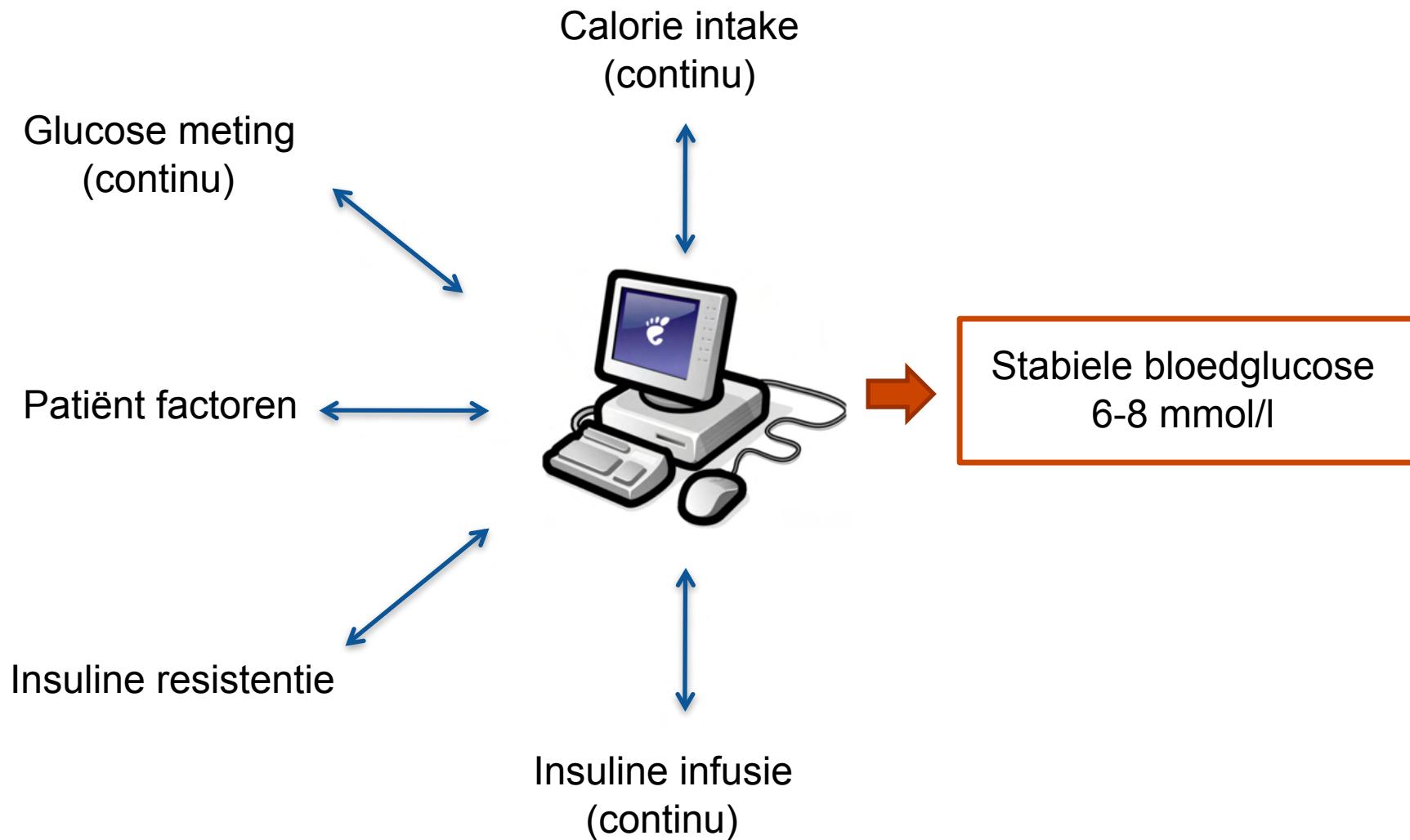
Oplossing?



Yamashita et al, Acta Anest Scand 2009



Glucose regulatie in de toekomst?



Conclusie

- Glucose is de belangrijkste brandstof voor het brein
- Bij kritisch zieke (neurologische) patienten:
 - Normoglycemie (6-8 mmol/l)
 - weinig variabiliteit