UniversityHospital Heidelberg

HÄMATOLOGIE HEUTE
ULM

Störungen des Folsäure-Stoffwechsel

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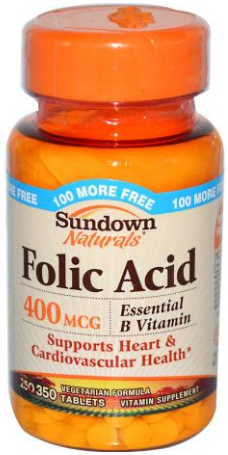
Folate (Vitamine B9)

- Early 1930: Treatment of megaloblastic anaemia with liver and brewers yeast
- 1941: Extraction from 4 tons of spinach
- Folium = Leaf
- Sources
  - Vegetables
  - Grains
  - Nuts
  - Brewers yeast

Folates

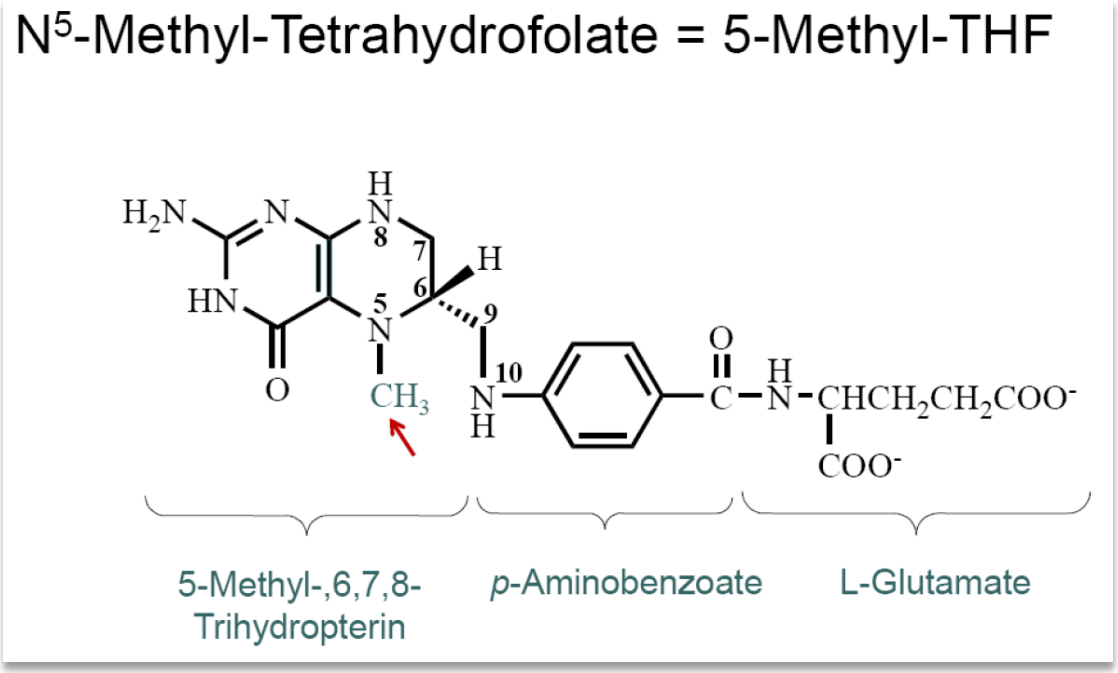
- Play an essential role in one-carbon methyl transfer reaction
- Involved in
  - DNA synthesis
  - Regulation of gene expression
  - Amino acid metabolism
  - Purine/pyrimidine synthesis



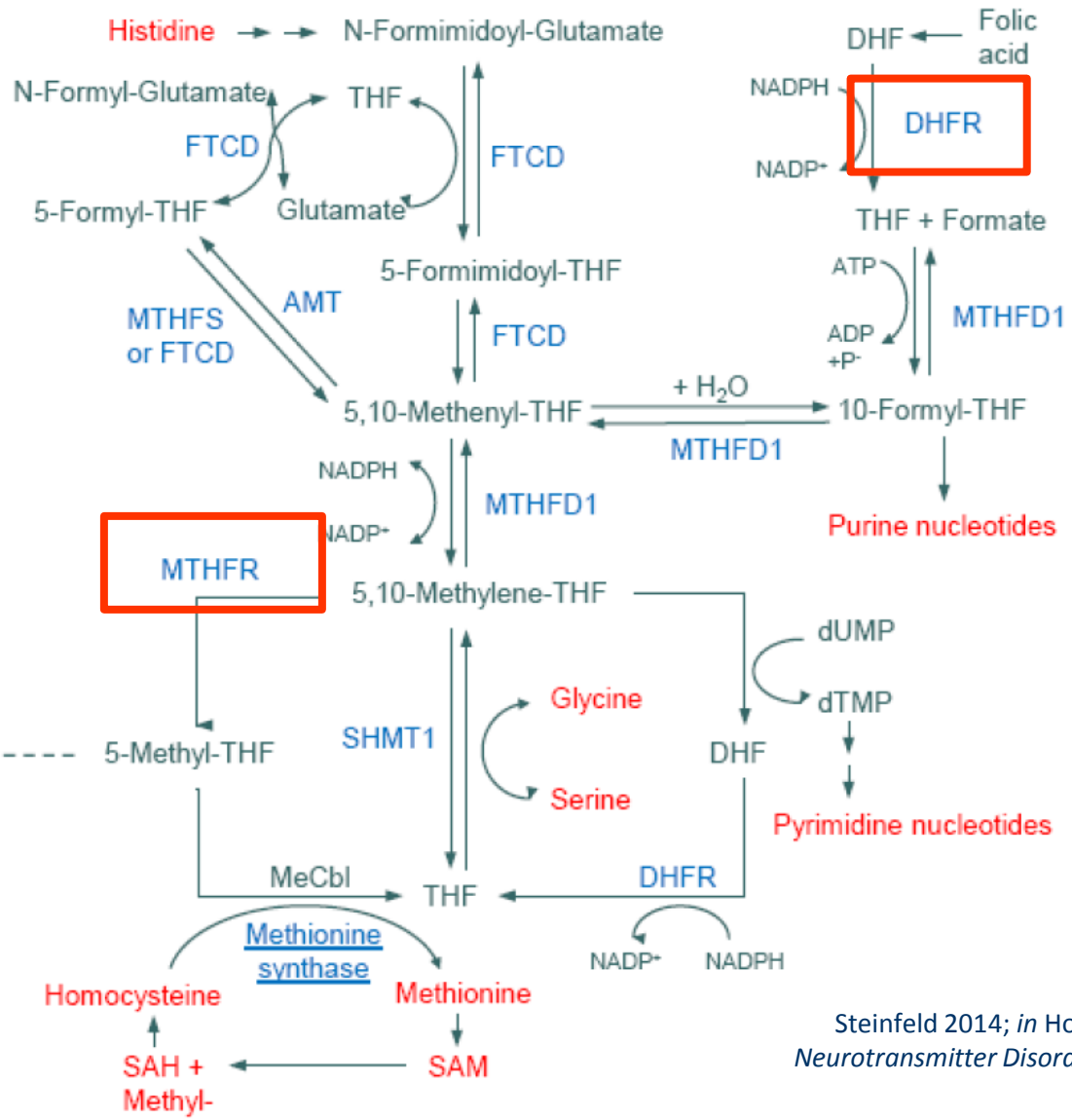
- Folic acid: Synthetic form used in supplements and fortified food
- Biologically active folic acid derivatives are generally 5,6,7,8-tetrahydrofolates

5-Methyltetrahydrofolate (5MTHF)

- Transported across the mucosa of the small intestine and the choroid plexus
- Widely distributed in blood stream



Folate metabolism



5MTHF Transport

Transport across intestinal mucosa and choroid plexus

- PCFT
- FOLR1

Steinfeld 2014; *in* Hoffmann, Blau *Congenital Neurotransmitter Disorders – A clinical approach*

Inherited disorder of folate metabolism

With anaemia and neurological symptoms

- Hereditary folate malabsorption (or Proton-coupled folate transporter deficiency)
- Dihydrofolate reductase deficiency

Hereditary folate malabsorption

Hereditary folate malabsorption

- Defect of proton coupled folate transporter PCFT (SLC46A1)
- PCFT defect results in **systemic folate deficiency** and **disturbed folate transport** into the central nervous system

- **Clinical findings**:
  - Early presentation!
  - Poor feeding and failure to thrive around 2 months of age
  - Megaloblastic anemia (partly pancytopenia)
  - Signs of humoral and cellular immunodeficiency (SCID-like)
  - Neurologic usually later, including developmental delays, cognitive and motor impairment, behavioral abnormalities, ataxia and other movement disorders, peripheral neuropathy, and seizures
  - Cortex or basal ganglia calcifications

Qiu et al; *Cell* 2006
Zhao et al; *Blood* 2007

Hereditary folate malabsorption II

- Biochemical findings

Folate (Serum)	5MTHF (CSF)	Blood count	Homocysteine (Plasma)	Methionine (Plasma)	MRI/CCT

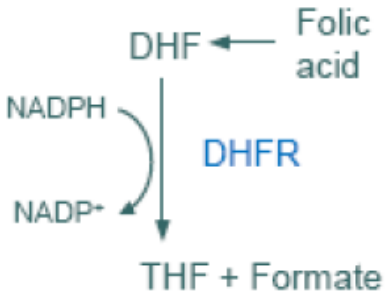
Hereditary folate malabsorption III

- Treatment & Outcome
  - 5-formyl-THF (= folinic acid 10-20 mg/kgBW)
  - i.m./i.v.?
  - NO Folic acid!
  - Prognosis regarding neurological symptoms difficult

Dihydrofolate reductase deficiency

Dihydrofolate reductase deficiency

- DHFR catalyzes the NADPH-dependent conversion of dihydrofolate to tetrahydrofolate
- Major target of methotrexate



Cario et al;. Am. J. Hum. Genet. 2011
Banka et al; Am. J. Hum. Genet. 2011

REPORT

Dihydrofolate Reductase Deficiency Due to a Homozygous *DHFR* Mutation Causes Megaloblastic Anemia and Cerebral Folate Deficiency Leading to Severe Neurologic Disease

Holger Cario,[1,*] Desirée E.C. Smith,[2] Henk Blom,[2] Nenad Blau,[3,4,5] Harald Bode,[1] Karlheinz Holzmann,[6] Ulrich Pannicke,[7] Karl-Peter Hopfner,[8] Eva-Maria Rump,[9] Zuleya Ayric,[10] Elisabeth Kohne,[1] Klaus-Michael Debatin,[1] Yvo Smulders,[11] and Klaus Schwarz[7,9]

Cario et al;. Am. J. Hum. Genet. 2011
Banka et al; Am. J. Hum. Genet. 2011

Dihydrofolate reductase deficiency II

- **Clinical findings**:
  - Infantile onset with failure to thrive
  - Megaloblastic anemia
  - Secondary microcephaly
  - Neurological symptoms follow (developmental delay, central hypotonia with poor head control, inability to fix and follow, and frequent focal seizures)
  - Brain MRI with cerebellar and cerebral atrophy thin corpus callosum and poor myelination of white matter.

Cario et al;. Am. J. Hum. Genet. 2011
Banka et al; Am. J. Hum. Genet. 2011

Dihydrofolate reductase deficiency III

- Biochemical findings

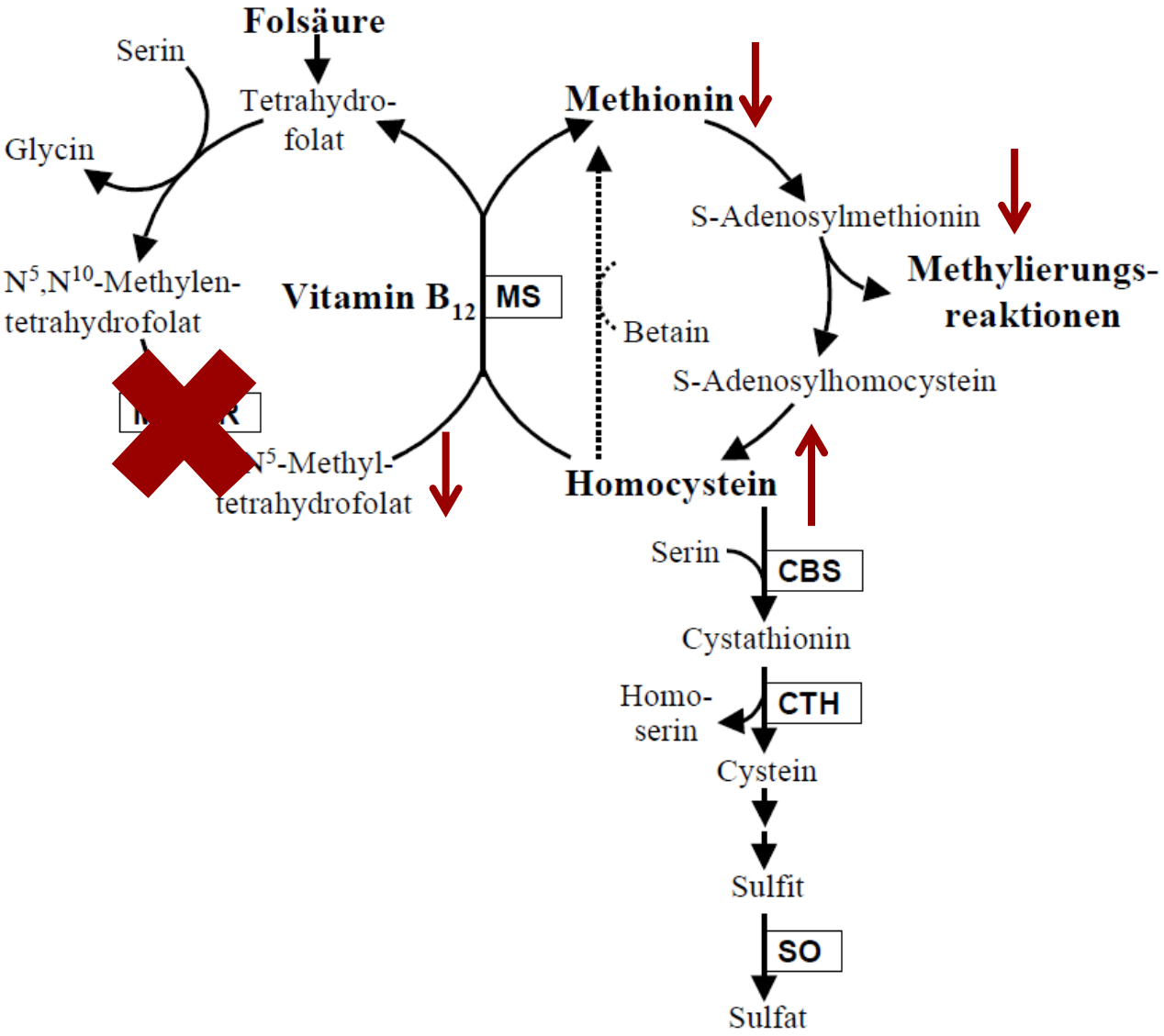
Folate (Serum)	5MTHF (CSF)	Blood count	Homocysteine (Plasma)	Methionine (Plasma)	MRI/CCT
normal	↓ (< 5 nM)	Megaloblastic anemia	**normal**	**normal**	Hypomyelin-isation, thin corpus callosum, brain atrophy

- Treatment & Outcome
  - 5-formyl-THF (= folinic acid 5-10 mg/kgBW)
  - i.m./i.v.?
  - NO Folic acid!

  - Prognosis regarding neurological symptoms difficult
  - Seizures!

5,10-Methylenetetrahydrofolate Reductase Deficiency

MTHFR deficiency



MTHFR deficiency

- **Clinical findings**:

  Onset and severity of symptoms vary significantly!

  – Neonatal form:

  Infantile spasms

  Developmental delay

  Motor and gait abnormalities, incoordination, paresthesias

  Stroke

  – Adult-onset

  Combination of progressive spastic paraparesis and polyneuropathy

  Variably behavioral changes & cognitive impairment

  Seizures

  Leukoencephalopathy

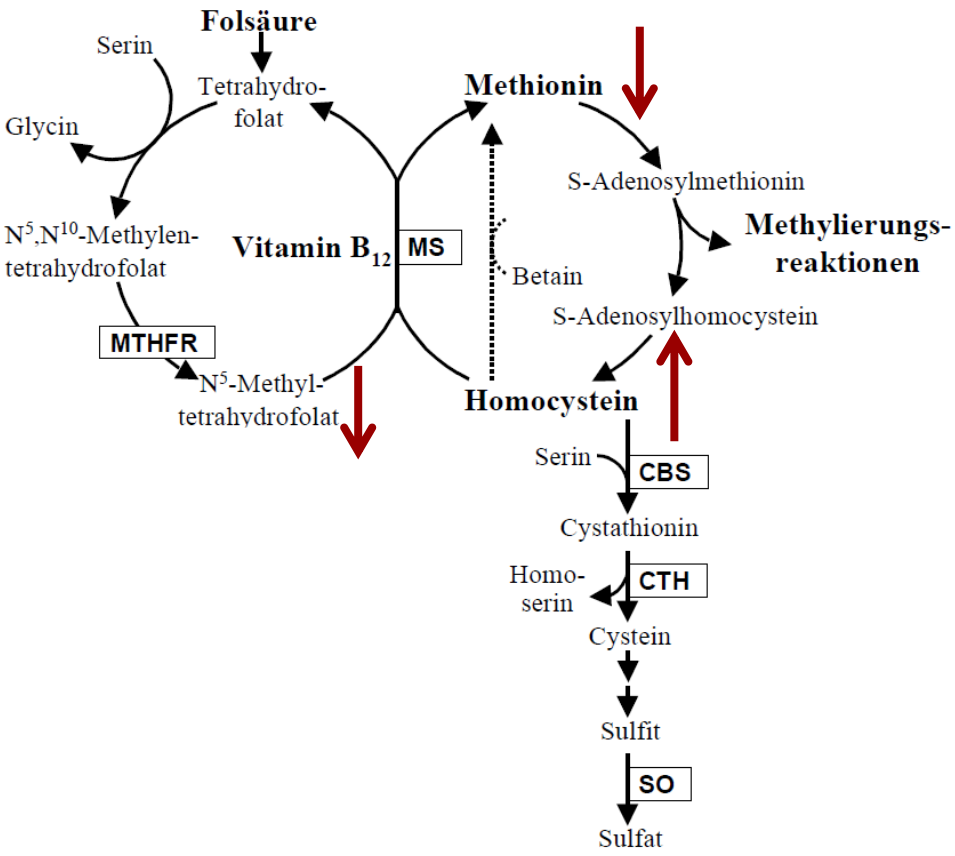
MTHFR deficiency

- Biochemical findings

Folate (Serum)	5MTHF (CSF)	Blood count	Homocysteine (Plasma)	Methionine (Plasma)	MRI/CCT
Variabel/↓	↓ (< 5 nM)	**normal**	↑↑	↓↓	Periventricular demyelination, Hydrocephalus

MTHFR deficiency

- Treatment & Outcome
  - Betaine neonates and infants 100–250 mg/kg/day; children and adults, 6–9 g/day; three divided doses
  - Folinic acid orally 15 mg/d
  - Hydroxycobalamin 0.5–1 mg orally or 1 mg IM monthly
  - Methionine orally 40–50 mg/kg/day
  - Vitamin B6 orally 100–250 mg/day



Cerebral Folate (Transport) Deficiency

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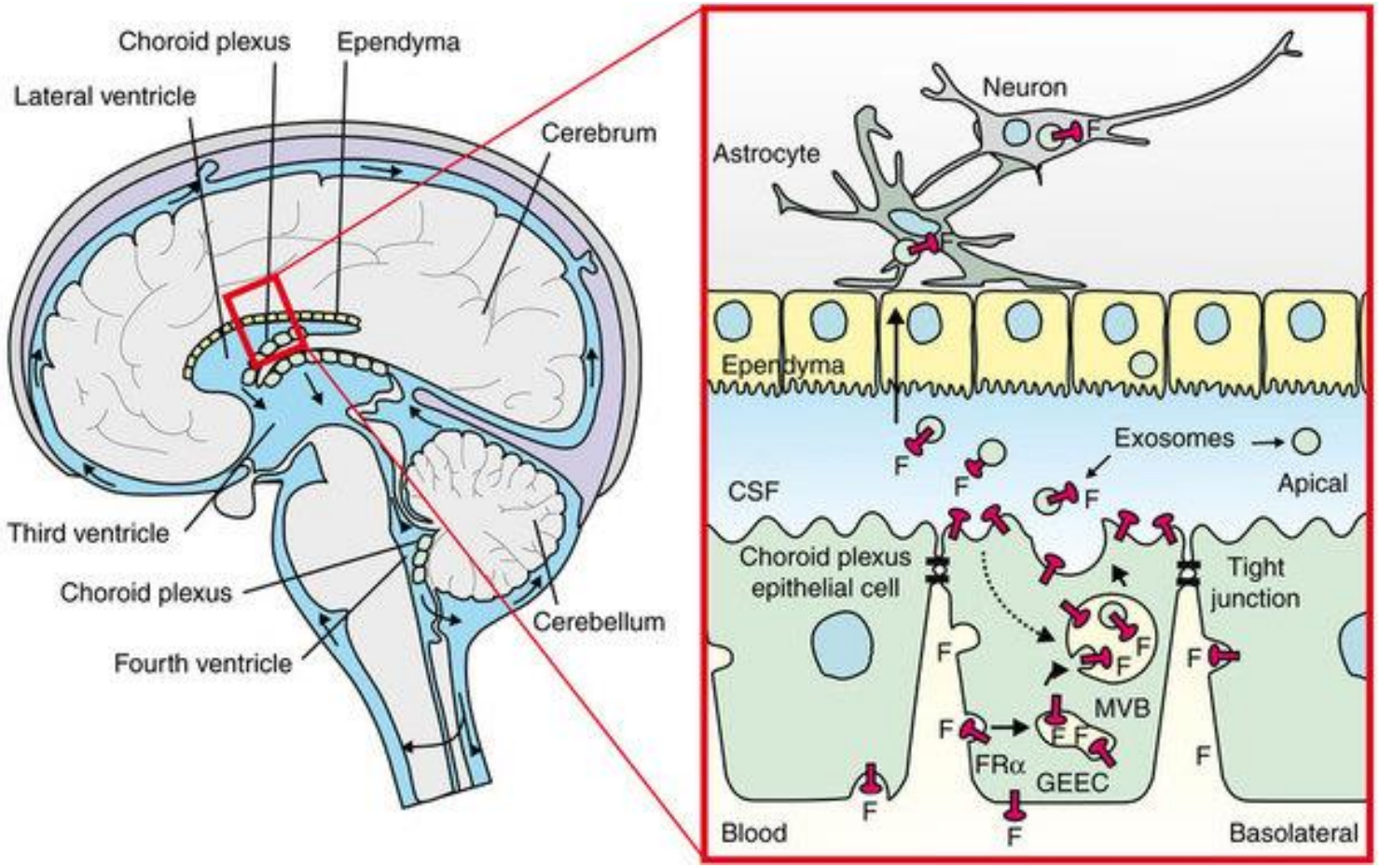

Grapp et al; Nat Commun. 2013

Folate receptor alpha (FRα) deficiency

- Severe decreased 5MTHF concentration in CSF
- Pathogenic mutation in *FOLR1* gene

- **Clinical findings**:
  - Symptomatic in late infancy (increased expression of FRß?)
  - **Developmental regression**
  - Short drop attacks then myoclonic epileptic seizures
  - **Ataxia**, truncal hypotonia and lower limb spasticity
  - Autistic-like behavior

  - MRI: delayed myelination and cerebellar and/or cerebral atrophy
  - MRS: low concentration of inositol and choline in the cerebral white matter

Cario et al;. Neurology 2009
Steinfeld et al; Am. J. Hum. Genet. 2009

Folate receptor alpha (Frα) deficiency

- Biochemical findings

Folate (Serum)	5MTHF (CSF)	Blood count	Homocysteine (Plasma)	Methionine (Plasma)	MRI/CCT
normal	↓ (< 5 nM)	**normal**	**normal**	**normal**	delayed myelination, cerebellar and cerebral atrophy, low concentration of inositol and choline

- Treatment & Outcome
  - 5-formyl-THF (= folinic acid 5-10 mg/kgBW)
  - Neurological symptoms = 50-100 mg i.v. 1 x/week
  - NO Folic acid!
  - Early treatment is mandatory

	Folate (Serum)	5MTHF (CSF)	Blood count	Homocysteine (Plasma)	Methionine (Plasma)	MRI/CCT
PCFT	↓	↓ (< 5 nM)	Megaloblastic anemia	↑	↓	Cortex or basal ganglia calcification
DHFR	**normal**	↓ (< 5 nM)	Megaloblastic anemia	**normal**	**normal**	Hypomyelin-isation, thin corpus callosum, brain atrophy
MTHFR	**Variabel /↓**	↓ (< 5 nM)	**normal**	↑↑	↓↓	Periventricular demyelination, Hydrocephalus
FRα	**normal**	↓ (< 5 nM)	**normal**	**normal**	**normal**	delayed myelination, cerebellar and cerebral atrophy, low concentration of inositol and choline

Thank you!


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