“Formulações de medicamentos para superar barreiras sangue-cérebro e sangue-líquor no tratamento de transtornos mentais

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PPG Psiquiatria UFRGS

Declaração de Conflito de interesses

- Nenhum conflito em relação ao tema da conferencia
  - Nenhuma participação acionária ou financeira ligada ao desenvolvimento de drogas para transporte em barreira sangue-cérebro

Medicamentos para ultrapassar barreiras do SNC

- Justificativa:
  - Por que drogas específicas? Existe real necessidade?
  - Evidência de barreiras influenciando o curso das doenças psiquiátricas e resposta a tratamento
    - Acesso ao SNC
    - Resistência a drogas
  - Tipos de barreiras
    - Moléculas envolvidas
  - Tipos de formulações
  - Perspectivas

Construção central

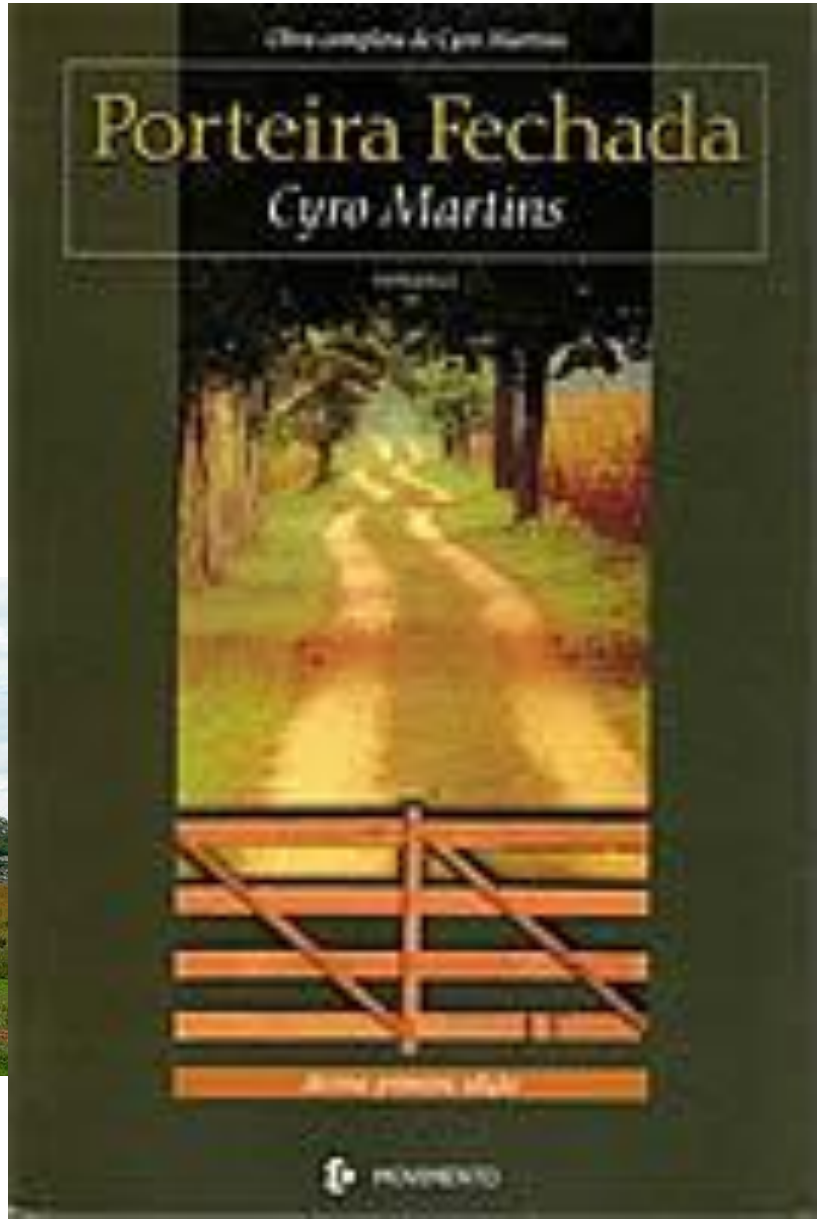
Homenagem a vida e obra
de Cyro Martins

Metáfora da fronteira gaúcha:
- tipos de fronteiras
- vantagens e desvantagens

Manejo adequado das fronteiras

Glossário de termos
- Cavalo de tróia
- Santuário
- Fronteiras & Barreiras

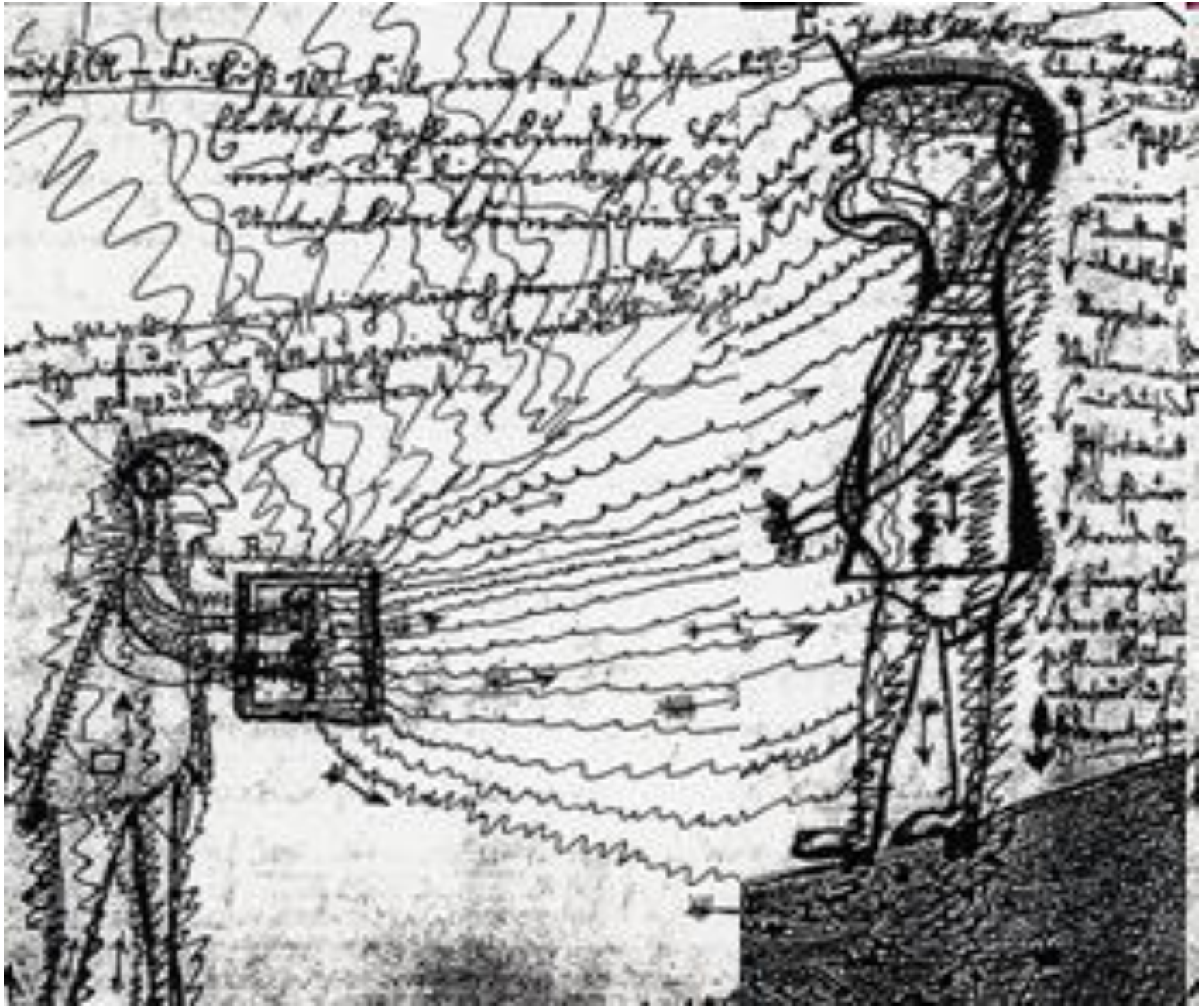
Fronteiras- Passagens - Limites



DUI CHECKPOINTS

Easy to tell when they are ahead.


ALLIED
CHECKPOINT
CHARLIE
Eingang
Entrance
Pass-
kontrolle
Nu das
güad
oder
nüsch
EAST-SIDE GA



Justificativa

- Limitação do efeito de tratamentos
- Progressão de doença mental
  - Esquizofrenia, T. Humor Bipolar
- Resistência-tolerância adquirida a drogas
- Necessidade de drogas mais efetivas
- Necessidade de drogas mais toleradas

Limitantes do Efeito de psicofármacos

- Absorção e distribuição
- Metabolização hepática
- Passagem para cérebro
- Ligação a locais específicos
- Eliminação do cérebro

- Foco nos fatores que modificam acesso ao cérebro

ELSEVIER

Neuroscience Letters 420 (2007) 45–48

www.elsevier.com/locate/neulet

Serum levels of brain-derived neurotrophic factor in patients with schizophrenia and bipolar disorder

Clarissa Severino Gama [a,b,e,*], Ana Cristina Andreazza [a,d], Maurício Kunz [a,b,d,e], Michael Berk [c,f,g], Paulo Silva Belmonte-de-Abreu [a,b,e], Flavio Kapczinski [a,b,d]

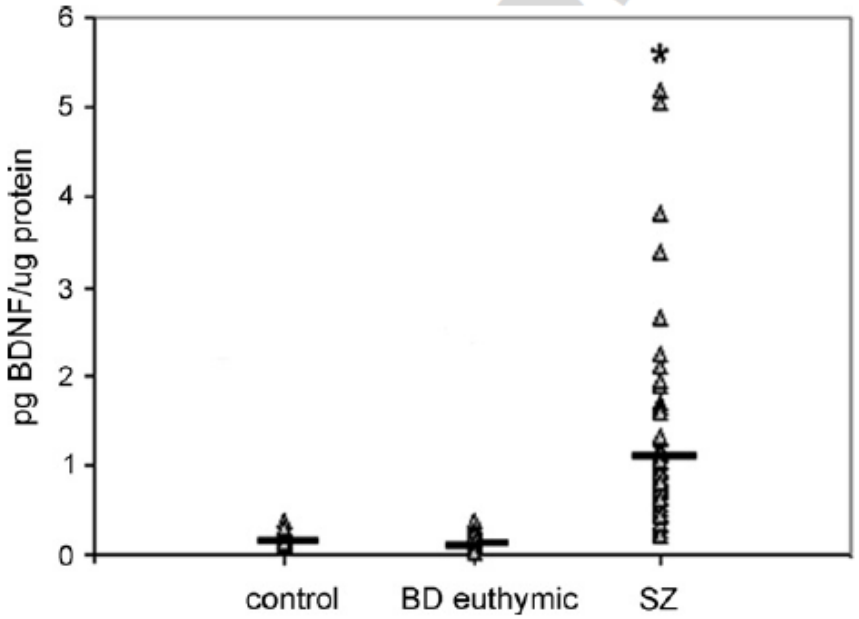
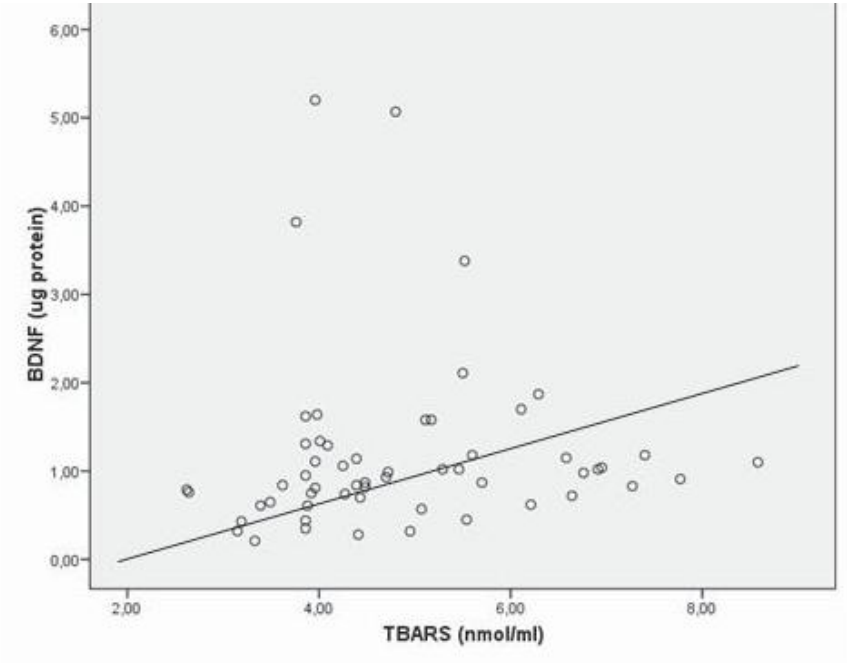


Fig. 1. Scatter plot of serum BDNF levels in controls, BD euthymic, and SZ patients. Mean levels are indicated by horizontal lines. ANOVA was performed to analyze variance between groups and multiple comparisons were assessed by Tukey test; (*) $p < 0.001$.

Níveis séricos do fator neurotrófico derivado do cérebro e dos produtos de reação com o ácido tiobarbitúrico em pacientes com esquizofrenia cronicamente medicados: correlação positiva

Clarissa Severino Gama,[1,2,3,4] **Michael Berk,**[3,5,6] **Ana Cristina Andreazza,**[1,2,7] **Flávio Kapczinski,**[1,2,7] **Paulo Belmonte-de-Abreu**[1,2,4]



ELSEVIER

Progress in Neuro-Psychopharmacology & Biological Psychiatry 30 (2006) 512 – 515

www.elsevier.com/locate/pnpbp

Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in schizophrenia: A study of patients treated with haloperidol or clozapine

Clarissa Severino Gama [a,*], Mirian Salvador [b], Ana Cristina Andreazza [b], Flavio Kapczinski [a], Paulo Silva Belmonte-de-Abreu [a]

Table 1
Serum SOD and TBARS levels in schizophrenic (schiz) patients and normal control subjects

	Schiz (n=17)	Normal (n=15)	t*	p
SOD (USOD/g)	7.1±3.0	4.0±1.6	3.592	0.001
TBARS (nmol/ml)	3.8±0.8	2.5±0.7	4.668	0.0001

Mean±S.D.
*Two samples Student's t test with equal variances; degrees of freedom: 30; p (two-tailed).

Table 2
Serum SOD and TBARS levels in schizophrenic patients treated with haloperidol or clozapine

	Haloperidol (n=10)	Clozapine (n=7)	t*	p
SOD (USOD/g)	6.9±3.5	7.4±2.1	−0.380	0.710
TBARS (nmol/ml)	3.4±0.7	4.4±0.7	−3.039	0.008

Mean±S.D.
*Two samples Student's t test with equal variances; degrees of freedom: 15; p (two-tailed).

ELSEVIER

Neuroscience Letters 433 (2008) 270–273

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Elevated serum thiobarbituric acid reactive substances in clinically symptomatic schizophrenic males

Clarissa Severino Gama[a,b,c,e,*], Mirian Salvador[h], Ana Cristina Andreazza[a,b,d,h], Maria Ines Lobato[a,b,e], Michael Berk[c,f,g], Flavio Kapczinski[a,b,c,d], Paulo Silva Belmonte-de-Abreu[a,b,e]

Table 1
Blood SOD and TBARS levels in males among DSM-IV schizophrenia subtypes

Schizophrenia forms	*N*	SOD (USOD/g)	*P*	TBARS (nmol/ml)	*P*
Paranoid	38	9.8 ± 5.1	0.500*	5.1 ± 1.7	0.837**
Disorganized	27	9.4 ± 4.1		5.0 ± 1.3	
Undifferentiated	3	12.7 ± 1.2		5.4 ± 1.4	

Mean ± S.D.
* ANOVA *P*-value for mean SOD levels between paranoid, disorganized and undifferentiated groups.
** ANOVA *P*-value for mean TBARS levels between paranoid, disorganized and undifferentiated groups.

Table 2
Blood SOD and TBARS levels in males among the three illness course patterns

Clinical course	*N*	SOD (USOD/g)	*P*	TBARS (nmol/ml)	*P*
Partial remission	18	10.4 ± 7.8	0.689*	4.9 ± 1.6	0.037**
Marked symptoms	19	10.1 ± 5.0		5.9 ± 2.0&	
Deteriorated	31	9.2 ± 4.5		4.7 ± 1.3&	

Mean ± S.D.
* ANOVA *P*-value for mean SOD levels between partial remission, marked symptoms and deteriorated groups.
** ANOVA *P*-value for mean TBARS levels between partial remission, marked symptoms and deteriorated groups.
& *P* = 0.037 (Tukey test) for mean TBARS levels between groups marked symptoms and deteriorated.

Neuroscience Letters 502 (2011) 143–146

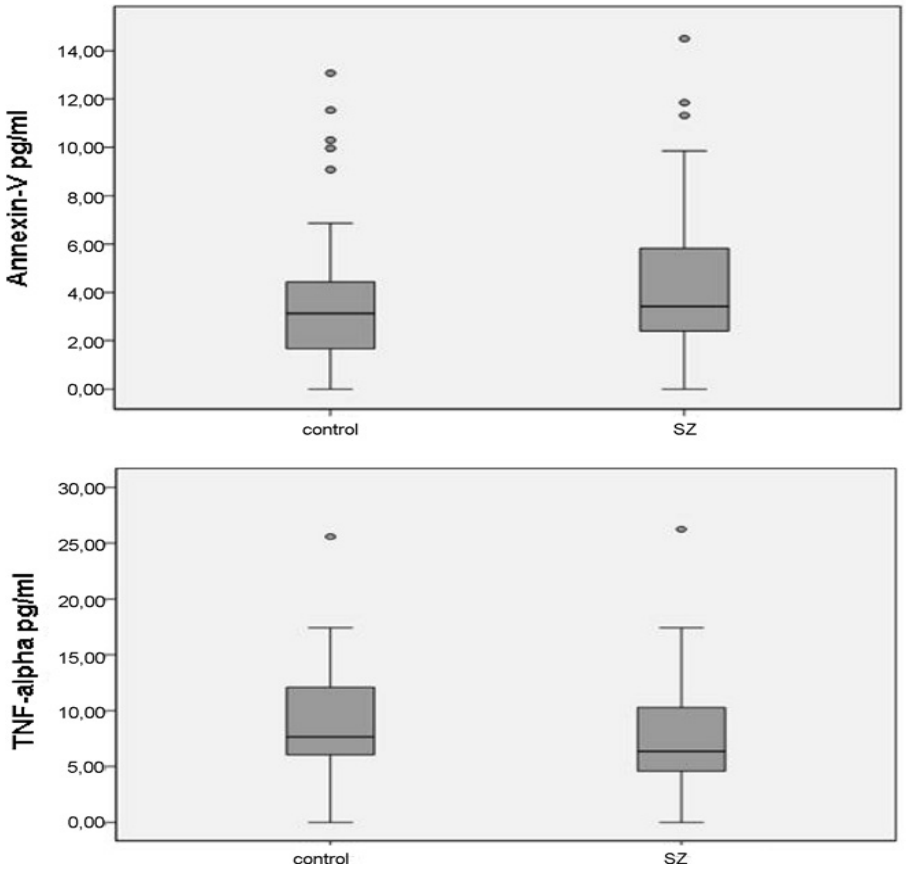
Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Increased annexin-V and decreased TNF-alpha serum levels in chronic-medicated patients with schizophrenia

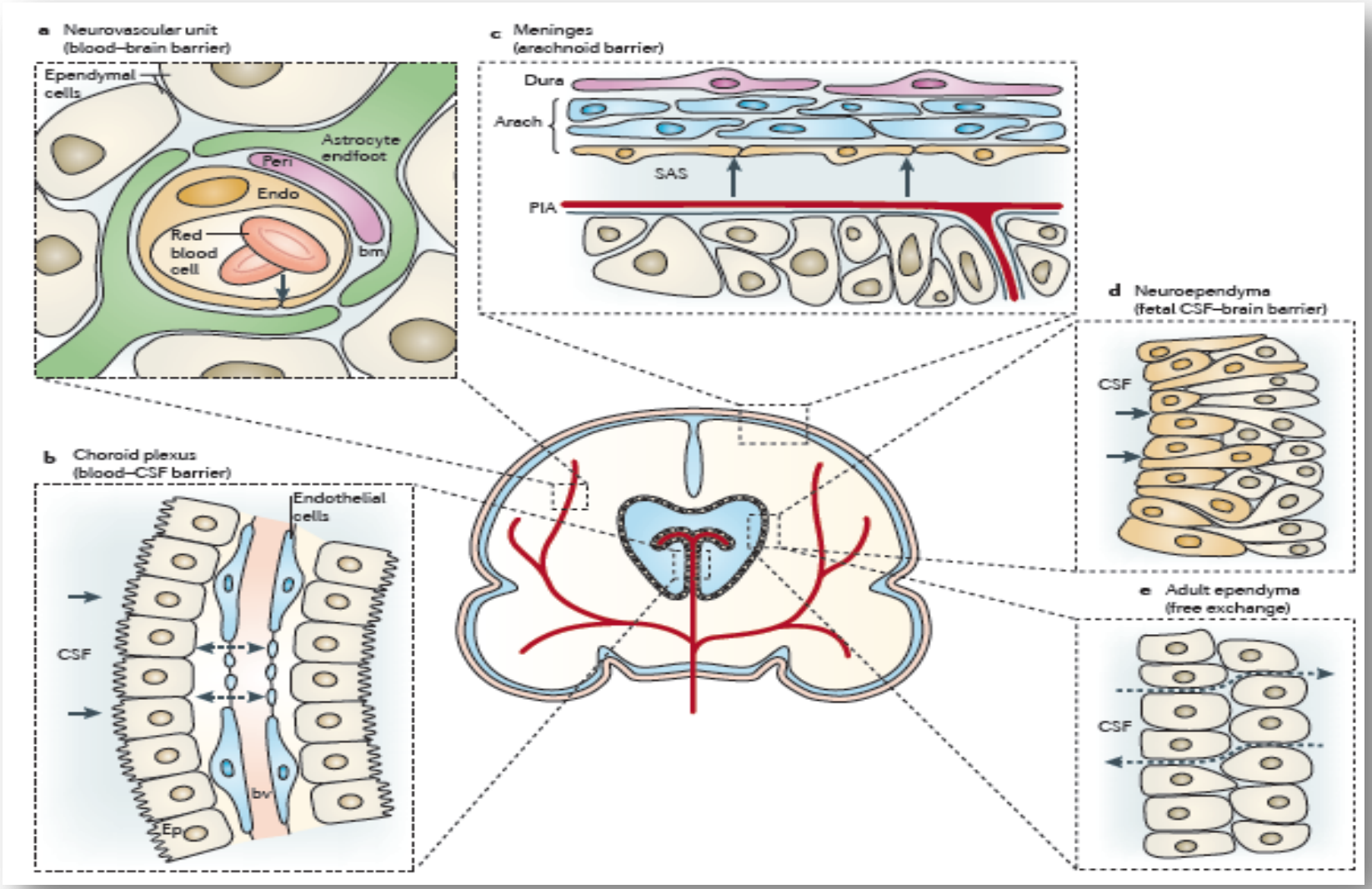
L.P. Francesconi[a,*], K.M. Ceresér[b,c], R. Mascarenhas[a], L. Stertz[c], C.S. Gama[b,c], P. Belmonte-de-Abreu[a,b,c]



A Unidade Neurovascular
NVU

- BBB: Barreira Sangue-Cérebro
- BCSF: Barreira Sangue-F. Cer-Espinhal
- BRB: Barreira Sangue-Retina
- BLB: Barreira Sangue-Labirinto

Barreiras do cérebro:



Journal of Cerebral Blood Flow & Metabolism (2009) 29, 921–932

www.jcbfm.com

Kinetic profile of the transcriptome changes induced in the choroid plexus by peripheral inflammation

Fernanda Marques[1], João C Sousa[1], Giovanni Coppola[2], Ana M Falcao[1], Ana João Rodrigues[1], Daniel H Geschwind[2], Nuno Sousa[1], Margarida Correia-Neves[1] and Joana A Palha[1]

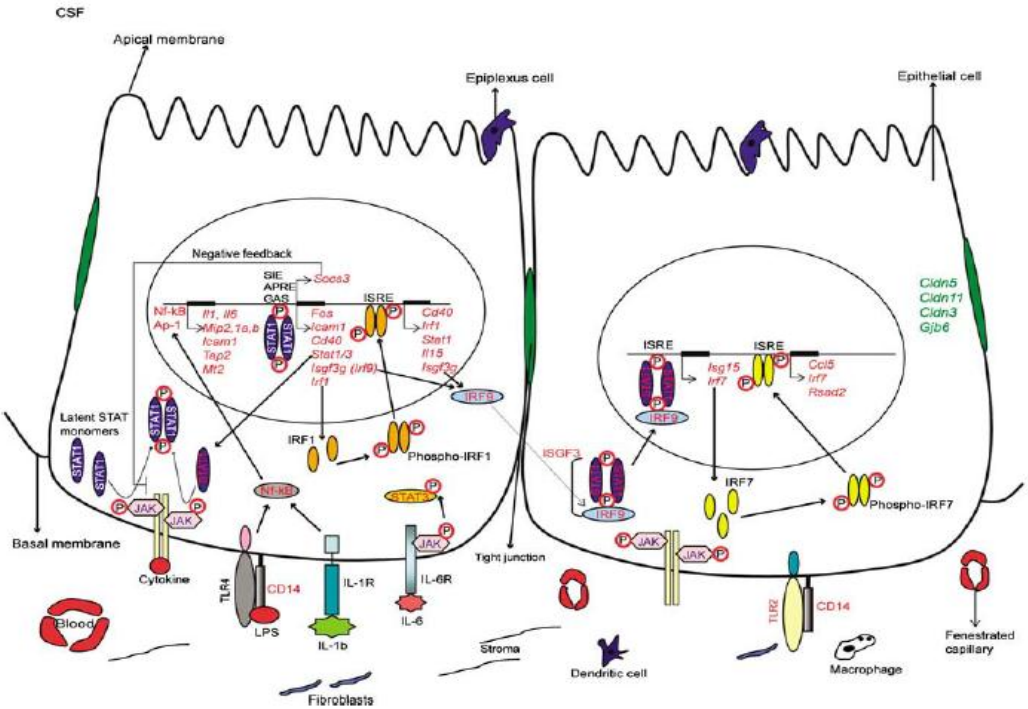
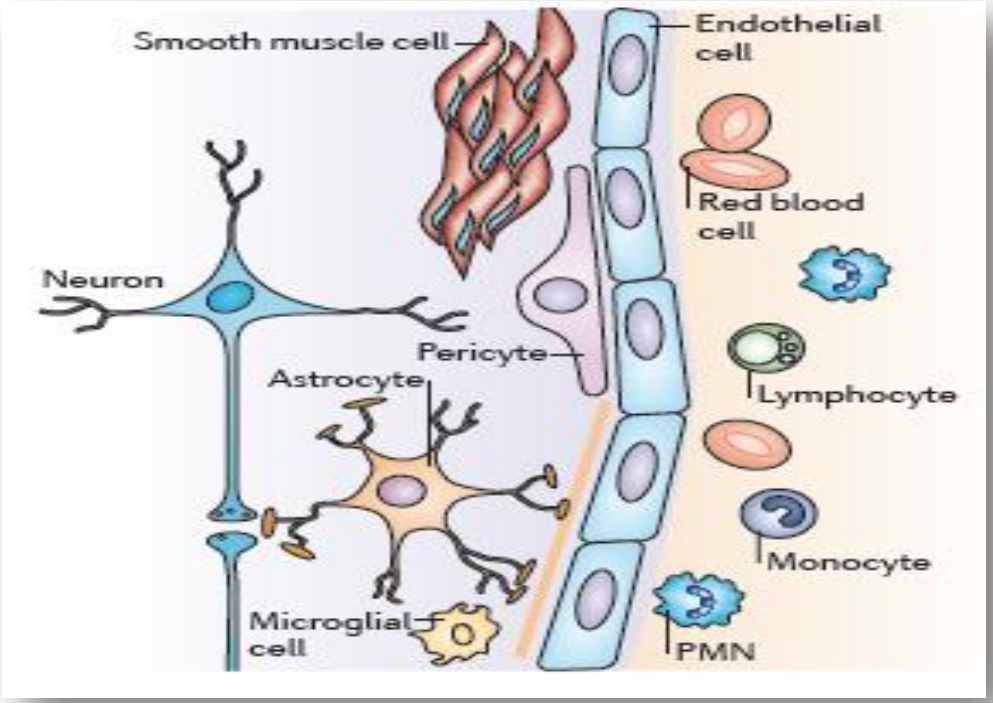


Figure 5 Suggested pathways of the CP epithelial cells response to peripheral inflammation. The genes whose expression was, at one or more time points, down-regulated are represented in green, and whose expression was up-regulated at one or more time points are represented in red.

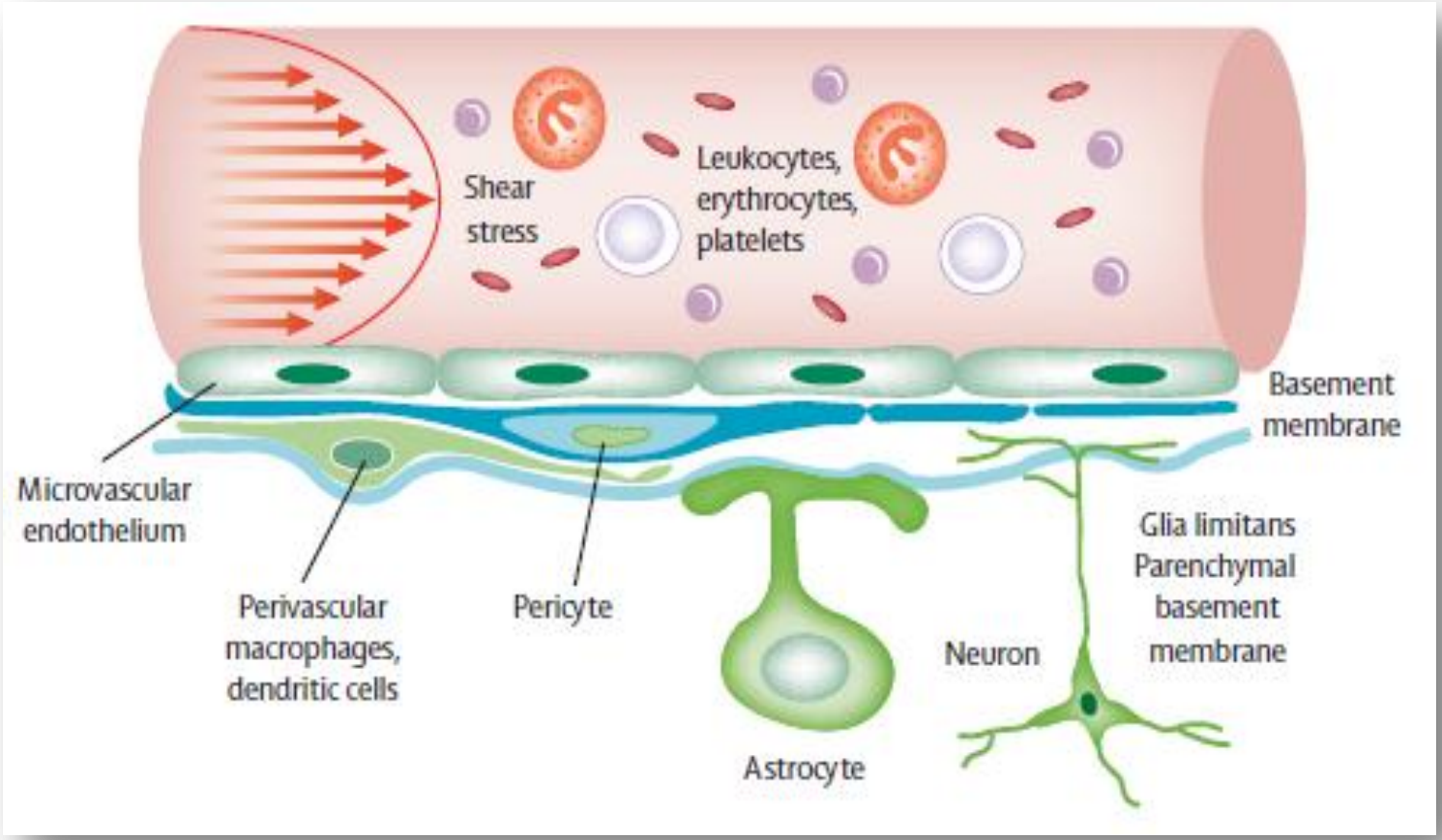
O plexo coróide é um elemento ativo de resposta a inflamação

Engaging neuroscience to advance translational research in brain barrier biology

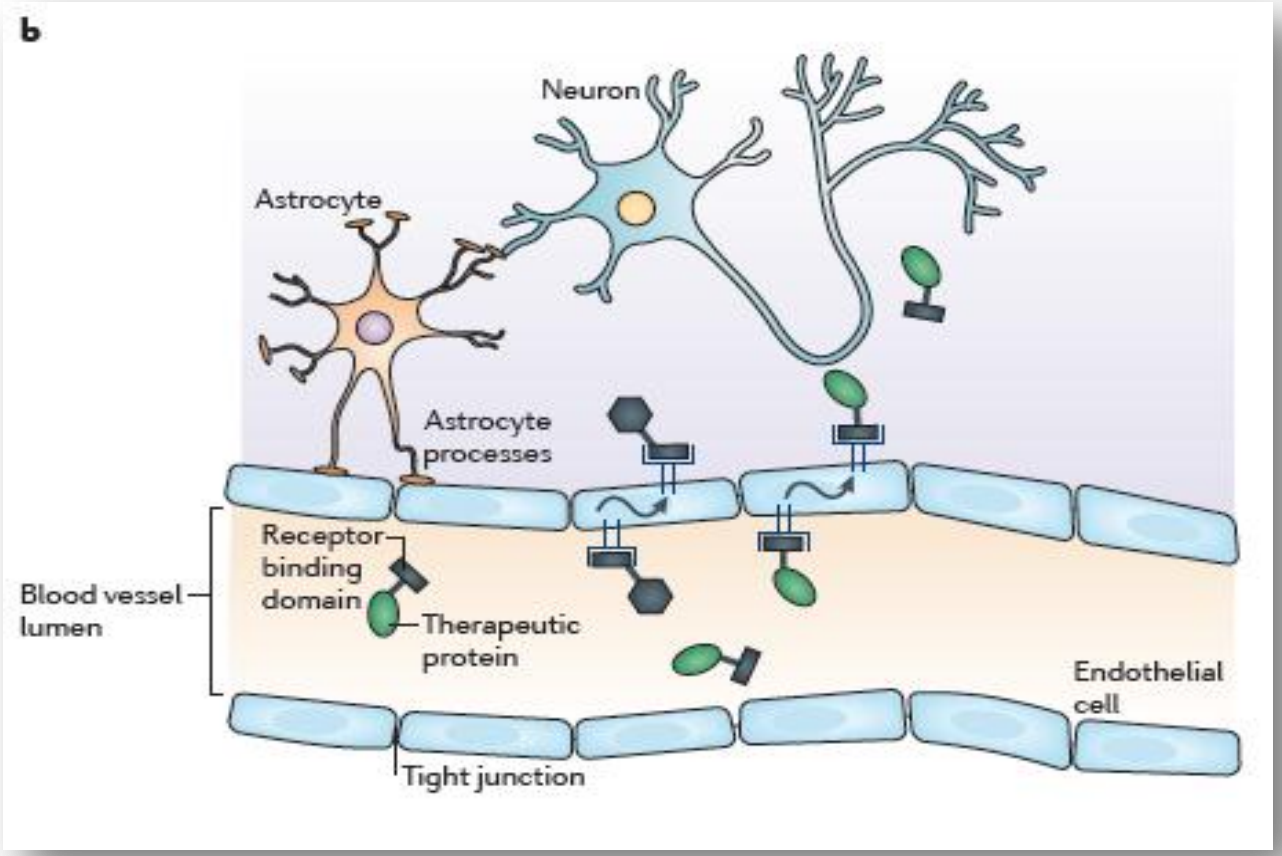
Edward A. Neuwelt, Björn Bauer, Christoph Fahlke, Gert Fricker, Constantino Iadecola, Damir Janigro, Luc Leybaert, Zoltán Molnár, Martha E. O'Donnell, John T. Povlishock, Norman R. Saunders, Frank Sharp, Danica Stanimirovic, Ryan J. Watts and Lester R. Drewes



NVU: Unidade neurovascular



Forma de transporte de drogas para dentro do Cérebro



BBB - BCSFB

- Funções:
  - Noção convencional:
    - controle de tráfico entra-sai do cérebro
  - Noção atual:
    - Atividade fisiológica dinâmica
    - Controle do fluxo sanguíneo cerebral
    - Controle do desenvolvimento neuronal
    - Participante de patologias de SNC:
      - D. Alzheimer, D. Parkinson, Esclerose Múltipla, Esquizofrenia

Neuropathology and Applied Neurobiology (2009), **35**, 132–146 doi: 10.1111/j.1365-2990.2008.01005.x

Review: Role of developmental inflammation and blood–brain barrier dysfunction in neurodevelopmental and neurodegenerative diseases

H. B. Stolp and K. M. Dziegielewska

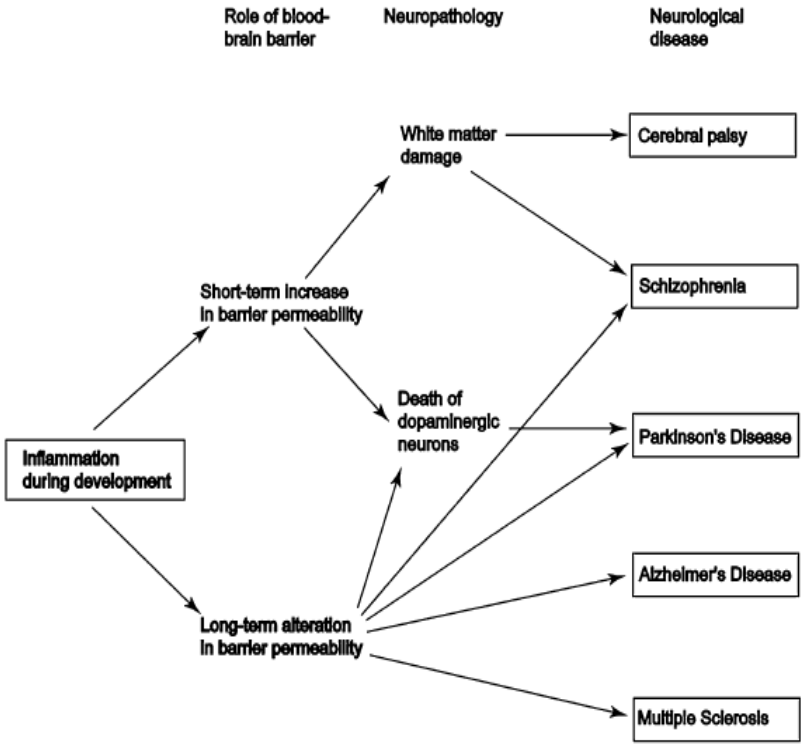
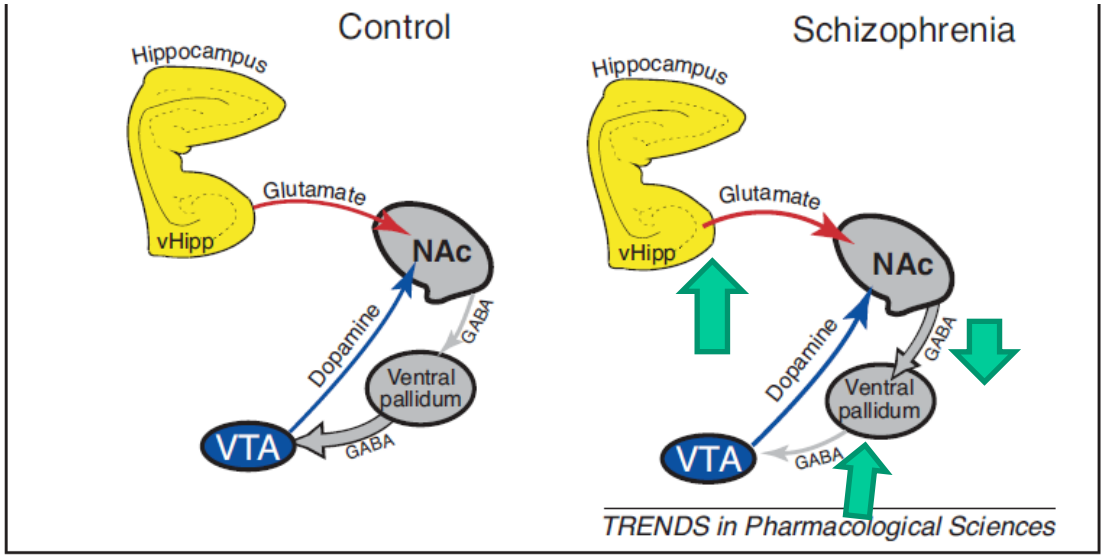


Figure 1. Schematic representation of a hypothesis showing a possible mechanism of inflammation-induced damage to the blood–brain barrier during early stages of brain development and consequences for later brain damage associated with number of neurological disorders, both neurodevelopmental and those normally considered neurodegenerative. Inflammation during early brain development leads to a short- and long-term increased permeability of the blood–brain barrier. The short-term changes result in immediate damage to the brain, which may lead to neurodevelopmental disorders, such as cerebral palsy, but also sensitize the brain to future damage. The long-term changes in blood–brain barrier function may change the brain's ability to cope with environmental exposure to neurotoxic chemicals over a lifetime, possibly increasing damage to the brain and accelerating onset of neurological diseases, such as Parkinson's disease and Alzheimer's disease.

Circuitos alterados em esquizofrenia

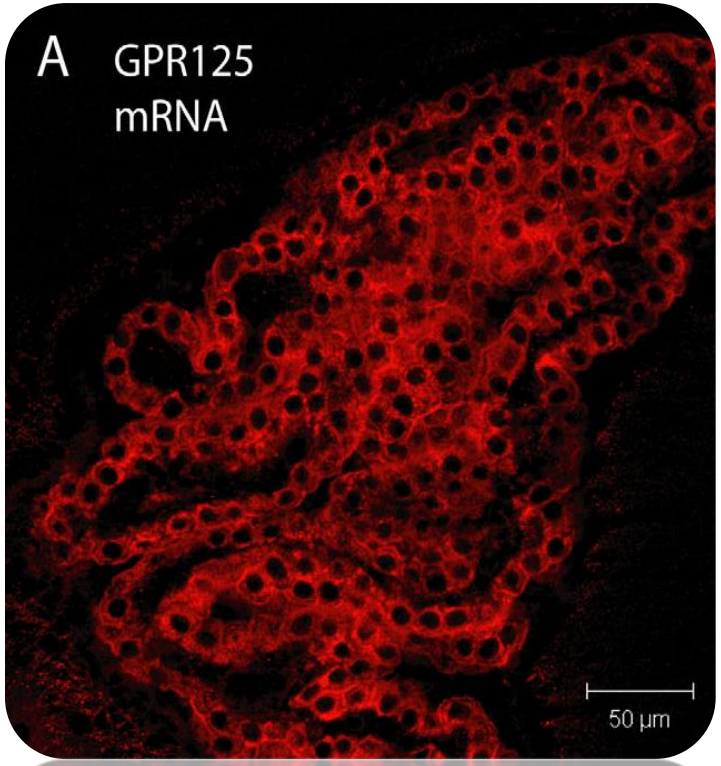


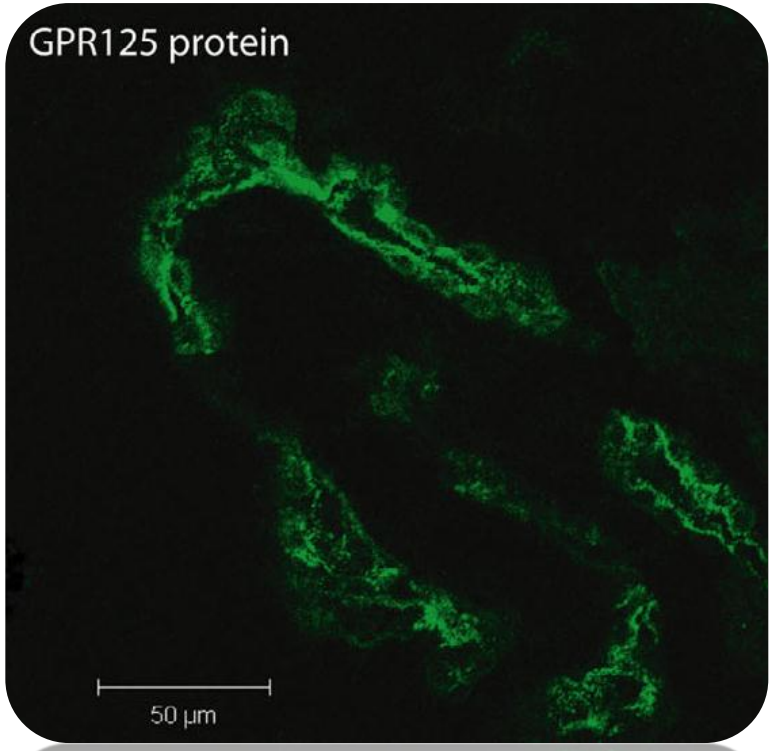
Meta
terap

Figure 1. The ventral hippocampus (vHipp) regulates dopamine neuron activity via a polysynaptic projection. Thus, the vHipp excites neurons in the nucleus accumbens that, in turn, inhibit ventral pallidal (VP) activity. Given that the VP provides an inhibitory tone to the dopamine neurons of the VTA, activation of the vHipp will result in an increase in dopamine neuron activity. In schizophrenia, hippocampal activity is pathologically enhanced, which leads to an enduring increase in dopamine

Expressão de GPR125 em plexo coróide:

Imunohistoquímica de RNAM de GPR125 e proteína GPR125 em plexo coróide





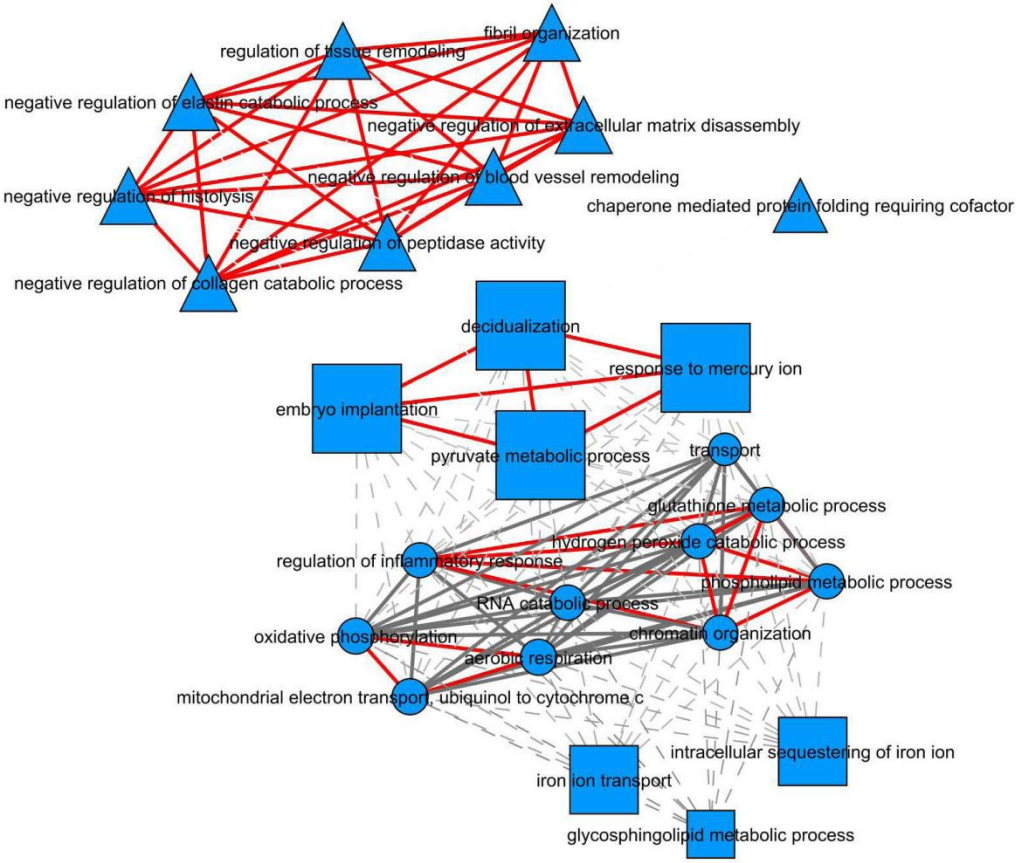
GPR125 belongs to the family of Adhesion G protein-coupled receptors (GPCRs): GPR125 expression was transiently increased (almost 2-fold) at 4 h after traumatic brain injury (TBI) followed by a decrease (approximately 4-fold) from 2 days onwards in the choroid plexus as well as increased expression (2-fold) in the hippocampus that was delayed until 1 day after injury.Palha e cols: BMC Neuroscience 2008, **9:97**

Genes de plexo coróide alterados na inflamação

Table 2 Clustering of the genes whose expression was altered in the choroid plexus upon peripheral LPS injection

Immune molecules	Chemokines: *Ccl4*, *Cxcl2*, *Cxcl13*, *Ccl4*, *Cxcl1*, *Ccl5*, *Ccl3*, *Cxcl16*, *Ccl7*, *Cxcl9*, *Ccl9*, *Ccl11*, *Ccl2*, *Ccl19*, *Cxcl10* ↑ and *Cxcl12* ↓	15↑1↓
	Interleukins: *Il1b*, *Il15*, *Il6* ↑	3↑
	Other molecules with cytokine activity: *Csf1*, *Csf3*, *Spp1* ↑	3↑
Antigen presentation pathway	Antigen presentation pathway: *H2T23*, *H2K1*, *Psmb8*, *Psmb9*, *Tap2* ↑ and *H2Eb1* ↓	5↑1↓
Signaling pathways	TLR and co-estimulatory molecules: *Cd14*, *Tlr2* ↑	2↑
	JAK/STAT signaling pathway: *Socs3*, *Cish*, *Socs2*, *Stat1*, *Stat3* ↑ and *Pias3* ↓	5↑1↓
	MAPK signaling pathway: *Map3k1*, *Map3k6*, *Map3k3*, *Map3k8*, *Fos*, *Junb* ↑ and *Mapk4* ↓	6↑1↓
	NF-KB signaling pathway: *Bcl3*, *Tnfrsf5*, *Egfr*, *Prkr*, *Il1b*, *Map3k3*, *Map3k8*, *Nfkb1*, *Nfkbia*, *Nfkbie*, *Ngfb*, *Relb*, *Ripk1*, *Tlr2*, *Tnfaip3* ↑ and *Hdac2* ↓	15↑1↓
	Complement signaling: *C2*, *C3*, *C6*, *Slp*, *H2Bf*, *Serping1* ↑	6↑
	Interferon signaling: *Ifit3*, *Ifitm1*, *Ifngr2*, *Irf1*, *If2*, *If7*, *Isgf3g*, *Mx1*, *Oas1g*, *Psmb8*, *Stat1* ↑	11↑
	IL-10 signaling: *Bcl3*, *Cd14*, *Fos*, *Il6*, *Il1b*, *Junb*, *Nfkbia*, *Nfkbie*, *Socs3*, *Stat3* ↑	10↑
	IL-6 signaling: *A2m*, *Bcl3*, *Cd14*, *Cebpb*, *Fos*, *Il6*, *Il1b*, *Junb*, *Nfkbia*, *Nfkbie*, *Stat3* ↑	11↑
Acute phase response signaling	Acute phase response: *A2m*, *Bcl3*, *C2*, *C3*, *Cebpb*, *H2Bf*, *Fos*, *Il6*, *Il1b*, *Junb*, *Map3k1*, *Nfkbia*, *Nfkbie*, *Ripk1*, *Saa1*, *Saa3*, *Serpina3n*, *Serping1*, *Socs2*, *Socs3*, *Stat3* ↑	21↑
Glucocorticoid receptor signaling	Glucocorticoid receptor signaling: *A2m*, *Bcl3*, *Ccl3*, *Ccl5*, *Ccl11*, *Cxcl13*, *Cdkn1a*, *Cebpb*, *Cxcl2*, *Dusp1*, *Fkbp5*, *Fos*, *Icam1*, *Il6*, *Il1b*, *Junb*, *Map3k1*, *Nfkb1*, *Nfkbia*, *Nfkbie*, *Sele*, *Stat1*, *Stat3* ↑ and *Tgfbr2* ↓	23↑1↓
Cell adhesion molecules	Tight junctions: *Cldn3*, *Cldn11*, *Cldn5* ↓	3↓
	Gap junctions: *Gjb6* ↓	1↓
	Leukocyte transendothelial migration: *Icam1*, *Madcam1*, *Selp*, *Sele* ↑ and *Pecam1* ↓	4↑1↓
	Extracellular matrix: *Pcdh7*, *Esm1*, *Ptn*, *Nid1*, *Nid2*, *Lama2*, *Dcn*, *Tgfbi*, *Emid2* ↓	9↓
Proteins that contribute to integrity of ECM	Proteases/proteases inhibitors: *Adamts1*, *Adamts4*, *Serping1*, *Serpina3n*, *Mmp13*, *Psmb8*, *Psmb9*, *Adam7*, *Usp18*, *Psme2b*, *Casp4*, *A2m*, *Timp1* ↑	13↑
Transporters	Solute carrier: *Slc7a5*, *Slc43a3*, *Slc15a2*, *Slc31a2*, *Slc38a2*, *Slc7a11* ↑ and *Slc6a6*, *Slc23a2*, *Slc29a4*, *Slc7a10*, *Slc9a3r2*, *Slco2b1*, *Slc5a6*, *Slc9a3r2*, *Slco1a4*, *Slc22a5* ↓	6↑10↓
	ABC transporter: *Tap2* ↑	1↑

Genes alterados em PC na inflamação



FLUIDS AND BARRIERS OF THE CNS

RESEARCH Open Access

Transcriptome signature of the adult mouse choroid plexus

Table 1 Most highly expressed genes found in the choroid plexus in normal physiological conditions

Symbol	Definition	E.value
Ubb	ubiquitin B	15.0
Igf2	insulin-like growth factor 2	14.6
Rpl41	ribosomal protein L41	14.5
Cox4i1	cytochrome c oxidase subunit IV isoform 1	14.1
Clu	clusterin	14.1
Psap	prosaposin	14.0
Chchd10	coiled-coil-helix-coiled-coil-helix domain containing 10	14.0
Arl6ip1	ADP-ribosylation factor-like 6 interacting protein 1	13.9
Atp5b	ATP synthase, H+ transporting mitochondrial F1 complex. beta subunit	13.9
Cst3	cystatin C	13.9
Clic6	chloride intracellular channel 6	13.8
Ttr	transthyretin	13.8
1500015O10Rik	RIKEN cDNA 1500015O10 gene	13.7
Grim19	genes associated with retinoid-IFN-induced mortality 19	13.7
Cox8a	cytochrome c oxidase, subunit VIIIa	13.7
Gapd	glyceraldehyde-3-phosphate dehydrogenase	13.7
Atp5h	ATP synthase. H+ transporting, mitochondrial F0 complex. subunit d	13.7
Uba52	ubiquitin A-52 residue ribosomal protein fusion product 1	13.6
Uqcrh	ubiquinol-cytochrome c reductase hinge protein	13.6
Ckb	creatine kinase. brain	13.6
Cox6a1	cytochrome c oxidase. subunit VI a, polypeptide 1	13.6
Gpx4	glutathione peroxidase 4	13.6
Rps14	ribosomal protein S14	13.6
Ppia	peptidylprolyl isomerase A	13.6
Rplp1	ribosomal protein. large, P1	13.6
Aldh2	aldehyde dehydrogenase 2, mitochondrial	13.6
Rnaset2	ribonuclease T2	13.5
Rps27a	ribosomal protein S27a	13.5
Rps29	ribosomal protein S29	13.5
Dbi	diazepam binding inhibitor	13.5
Atp5j2	ATP synthase, H+ transporting. mitochondrial F0 complex, subunit f. isoform 2	13.5
Grina	glutamate receptor, ionotropic. N-methyl D-asparate-associated protein 1 (glutamate binding)	13.5
1110020P15Rik	RIKEN cDNA 1110020P15 gene	13.5
Atp1a1	ATPase, Na+/K+ transporting. alpha 1 polypeptide	13.5
Fth1	ferritin heavy chain 1	13.4
Ptgds	prostaglandin D2 synthase (brain)	13.4
Atp5g3	ATP synthase. H+ transporting, mitochondrial F0 complex. subunit c (subunit 9), isoform 3	13.4
Cd81	Cd81 antigen	13.4
Ndufa1	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex. 1	13.3
Atp1b1	ATPase. Na+/K+ transporting, beta 1 polypeptide	13.2
Cd63	Cd63 antigen	13.2
Cox5b	cytochrome c oxidase. subunit Vb	13.2
Ubc	ubiquitin C	13.2
Sostdc1	sclerostin domain containing 1	13.2
Rps20	ribosomal protein S20	13.2
Ubl5	ubiquitin-like 5	13.1
Aplp2	amyloid beta (A4) precursor-like protein 2	13.1
Scd2	stearoyl-Coenzyme A desaturase 2	13.1
Rbp1	retinol binding protein 1. cellular	13.1
Ndufa4	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4	13.1
Rpl3	ribosomal protein L3	13.1

Tipos de transporte em BBB

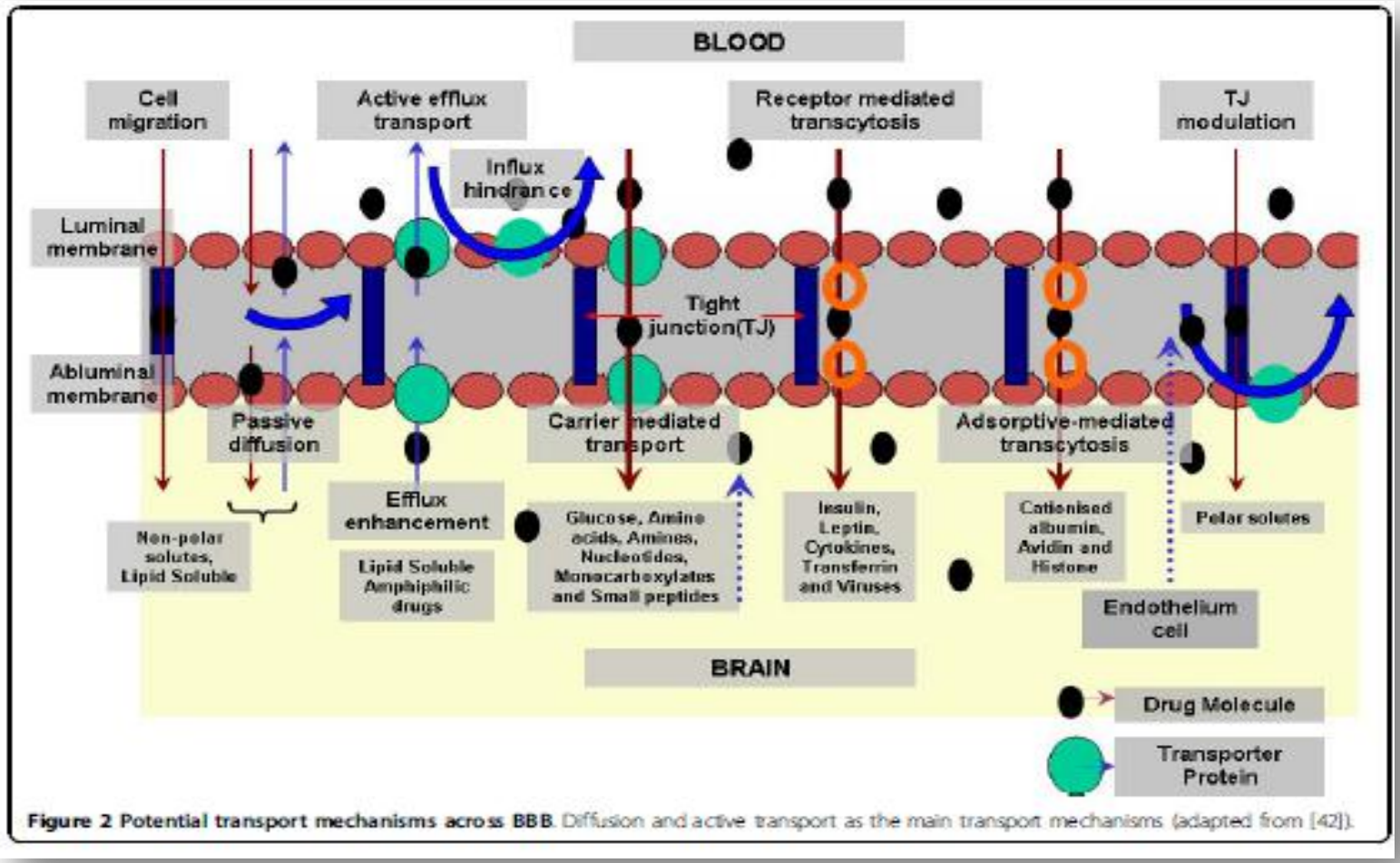


Figure 2 Potential transport mechanisms across BBB. Diffusion and active transport as the main transport mechanisms (adapted from [42]).

Neuropathology and Applied Neurobiology (2009), **35**, 132–146 doi: 10.1111/j.1365-2990.2008.01005.x

Review: Role of developmental inflammation and blood–brain barrier dysfunction in neurodevelopmental and neurodegenerative diseases

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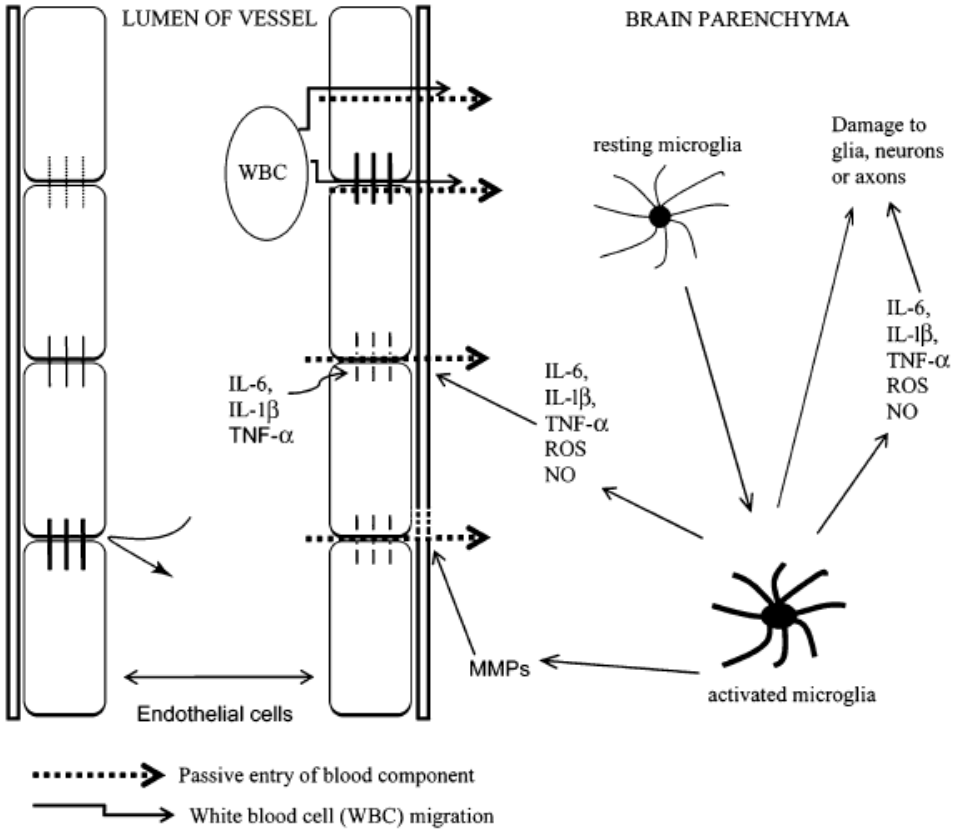
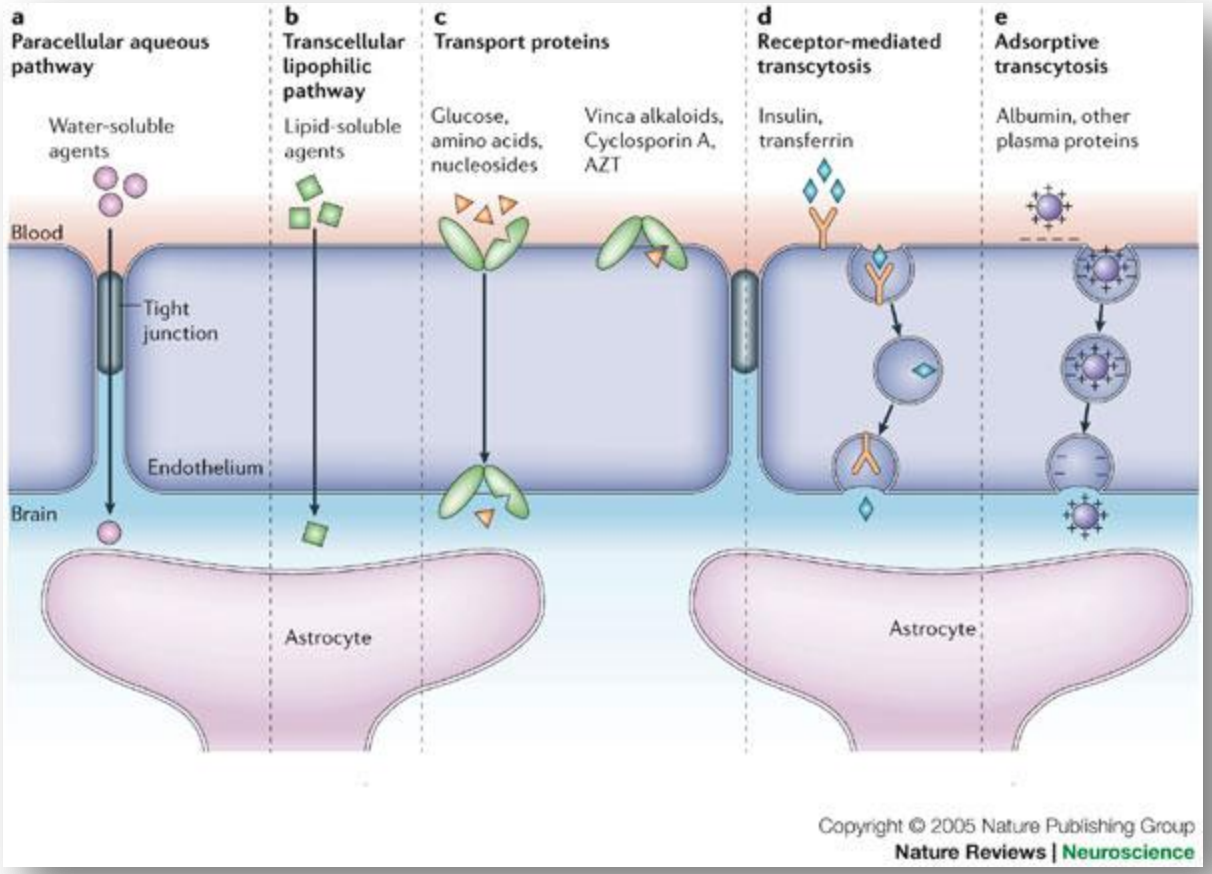
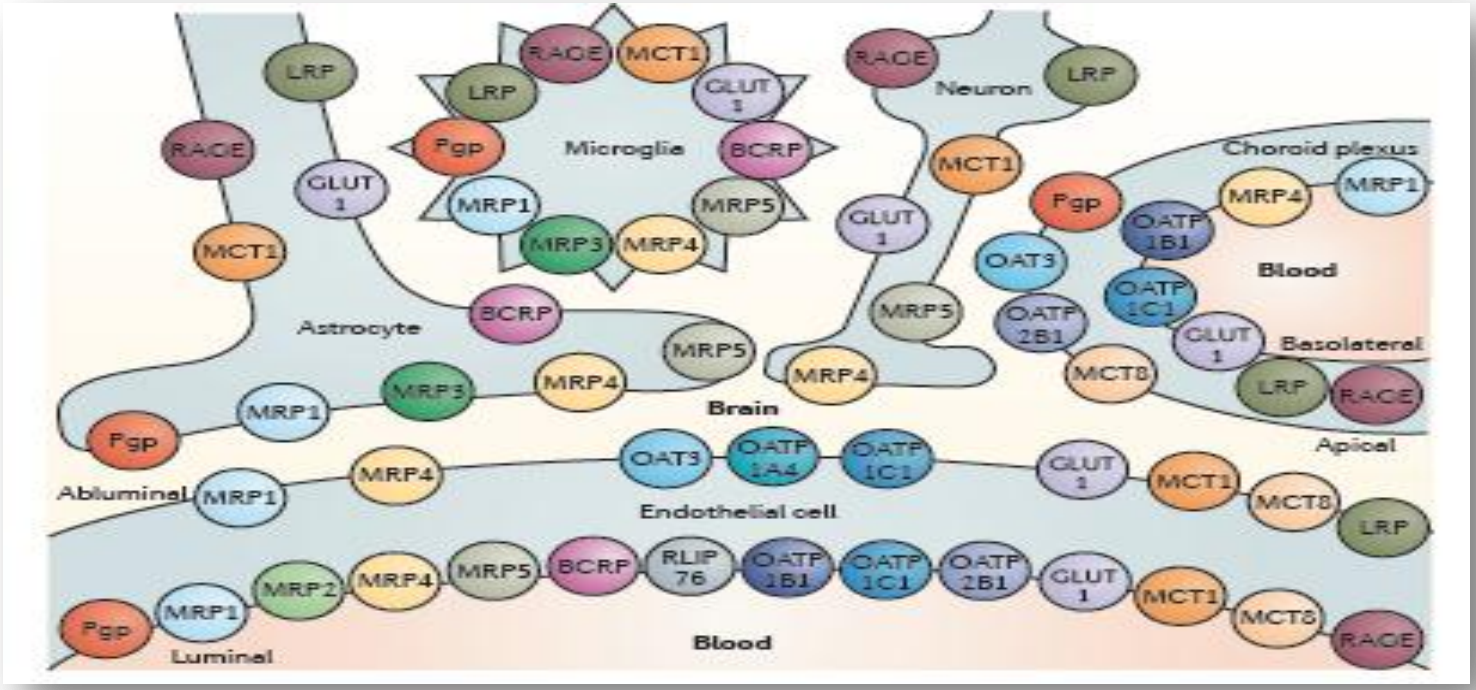


Mecanismos de passagem em BBB

Tipos de passagem em NVU

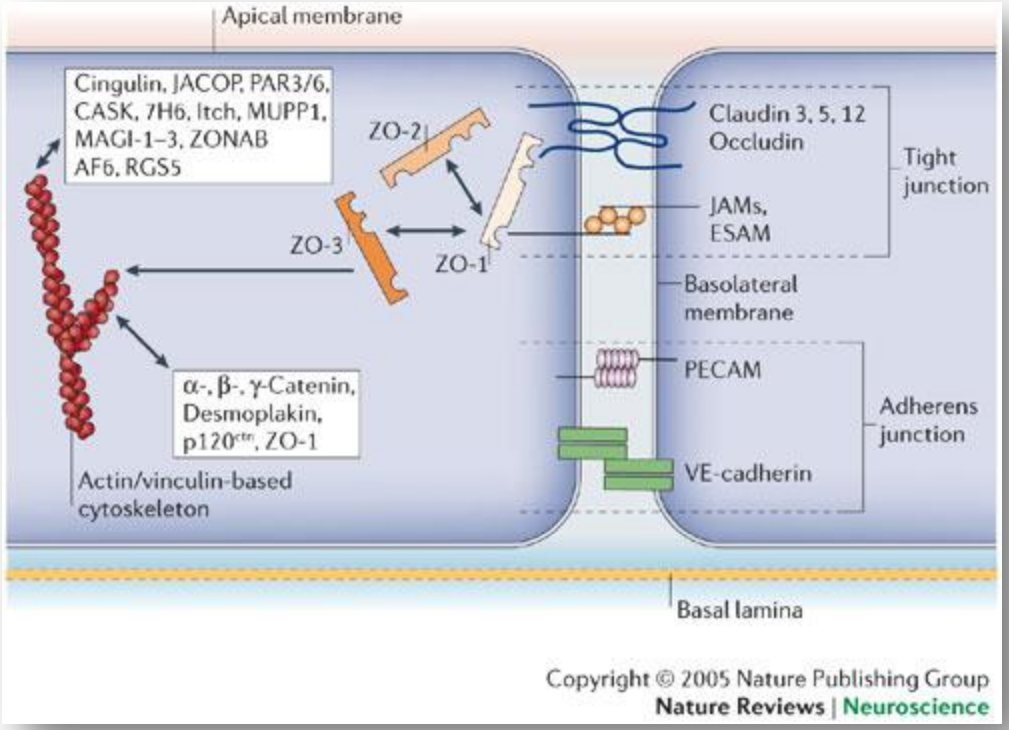


Transportadores primários da NVU



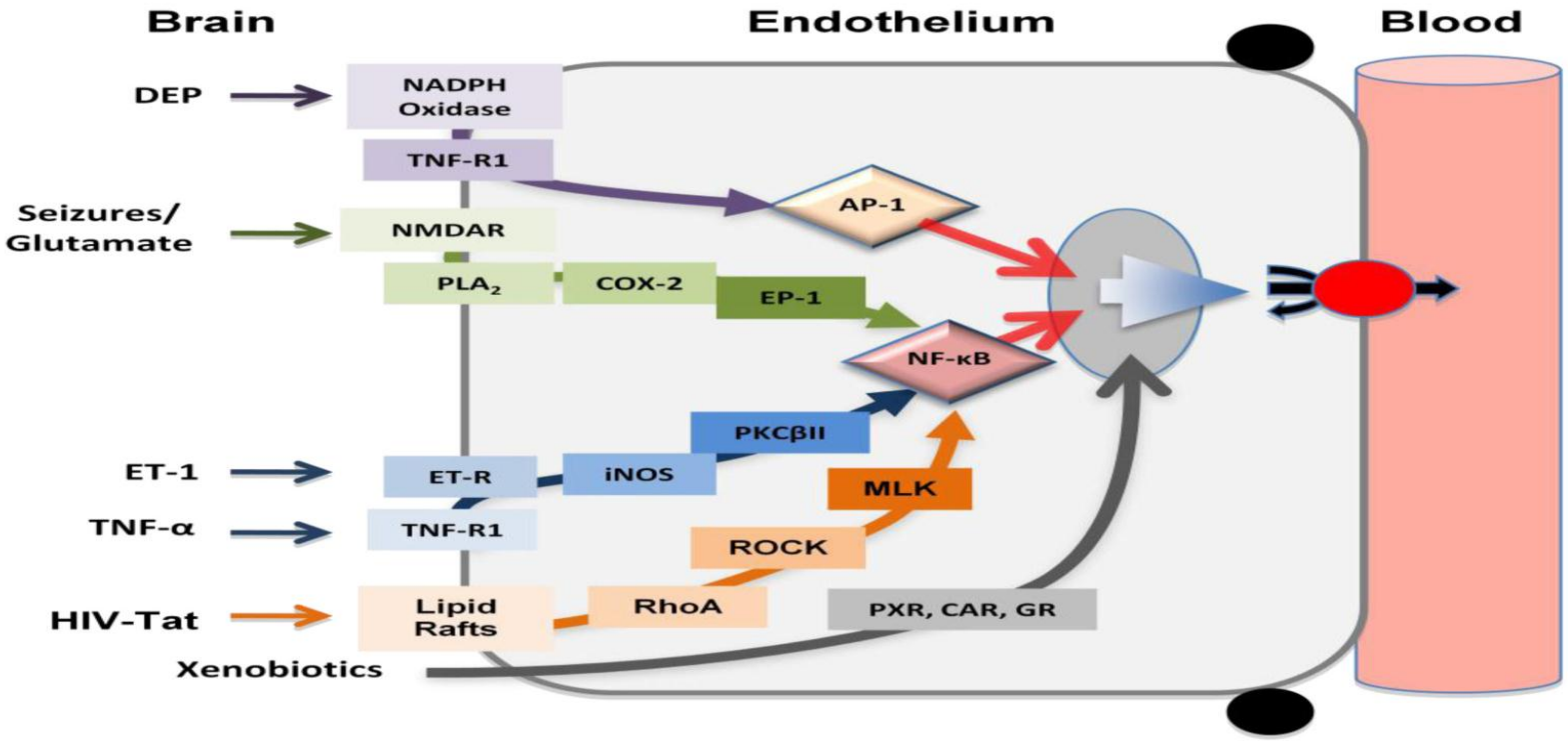
BCRP: Breast cancer resistance protein: ABC transporter G family member 2
GLUT: solute carrier family 2, facilitated glucose transporter member
LRP: low-density lipoprotein receptor related protein family member
PGP: licoproteina P, MRP: multidrug resistance associated protein family member

Moléculas ativas no transporte Barreira Sangue-cérebro



Abbott NJ *et al.* (2006) Astrocyte–endothelial interactions at the blood–brain barrier *Nat. Rev. Neuro.* 7: 41–53

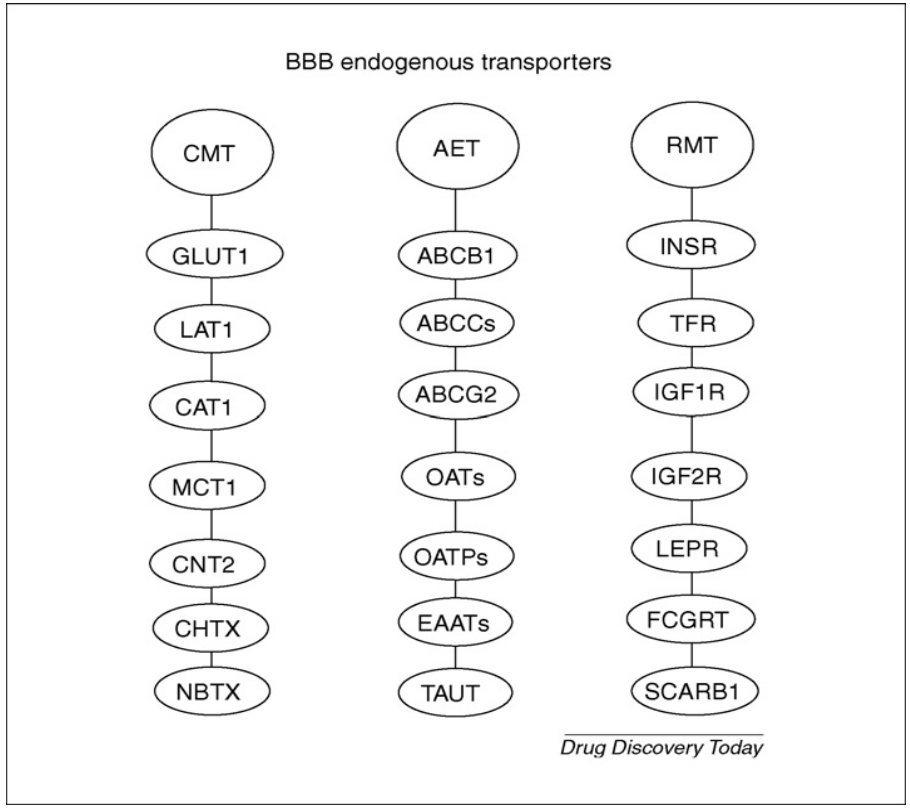
Transporte de drogas e xenobióticos Cérebro-Sangue



	PXR	CAR	GR	FXR	TNF-α	DEP	Glu
P-gp	+	+	+		+	+	+
Mrp2	+	+		+	-	+	
Mrp4	NC				-	NC	
Bcrp	+	+	+		NC	+	
Mrp1	NC				NC	+	

Endogenous blood–brain barrier transporters.

The transporters are grouped into three categories: carrier-mediated transport (CMT), active efflux transport (AET) and receptor-mediated transport (RMT).Abbreviations: GLUT1, glucose transporter, member 1 (SLC2); LAT1, large neutral amino acid transporter, member 1 (SLC7); CAT1, cationic amino acid transporter, member 1(SLC7); MCT1, monocarboxylic acid transporter, member 1 (SLC16); CNT2, concentrative nucleoside transporter, member 2 (SLC28); CHT, choline transporter (SLC5); NBT, nucleobase transporter; ABCB1, adenosine triphposphate-binding cassette (ABC) transporter, subfamily B, member 1, also called P-glycoprotein; ABCC, ABC transporter, subfamily C; ABCG2, ABC transporter, subfamily G, member 2; OAT, organic anion transporter (SLC22); OATP, organic anion-transporting polypeptide (SLC21); EAAT, glutamic acid amino acid transporter (SLC1); TAUT, taurine transporter (SLC6); INSR, insulin receptor; TFR, transferrin receptor; IGFR, insulin-like growth factor receptor; LEPR, leptin receptor; FCGRT, Fc fragment of IgG receptor transporter, also called neonatal Fc receptor (FCRN); SCARB1, scavenger receptor, class B, member 1.

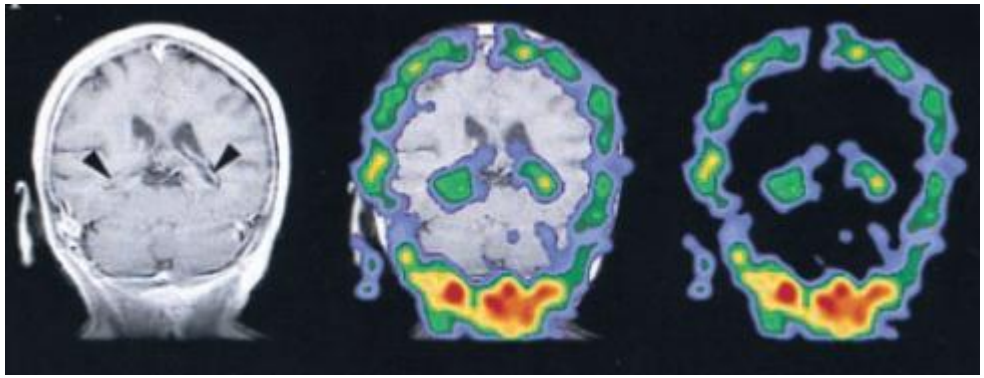


Glicoproteína P/ MDR e permeabilidade

Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 3900–3905, March 1999
Medical Sciences

Choroid plexus epithelial expression of *MDR1* P glycoprotein and multidrug resistance-associated protein contribute to the blood–cerebrospinal-fluid drug-permeability barrier

VALLABHANENI V. RAO*†, JULIE L. DAHLHEIMER*†, MARK E. BARDGETT‡, ABRAHAM Z. SNYDER*, RICK A. FINCH§, ALAN C. SARTORELLI§, AND DAVID PIWNICA-WORMS*†¶



Psychiatry Research: Neuroimaging 183 (2010) 151–156

Contents lists available at ScienceDirect

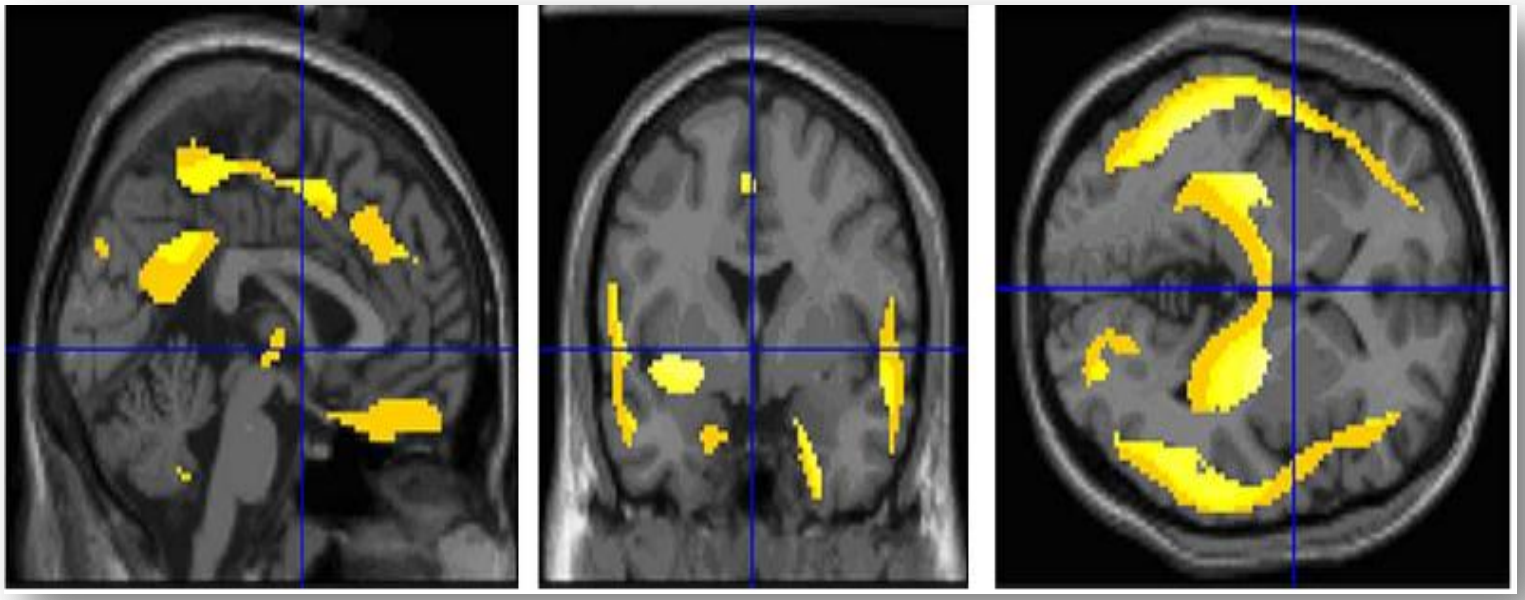
Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Regional increase in P-glycoprotein function in the blood-brain barrier of patients with chronic schizophrenia: A PET study with [^{11}C]verapamil as a probe for P-glycoprotein function

Onno L. de Klerk [a,b,*], Antoon T.M. Willemsen [c], Fokko J. Bosker [a], Anna L. Bartels [d], N. Harry Hendrikse [e], Johan A. den Boer [a], Rudy A. Dierckx [c]

[11C]verapamil-PET : aumento local de P-gp em esquizofrenicos medicados. Relacionado a resistencia a antipsicóticos em esquizofrenia.



Drogas inteligentes

Strategies to advance translational research into brain barriers

Edward Neuwelt, N Joan Abbott, Lauren Abrey, William A Banks, Brian Blakley, Thomas Davis, Britta Engelhardt, Paula Grammas, Maiken Nedergaard, John Nutt, William Pardridge, Gary A Rosenberg, Quentin Smith, Lester R Drewes

Lancet Neurol 2008; 7: 84–96

There is a paucity of therapies for most neurological disorders—from rare lysosomal storage diseases to major pub

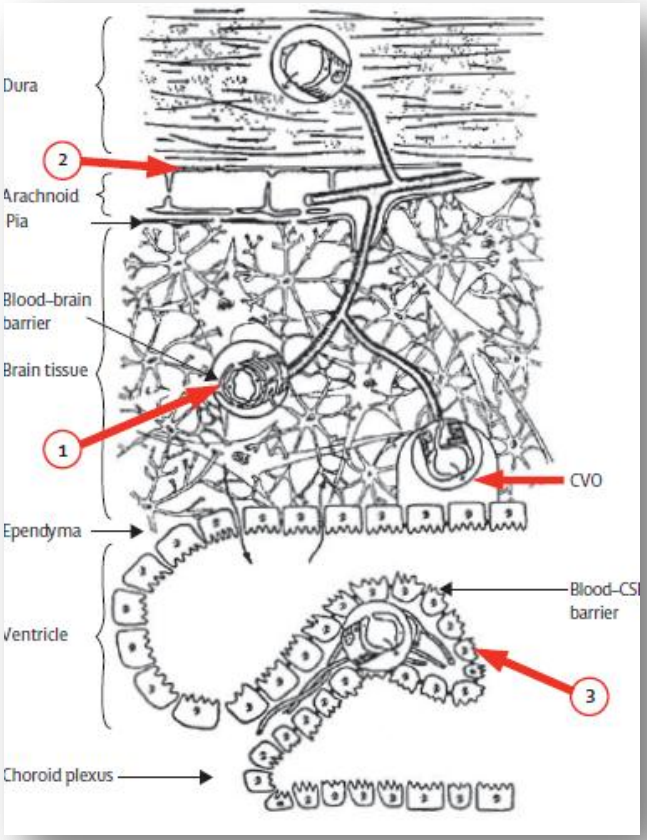


***Figure 6:* Barrier sites in the CNS**

The three main sites of barriers in the CNS. (1) The brain endothelium, which forms the BBB. (2) The arachnoid epithelium, which forms the middle layer of the meninges. (3) The choroid plexus epithelium, which secretes CSF. At each site, the physical barrier formed by the tight junctions reduces the permeability of the paracellular (intercellular cleft) pathway. In the circumventricular organs (CVO), which contain neurons that are specialised for neurosecretion or chemosensitivity, the endothelium is leaky, which enables tissue–blood exchange; however, because these sites are separated from the rest of the brain by an external glial barrier and separated from the CSF by a barrier at the ependyma, CVOs do not form a path across the BBB. Reproduced with permission from Elsevier.[56] The other specialised endothelial barriers covered in this report are similar to the brain endothelial barrier, whereas the other epithelial barriers (eg, eye, nerve, or labyrinth) have regional specialisations.

Bhaskar *et al. Particle and Fibre Toxicology* 2010, **7**:3
http://www.particleandfibretoxicology.com/content/7/1/3

PARTICLE AND FIBRE TOXICOLOGY

REVIEW Open Access

Multifunctional Nanocarriers for diagnostics, drug delivery and targeted treatment across blood-brain barrier: perspectives on tracking and neuroimaging

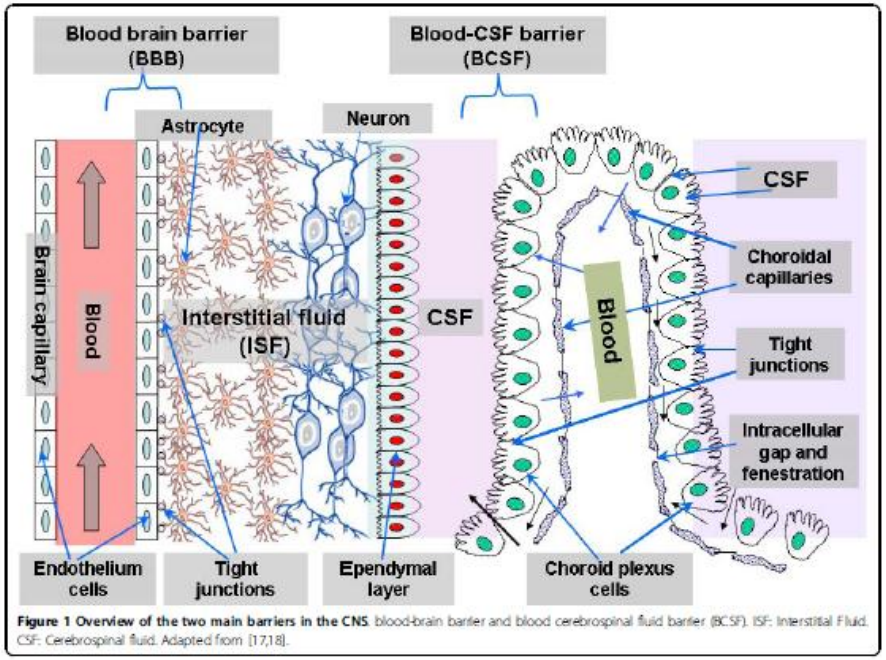
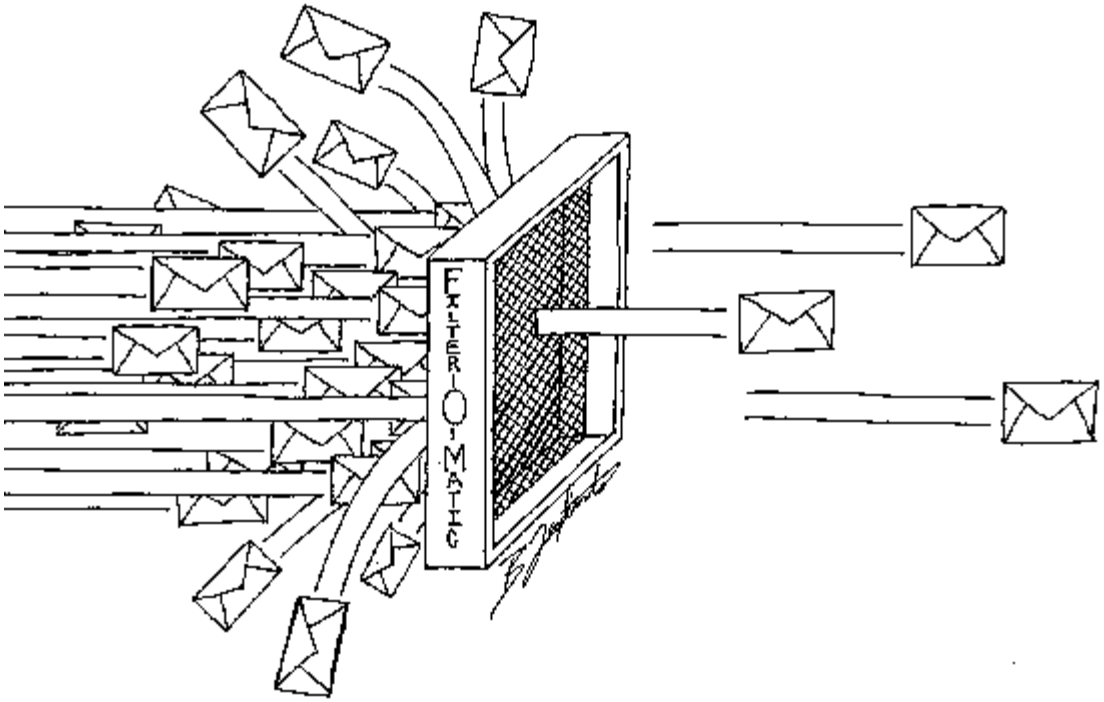


Figure 1 Overview of the two main barriers in the CNS. blood-brain barrier and blood cerebrospinal fluid barrier (BCSF). ISF: Interstitial Fluid. CSF: Cerebrospinal fluid. Adapted from [17,18].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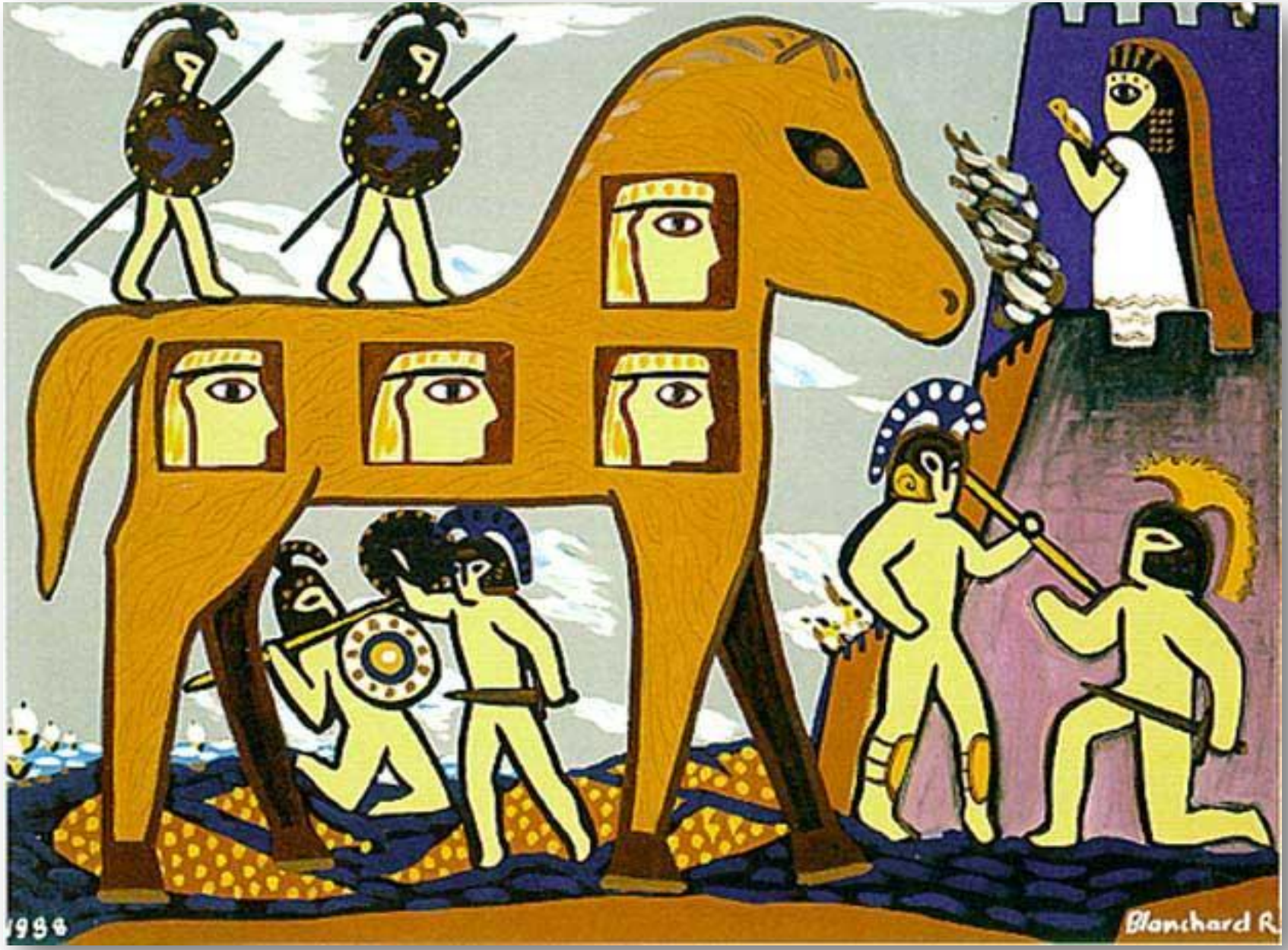
1994
Blanchard R.

Mecanismos de transporte de drogas na BBB

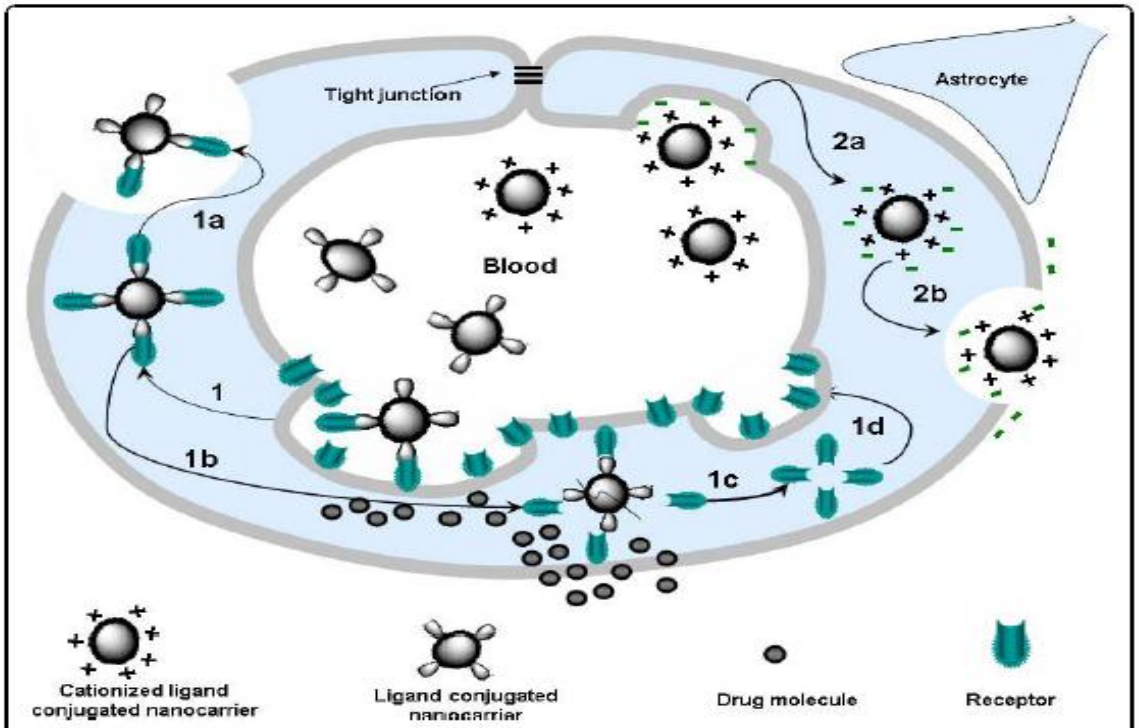

Figure 3 Mechanisms of drug transport through the BBB using nanocarriers conjugated to receptor-specific ligands and cationized ligands. (1) Receptor-mediated endocytosis of the nanocarrier; (1a) Exocytosis of the nanocarrier; (1b) Dissociation of the receptor from the ligand-conjugated nanocarrier and acidification of the vesicle leading to the degradation of the nanocarrier and the release of the drug into the brain; (1c and 1d) Recycling of receptors at the luminal cytoplasmic membrane; (2a) Adsorptive-mediated endocytosis of the nanocarrier conjugated to cationized ligands; (2b) Exocytosis of positively charged nanocarriers (adapted from [66]).

Modelo de Nanopartícula para passagem em BBB

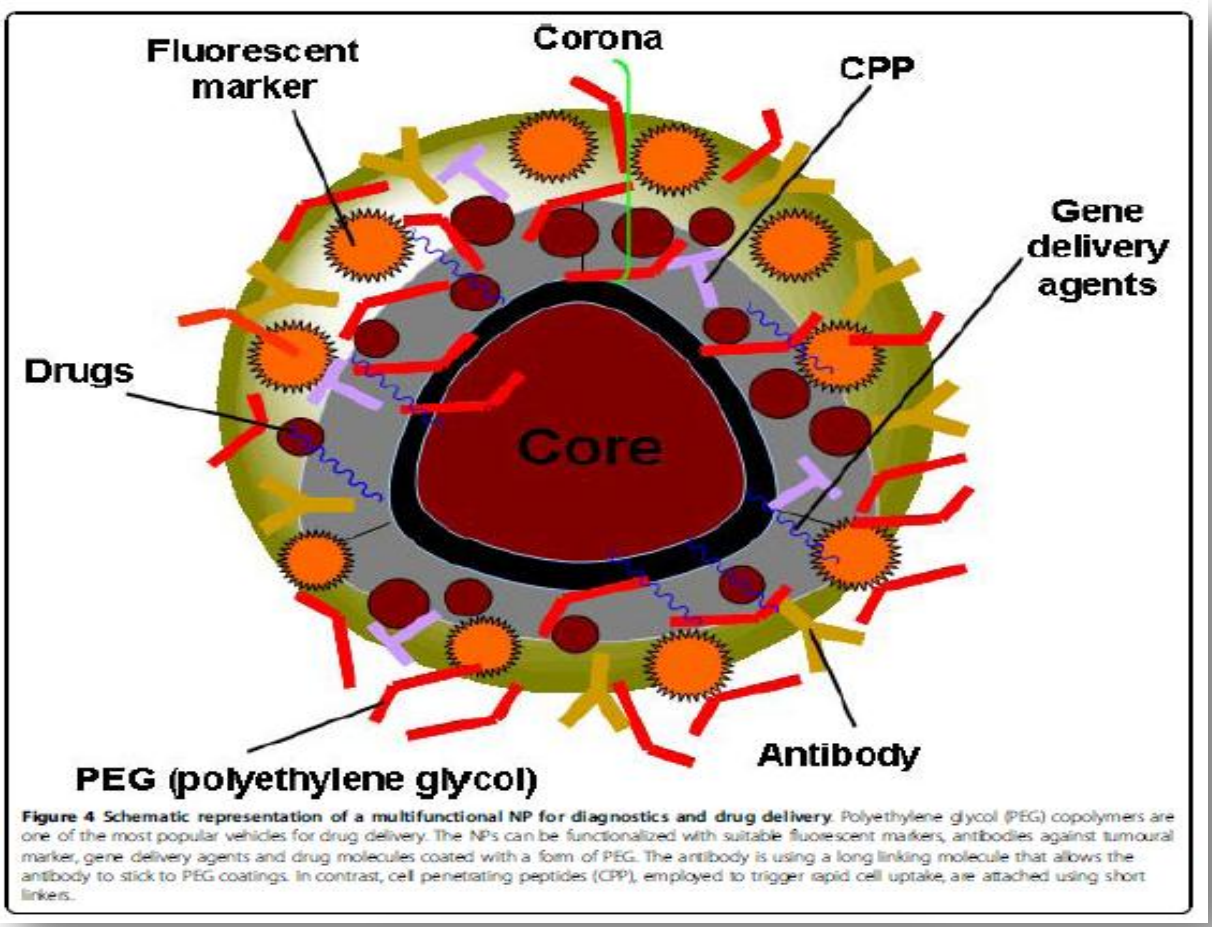

Figure 4 Schematic representation of a multifunctional NP for diagnostics and drug delivery. Polyethylene glycol (PEG) copolymers are one of the most popular vehicles for drug delivery. The NPs can be functionalized with suitable fluorescent markers, antibodies against tumoural marker, gene delivery agents and drug molecules coated with a form of PEG. The antibody is using a long linking molecule that allows the antibody to stick to PEG coatings. In contrast, cell penetrating peptides (CPP), employed to trigger rapid cell uptake, are attached using short linkers..

Bhaskar *et al. Particle and Fibre Toxicology* 2010, **7**:3
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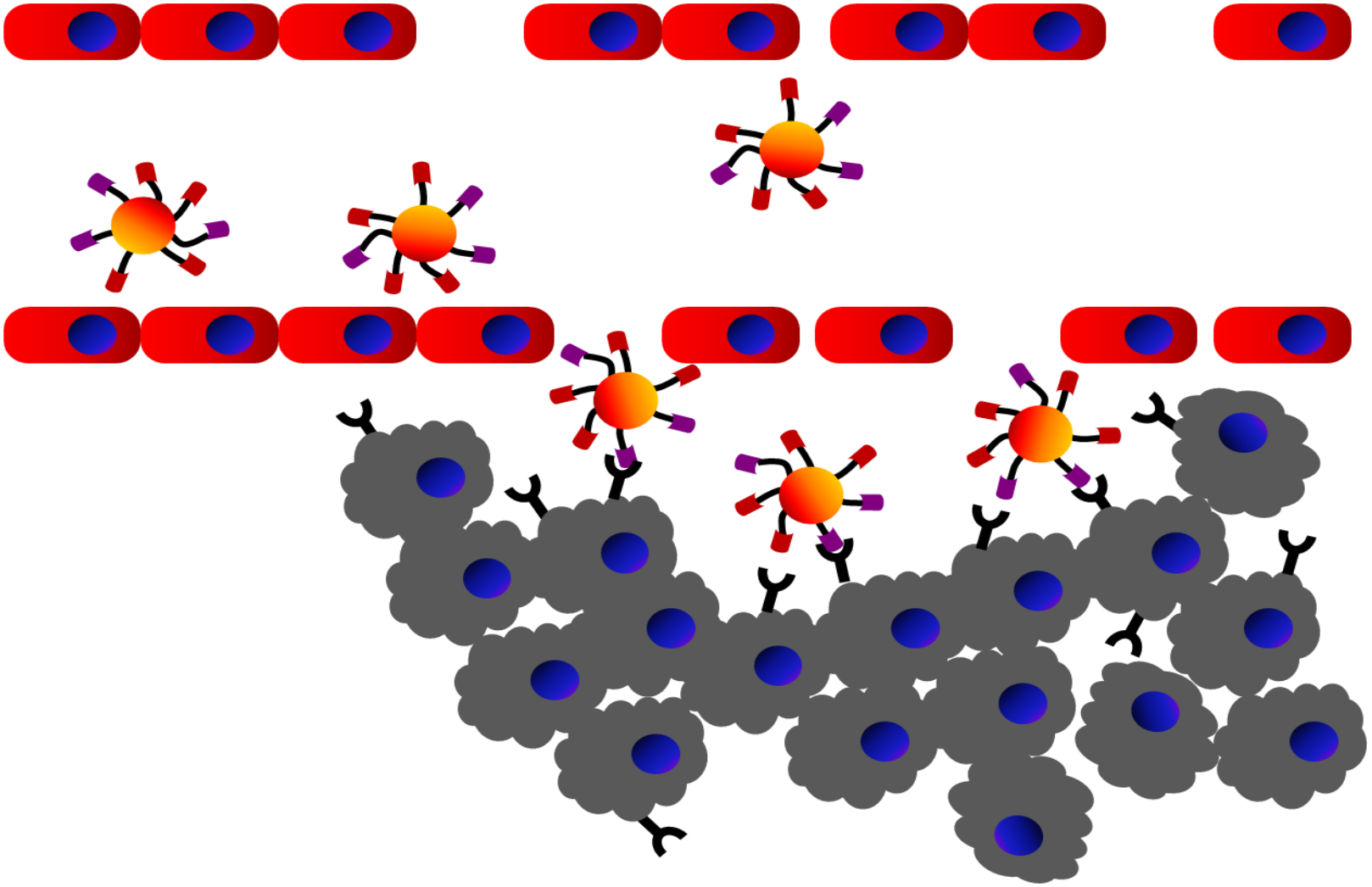
Nanopartículas e passagem SNC



Strategies to advance translational research into brain barriers

Edward Neuwelt, N Joan Abbott, Lauren Abrey, William A Banks, Brian Blakley, Thomas Davis, Britta Engelhardt, Paula Grammas, Maiken Nedergaard, John Nutt, William Pardridge, Gary A Rosenberg, Quentin Smith, Lester R Drewes

Lancet Neurol 2008; 7: 84-96

Bhaskar *et al. Particle and Fibre Toxicology* 2010, **7**:3
http://www.particleandfibretoxicology.com/content/7/1/3

Agentes candidatos para transporte de drogas em BBB

Table 1 Effect of different agent(s)/condition(s) on BBB

Agent/condition	Effect on BBB
Bradykinin, RMP-7	Transient increase of permeability, activates B2 receptors
VEGF, HIF-1, Deferoxamine,	Increase of permeability and leakage
TNF-alpha, IL-1beta	Moderate increase of permeability
Tat, Nef, gp120 + IFN-gamma	HIV-1-associated dysfunction
Low magnetic field (0.15 T)	Moderated increase of permeability
Metalloproteinases	Increase of permeability
LTC4	Leukotriene-induced permeability
Lipopolysaccharide	Enhance the passage of regulatory proteins
P85	Increase permeability by inhibiting the drug efflux transporter Pgp
endothelin-1	Dramatic increase of permeability after intracisternal administration
tPA	Increase permeability via Akt phosphorylation
PTX	Increased permeability by altering endothelial plasticity and angiogenesis

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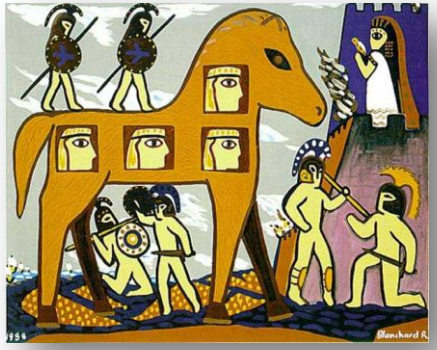
Table 2 NP based drug delivery systems: a list of NP conjugated platforms for delivery across the BBB

NP Platform	Drug (and effects)
PBCA NP coated with Polysorbate 80	dalargin (analgesic)
PBCA NP coated with Polysorbate 80	doxorubicin (DOX) (anti-tumour antibiotic)
PBCA NP coated with Polysorbate 80	kytorphin (analgesic)
PBCA NP	NMDA receptor antagonist MRZ 2/576 (antagonist)
PBCA NP coated with Polysorbate 80	tubocurarine (Increased BBB permeability)
PEG-PHDCA	PrPres Specific Drug in Prion Disease
PBCA NP coated with Polysorbate 80	tacrine (Anti Alzheimer's Drug)
PBCA NP coated with Polysorbate 80	rivastigmine (Anti Alzheimer's Drug)
PBCA NP coated with Polysorbate 80	gemcitabine (anti glioma drug)
DMAEMA/HEMA (pH sensitive)	paclitaxel
LDC-polysorbate 80 NPs	diminazene (anti human African tryparosomiasis (HAT))
DO-FUdR-SLN	5-fluoro-2'-deoxyuridine (FUdR) (Very efficient in brain targeting)
PBCA NPs, MMA-SPM NPs, and SLNs	stavudine (D4T), delavirdine (DLV), and saquinavir (SQV) (anti HIV agents and enhanced BBB permeability)
PBCA NPs coated with apolipoprotein B and E	loperamide and dalargin (increased BBB permeability)



Cavalos de tróia para transporte de drogas para o cérebro

Therapeutic effects in brain following intravenous administration of peptides, recombinant proteins or non-viral gene medicines attached to molecular Trojan horses

Peptide	Gene therapy	Species	Pharmacological effect	Reference
VIP	–	Rat	Increase in cerebral blood flow	[63]
BDNF	–	Rat	Complete neuroprotection of hippocampal CA1 neurons in transient forebrain ischemia	[64]
BDNF	–	Rat	65–70% Reduction in stroke volume in permanent or reversible middle cerebral artery occlusion	[65,66]
FGF-2	–	Rat	80% Reduction in stroke volume in permanent or reversible middle cerebral artery occlusion	[68]
$A\beta^{1-40}$	–	Mouse	Imaging brain amyloid *in vivo* with peptide radiopharmaceutical	[69]
EGF	–	Rat	Early detection of brain cancer *in vivo* with peptide radiopharmaceutical	[70]
PNA	–	Mouse, rat	Imaging gene expression *in vivo* with antisense radiopharmaceutical	[71,72]
–	EGFR antisense	Mouse	100% Increase in survival time in intra-cranial human brain cancer	[73]
–	RNAi	Mouse	90% Increase in survival time in intra-cranial human brain cancer	[74]
–	TH	Rat	Complete normalization of strialtal enzyme activity in experimental Parkinsons disease	[75]

Abbreviations: VIP, vasoactive intestinal peptide; BDNF, brain-derived neurotrophic factor; FGF, fibroblast growth factor; EGF, epidermal growth factor; EGFR, EGF receptor; PNA, peptide nucleic acid; RNAi, RNA interference; TH, tyrosine hydroxylase.

Pardriedge, 2007

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Review

Strategy for effective brain drug delivery

M. Intakhab Alam[a], Sarwar Beg[a], Abdus Samad[b], Sanjula Baboota[a,*], Kanchan Kohli[a], Javed Ali[a], Alka Ahuja[c], M. Akbar[d]

Table 4
Brief account on drug molecules being used by several approaches for brain targeting.

Drug	Problem	Approach	Inference	Reference
Dopamine, Morphine	High water solubility and lower lipid solubility	Transnasal route	Observed satisfactory cerebral concentration due to crossing of olfactory CSF through nasal mucosa and get available into general CSF	Dahlin et al., 2000; Westin et al., 2005
NAD^+ (antioxidant co-factor)	–	Intranasal route	Decreased brain injury in a rat model of transient focal ischemia	Ying et al., 2007
Gallotannin (a PARG inhibitor)	–	Intranasal route	Decreased frequency of ischemic brain injury in rats	Wei et al., 2007
Olanzapine (antipsychotic agent)	Lesser uptake drug due to hydrophobicity	Given in microemulsion formulation containg mucoadhesive polymer intranasally	Significantly higher concentration achieved in brain microenvironment due to increased solubility and mucoadhesive nature	Kumar et al., 2008a
Cytosine arabinoside (an anticancer agent)	–	Given by intracerebral injection	Results showed superior cerebral blood level as compared to intraventricular, transnasal and i.v. route due to convection enhanced diffusion	Groothuis et al., 2000
GDNF (glial derived neurotrophic factor) (for treating parkinsonism)	Difficult to administer by any other route due to its deviation from cerebrospinal fluid flow tracts	Administered via intra-cerebroventricular injection	Achieved better cerebral concentration to treat parkinsonism	Nutt et al., 2003; Pardridge, 1995b
Cytosine arabinoside (for treating neoplastic meningitis)	Rapid turnover from cerebral environment due to leakage of CSF and lower half life	Given in a suspension formulation containg multivesicular lipid "DepoCyt" of size 3–30 Am intraventricularly	Observation showed increased half life of drug from 0.74 to 156 h with sustained release profile of drug delivery	Murry and Blaney, 2000
Nerve growth factor	–	Given in the form of intracerebral implant device surgically into brain	Showed gradual improvements in patient showing spinal cord damage	Kennedy and Bakay, 1998
Etoposide (for treating metastatic brain tumors)	Drug shows lesser concentration in brain	Instigated in the form of reservoir type osmotic pump (Omayama, MiniMed PIMS system, Medtronic SynchroMed system osmotic systems) by implantation	Showed 100-fold much effective concentration as earlier	Ommaya, 1984; Huynh et al., 2006
Lomustine (BCNU). (anticancer)	Due to lower residence time of the drug in cerebral microenvironment due to leakage by ISF	Give in the form of a monolithic or matrix based depot preparation injected into brain micro blood vessels	Satisfactory cerebral concentration of drug was achieved by slow diffusion of drug from depot site into brain cells by active transport from endothelial cells approximately upto 6 weeks	Quinones-Hinojosa, Brem, 2008
Dalargin, Kyotorphin (analgesic)	Due to high molecular weight these peptides are unable to cross junctional BBB	Peptides are given in poly butyl cyanoacrylate nanoparticles coated with polysorbate-80 to protect from opsonisation	Considerable cerebral peptide concentration achieved with decreased frequency of algesic attacks	Schronder et al., 1998
Doxorubicin	–	Given in the form of nanoparticle system which is coated polysorbate-80.	Because of very small size nano particles travelled in brain intact by releasing the drug in brain micro environment directly and due to endocytotic uptake	Gulayaev et al., 1999

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Table 1

Summary of the physiological approaches to deliver therapeutic molecules in the brain parenchyma.

Method	Molecules used	Stage of development	Potential problems
Use of specific transporters	Large amino acid carrier has been used by L-Dopa	Clinic for PD	Dosage and side effects
Receptor-mediated			
Transferrin receptor	Small and large molecules conjugated to mAbs or expressed as fusion proteins	Preclinical	To get therapeutical concentration in the brain parenchyma Toxicity
	Liposomes and nanoparticles coated with mAbs	Preclinical	Mechanism not known, high quantities needed Toxicity
	Nanoparticles coated with transferrin	Preclinical	Mechanism not known Toxicity
Insulin receptor	Small and large molecules conjugated to mAbs or expressed as fusion proteins	Preclinical	To get therapeutical concentration in the brain parenchyma Toxicity
	Liposomes and nanoparticles coated with mAbs	Preclinical	To get therapeutical concentration in the brain parenchyma
Low-density lipoprotein receptor related protein (LRP)	Receptor Associated Protein (RAP) (fragment): ligand to LRP conjugated to small and large molecules or expressed as fusion protein	Preclinical	Potential toxicity Potential diminution of the affinity for LRP after modification Immunogenicity
	Melanotransferrin (p97): ligand of LRP conjugated to small molecules or expressed as a fusion protein	Preclinical	Large protein High cost of production High quantities needed Immunogenicity
	ApoE or ApoB a LRP ligand binding to nanoparticles coated with polysorbate-80 loaded with small anti-cancer agents	Preclinical	Mechanism not known Potential toxicity Potential disruption of the BBB
	LRP binding domain of the apolipoprotein B (peptide of 38 amino acids) LRP ligand expressed with proteins	Preclinical	Not tested on active molecules (anti-cancer agents or others) or in human

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Various BBB- disrupting agents and permeation enhancers along with their mechanisms and drug molecules being transported into brain.

Type	Disrupting agent	Disruption mechanism	Molecules	Inferences	References
Chemical (Hypertonic solutions)	Mannitol	By shrinking of brain capillary endothelial cells leads to transient opening of paracellular route of access to the brain.	Methotrexate	Showed 10 to 100-fold increase in concentration (paracellular transport)	Rapoport, 2000
	Bradykinin (a plasma kinin of decapeptide nature) and Bradykinin analogue (Labradimil)	Modulates the BBB by B2 receptor mediated movement of junctional protein actin/myosin by expressing on endothelium of luminal membrane	Radiolabelled tracers	Increased concentrations are maintained for at least 90 min	Emerich et al., 2001
	Alkylglycerols (monoacetyl and diacetyl glycerol; 1-O-hexyldiglycerol)	Induce junctional osmotic pressure to attain transient opening for drug entry (Like mannitol)	Methotrexate, Erucylphosphocholine (ErPC)	A 17-fold increase in ErPC delivery to the tumor	Erdlenbruch et al., 2003; Erdlenbruch et al., 2002
Physical (Electromagnetic radiation)	Ultrasonic waves	Thermal effect of radiation leads to altered permeability and generalized opening.	Optison™ (a marketed product containg perfluorocarbon as a ultrasound contrast agent) used for imaging brain micro-environment and tumors	Showed better predictive and illustrated view of the cerebrovascular environment	Hynynen, 2008; McDannold et al., 2007
		Cavitation effect produced due to air filled pockets. Formation of micro-bubbles by ultrasound contrast agent.			
	Primary alcohols (Glycerol, PEG 400)	Due to membrane destabilization which leads to BBB disruption and entry of drug into brain		Better CNS drug concentration achieved	
Permeation enhancers	Surfactants [Sodium dodecyl sulphate, Dimethylsulfoxide, Polysorbate (Tween-80), Polyethylene glycol hydroxy stearate]		Kyotorphin, an oligopeptide used as analgesic normally does not cross the BBB is given with Tween-80	Superior peptide concentration achieved in brain micro-environment	Sakane et al., 1989
	Incomplete freund's		Amyloid β peptide (a		Schenk et al., 1999;

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Permeation enhancers	Surfactants [Sodium dodecyl sulphate, Dimethylsulfoxide, Polysorbate (Tween-80), Polyethylene glycol hydroxy stearate]	Kyotorphin, an oligopeptide used as analgesic normally does not cross the BBB is given with Tween-80	Superior peptide concentration achieved in brain micro-environment	Sakane et al., 1989
	Incomplete freund's adjuvant (IFA) are mineral oil emulsions formed from mineral oil like liquid paraffin	Amyloid β peptide (a protein found deficient in Alzheimer's disease patient)		Schenk et al., 1999; Rabchevsky et al., 1999

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Table 6
Different nanoparticulate carrier system for brain targeting.

Carrier system	Drug molecule	Polymers/reagents	Mechanism/Inference	References
Polymeric nanoparticles	Amphotericin B (AmB)	Poly(lactic acid)-b-poly(ethylene glycol) coated with polysorbate 80 (Tween-80)	Enhanced concentration in mice brain indicating increased permeability across the BBB.	Ren et al., 2009
	Loperamide	Poly(d,l-lactide-co-glycolide), surface-decorated with the peptide Gly-l-Phe-d-Thr-Gly-l-Phe-l-Leu-l-Ser(O-beta-d-glucose)-CONH(2)	Effective carrier of Loperamide for brain targeting when administered intravenously	Vergoni et al., 2009
	Iron oxide	Magnetic iron oxide nanoparticles (MNP) coated with gum arabic	Superior ability for tumor targeting and intracellular drug delivery	Zhang et al., 2009
	Estradiol	Chitosan	Prominent blood and CSF concentration after intranasal administeration	Wang et al., 2008
	Paclitaxel	Biotinylated Poly lactic acid-poly ethylene glycol	Increased anti-tumoral activity	Pulkkinen et al., 2008
	Tacrine	Poly(n-butylcyanoacrylate) (surface functionalized by 1% polysorbate-80)	Enhanced brain concentration after intravenous administration in rats	Wilson et al., 2008
	Paclitaxel	Poly(lactide) (PLA) nanoparticles decorated with D-alpha-(tocopheryl polyethylene glycol succinate)	Better therapeutic concentration in MCF-7 breast cancer cells	Pan and Feng, 2008
	Loperamide	Poly(d,l-lactide-co-glycolide) (PLGA) derivatized with H(2)N-Gly-l-Phe-d-Thr-Gly-l-Phe-l-Leu-l-Ser(O-beta-d-Glucose)-CONH(2) [g7] (g7-Np)	Higher BBB concentration with sustained release profile.	Tosi et al., 2007
	Nimodipine	Methoxy poly(ethylene glycol)-poly(lactic acid)	Intranasal administration showed higher concentrations in blood, cerebrospinal fluid and brain tissues due to direct nose-brain transport	Zhang et al., 2006
	Dalargin (a leu-enkephalin analogue)	Poly(butylcyanoacrylate) surface decorated with polysorbate-80	Intravenous delivery showed superior concentration in capillary endothelium and cerebral neurons	Aliautdin et al., 1996
	Ferumoxtran-10	Iron oxide coated with dextran	Showed different visualization enhancement patterns in a variety of CNS lesions with inflammatory components than gadolinium.	Manninger et al., 2005.
Nanoemulsion	Risperidone	Capmul MCM as the oil phase along with mucoadhesive polymers	Upon intranasal administration showed promising cerebral as well as CSF concentration.	Kumar et al., 2008b.
	Paclitaxel	Pine-nut oil containg high concentrations of essential polyunsaturated fatty acid (PUFA)	Showed higher cytotoxic effect in human glioblastoma brain tumor cells	Desai et al., 2008
	Saquinavir	Edible oils rich in essential polyunsaturated fatty acids (PUFA) and surfactant Lipoid-80 and deoxycholic acid.	Enhanced oral bioavailability and brain concentration achieved effective antiretroviral therapy	Vyas et al., 2008
Nanosuspension	Indinavir	Nanosuspension formulations were prepared by high pressure homogenization	Increased central nervous system concentration of drug due to enhanced biodistribution	Dou et al., 2009
	Atovaquone	Nanosuspension coated with apolipoprotein E (apoE) and stabilized by polysorbate 80, poloxamer 184, or poloxamer 338	Improved uptake into brain and reduced *T. gonadi* infection	Shubar et al., 2009
Nanogel	Oligonucleotides (ODN)	Nanogels prepared from poly(ethylene glycol) and polyethylenimine	Illustrated higher concentration in brain microvessels when observed in bovine brain	Vinogradov et al., 2004
	5-fluorouracil	Copolymeric micelles of N-isopropylacrylamide (NIPAAM) and N-vinylpyrrolidone (VP) cross-linked with N,N′-methylenebisacrylamide (MBA), coated with polysorbate-80	In vivo scintigraphy showed higher concentration across BBB	Sheetal et al., 2006

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Review

Strategy for effective brain drug delivery

M. Intakhab Alam[a], Sarwar Beg[a], Abdus Samad[b], Sanjula Baboota[a,*], Kanchan Kohli[a], Javed Ali[a], Alka Ahuja[c], M. Akbar[d]

Table 6 (*Continued*)

Carrier system	Drug molecule	Polymers/reagents	Mechanism/Inference	References
Nanosphere	CTPB (N-(4-chloro-3-trifluoromethylphenyl)-2-ethoxybenzamide), (responsible for histone acetyltransferase (HAT) dependent gene expression)	Glucose-derived carbon nanospheres	Evaluated BB crossing ability which is confirmed by the transport of membrane-impermeable molecule CTPB.	Selvi et al., 2008
	-	Nanospheres made from poly(ethylene glycol) (PEG)-coated hexadecylcyanoacrylate	Attained higher brain concentration due to convection enhanced diffusion (CED) and higher affinity of PEG towards BBB endothelium	Brigger et al., 2002
Solid lipid nanoparticle (SLN)	Etoposide	Tripalmitin as solid fat	Explained better drug concentration in dalton's lymphoma when injected by subcutaneous, intravenous or intraperitoneal routes.	Harivardhan et al., 2005
	5-fluoro-2'-deoxyuridine (FUdR)	Octanoic acid and Pluronic F-68 and F-127	Improved the ability of drug to penetrate blood–brain barrier	Wang et al., 2002
	Camptothecin	Stearic acid, Soybean lecithin and Poloxamer 188	Showed effective drug targeting with promising sustained release profile along with dose reduction and decreased systemic toxicity	Yang et al., 1999
	Temozolomide	Stearic acid, Lecithin, Poloxamer188, Tween 80	Achieved higher cerebral concentration with potential reduction of cardiac and nephric cytotoxicity	Huang et al., 2008
Nanoliposome	Tempamine	Lipid	Therapeutically active for neurodegenerative diseases involving oxidative damage (multiple sclerosis)	Kizelsztein et al., 2009

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Development and evaluation of olanzapine-loaded PLGA nanoparticles for nose-to-brain delivery: *In vitro* and *in vivo* studies

U. Seju, A. Kumar, K.K. Sawant *

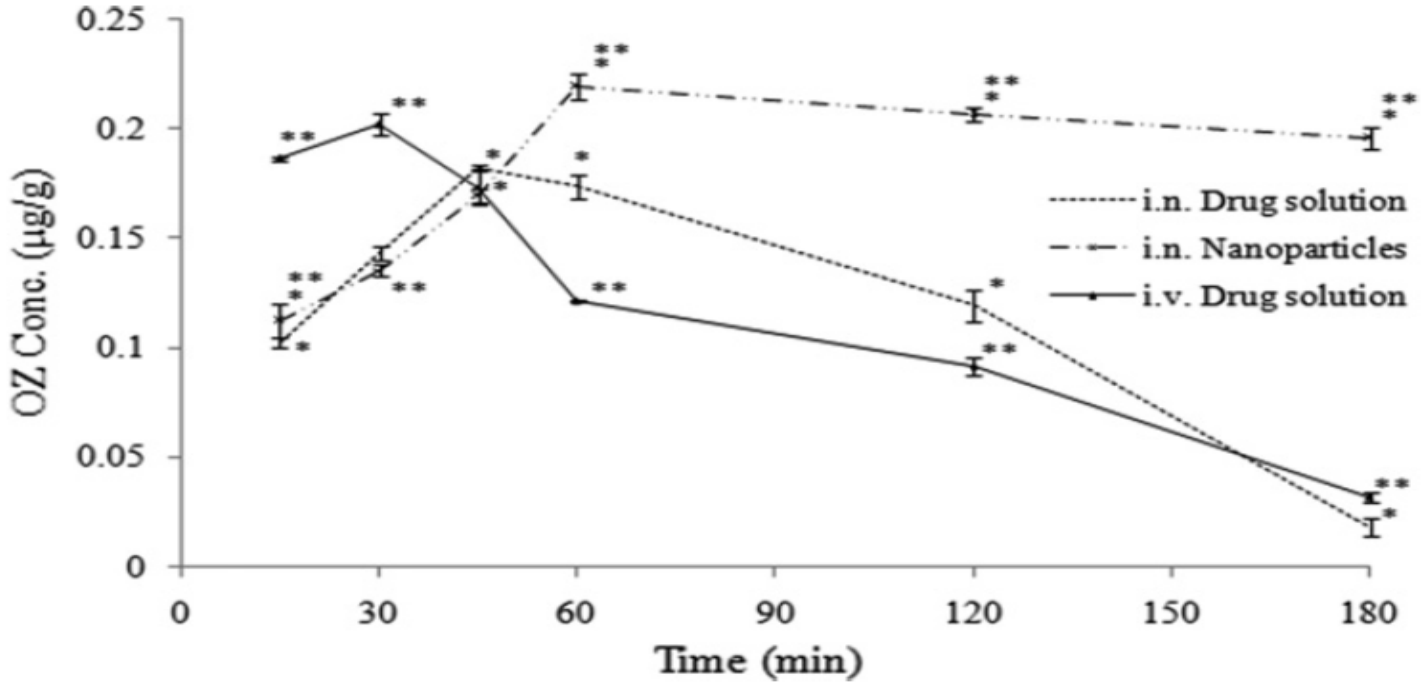

Fig. 6. Time profile of OZ concentration in brain after IN administration of NP and drug solution and IV administration of drug solution in rats. The values represent mean ± SD of six animals (some error bars are too small to be shown). $^{*}p < 0.05$;

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Research paper

Efficacy of surface charge in targeting pegylated nanoparticles of sulpiride to the brain

Tapan Parikh *, Murali Mohan Bommana, Emilio Squillante III

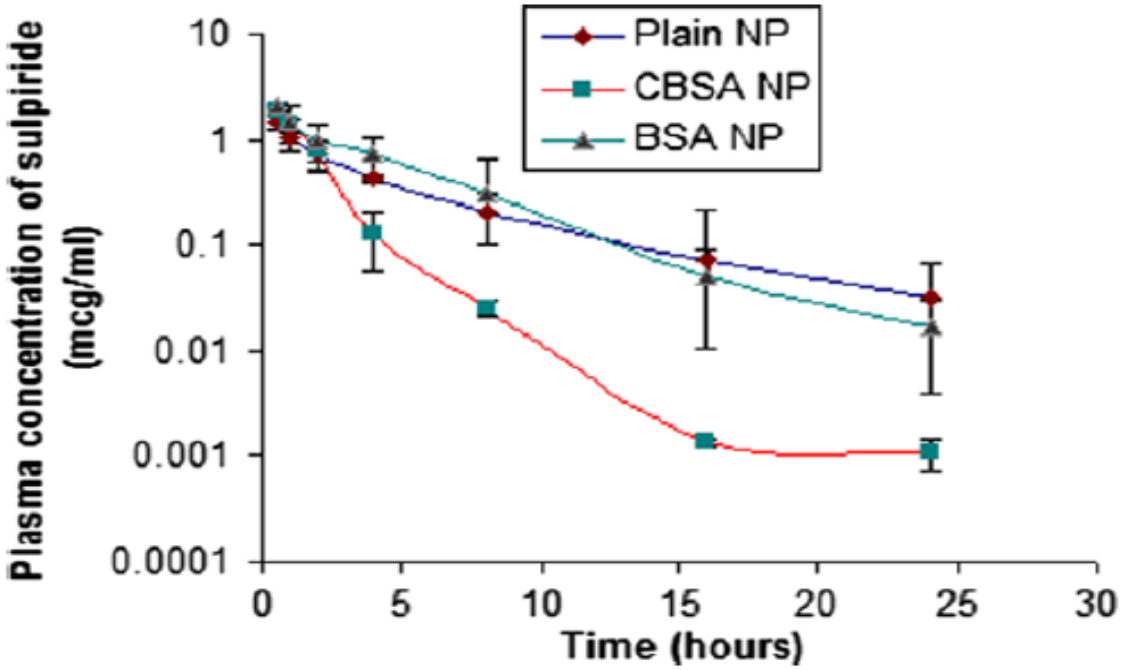
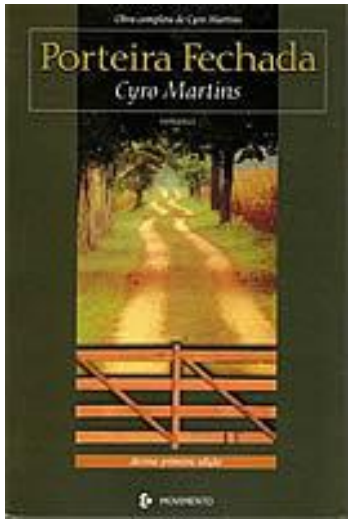


Fig. 5. Sulpiride plasma concentrations (mcg/ml) of Sprague Dawley rats ($n = 5$) for (1) plain nanoparticles (—◆—), (2) BSA nanoparticles (—■—), and (3) CBSA nanoparticles (—▲—) vs. time (h), respectively. A lower percentage plasma dose release profile for CBSA nanoparticle (60.42 ± 8.57%) obtained when compared to BSA nanoparticles (86.23 ± 18.32%) and uncoated nanoparticles (82.35 ± 12.25%). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Estudos de uso de drogas com Cavalos de Tróia emPsiquiatria

1: Patel S, Chavhan S, Soni H, Babbar AK, Mathur R, Mishra AK, Sawant K. Brain targeting of risperidone-loaded solid lipid nanoparticles by intranasal route. J Drug Target. 2011 Jul;19(6):468-74.
2: Kumar M, Misra A, Pathak K. Formulation and characterization of nanoemulsion of olanzapine for intranasal delivery. PDA J Pharm Sci Technol. 2009 Nov Dec;63(6):501-11.
3: Parikh T, Bommana MM, Squillante E 3rd. Efficacy of surface charge in targeting pegylated nanoparticles of sulpiride to the brain. Eur J Pharm Biopharm. 2010 Mar;74(3):442-50. Epub 2009 Nov 24.
4: Kumar M, Misra A, Babbar AK, Mishra AK, Mishra P, Pathak K. Intranasal nanoemulsion based brain targeting drug delivery system of risperidone. Int J Pharm. 2008 Jun 24;358(1-2):285-91. Epub 2008 Mar 27. PubMed PMID: 18455333.



Futuro

- "drogas inteligentes":
  - Reverter resistência (induzidas por MDR-GP)
  - Diminuir dose necessária
  - Modificar o alvo específico
  - Novas utilidades de velhas drogas

O possível e o não possível: equipe