NEUROTRANSMITTER DISORDERS, BH_4

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“PEDIATRIC NEUROTRANSMITTER DISEASES” IS AN UMBRELLA TERM FOR GENETIC DISORDERS THAT AFFECT THE METABOLISM OF NEUROTRANSMITTERS (SYNTHESIS AND BREAKDOWN)

EPILEPSY IN IEM

- Only a small percentage (< 2%?) of individuals with epilepsy have an IEM.
- In 20% of cases, seizures are untreatable or very difficult control because of:

– Diffuse or localized structural brain abnormality

– Epileptic encephalopathy (Lennox-Gastaut, etc.)

– IEM

- Seizures are a very common symptom in IEM:

– Major manifestation or

– One among many other problems.

– Not always refractory to AED

NEONATAL METABOLIC EPILEPTIC ENCEPHALOPATHY

- Urea Cycle Disorders
- Methylmalonic, Propionic Acidurias, etc.
- Marple Syrup Urine Disease
- Non-ketotic Hyperglycinemia
- Pyridoxine-dependant Epilepsy
- Biotinidase Deficiency
- Perinatal Hypophosphatasia
- Adenylsuccinate Lyase Deficiency
- MTHFR Deficiency
- D-/D-,L-2-Hydroxyglutaric Aciduria
- Congenital Disorders of Glycosylation
- 3-Phosphoglycerate Dehydrogenase Deficiency
- GABA-T Deficiency
- Congenital Glutamine Deficiency
- Glutamate Transporter Deficiency
- (Creatine Deficiency Disorders)

Blue indicates disorders, for which specific treatments exists.

G.F. Hoffmann: Inherited metabolic disorders presenting as epileptic encephalopathy

INFANTILE METABOLIC ENCEPHALOPATHY

- ✓ GLUT1 Deficiency
  - ✓ Urea Cycle Disorders
  - ✓ Methylmalonic, Propionic Acidurias, etc.
  - ✓ Marple Syrup Urine Disease
  - ✓ Non-ketotic Hyperglycinemia
  - ✓ Pyridoxine-dependant Epilepsy
  - ✓ Biotinidase Deficiency
  - ✓ Menke disease
  - ✓ (Canavan disease)
  - ✓ Sulphite Oxidase/ Molybdenum Cofactor Deficiency
  - ✓ Generalized Peroxisomal Disorders
  - ✓ Mitochondriopathies (especially MERRF)
  - ✓ Congenital Disorders of Glycosylation
  - ✓ Smith-Lemli-Opitz syndrome
  - ✓ Adenylsuccinate Lyase Deficiency
  - ✓ D-/D-,L-2-Hydroxyglutaric Aciduria
  - ✓ Folate Receptor Defect
  - ✓ MTHFR Deficiency
  - ✓ Creatine Deficiency Disorders
  - ✓ CAD (multifunctional enzyme complex, first steps of de novo pyrimidine biosynthesis)
- ✓ Neuronal Ceroid Lipofuscinoses (NCL)

G.F. Hoffmann: Inherited metabolic disorders presenting as epileptic encephalopathy

JUVENILE & ADULT ONSET

- Acute intermittent porphyria
- Adrenoleukodystrophy, X-linked
- GM1-gangliosidosis
- Mitochondriopathies
- Neuronal ceroid lipofuscinoses
- Niemann-Pick type C disease
- Sialidosis I

G.F. Hoffmann: Inherited metabolic disorders presenting as epileptic encephalopathy

WHICH DIAGNOSTIC TESTS? TODAY

- Amino acids in plasma/urine
- Organic acids in urine
- Acylcarnitines in plasma
- Aminoacids in plasma/CSF
- Orotic acid in urine
- Amino acids in plasma
- Neurotransmitters

INDICATIONS FOR NEXT GENERATION SEQUENCING

Panel diagnostics (out of massive parallel sequencing)

- Mitochondrial diseases
- Mental Retardation
- Epilepsy
- Dystonia
- Ataxia
- Ophtalmological disorders
- Liver failure
- **In parallel: Comprehensive metabolic investigations**

NEUROTRANSMITTER DISORDERS

METABOLISM AND/OR TRANSPORT OF

BIOGENIC AMINES

GLUTAMATE

γ-AMINOBUTYRIC ACID (GABA)

GLYCINE

http://lyrobossite.free.fr/Structure_II_L'axone.htm

THE CLINICAL DIAGNOSIS OF INHERITED NEUROTRANSMITTERS DISORDERS IS VERY DIFFICULT

AND NEEDS SPECIALIZED DIAGNOSTIC PROCEDURES FOR DETECTION

Analysis of neurotransmitter disorders requires

LUMBAR PUNCTURE

Because there is a rostrocaudal concentration gradient of biogenic amine metabolites in cerebrospinal fluid

the standard protocol is critical

Fraction I – BIOGENIC AMINE METABOLITES / 5-MTHF (0,5 ml of CSF)
Fraction II – AMINO ACIDS (1 ml of CSF)
Fraction III – ROUTIN BIOCHEMICAL ANALYSIS (1-2 ml of CSF)
Fraction IV - GABA (1 ml of CSF)
Fraction V - PTERIN (1 ml of CSF)

MONOAMINES

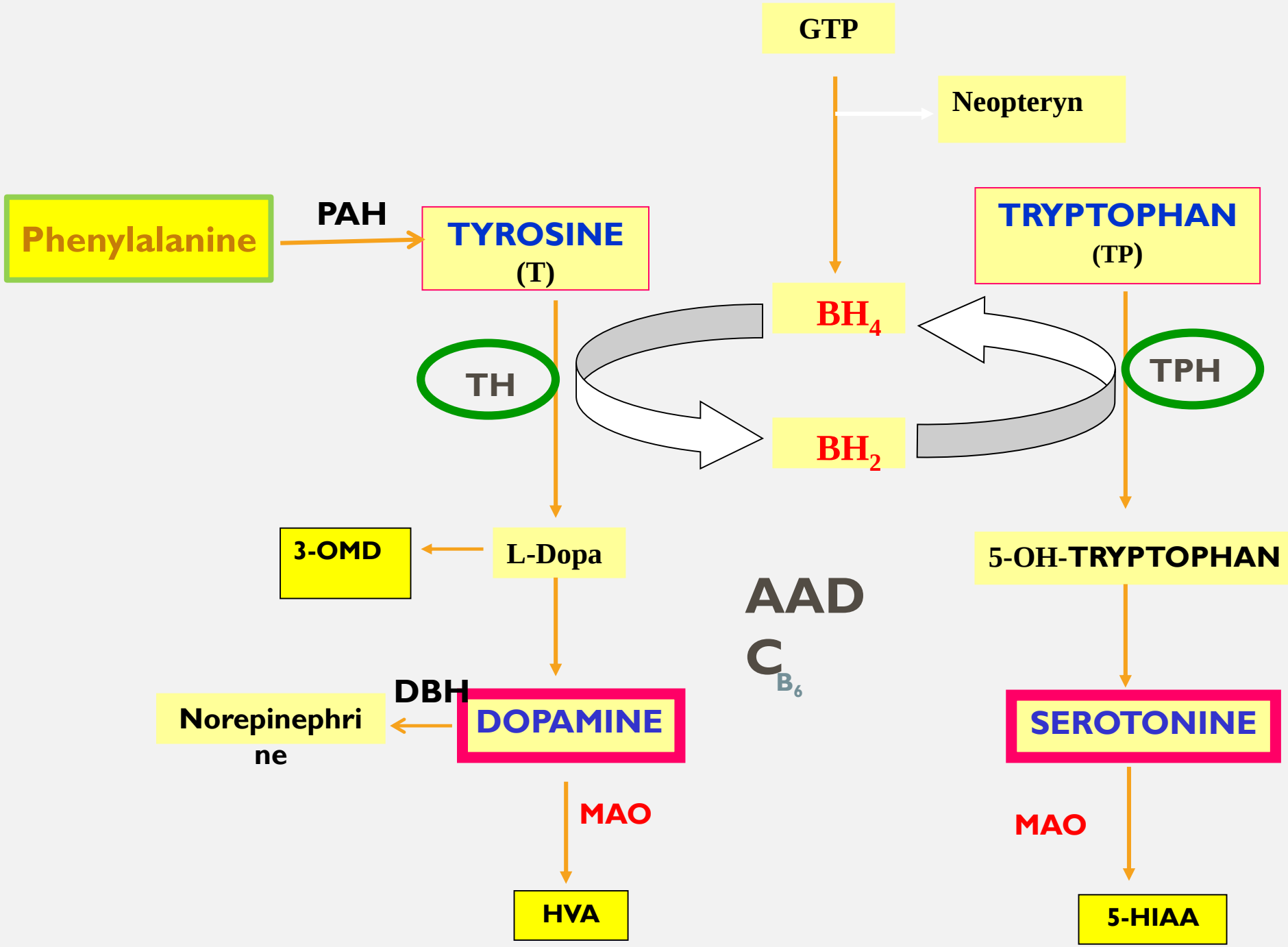
↓

Biogenic amines

↓

CATECHOLAMINES: DOPAMINE + NOREPINEPHRINE

SEROTONIN


GTP
Neopteryn
Phenylalanine
PAH
TYROSINE
(T)
TRYPTOPHAN
(TP)
BH4
TH
TPH
BH2
3-OMD
L-Dopa
5-OH-TRYPTOPHAN
AAD
CB6
DBH
Norepinephrine
DOPAMINE
SEROTONINE
MAO
MAO
HVA
5-HIAA

INHERITED DISORDERS
AFFECTING MONOAMINES METABOLISM

or

TETRAHYDROBIOPTERIN DEFICIENCY

and

INHERITED DISORDERS AFFECTING MECHANISMS CONTROLLING NEUROTRANSMISSION

cause syndromes of

MONOAMINE NEUROTRANSMITTER DEFICIENCY

with

ABNORMAL PATTERN OF MONOAMINE METABOLITES

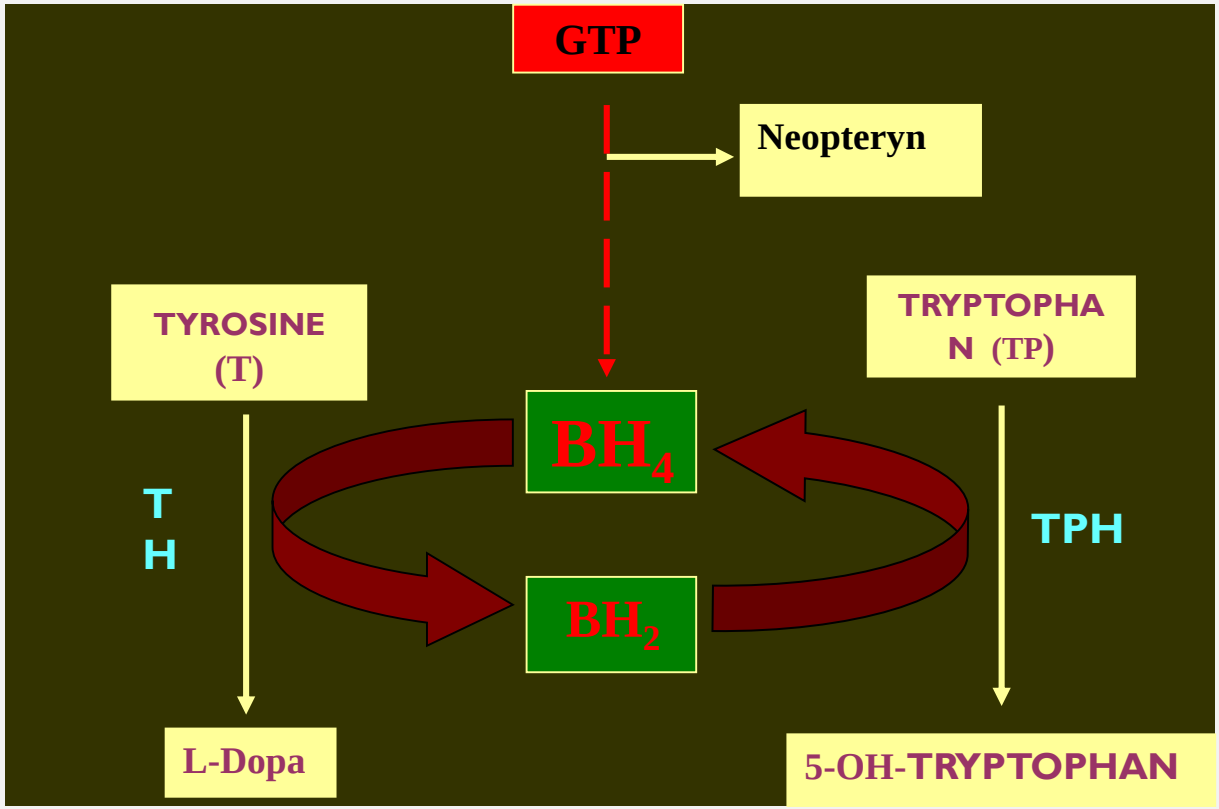
IN CEREBROSPINAL FLUID

REFERENCE VALUES

	0- 6 m	6 – 12m	1 – 4 yrs	> 4 yrs
HVA [nmol/L]	300 - 1000	300 - 1000	200 - 800	100 - 600
5-HIAA [NMOL/L]	300 - 1000	200 - 800	100 - 600	< 50
3-OMD [NMOL/l]	100 - 300	< 100	<50	<50

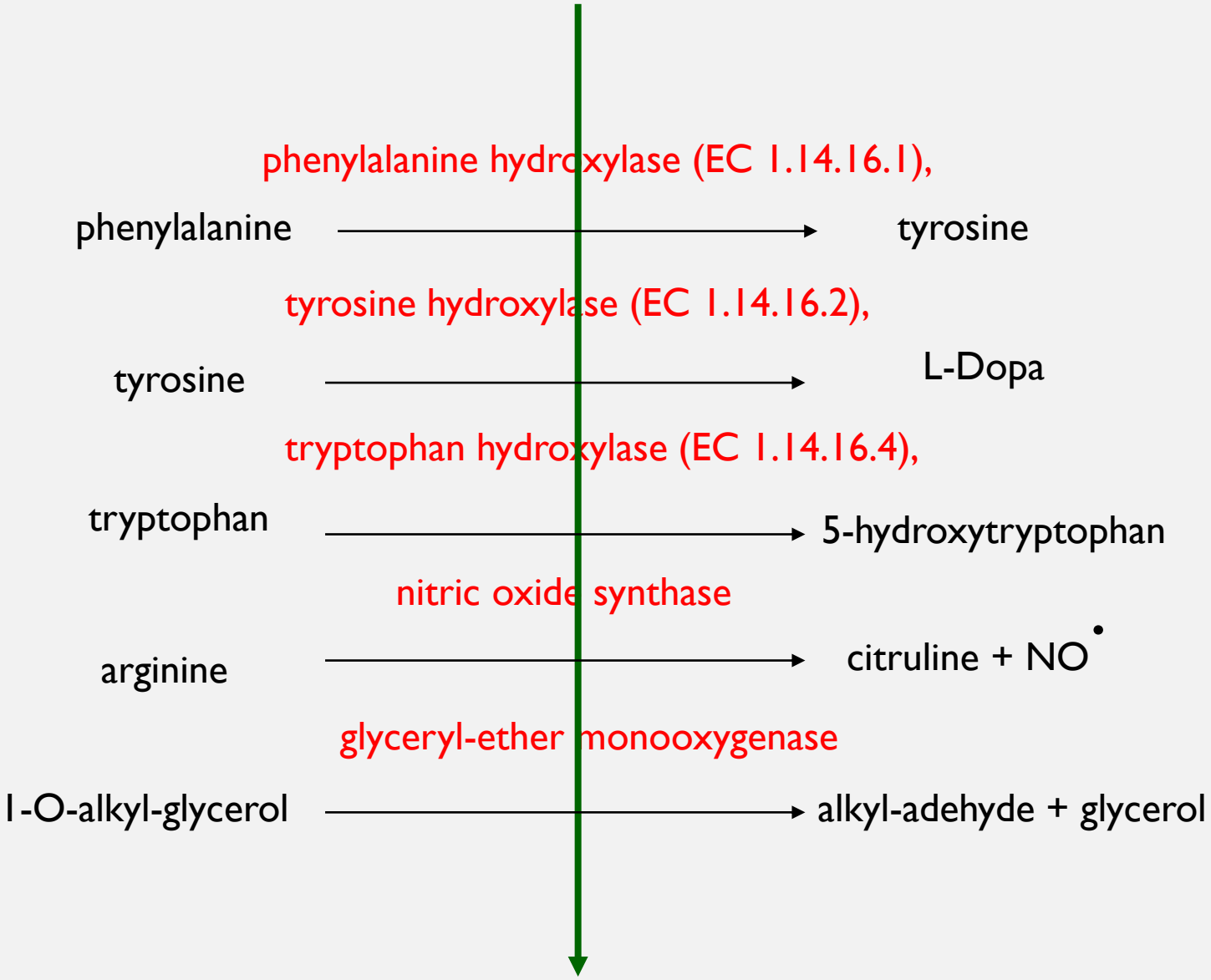
SYNTHESIS OF THE NEUROTRANSMITTERS CAN BE SEVERELY COMPROMISED WHEN THERE ARE DEFECTS AFFECTING THE ENZYMES INVOLVED

BH_4



TETRAHYDROBIOPTERIN (BH_4)

IS THE COFACTOR FOR



QUINONOID DIHIDROBIOPTERIN ($Q\text{-}BH_2$)

TETRAHYDROBIOPTERIN IS ALSO COFACTOR FOR THE PHENYLALANINE HYDROXYLASE IN THE LIVER

DEFECTS OF TETRAHYDROBIOPTERIN METABOLISM
ARE IDENTIFIED
BECAUSE OF THE PRESENCE OF HYPERPHENYLALANINEMIA
FOLLOWING NEWBORN SCREENING

THESE DEFECTS MAY PRESENT PHENOTYPICALLY
WITH OR WITHOUT
HYPERPHENYLALANINEMIA

CLINICAL SYMPTOMS
ARGTPCH, PTPS, AND DHPR DEFICIENCIES

Neonatal period (hyperphenylalaninemia)

- poor sucking,
- decreased spontaneous movements,
- “floppy baby”

ARGTPCH, PTPS, AND DHPR DEFICIENCIES

Infancy and childhood

- disturbance of tone and posture
- abnormal movements
- hypersalivation and swallowing difficulties
- mental retardation
- convulsions (grand mal or myoclonic attacks),
- drowsiness,
- irritability
- recurrent hyperthermia without infections
- diurnal fluctuation

ADGTPCH, SR

without hyperphenylalaninemia

- dystonia (lower limbs, trunk, arms, neck)
- parkinsonism (associated with tremor, rigidity, bradykinesia)
- oculogyric crises (only SR)
- psychomotor retardation (only SR)

MRI of the brain – normal
mild cerebral atrophy

EEG – normal
epileptiform potentials

IN SOME NEUROLOGICAL DISORDERS SECONDARY ABNORMALITIES OF MONOAMINES METABOLITES PATTERN ARE OBSERVED (HVA and 5-HIAA)

the group of patients with low biogenic amine

metabolites values in CSF

Lesch–Nyhan disease

Alexander disease

mitochondrial encephalopathies

pontocerebellar hypoplasia

other encephalopathies

Patients with basal ganglia involvement did not manifest lower values of neurotransmitters

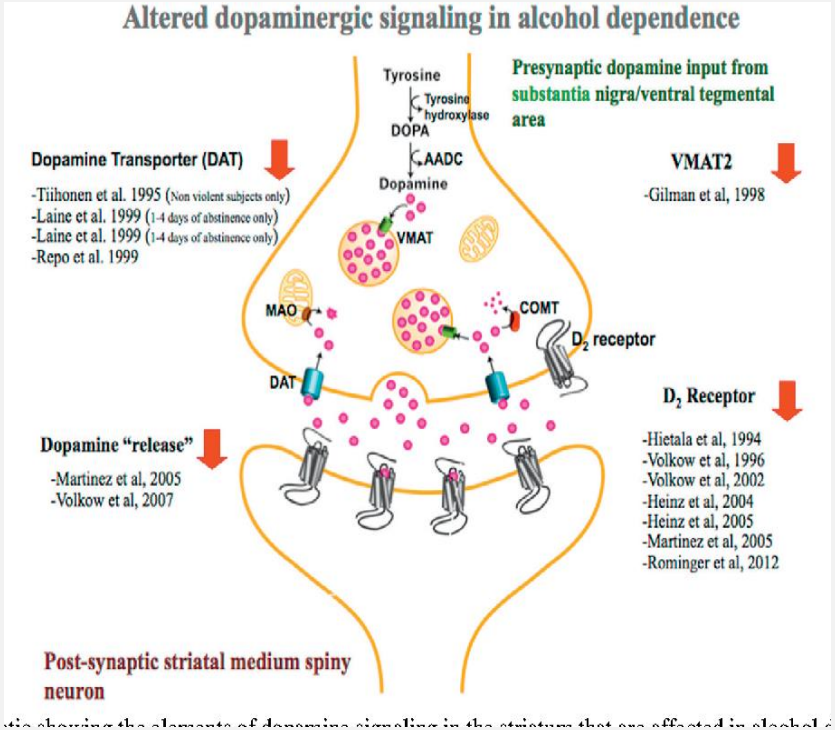
García-Cazorla A. and all.; *Developmental Medicine & Child Neurology* 2007, 49: 740–744

- TH is responsible for the synthesis of l-dopa, a precursor of catecholamines, which can be methylated to 3-OMD and its final product - vanillyllactic acid (VLA) or decarboxylated to dopamine;

- Dopamine is stored in presynaptic vesicles and then released into the synaptic cleft;

- The complex process is regulated by transporters that play a key role in dopaminergic neurotransmission

- The biochemical diagnosis of THD is based only on the analysis of AB metabolites in CSF and genetic tests



CEREBRAL FOLATE DEFICIENCY

The presence of folate deficiency in the central nervous system in the presence of normal peripheral folate constitutes the syndrome of cerebral folate deficiency (CFD).

CFD can be secondary to:

- drug-induced folate deficiency,
- DHPR deficiency,
- 3-phosphoglycerate dehydrogenase deficiency,
- AADC deficiency.

Folate is an essential cofactor in DNA synthesis and methylation reactions and is a critical determinant of embryonic CNS development. In its various forms, folic acid participates in the synthesis of:

- purines and pyrimidines,
- the metabolism of serine, histidine, methionine, homocysteine and glycine.

CEREBRAL FOLATE DEFICIENCY (CFD) IS DEFINED AS ANY NEUROLOGICAL SYNDROME ASSOCIATED WITH A LOW CEREBROSPINAL FLUID (CSF) CONCENTRATION OF 5-METHYLTETRAHYDROFOLATE (5MTHF) IN THE PRESENCE OF NORMAL PERIPHERAL FOLATE STATUS

Reference values for 5-MTHF in CSF

	1 – 4 yrs	> 4 yrs
5-MTHF [nmol/L]	72 - 227	40 - 180

Hyland K. et all 2010

CEREBRAL FOLATE DEFICIENCY

- deceleration of head growth from the age of 4 to 6 mo
- irritability, and sleep disturbances
- delayed acquisition of neurodevelopmental milestones
- poor postural control
- cerebellar ataxia
- dyskinesias
- paraparesis with pyramidal deficits
- autistic features
- epilepsia (myoclonic-astatic seizures, absences and generalized tonic-clonic seizures)

Hyland K. et all 2010

GLYCINE ENCEPHALOPATHY

- Glycine, the simplest amino acid with a single amino and carboxyl group, may accumulate to pathological levels in a disorder of the glycine cleavage system, leading to nonketotic hyperglycinemia (NKT), or glycine encephalopathy.

Serine + Tetrahydrofolate $\xrightarrow[\text{hydroxymethyltransferase}]{\text{PLP Serine}}$ Glycine + metyltetrahydrofolate

- Defects of the glycine cleavage system are detected by a ratio of CSF to plasma glycine: N:> 0.08.

GLYCINE

- Structural amino acid
- Metabolic intermediate
- Conjugates for detoxification
- Neurotransmitter (inhibitory in spinal cord)
- Adjuvant to NMDA receptor

NONKETOTIC HYPERGLYCINEMIA

NEONATAL SEVERE

- lethargy progressing to coma
- hypotonia
- seizures
- hypoventilation, and apnea
- EEG - burst-suppression pattern
- severe mental retardation
- severe myoclonic and generalized seizure disorder
- spastic quadriplegia

NONKETOTIC HYPERGLYCINEMIA

VARIANT LATE-ONSET

- late onset in infancy or childhood
- seizures
- moderate mental retardation
- ataxia
- hyperactivity and/or chorea

CLINICAL SYMPTOMS

- developmental delay
- prominent language deficits
- hypotonia
- ataxia
- seizures
- MRI - increased signal in the globus pallidus

NON-KETOTIC HYPERGLYCINAEMIA

Treatment

- Sodium benzoate lowers plasma glycine
- Dextromethorphan / ketamine
- Anticonvulsants

Confirmatory tests

- Enzyme assay
  - Liver
  - Transformed lymphoblasts
- Mutation analysis

Prenatal diagnosis

- Enzyme assay on CVB (uncultured)
  - Sometimes equivocal
- Mutation analysis

SECONDARY HYPERGLYCINAEMIA

- Sodium valproate
- Organic acidaemias
- Pyridoxine / Pyridoxal-P dependency

PYRIDOXINE RESPONSIVE EPILEPSY

- Onset usually neonatal, maybe up to 2 yrs
- Multiple seizure types
- Usually resistant to anticonvulsants
- Seizures
- Often fetal distress, acidosis, hypotonia
- Usually dramatic response to IV pyridoxine

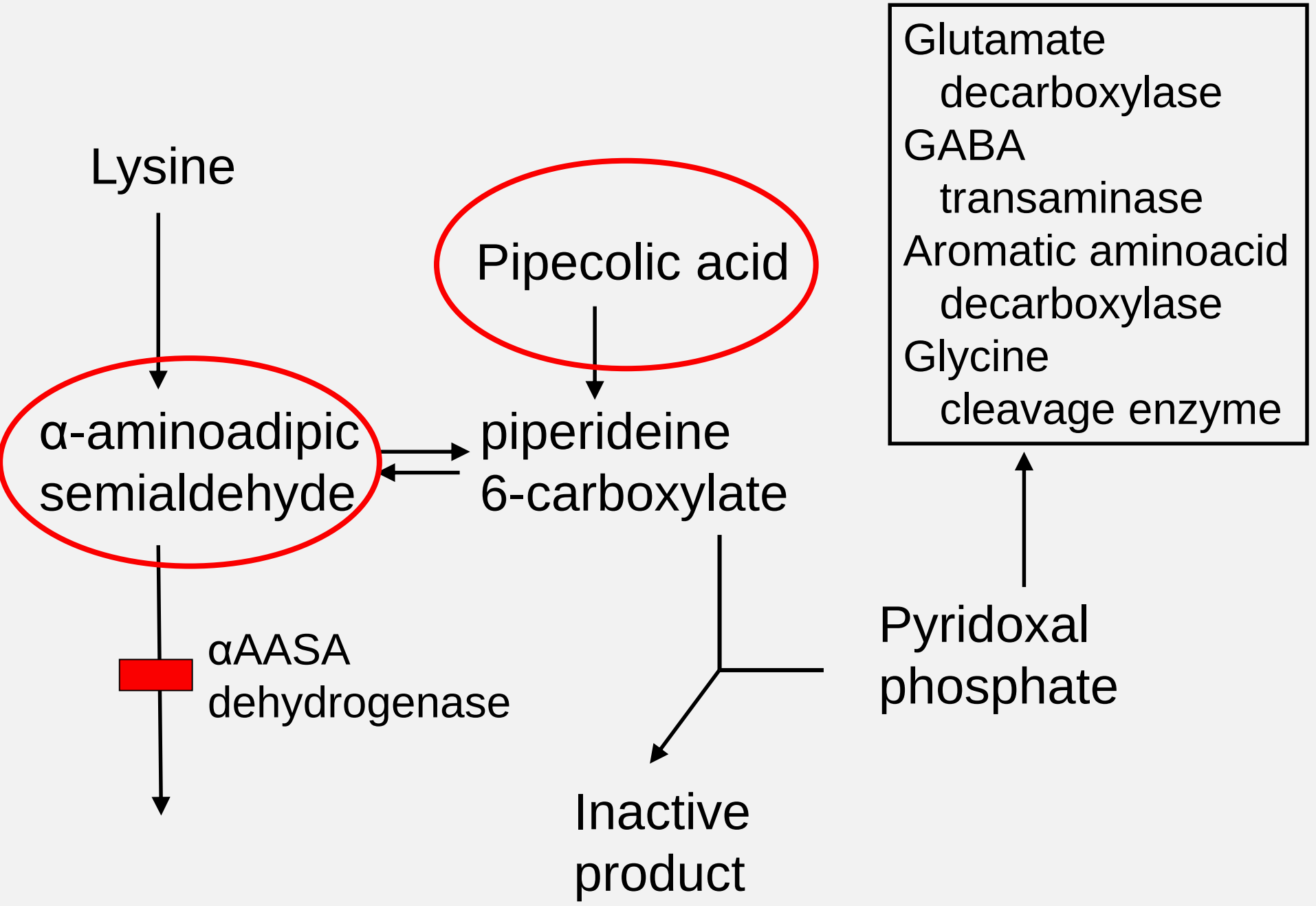
±Apnoea / hypotension for 24 hours

PYRIDOXINE RESPONSIVE EPILEPSY

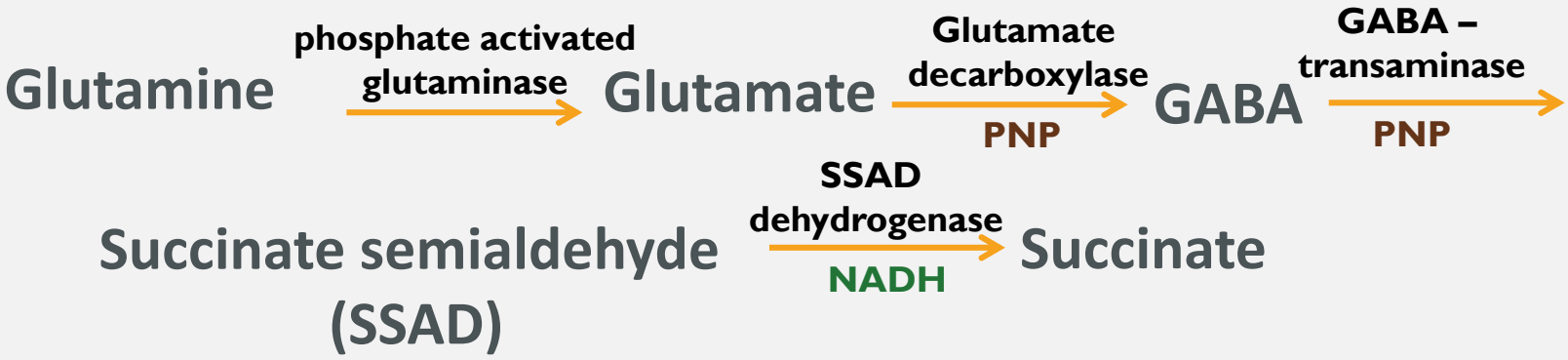
Treatment

- Pyridoxine 5-10 mg/kg/day

  (peripheral neuropathy with high doses)

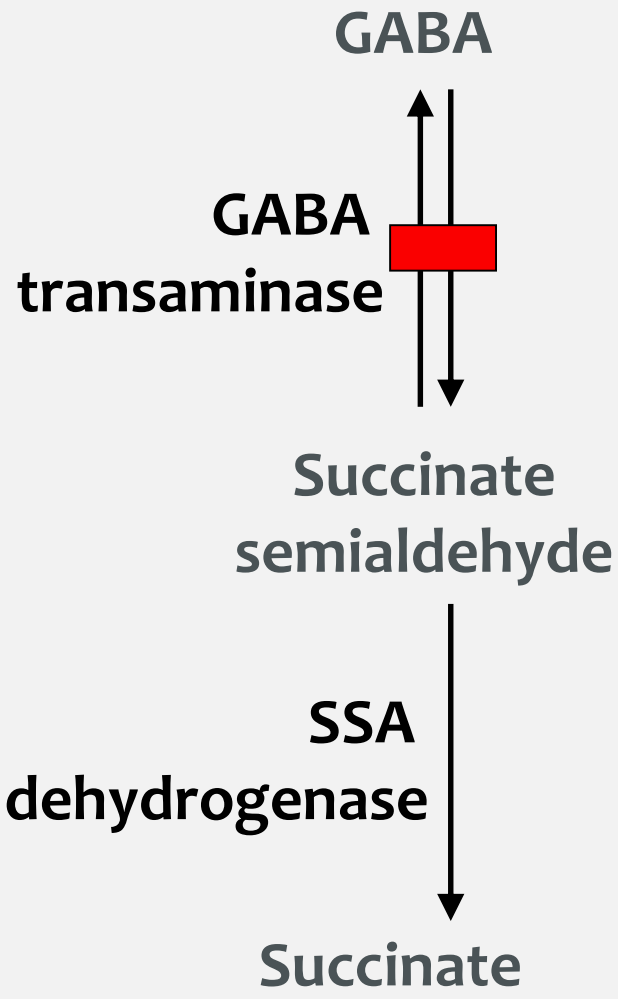

Lysine
Pipecolic acid
α-aminoadipic semialdehyde
piperideine 6-carboxylate
αAASA dehydrogenase
Inactive product
Glutamate decarboxylase
GABA transaminase
Aromatic aminoacid decarboxylase
Glycine cleavage enzyme
Pyridoxal phosphate

Metabolism of Glutamate and GABA



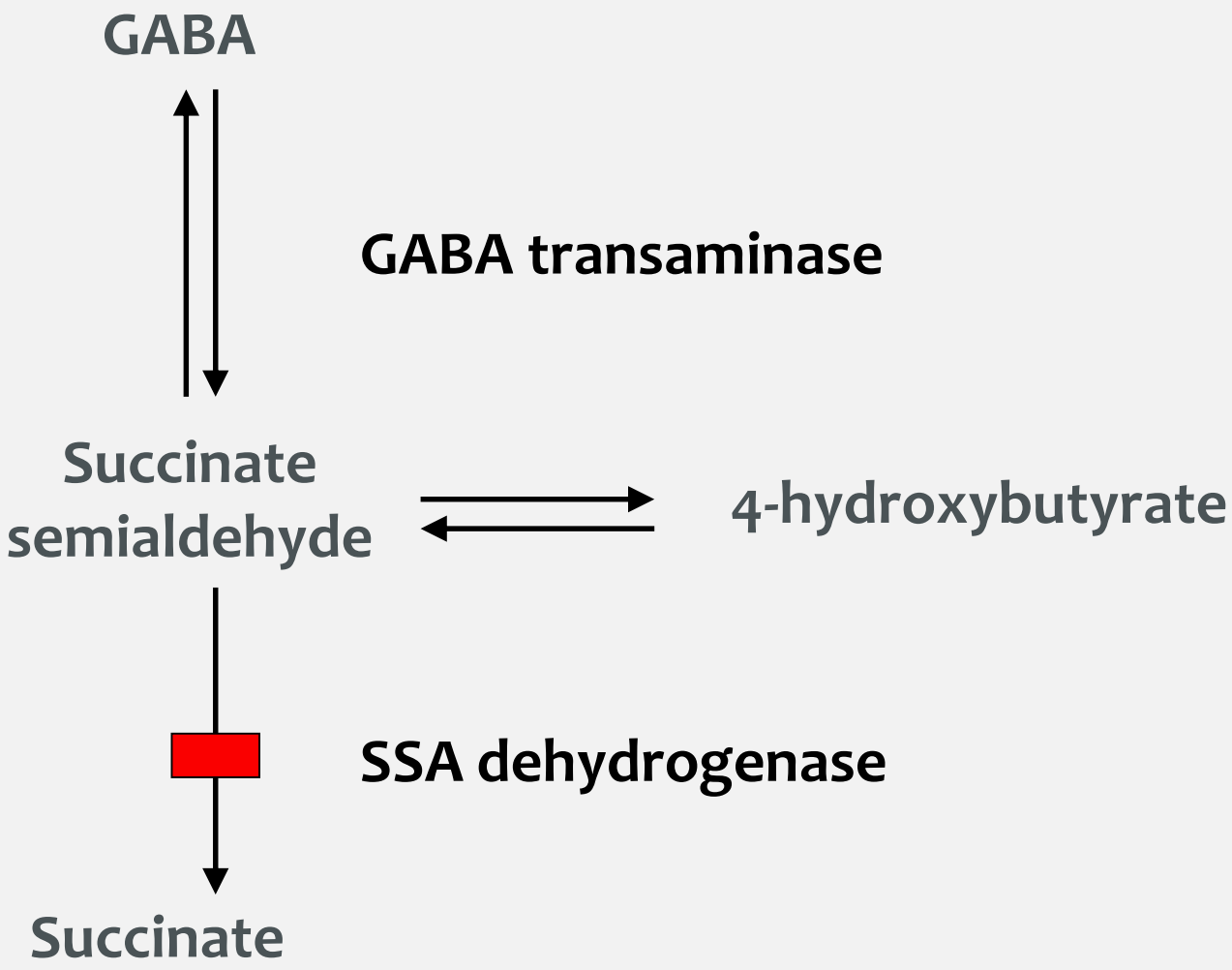
The functional status of the central nervous system (CNS) is based on a highly regulated balance between excitatory and inhibitory circuits.

Based on the fact that these neurotransmission systems to a large extent are using the two amino acids Glutamate and GABA as transmitters in excitation and inhibition, respectively.



GABA transaminase deficiency

- 2 families reported
- Seizures
- Severe developmental delay
- Diagnosis by CSF GABA


GABA
GABA transaminase
Succinate semialdehyde
4-hydroxybutyrate
SSA dehydrogenase
Succinate

SSADH DEFICIENCY

- Developmental impairment esp. speech
- Behaviour problems
- Ataxia
- Seizures
- Diagnosis: 4-hydroxybutyrate on urine OA
- Treatment: supportive

(vigabatrin ineffective)

NEUROTRANSMITTER DISORDERS: SUMMARY

- Present with seizures, developmental impairment, extrapyramidal or eye movement disorders, startle, hypotonia, sleep or behaviour problems etc
- Mostly in neonates or infants but sometimes later
- Awareness is essential
- Specific treatment is needed for some disorders
- Consider therapeutic trial (B6, Dopa)
- Some disorders detected by OAs, AAs
- Specialist analysis of CSF is required for others
- Protocol for CSF collection is important