Models of the Choroid Plexus Epithelium

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Abstract

- Short overview about brain diseases and CNS barriers
- Structure and function of the Choroid Plexus
- Ex vivo / in vitro models to study CP function
- **Active transporters in the CP**

Reasons to study CNS-Barriers

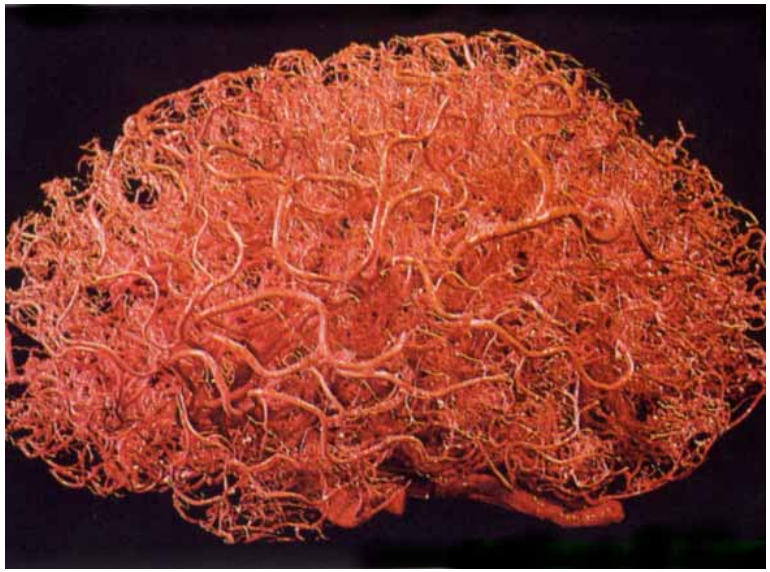
- 25 % of all human beings develop one or more mental disturbances
- 24 Mio human beings worldwide suffer from Schizophrenia
  direct costs of treatment in the USA: 0.5 % of the gross domestic product (GDP)
- appr. 37 Mio. human beings with dementia - the majority of them with Alzheimers disease; 3. largest health problem in the US annual costs appr. 70.000.000.000 $
- ca. 50 Mio. human beings with Epilepsy, more than 80% in developing countries

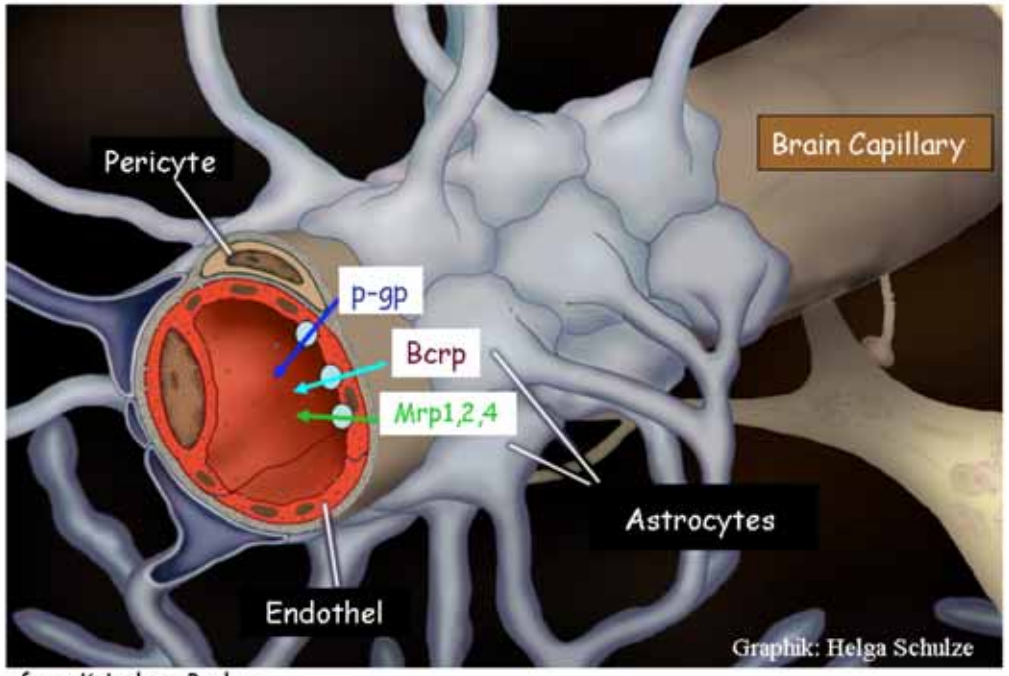
Therapeutic Problems

Drug resistance is one of the most important obstacle in the successful therapy of CNS diseases with the consequence, that - compared to other indications - there are relatively few successful CNS drugs on the market.

major problem : restricted access to the brain

Brain Capillaries

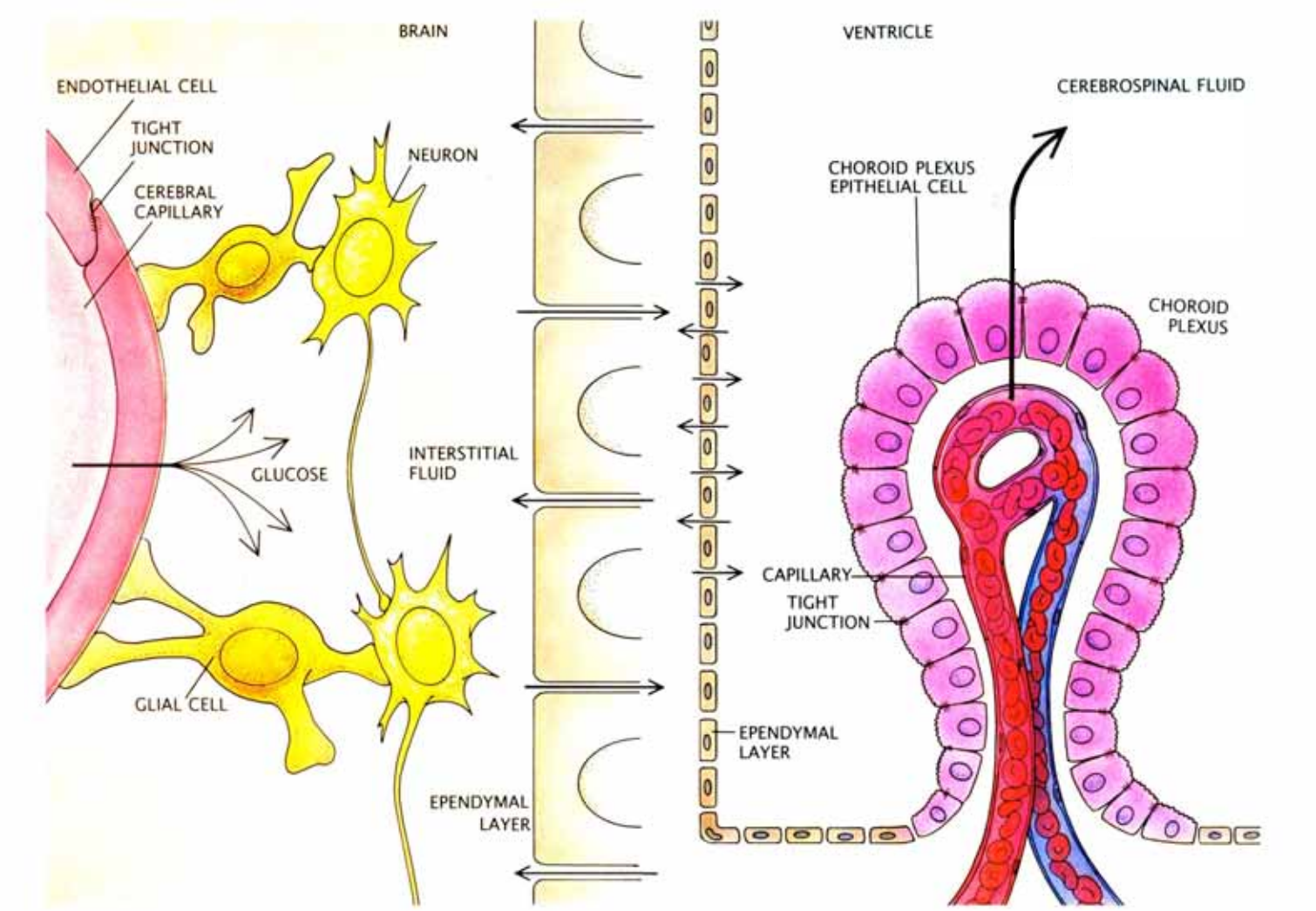




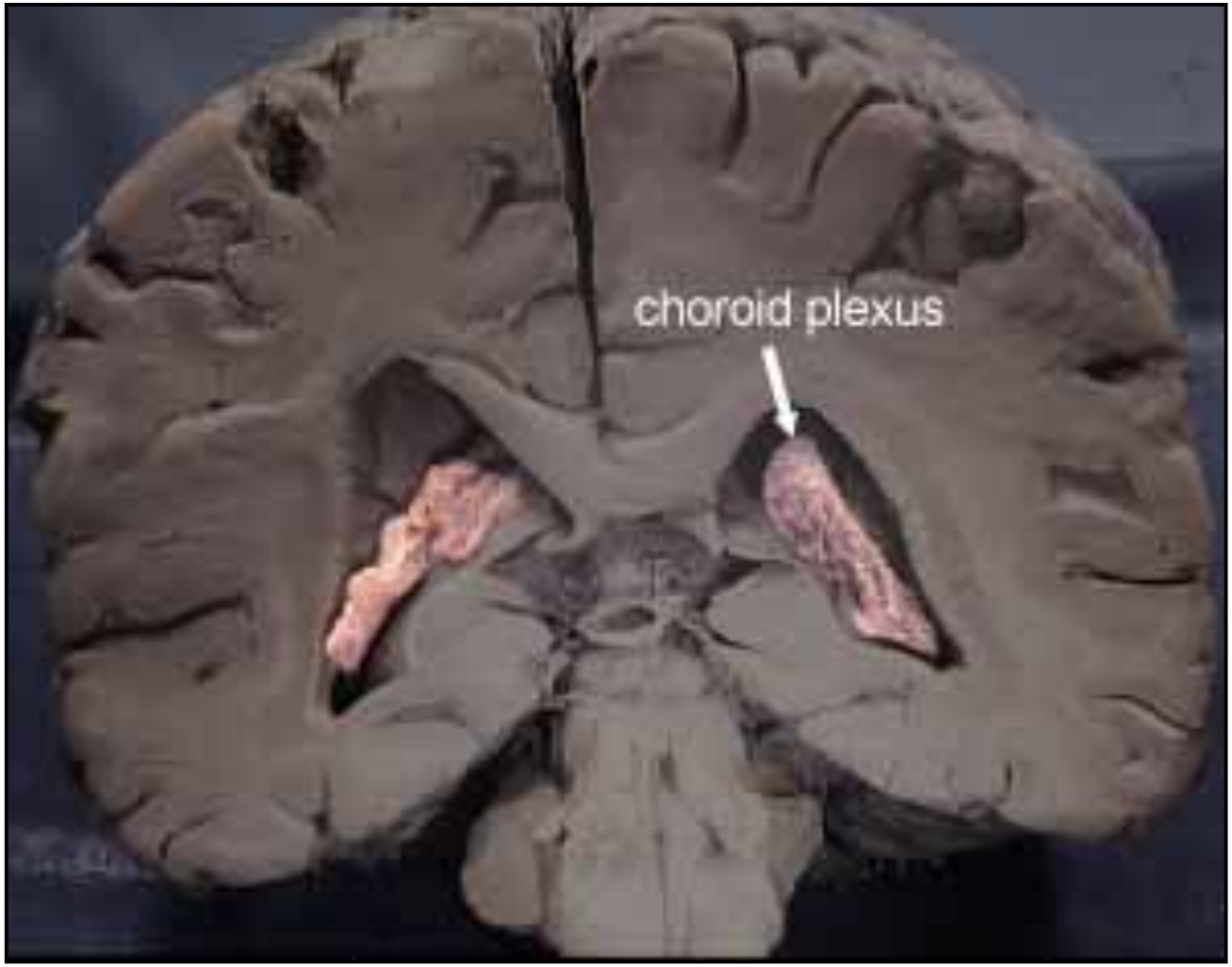
from: K. Ladage, Bochum

Human brain:	0.1% of Volume
Length:	600 km
Surface:	10-12 m^2

Blood-Brain Barrier and Blood-CSF Barrier



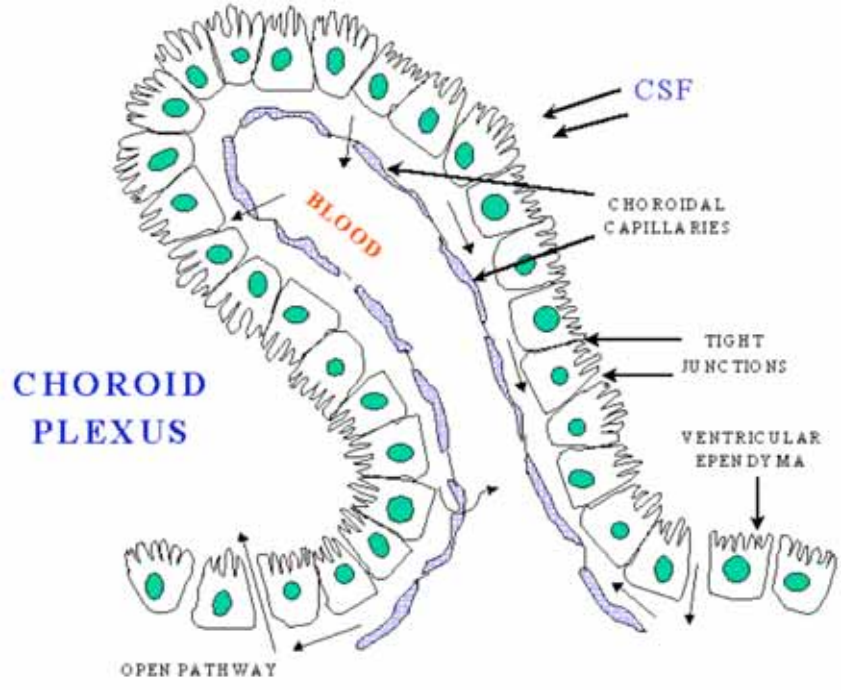
Choroid Plexus



from: www.sci.uidaho.edu

Function of the Choroid Plexus

First demonstrated 1913 by Goldmann



- production of CSF (appr. 21 ml/h)
- active regulation of molecules in the CSF
- polar epithelium
- fenestrated capillaries
- epithelial resistance of appr. 200 Ω cm^2

Models to study Choroid Plexus Function

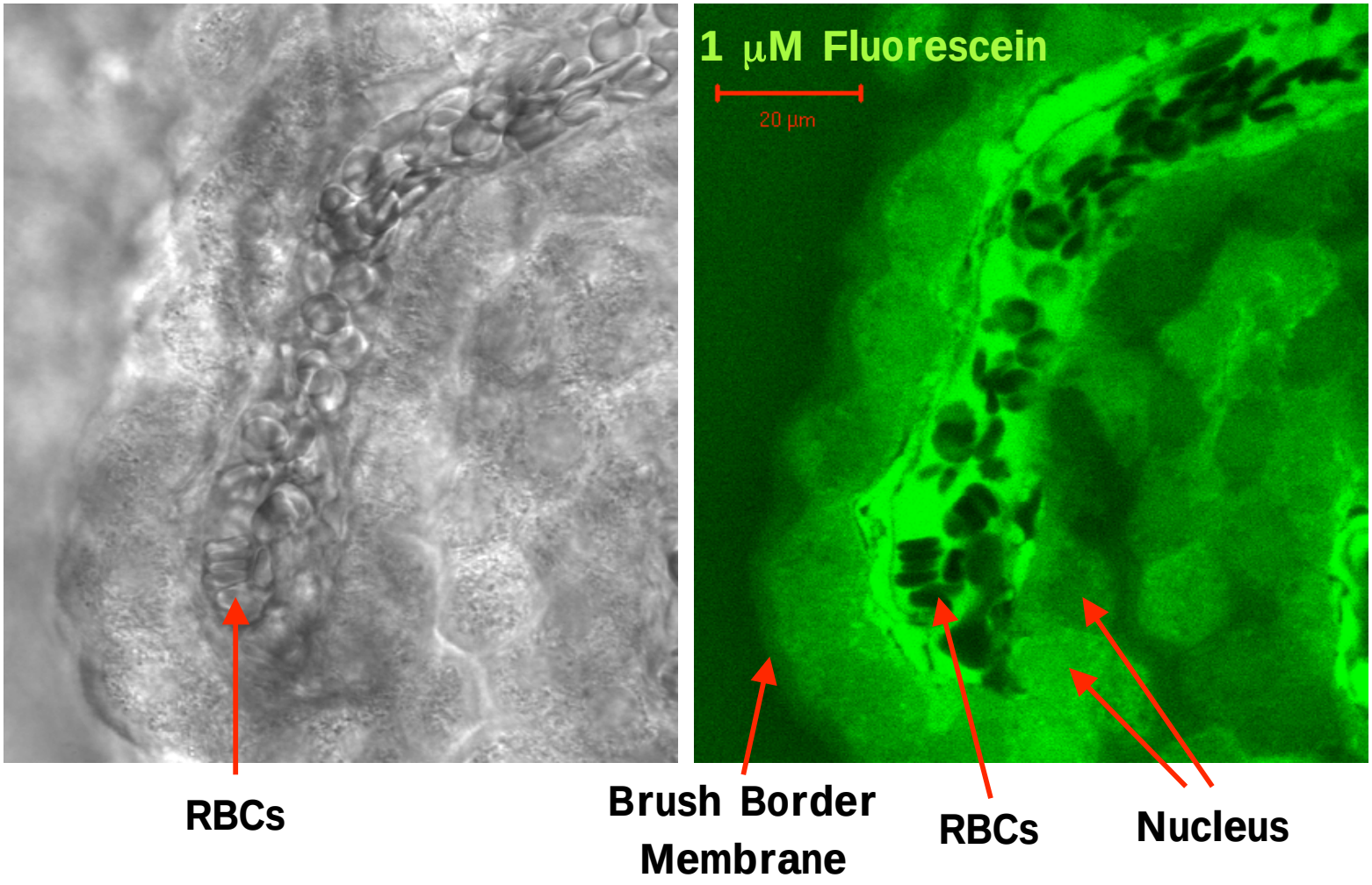
Freshly isolated tissue [rat, pig, shark (large CP, long viability)]

especially useful to study transport from CP to blood

Freshly isolated cell monolayers [pig]

useful to study CSF production; permeation studies
metabolism

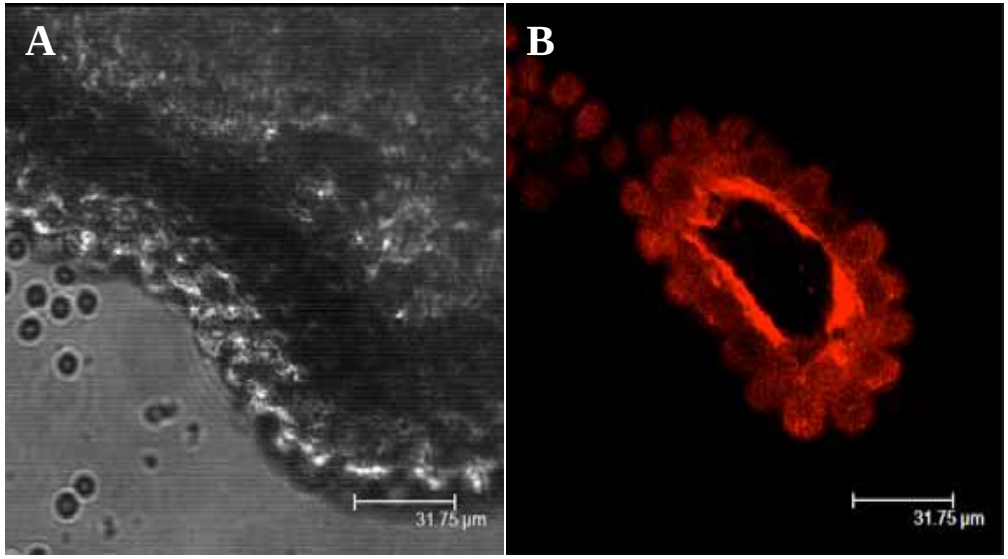
Studies with intact Tissue

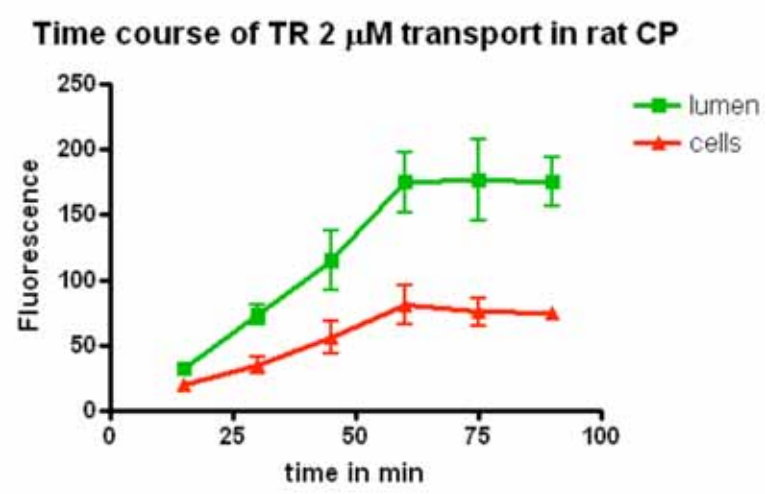


Breen et al., Am. J. Physiol. 282, F877-85, 2002
Baehr et al., Am. J. Physiol., 291, R464-472, 2006

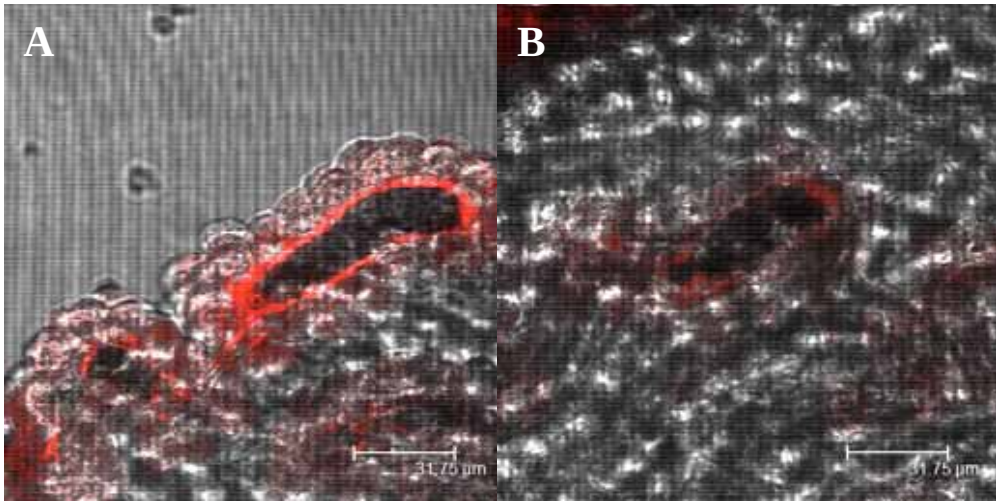
Studies with intact Tissue

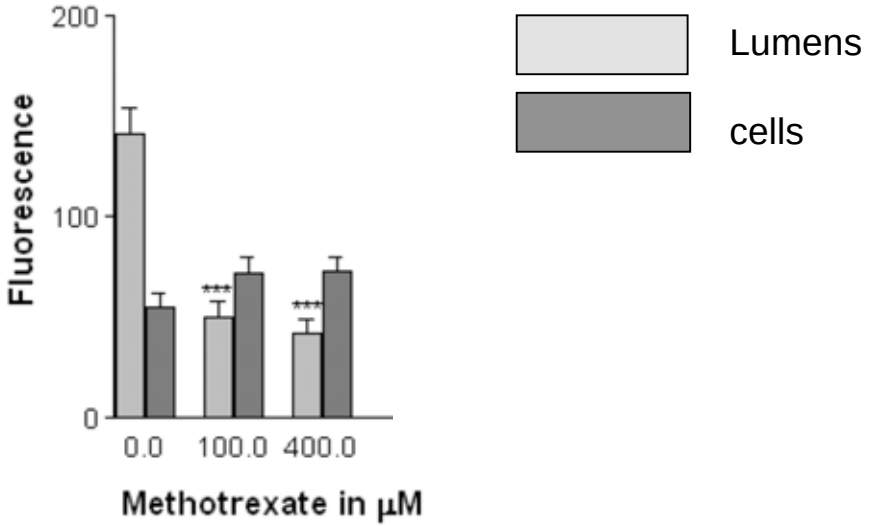
Incubation with fluorescent compounds being substrates for distinct transporters



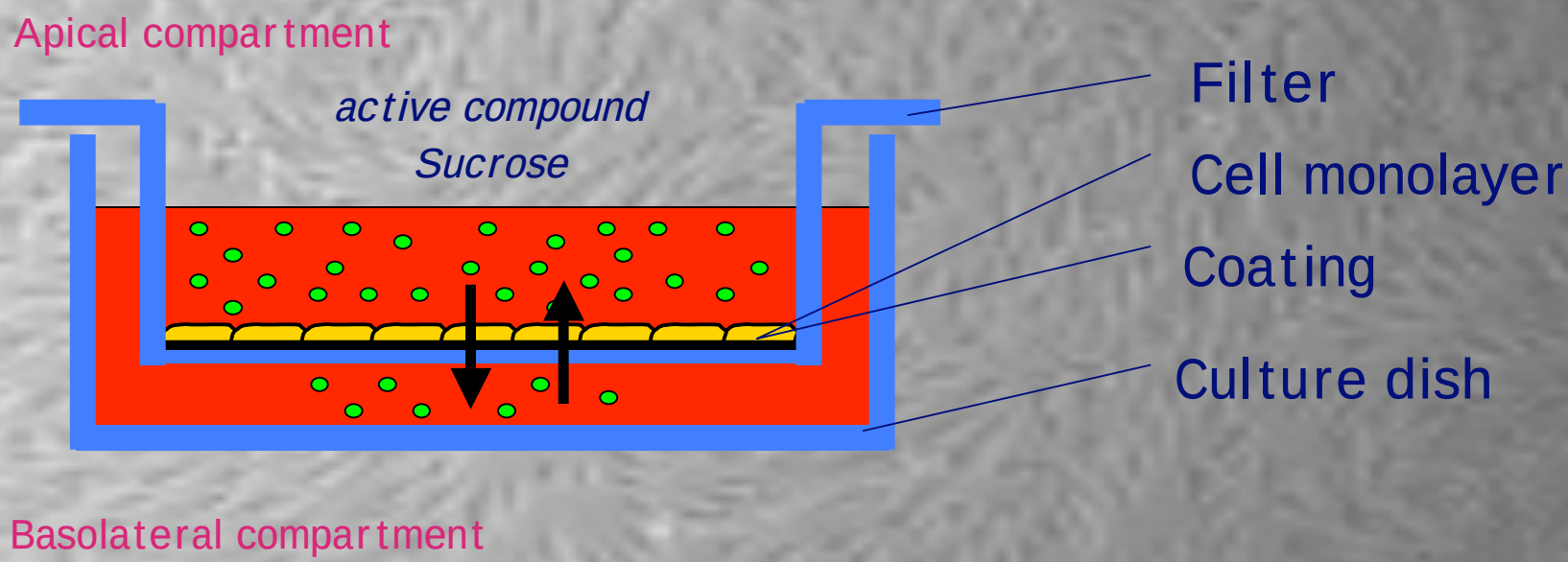


Inhibition of TR-transport (Example: Methotrexate)



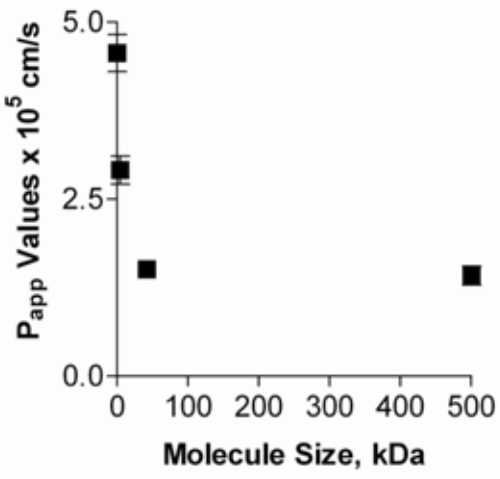


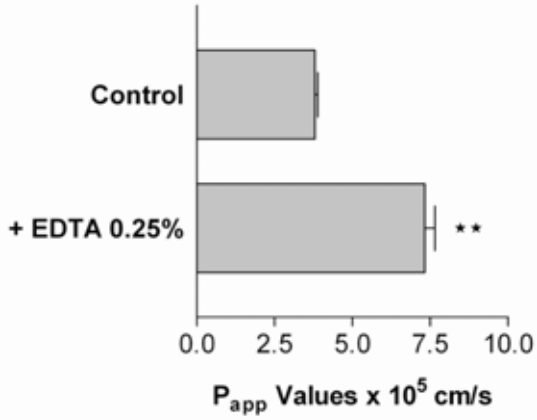
In vitro – cell cullture



Functionality of isolated cells

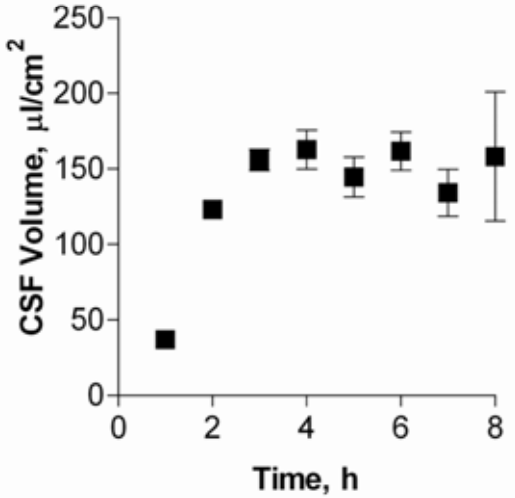
Formation of tight monolayers





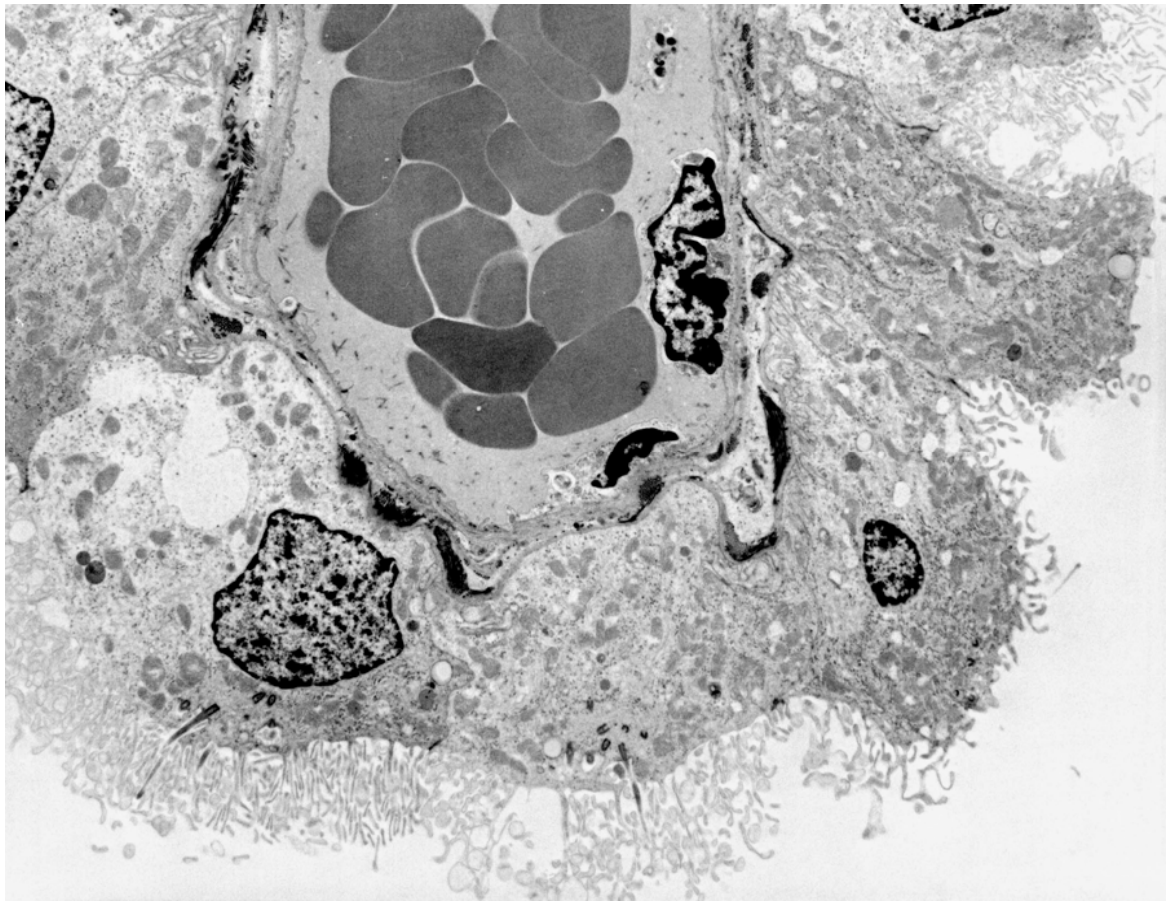
Exclusion of high molecular compounds
Permeability is influenced by EDTA

Active fluid excretion



Cells are able to accumulate
fluid in the apical compartment

Transporters in the CP



D.S. Miller

Transporters in the Choroid Plexus

SLC21 family

Oatp

SLC22 family

OAT

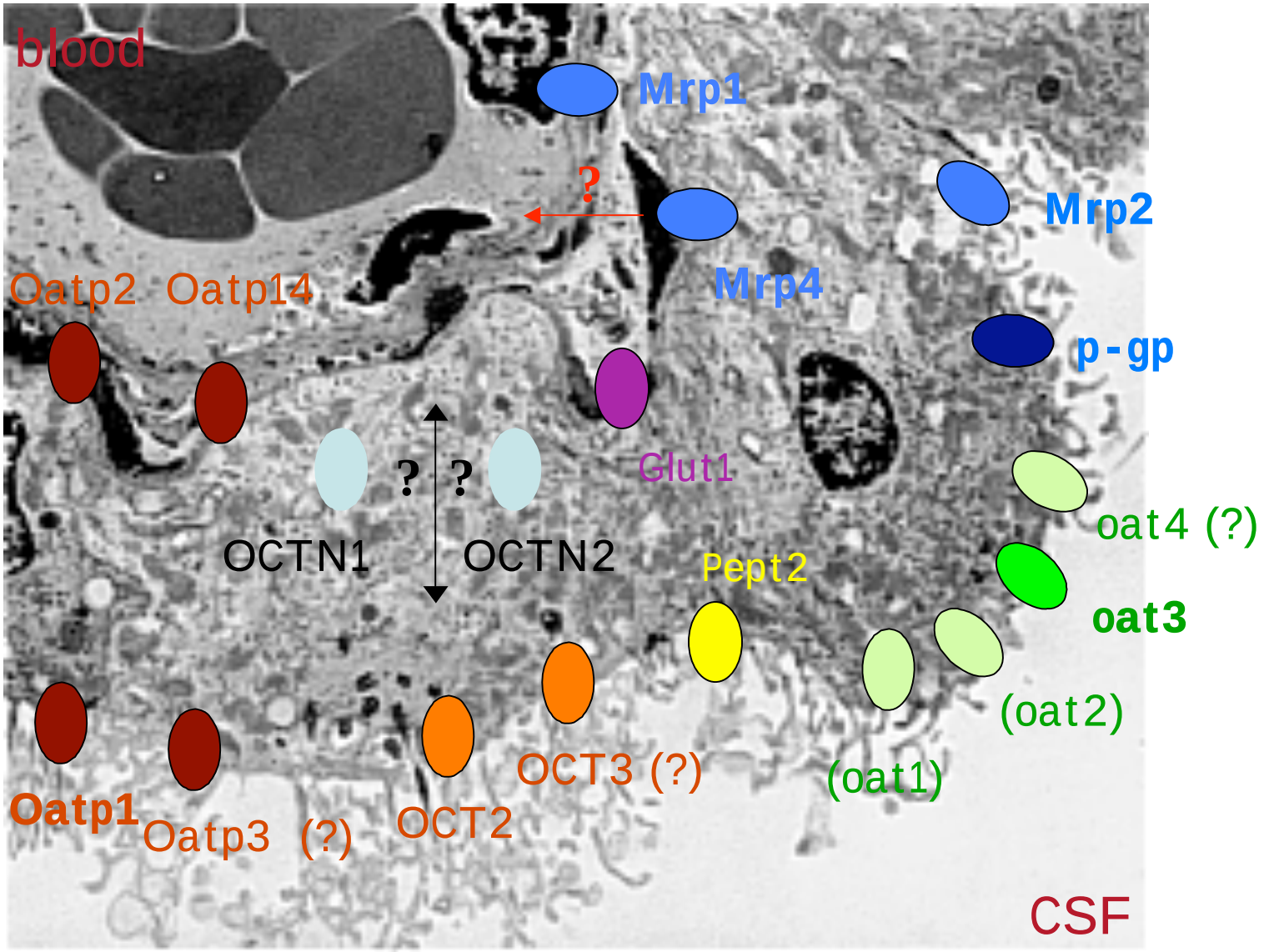
OCT

OCTN

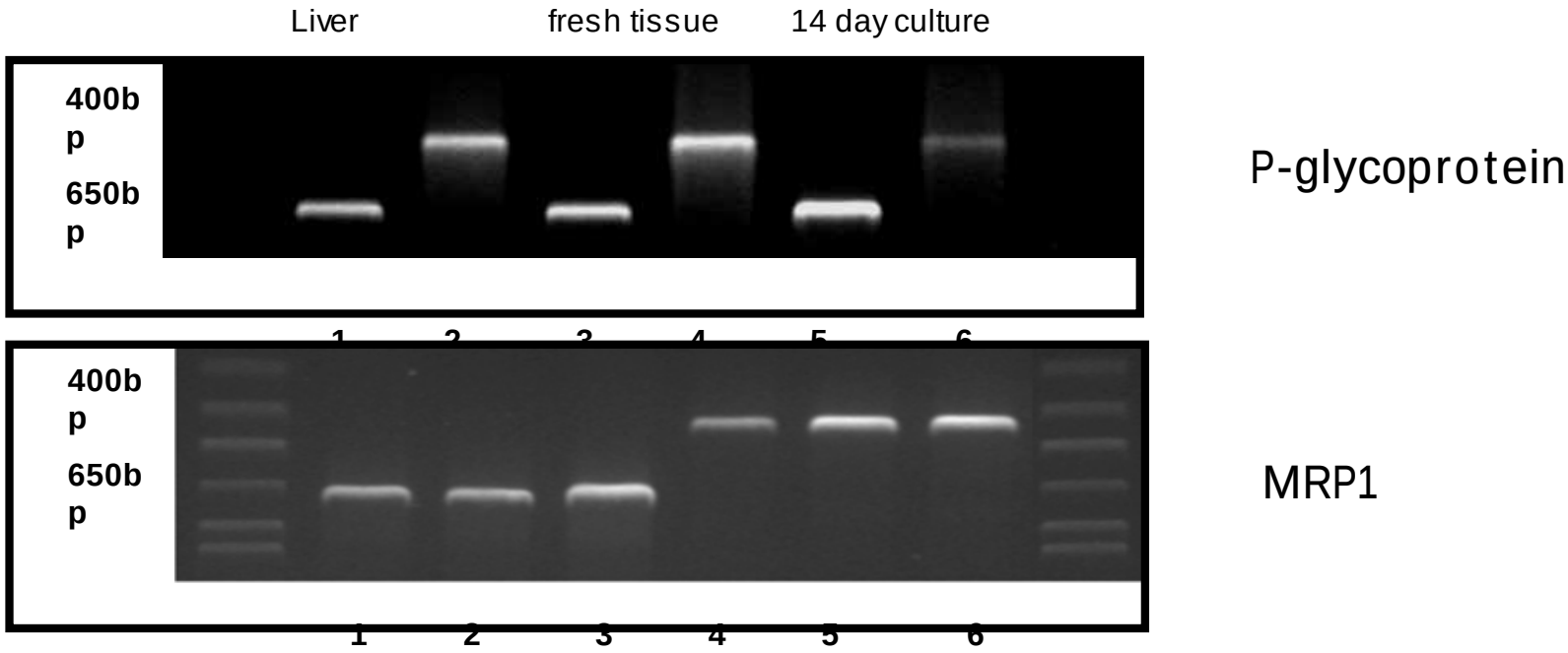
ABC families

MDR1, p-gp

Mrp



Is it possible to study ABC-Transporters?



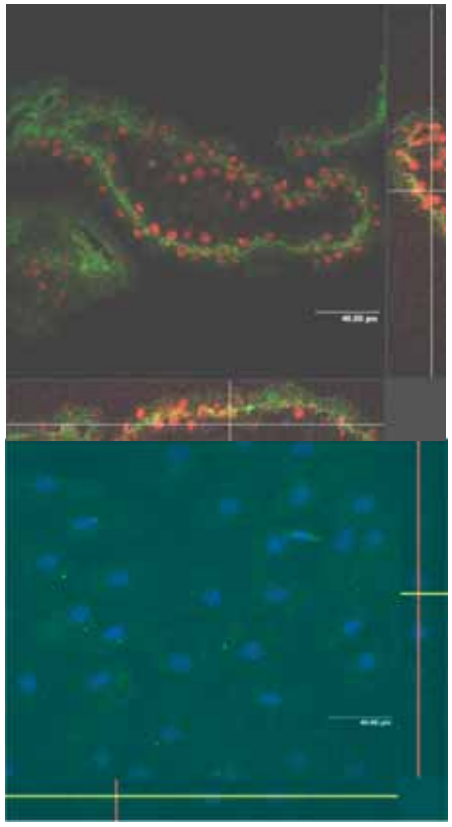
P-glycoprotein

MRP1

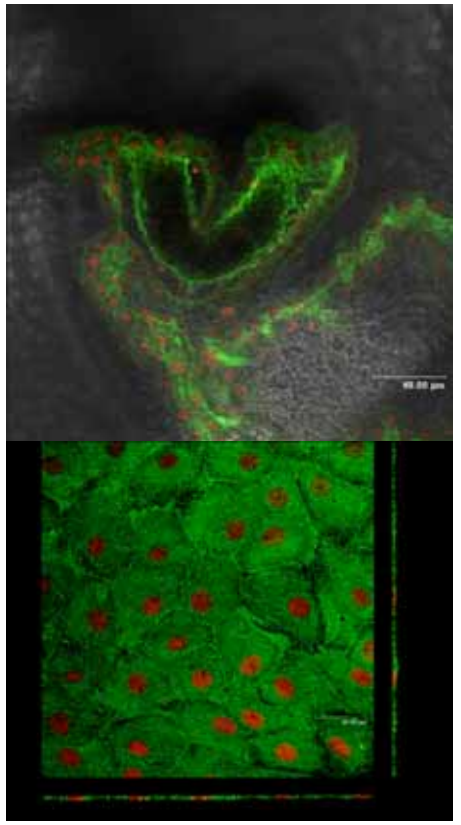
Expression of p-gp decreases with culture time

Expression of Mrp1 remains constant

Is it possible to study ABC-Transporters?



P-gp is localized in subapical domains
only very weak immunostaing in cultured cells



Mrp1 is localized on the
basolateral side;
strong immunostaining

Take Home Message

- The Choroid Plexus represents the second important barrier between blood and brain beside the blood brain barrier
- Two models are available: freshly isolated tissue and isolated cell monolayers
- ABC-Transporters are expressed in CP tissue.
  However P-glycoprotein expression is rather low and the protein exhibits only a sub-apical localization

Acknowledgements

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