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Pediatric Endocrinologist

Now, The patient is a 5 years old boy.

He visited in clinic in 1 year old with
abnormal movement (myoclonus and dystonia)

His mother complained about seizure like movements and treatment with phenobarbital and after 3 months adding clobazam.

Dystonia

Involuntary, slow, sustained contraction of agonist and sometimes antagonist muscles cause twisting and abnormal posturing.

The condition can affect one part of your body (**focal dystonia**), two or more adjacent parts (**segmental dystonia**), or all parts of your body (**general dystonia**)

He had been referred for working up for metabolic disorders
Metabolic assessments had done for him

acylcarnitine profile
Plasma Amino acids profile
Organic acids profile

- Almost without any significant point

Treatable metabolic seizures

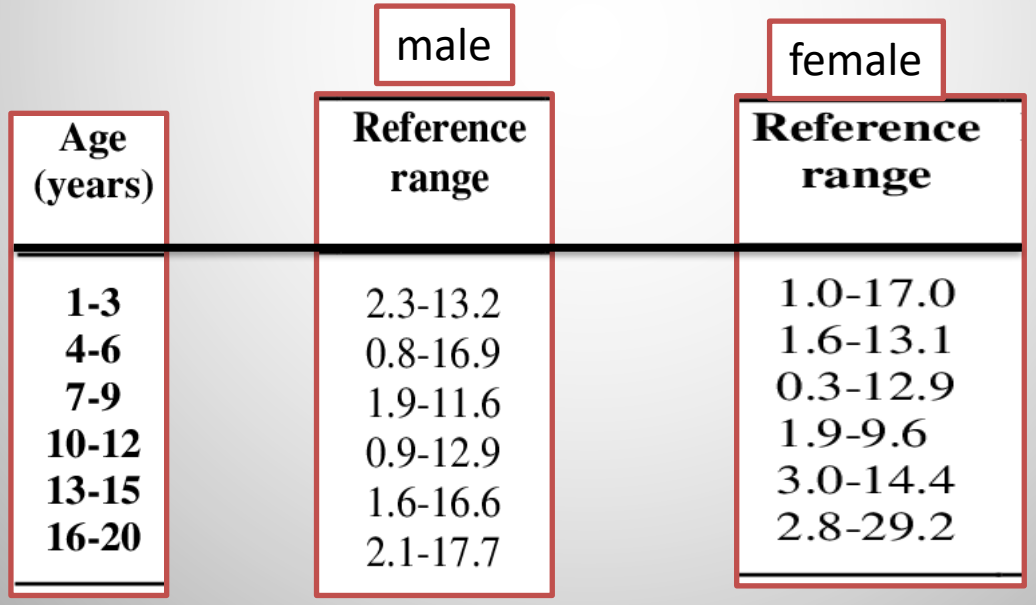
Disease Category	Intervention
Vitamin dependencies	
Pyridoxine dependency	Pyridoxine, ±folinic acid
Pyridoxal-5-phosphate dependency	Pyridoxal-5-phosphate, ±pyridoxine
Biotinidase deficiency	Biotin
Transportopathies	
GLUT-1 deficiency	Ketogenic diet
Cerebral folate deficiency	Folinic acid
Biotin thiamine responsive disorder	Thiamine, biotin
Amino or organic acidopathies	
Serine synthesis disorders	Serine and glycine
Mb-cofactor deficiency (type A)	cPMP (see text)
Cobalamin C deficiency	Cobalamin and betaine
Glutaric acidemia type I	Carnitine and protein restriction
Creatine synthesis disorders	Creatine, ornithine, and arginine restriction
Neurotransmitter disorders (BH4)	
Urea cycle disorders	Nitrogen scavengers, dialysis, and protein restriction
PTPS deficiency	BH4, monoamine precursors, and MAOIs
DHPR deficiency	Folinic acid and monoamine precursors
Glucose homeostasis disorders	
DEND	Sulfonylureas
HI-HA	Protein restriction and diazoxide
Mitochondrial disorders	
Pyruvate dehydrogenase deficiency	Ketogenic diet

Untreatable metabolic seizures

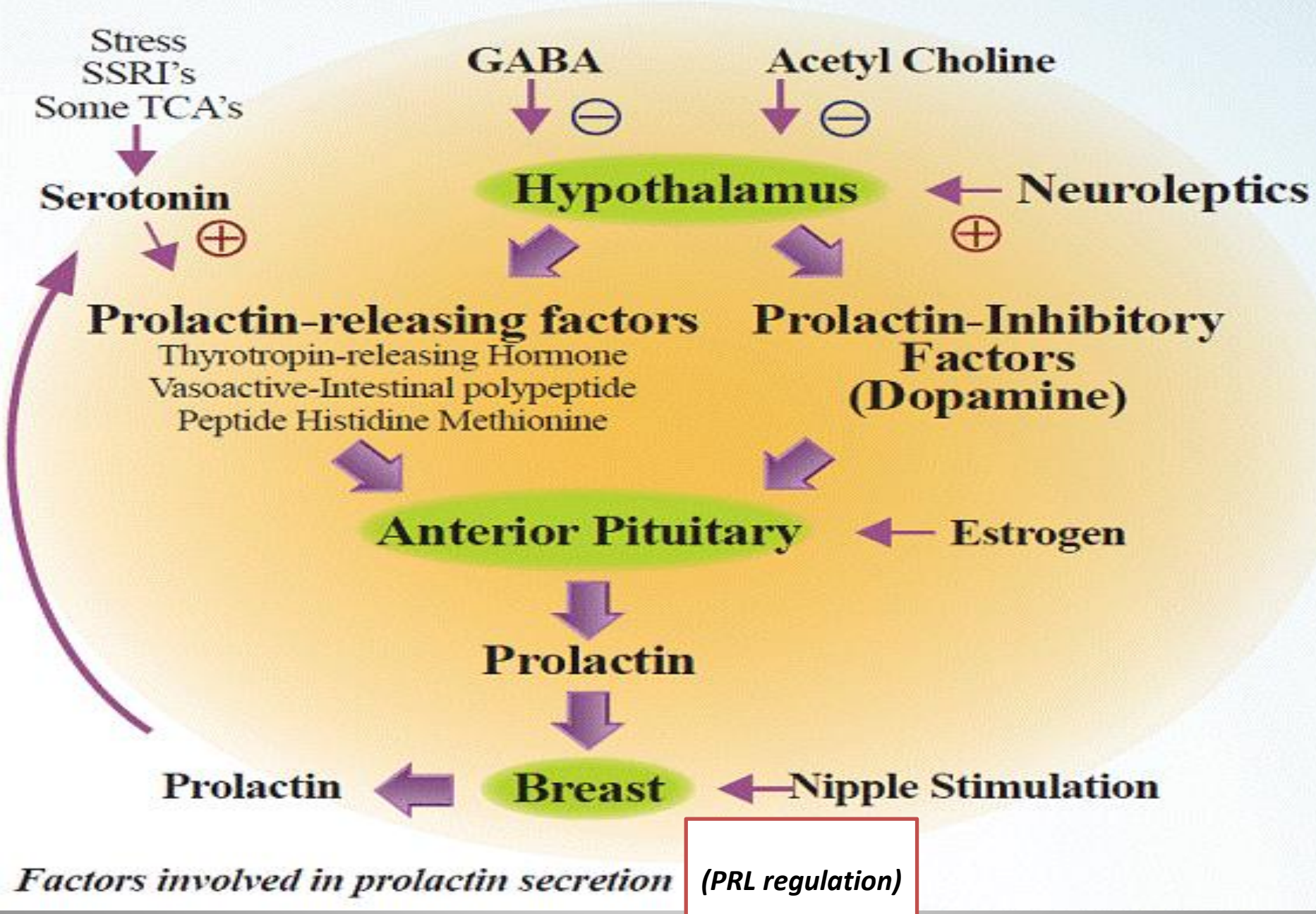
Nonketotic hyperglycinemia		Elevated CSF: plasma glycine ratio
Zellweger syndrome		Elevated VLCFA, phytanic and pristanic acids
Neonatal adrenoleukodystrophy		Elevated VLCFA, phytanic and pristanic acids
Molybdenum cofactor disease		Sulfite test in fresh urine, fibroblast studies, uric acid
Sulfite oxidase deficiency		Sulfite test in fresh urine, fibroblast studies
GABA transaminase deficiency		GABA in CSF
Adenylosuccinate lyase deficiency		Modified Bratton–Marshall test, purines in urine
Respiratory chain disorders and PDHc deficiency		Lactate elevation in CSF, plasma and urine, activity of respiratory chain enzymes and PDHc in muscle and fibroblasts
Glutamate transporter deficiency		Glutamate oxidation in fibroblasts, genetic studies (sequencing of *SLC25A22*)
Congenital glutamine deficiency		Extremely low levels of plasma, urine, and CSF glutamine
Neonatal form of neuronal ceroid lipofuscinosis		Cathepsin D activity
Asparagine synthetase deficiency[a]		No biomarker. ASNS gene
Hyperprolinemia due to *SLC25A22* mutations		High plasma proline, low glutamate in the CSF, accumulation of lipids in fibroblasts

Prolactin checking

PRL=23ng/ml

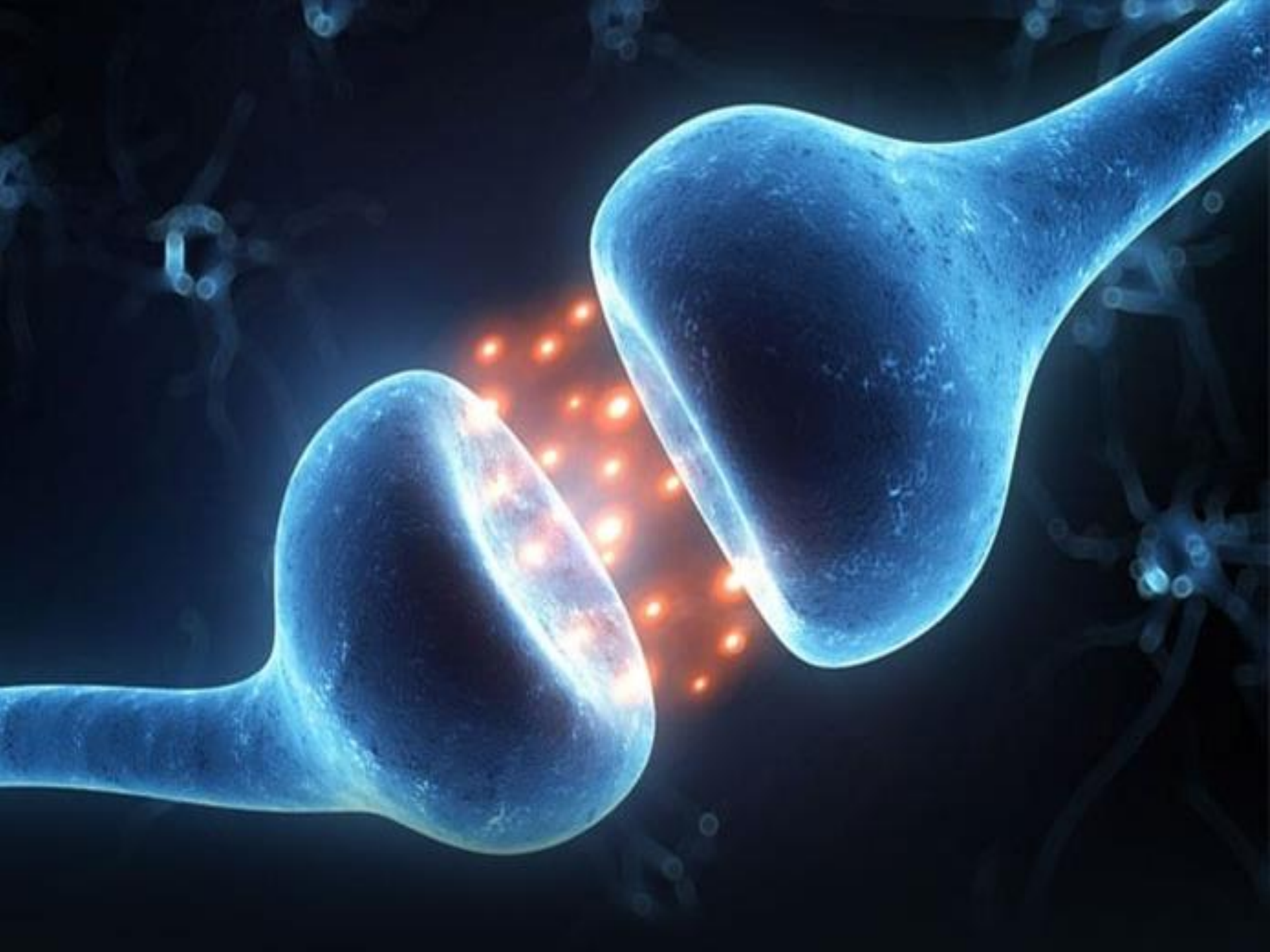


Age (years)	male Reference range	female Reference range
1-3	2.3-13.2	1.0-17.0
4-6	0.8-16.9	1.6-13.1
7-9	1.9-11.6	0.3-12.9
10-12	0.9-12.9	1.9-9.6
13-15	1.6-16.6	3.0-14.4
16-20	2.1-17.7	2.8-29.2

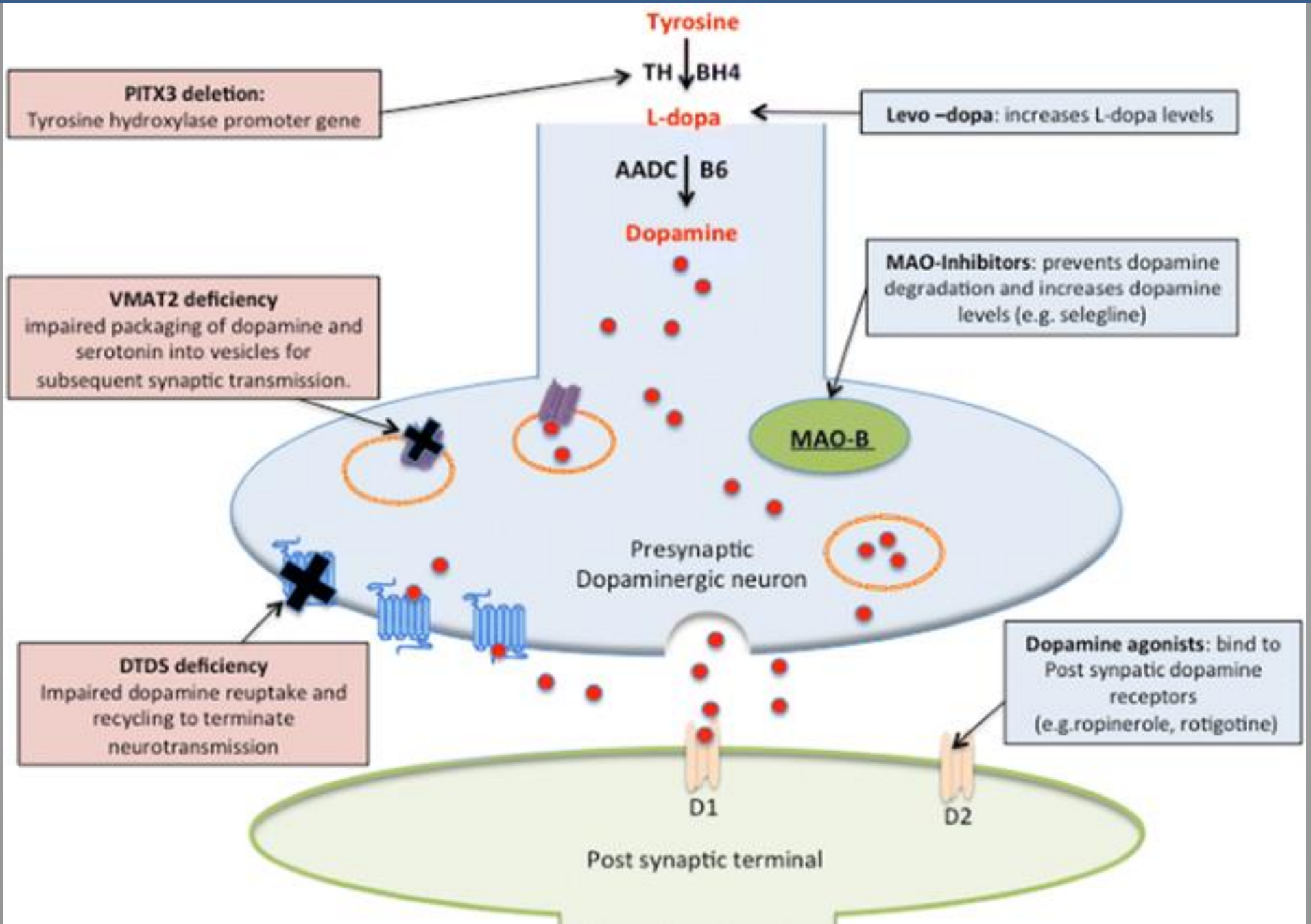


Factors involved in prolactin secretion

(PRL regulation)



Schemaic diagram of neurotransmitter disorders



Neurotransmitter disorders

heterogeneous group of inherited neurometabolic disorders caused by the defects in the synthesis, degradation and transport of neurotransmitters including:

-**Monoamines neurotransmitters (amines)**

(catecholamines (dopamine& norepinephrine & epinephrine)

and

Indolamines (serotonin & histamin)

-Amino acides

(glycine& aspartate & glutamate & gamma-amino butyric acid)

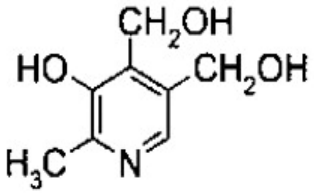
-**esters**

acetylcholine

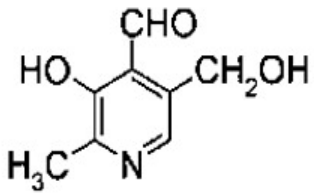
Neurotransmiter disorders

Primary disorders

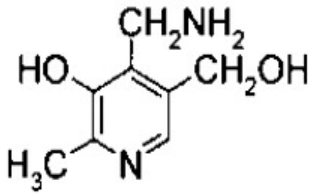
- Cofactor deficiency
  - VITAMIN B6
    - PNPO deficiency
    - Pyridoxine -dependent epilepsy
  - BH4
    - Phenylalanine normal
      - Autosomal dominant GTP-CH I deficiency
      - Sepiapterin reductase deficiency
    - Phenylalanine abnormal
      - Autosomal recessive GTP-CH I deficiency
      - PTPS deficiency
      - Dihydropteridine reductase deficiency
- enzyme deficiency
  - Tyrosine hydroxylase
  - AADC
  - Dopamine β-hydroxylase
  - Monoamine oxidase
- PITX3 (*TH* promoter)
- Defective Transport And or reuptake
  - DAT
    - DAT deficiency syndrome
- Defective Vesicle Formation And or packaging
  - VMAT2
    - Brain dopamine –serotonin vesicular transport disease



Pyridoxine (PN)



Pyridoxal (PL)



Pyridoxamine (PM)

pyridoxal kinase(PK)

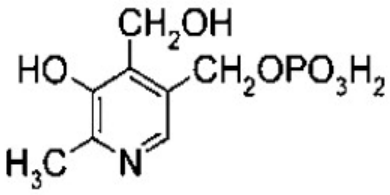
Phosphatase

pyridoxal kinase(PK)

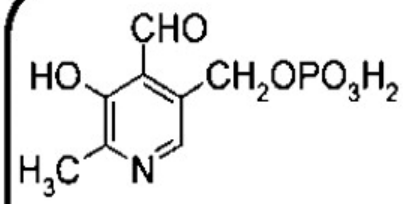
Phosphatase

pyridoxal kinase(PK)

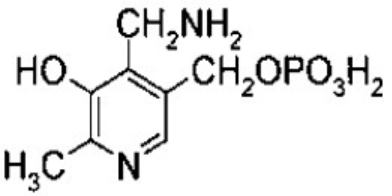
Phosphatase



Pyridoxine phosphate (PNP)



Pyridoxal phosphate (PLP)



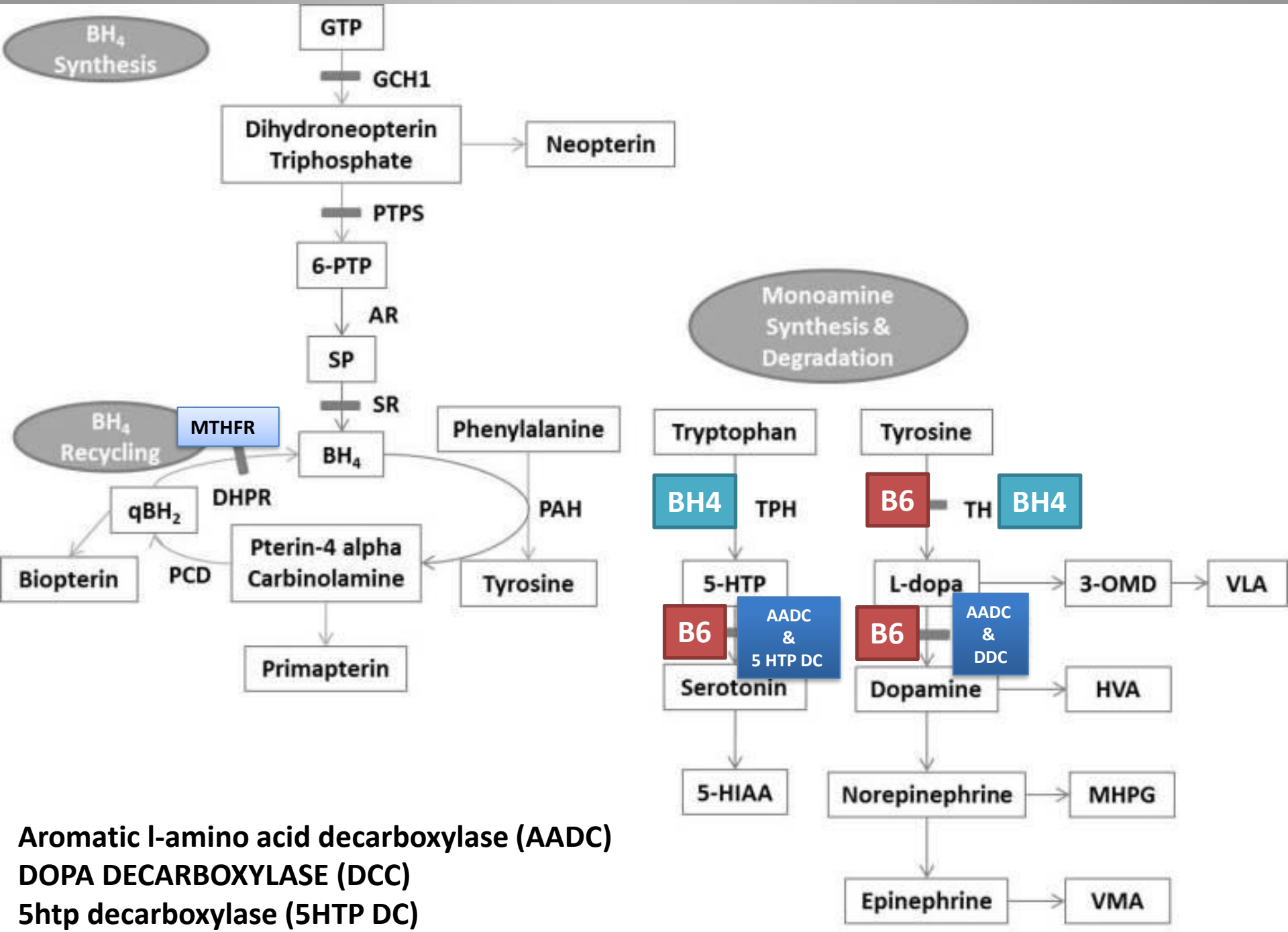
Pyridoxamine phosphate (PMP)

RIBOFLAVINE (COFACTOR)V

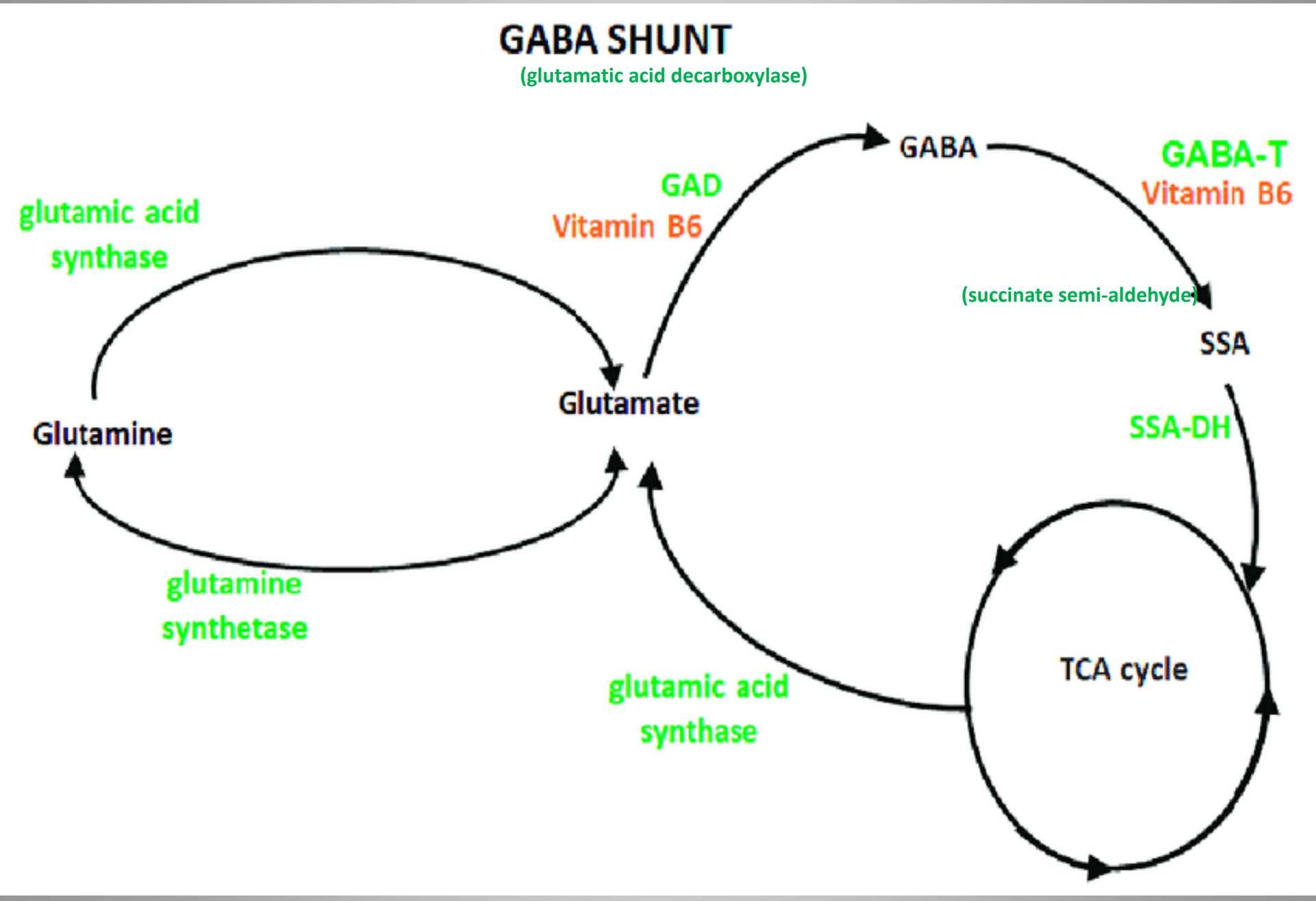
Pyridox(am)ine phosphate oxidase (PNPO)

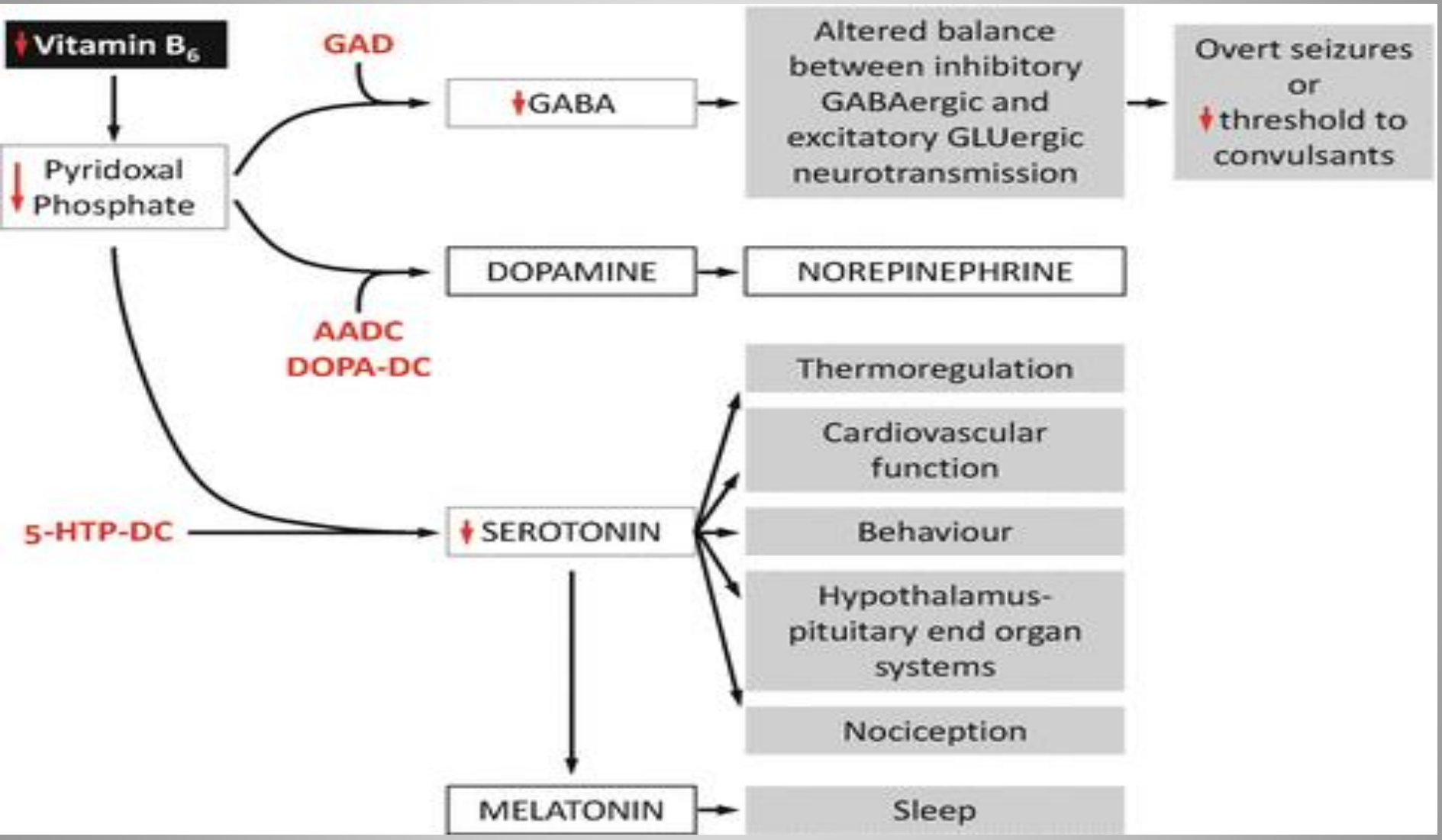
RIBOFLAVINE (COFACTOR)V

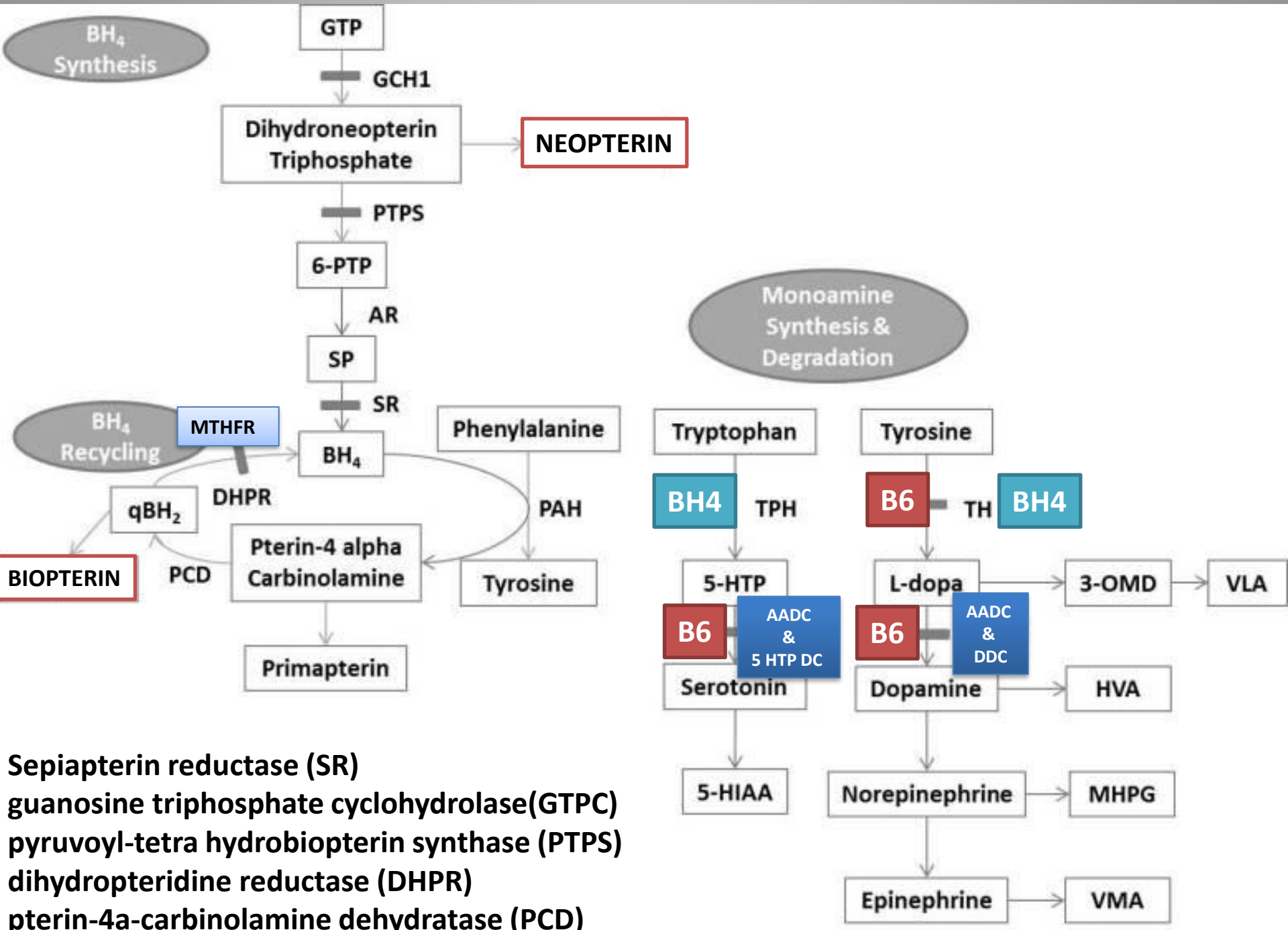
Pyridox(am)ine phosphate oxidase (PNPO)



Aromatic l-amino acid decarboxylase (AADC)
DOPA DECARBOXYLASE (DCC)
5htp decarboxylase (5HTP DC)


GABA SHUNT
(glutamatic acid decarboxylase)
GABA
GABA-T
Vitamin B6
GAD
Vitamin B6
glutamic acid
synthase
(succinate semi-aldehyde)
SSA
Glutamate
Glutamine
SSA-DH
glutamine
synthetase
TCA cycle
glutamic acid
synthase


↓Vitamin B6
GAD
↓GABA
Altered balance between inhibitory GABAergic and excitatory GLUergic neurotransmission
Overt seizures or ↓threshold to convulsants
↓ Pyridoxal Phosphate
DOPAMINE
NOREPINEPHRINE
AADC
DOPA-DC
Thermoregulation
Cardiovascular function
5-HTP-DC
↓SEROTONIN
Behaviour
Hypothalamus-pituitary end organ systems
Nociception
MELATONIN
Sleep



Sepiapterin reductase (SR)
guanosine triphosphate cyclohydrolase(GTPC)
pyruvoyl-tetra hydrobiopterin synthase (PTPS)
dihydropteridine reductase (DHPR)
pterin-4a-carbinolamine dehydratase (PCD)

Diagnostic Tests

Diagnostic protocols and interpretation of results are as follows:

Urine or blood pterin analysis and blood DHPR enzyme activity assay

All infants found to have **HPA on newborn screening** should have blood DHPR and urine or blood pterin analysis.

Interpretation of results of investigations in disorders of biopterin metabolism

Deficiency	Blood PHE µmol/L	Blood or urine biopterin	Blood or urine neopterin	Blood or urine primapterin	CSF 5HIAA and HVA	blood DHPR activity
PAH	>120	↑	↑	–	N	N
GTPCH	90–1200	↓↓	↓↓	–	↓	N
PTPS	240–2500	↓↓	↑↑	–	↓	N
DHPR	180–2500	↓↓	N or ↑	–	↓	↓
PCD	180–1200	↓	↑	↑↑		N

Unlike other disorders of tetrahydrobiopterin deficiency, sepiapterin reductase deficiency is not associated with elevated phenylalanine levels and, consequently, will not be detected upon newborn screening.

dominant form of GTPCH deficiency
and
sepiapterin reductase (SR) deficiency

also **lead to CNS amine deficiency**
But
are **associated with normal blood PHE**