Great Ormond Street Hospital for Children NHS Foundation Trust

University College London Hospitals NHS Foundation Trust

# CSF Neurotransmitters Disorders (Dopamine and Serotonin)


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NHS England

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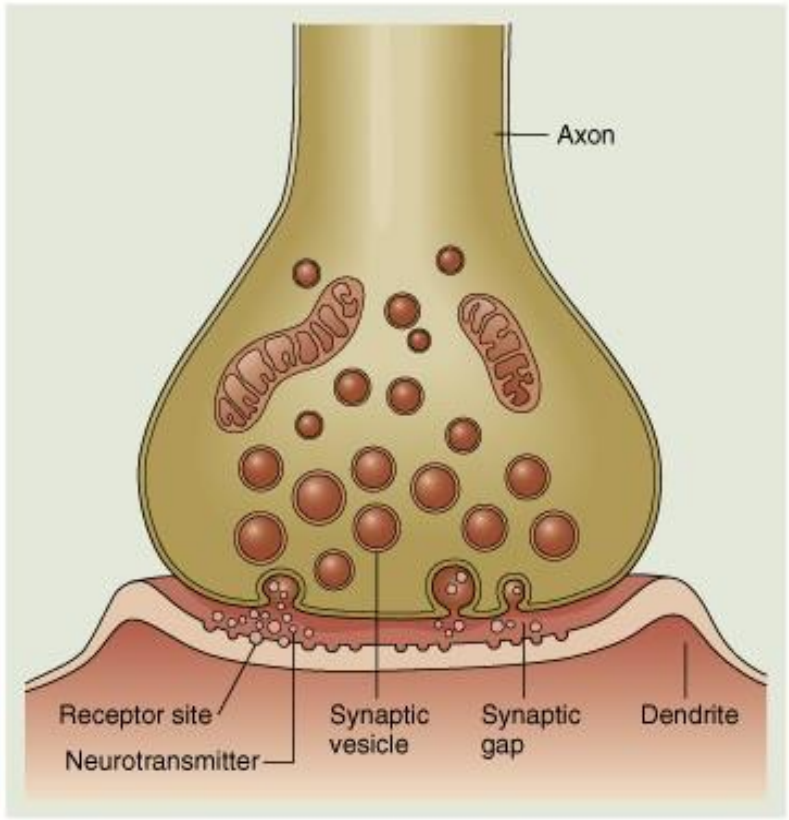
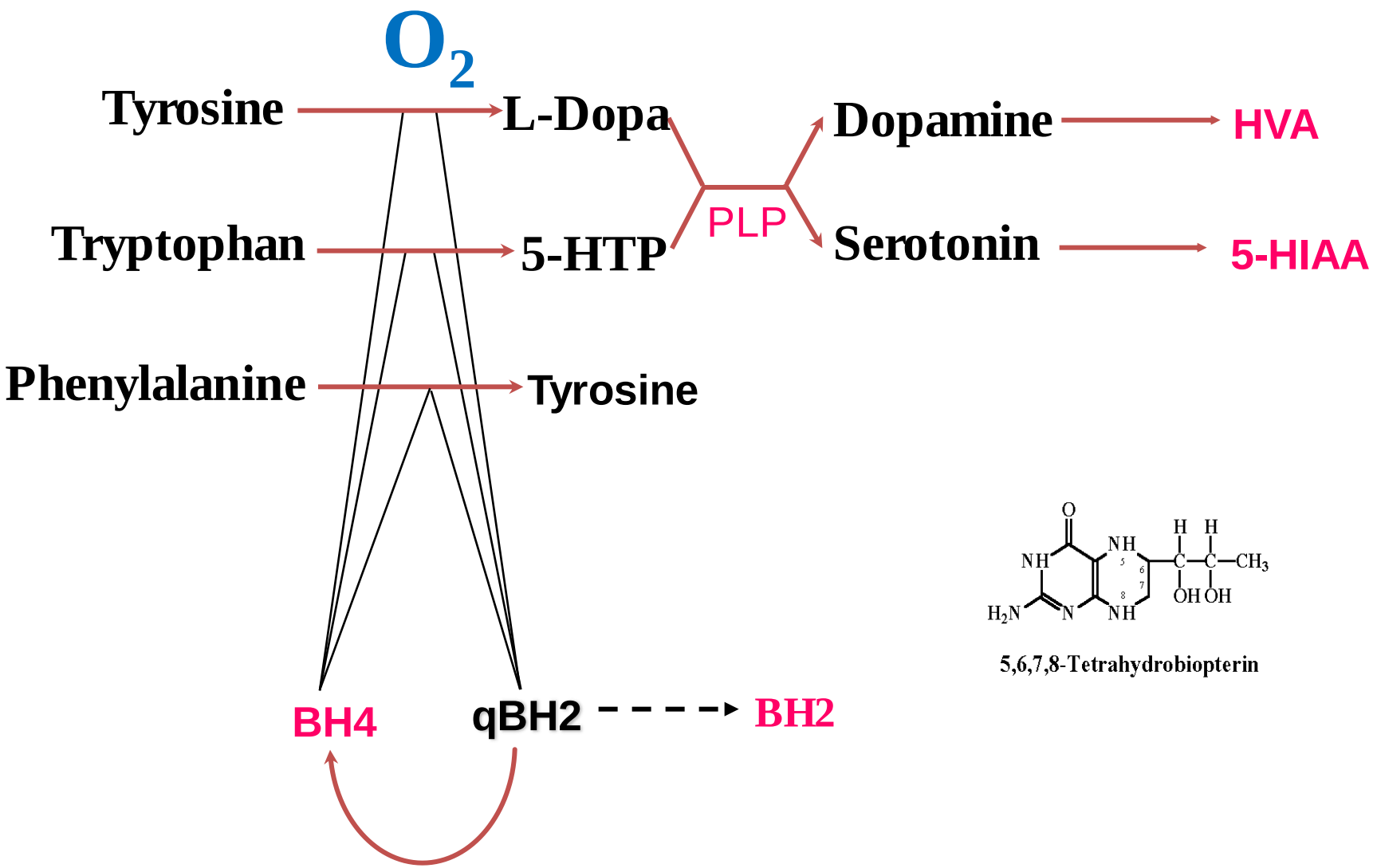
# Chemical Neurotransmission

- Neurotransmitters – *Substances that upon release from nerve terminals, act on receptor sites at post-synaptic membranes to produce either excitation or inhibition of the target cell*









5,6,7,8-Tetrahydrobiopterin

# Clinical Symptoms

**DOPAMINE DEFICIENCY**

- Movement disorders
- Dystonia
- Parkinsonism
- Chorea, hyperkinesia
- Myoclonus
- Ocular symptoms
- Abnormal peripheral tone
- Abnormal neurodevelopment
- Microcephaly
- Bulbar dysfunction
- Epilepsy

**NOREPINEPHRINE/EPINEPHRINE**

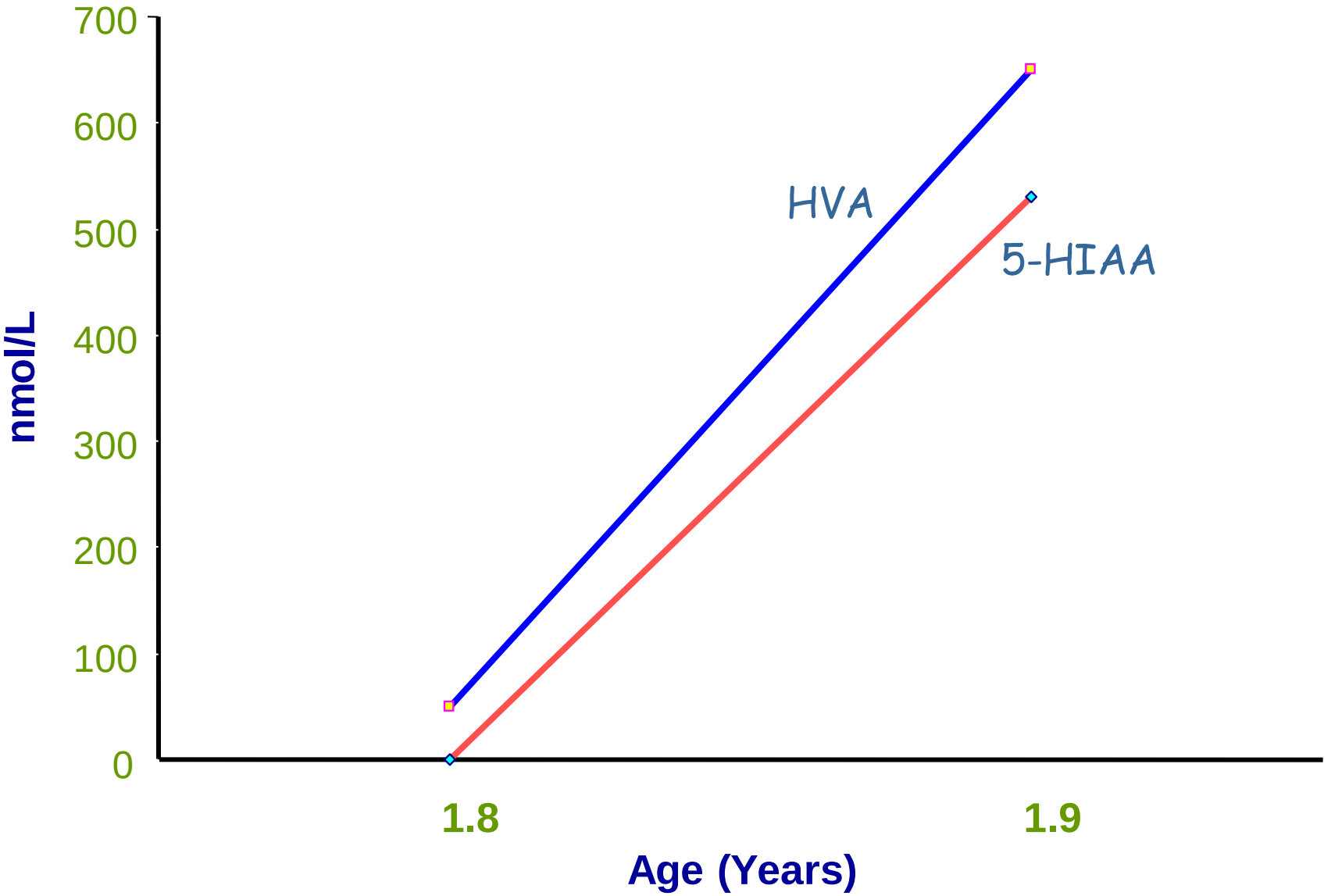
- Autonomic dysfunction
- Sleep disturbance
- Temperature instability

**SEROTONIN DEFICIENCY**

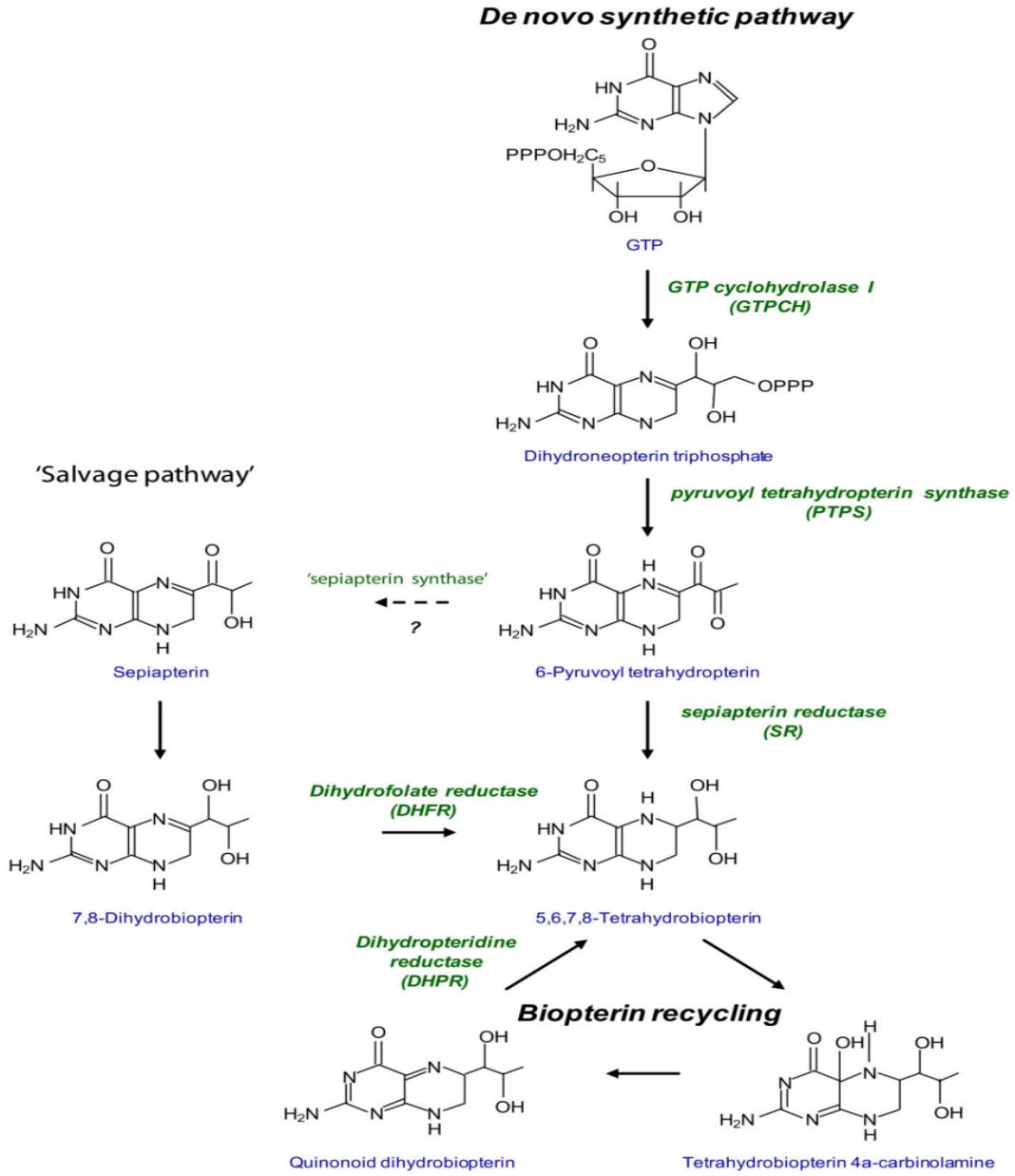
- Temperature instability
- Sweating
- Mood
- Movement disorders

*Kurian et al 2011*

# DHPR Deficiency – Response to Treatment



# Tetrahydrobiopterin Metabolism




*Nitric Oxide*. 2011 August 01; 25(2): 81–88. doi:10.1016/j.niox.2011.04.004.

# Disorders of BH4 metabolism

**With Hyperphenylalaninemia**

GTP cyclohydrolase I (GTPCH) deficiency;

Phe = 90-1200 umol/L

*6-Pyruvoyl-tetrahydropterin synthase (PTPS) deficiency;*

Phe = 240-2500 umol/L

Dihydropteridine reductase (DHPR) deficiency;

Phe = 180-2500 umol/L

Pterin-4a-carbinolamine dehydratase (PCD) deficiency;

Phe = 180-1200 umol/l

**Without hyperphenylalaninemia**

*Sepiapterin reductase deficiency (SR).*

*Dopa-responsive dystonia (DRD) due to GTPCH deficiency*;

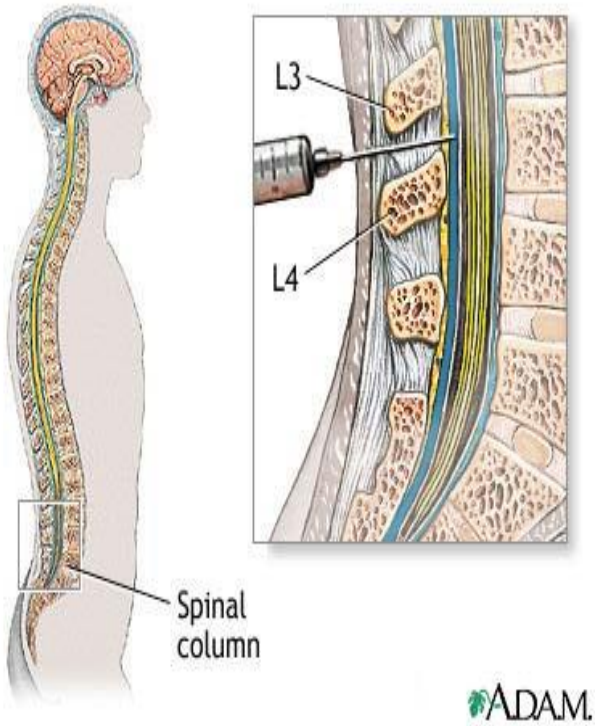
# CSF – Sample Requirements

**(Lab Specific – Check)**

- *Tube 1* 0.5ml **HVA & 5-HIAA**
- *Tube 2* 0.5ml **5-MTHF & PLP**
- *Tube 3* 1.0ml **Pterins**

(DTE/DETAPAC)

Rostro-caudal Gradient




***Collect at bedside and freeze immediately (not the form !)***

***Age related reference ranges***

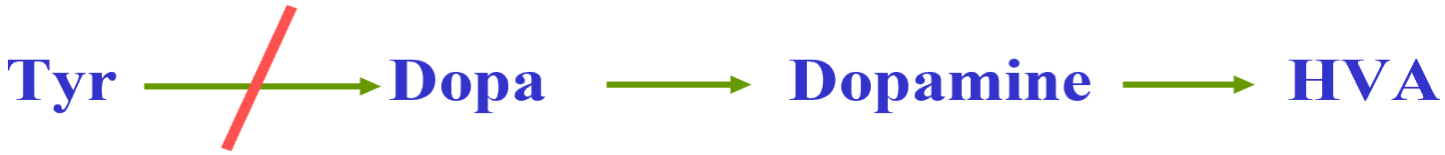
***Clinical Details and Drugs***

ERNDIM
QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

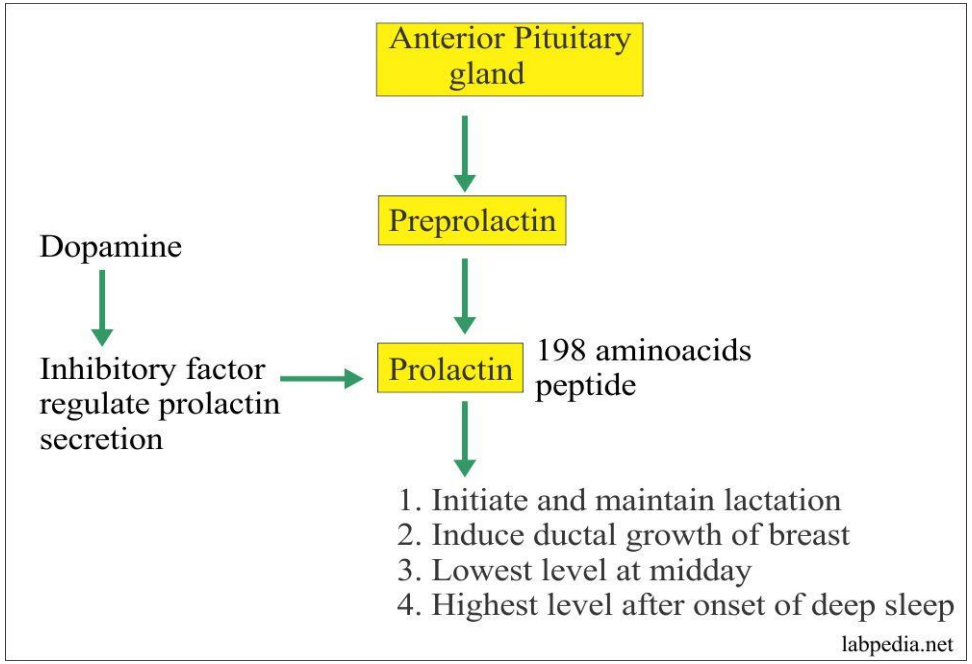
# Tyrosine Hydroxylase Deficiency

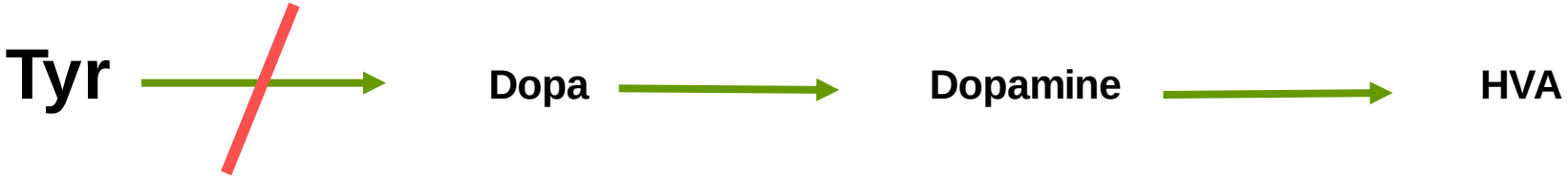
- Parkinsonian, ptosis, drooling, myoclonic jerks, severe head lag and truncal hypotonia.

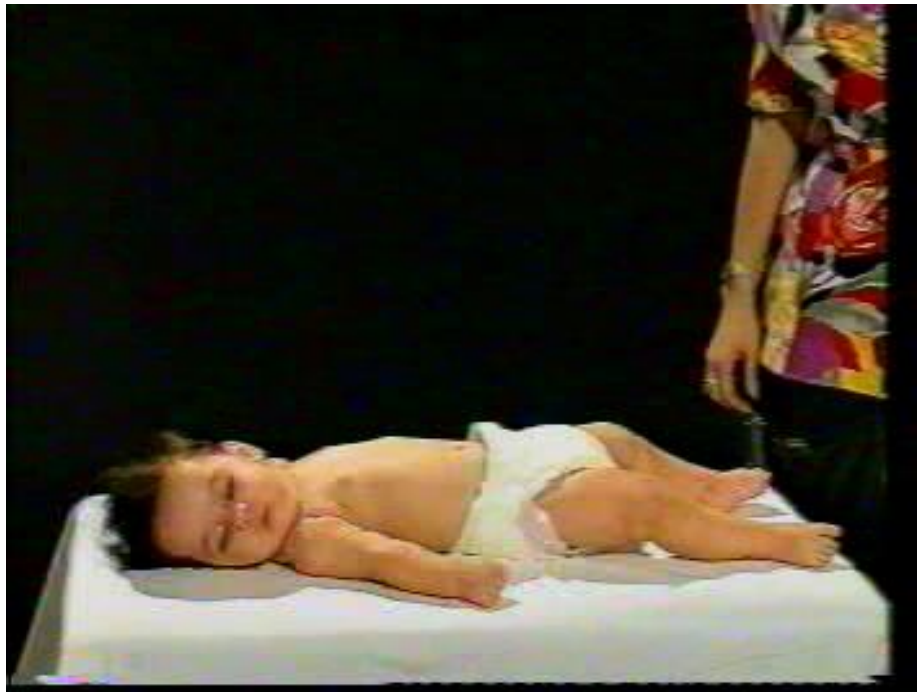
| CSF | Value nmol/L (Reference Range) |
|---|---|
| HVA | **<10** (154-867) |
| HIAA | **137** (68-451) |
| Neopterin | **9** (7-61) |
| BH2 | 8 (0.4-13.9) |
| BH4 | **36** (8-57) |
| 5-MTHF | **126** (52-178) |




Serum Prolactin 706 (86 – 324 mU/ml)

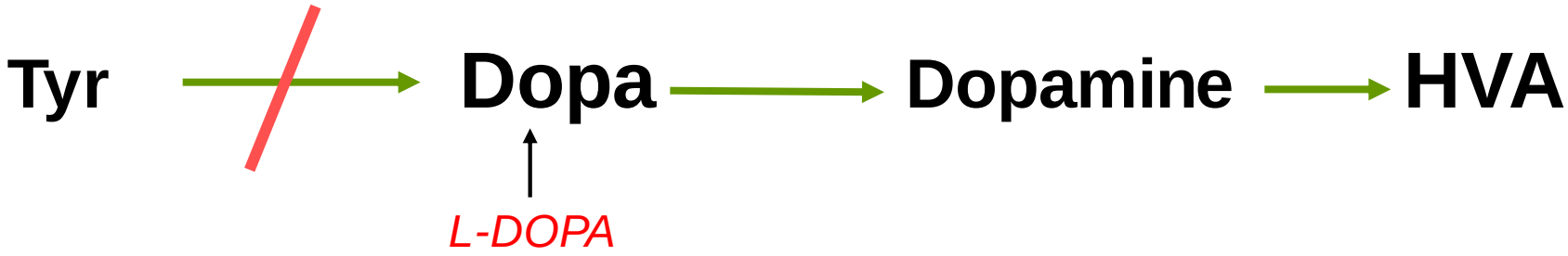




https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.870130226

# Treating the Dopamine deficiency




https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.870130226

# AADC Deficiency

- MRI brain scan normal
- very floppy
- Long episodes of arching and eye deviation
- Generalised hypotonia,
- mixed complex movement disorder

Normal phenylalanine

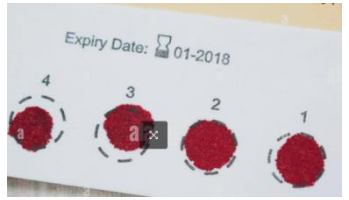
- Serum prolactin **900** (85 – 250 mU/ml)
- CSF neurotransmitters

| CSF | Value (Reference Range) |
|---|---|
| HVA | **48** (176-851 nmol/L) |
| 5-HIAA | **13** (68- 451 nmol/L) |
| Neopterin | 11 (7-65 nmol/L) |
| BH2 | 12 (0.4-13.9 nmol/L) |
| BH4 | 43 (19-56 nmol/L) |
| 3-O-methyl-dopa | **1543** (<100 nmol/L) |
| 5-MTHF | 60 (72-305) |

- Urine organic acids

**Peak of vanillylactate**


Vanillactic acid




3-Methyldopa

Tyrosine → L-Dopa → Dopamine → HVA

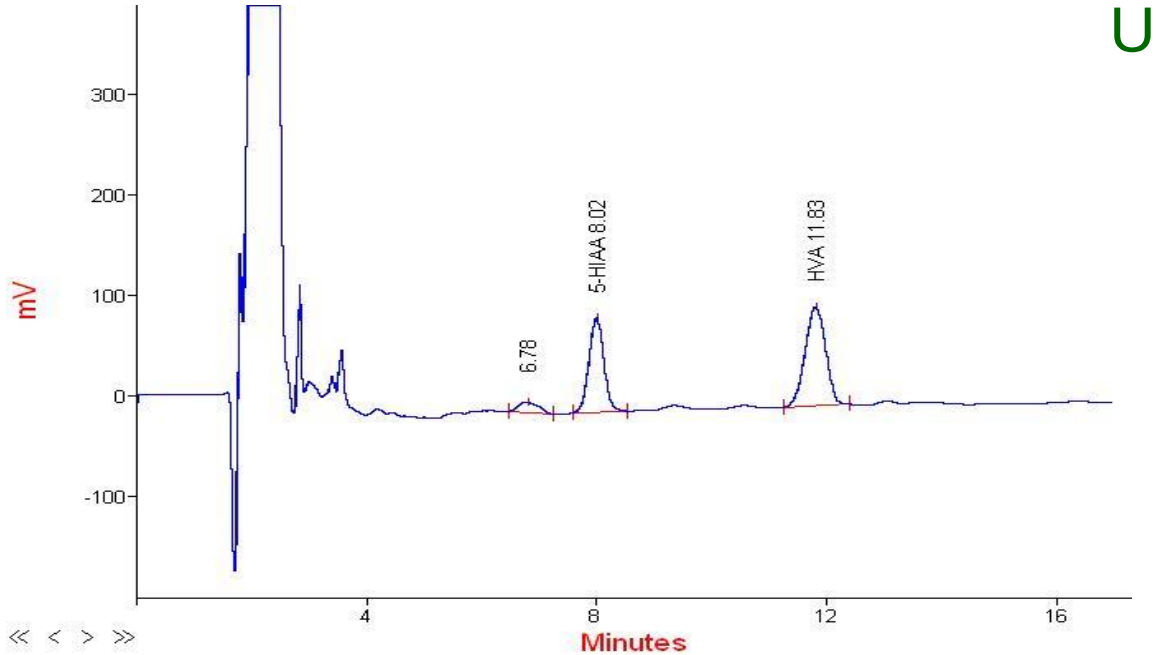
Tryptophan → 5-HTP → Serotonin → 5-HIAA

BH4

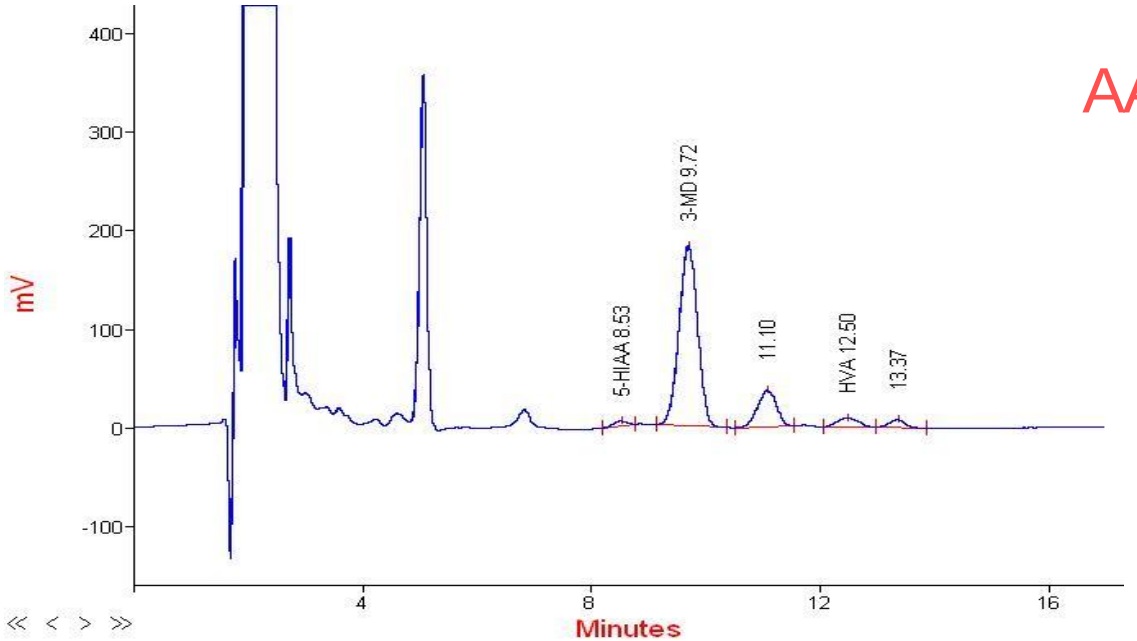
AADC

PLP

Unaffected




AADC Def



# L-Dopa Responsive Dystonia

- Hereditary progressive dystonia (Segawa et al., 1971).
- Autosomal Dominant – Female predominance (4:1).
- GTP cyclohydrolase – a causitive gene (Ichinose et al., 1994)

*Mutations in gene cause at least 2 disorders*:-

AR – present within 6 months, hyperphenylalaninaemia & marked impaitment of dopamine and serotonin turnover.

AD - DRD. Residual activity 2-20%.

# AD – GTP Cyclohydrolase Deficiency

- From beginning of ambulation, walked on toes
- Gradually got worse over early childhood
- Some hand cramping when writing
- Cognition normal
- Normal speech
- Given a diagnosis of 'cerebral palsy'
- Therapeutic trial of L-dopa

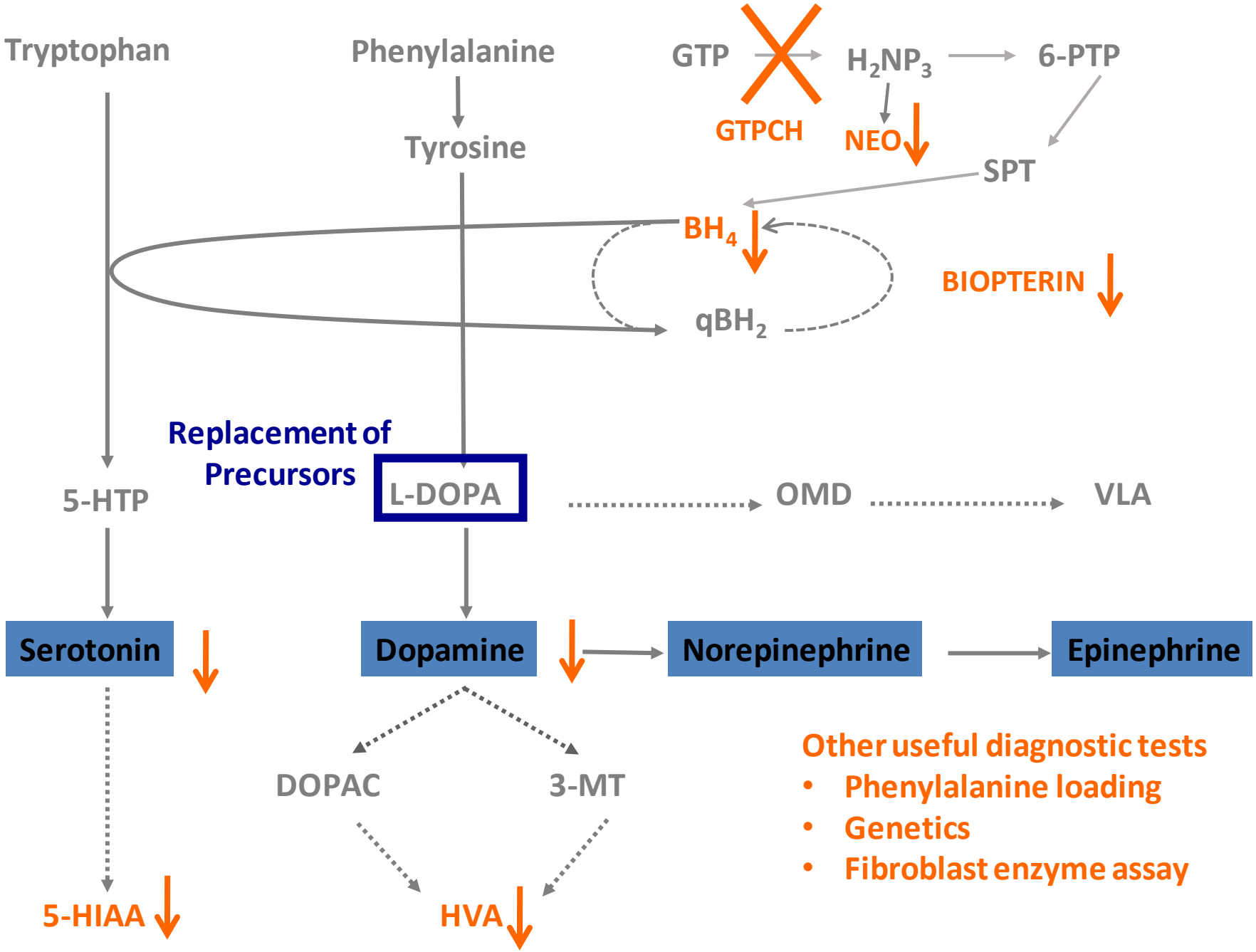
    Cessation of toe walking

    Able to run

    Virtually normalised

| CSF | Value nmol/L (Reference Range) |
|---|---|
| HVA | **155** (154-867) |
| HIAA | **85** (89-367) |
| Neopterin | **6** (7-61) |
| BH2 | 6.4 (0.4-13.9) |
| BH4 | **8** (8-57) |
| 5-MTHF | 126 (52-178) |

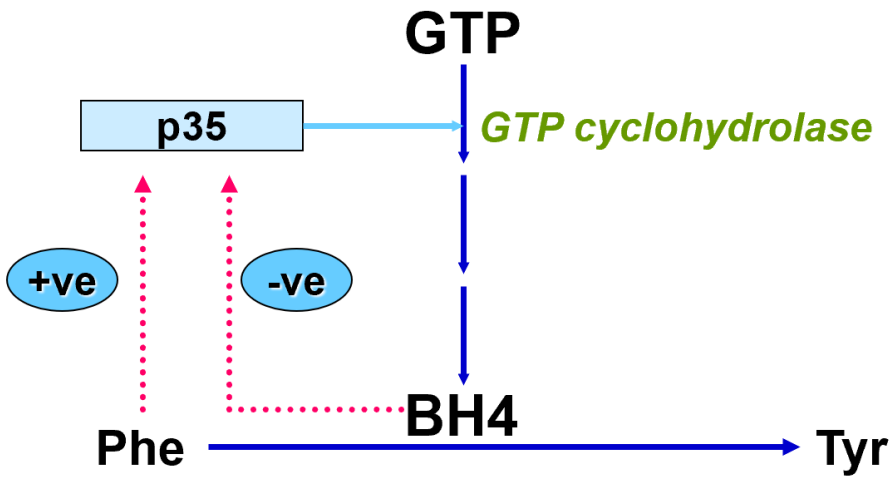
No Hyperphenylalaninaemia

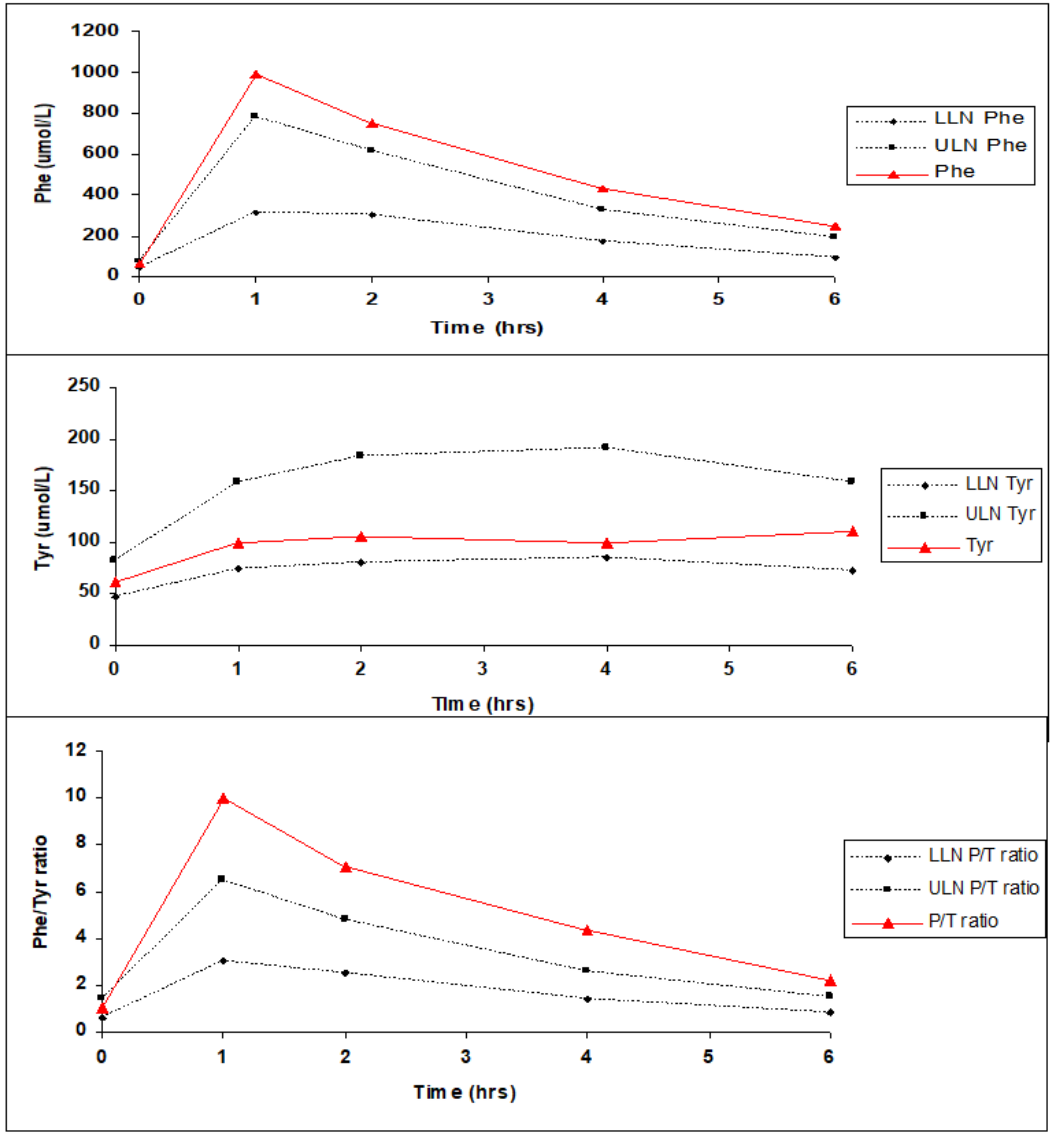



**Other useful diagnostic tests**

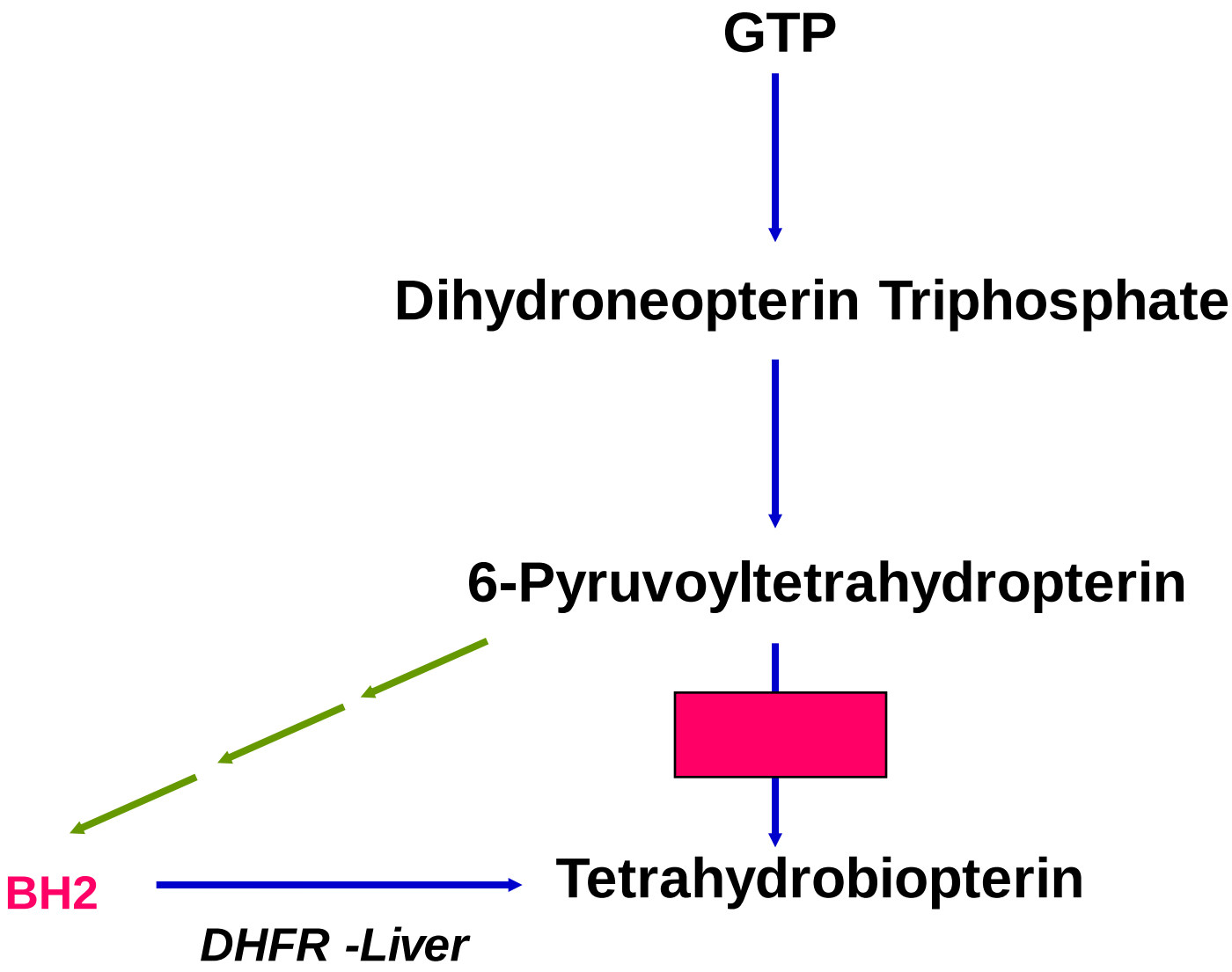
- Phenylalanine loading
- Genetics
- Fibroblast enzyme assay

# Phenylalanine Loading Test



# Sepiapterin Reductase Deficiency



# Sepiapterin Reductase Deficiency

Sex; Male. Dob; 31/12/1987. Sample; 09/05/2003. Dystonia responsive to L-DOPA. No hyperphenylalaninaemia. DHPR normal.

| | | |
|---|---|---|
| **HVA:** | **23** | **(71- 565 nmol/L)** |
| **5-HIAA:** | **2** | **(58- 220 nmol/L)** |
| **BH4:** | **11** | **(9- 39 nmol/L)** |
| **BH2:** | **64** | **(0.4- 13.9 nmol/L)** |
| **Total Neopterin:** | **19** | **(7- 65 nmol/L)** |

# Increased Dopamine Turnover

First female child of consanguineous parents. 36 week gestation.
Feeding difficulties from birth. 6 months reduced movements and failure to achieve milestones. 9 months able to smile but general paucity of movements. Rigidity of all limbs suggestive of dopamine deficiency. Left convergent squint but no abnormal eye movements detected.

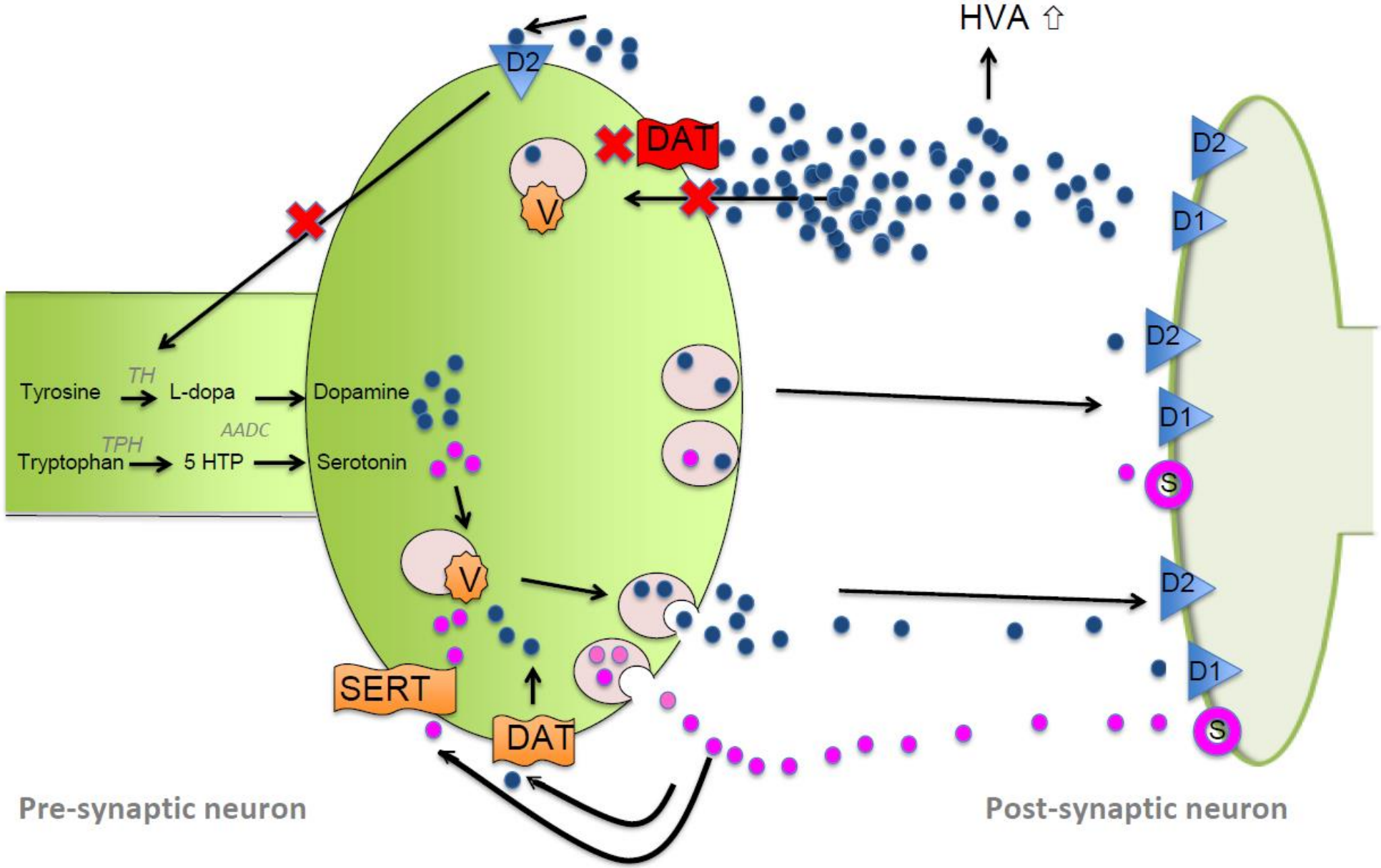
**HVA:** **1705** **(154–867 nmol/L)**

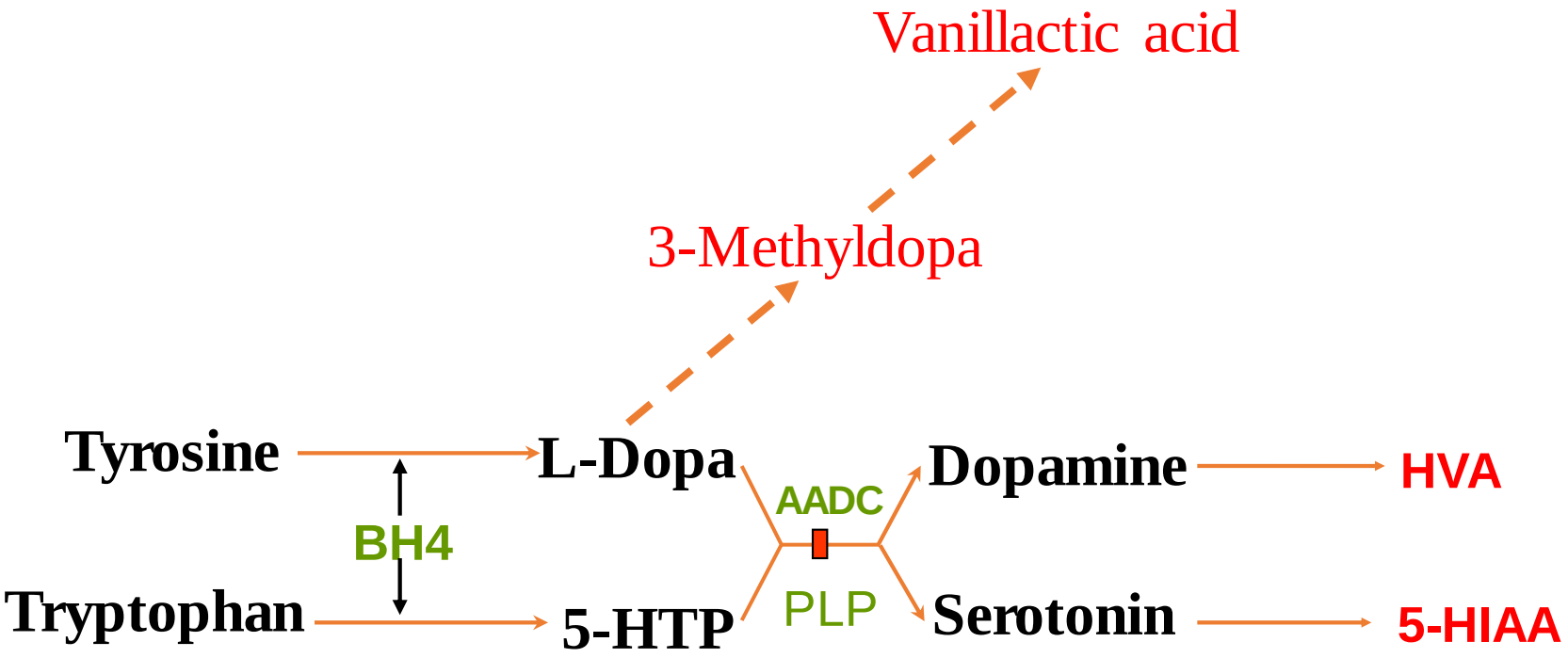
**5-HIAA:** **250** **(89-367 nmol/L)**

Pterin profile and 5-MTHF status unremarkable

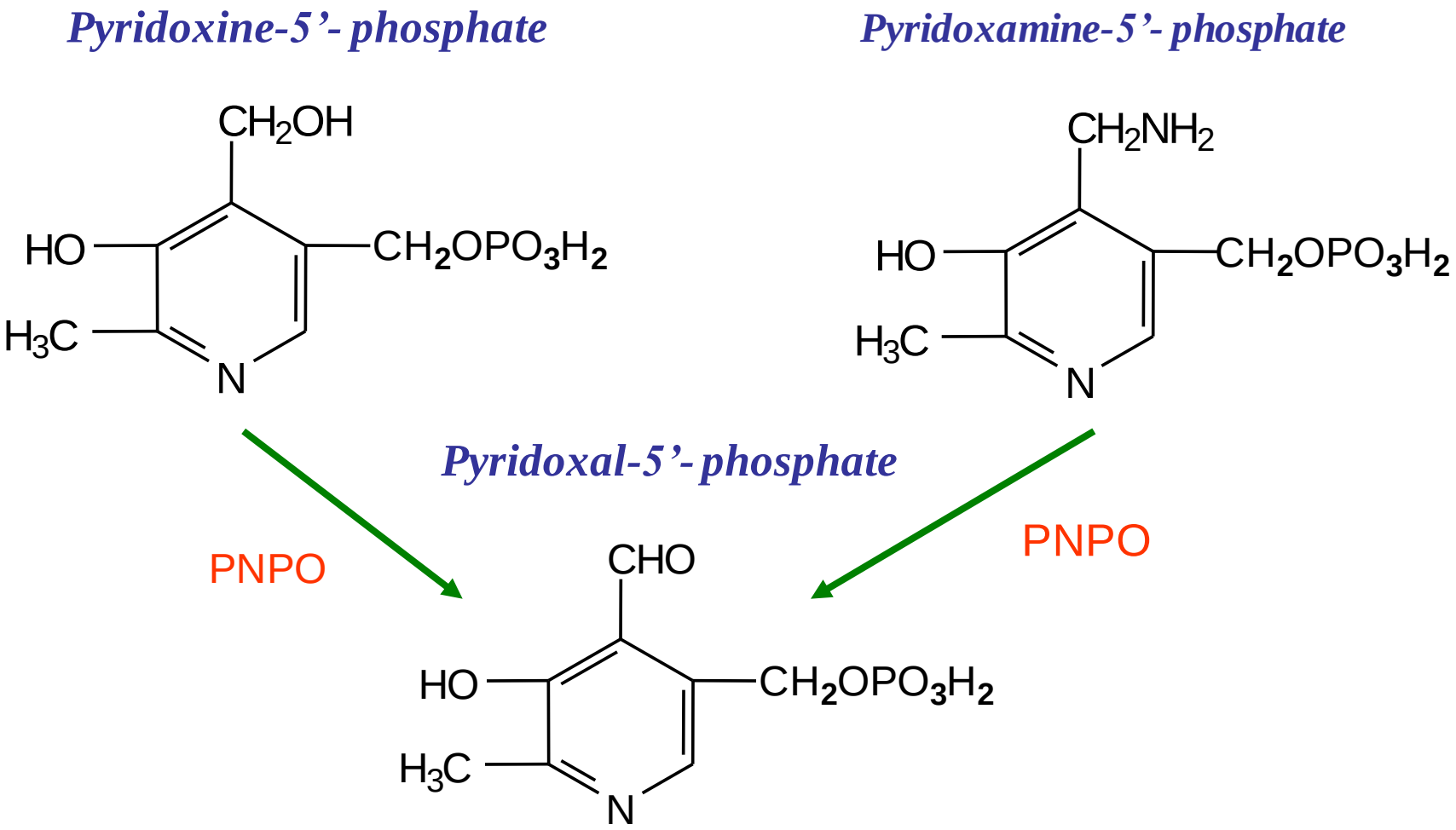
Elevated urinary HVA

**Serum Prolactin; 915 (<500 mU/ml)**


HVA ⇧
D2
DAT
V
D2
D1
D2
D1
S
Tyrosine
TH
L-dopa
Dopamine
AADC
TPH
Tryptophan
5 HTP
Serotonin
V
D2
D1
S
SERT
DAT
Pre-synaptic neuron
Post-synaptic neuron

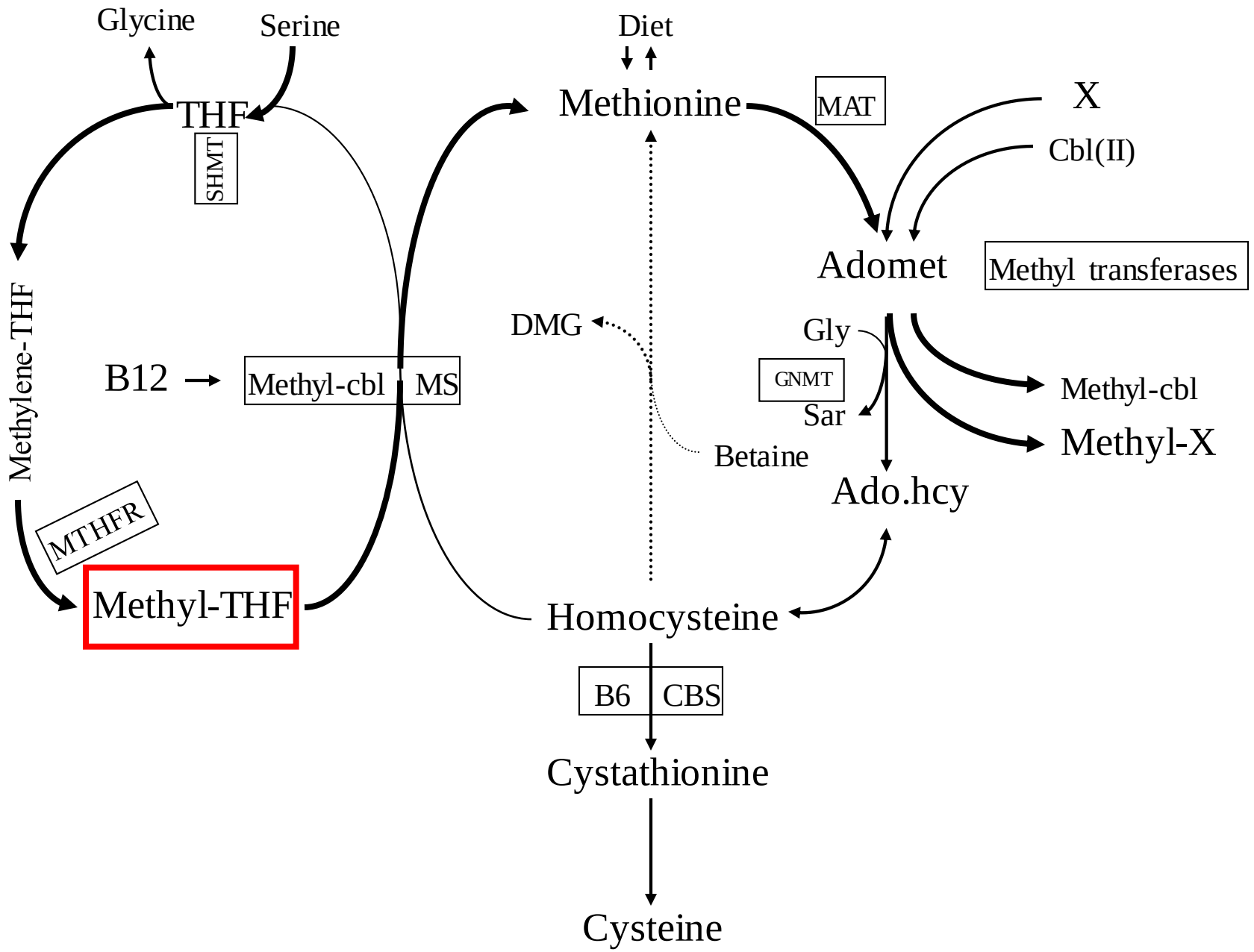

Vanillactic acid
3-Methyldopa
Tyrosine
L-Dopa
Dopamine
HVA
AADC
BH4
Tryptophan
5-HTP
PLP
Serotonin
5-HIAA

# Vitamin $B_6$ Metabolism

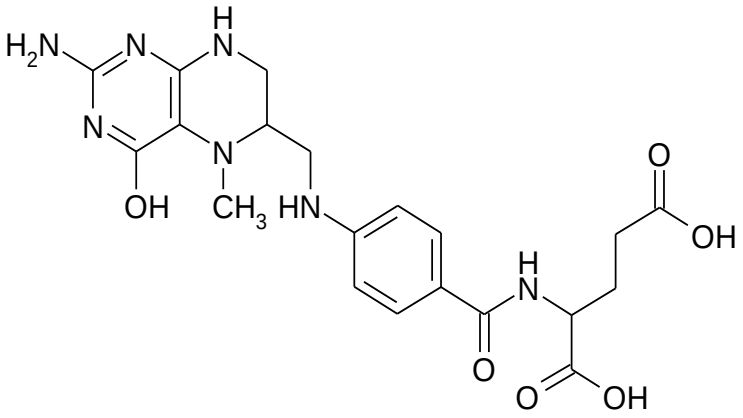


# PNPO Deficiency

- Neonatal epileptic encephalopathy
- Fetal distress, prenatal seizures, low Apgar
- Pseudo AADC deficiency – Not consistent
- ↑ Glycine & Threonine – Not consistent
- ↑ Vanillactate excretion – Consistent ?

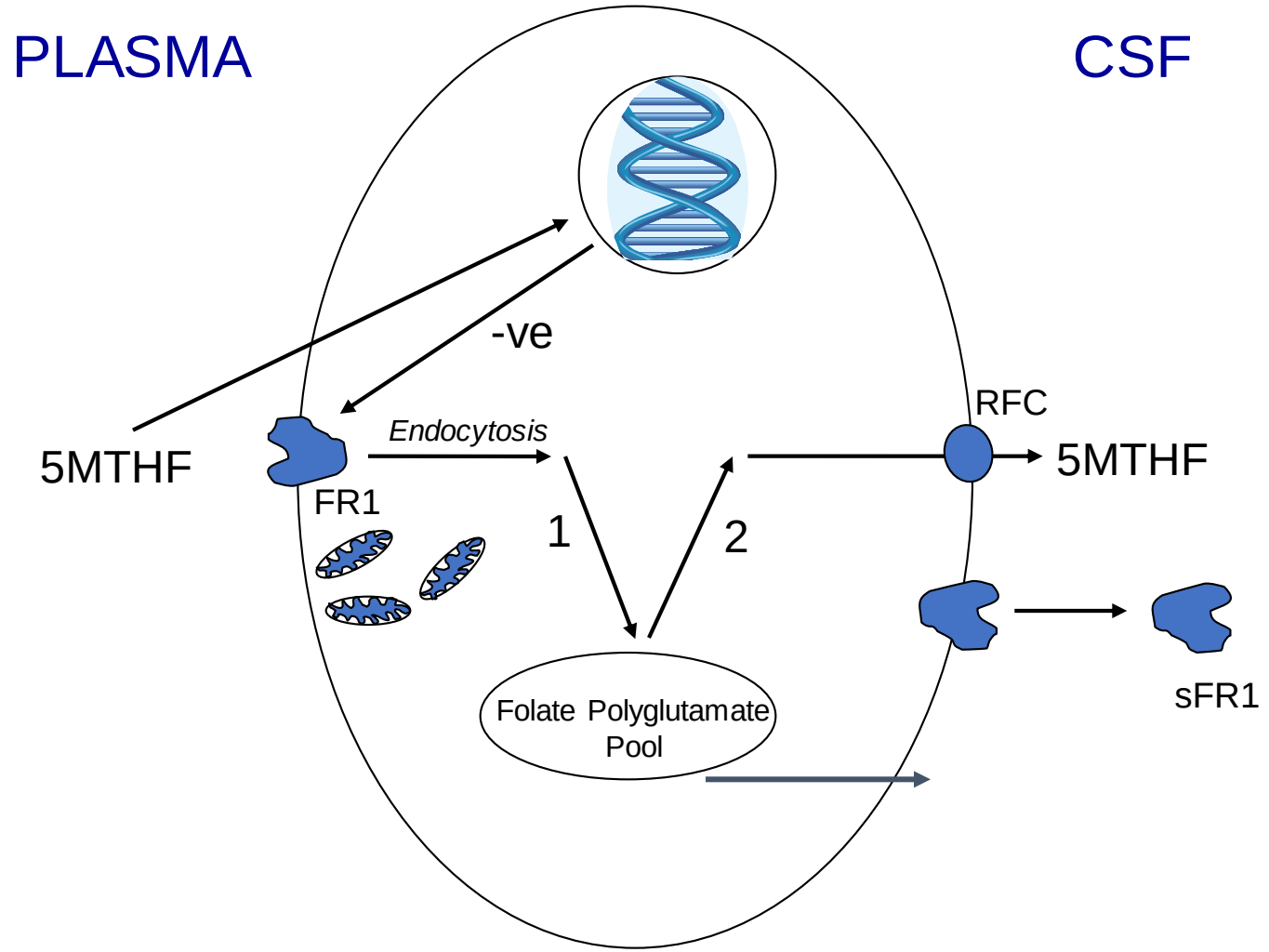

Glycine
Serine
THF
SHMT
Methylene-THF
MTHFR
Methyl-THF
B12
Methyl-cbl
MS
Diet
Methionine
MAT
X
Cbl(II)
Adomet
Methyl transferases
DMG
Gly
GNMT
Sar
Betaine
Methyl-cbl
Methyl-X
Ado.hcy
Homocysteine
B6
CBS
Cystathionine
Cysteine

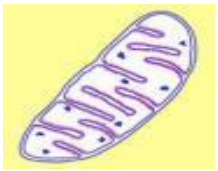
# CSF 5-MTHF Deficiency




- MTHFR deficiency
- AADC deficiency
- 3-Phosphoglycerate dehydrogenase def
- Rett syndrome
- Aicardi Goutieres
- DHPR deficiency
- Mitochondrial disorders
- L-dopa treatment
- Folic Acid treatment
- Folate transport deficiency
- Blocking antibodies
- Methotrexate
- Anticonvulsants
- Steroids
- Co-trimoxazole

Cerebral Folate Deficiency - Neurological syndrome associated with low CSF 5-MTHF and normal peripheral folate.



$O_2^{\cdot -}$ → ↓5MTHF

ARTICLE

# Folate Receptor Alpha Defect Causes Cerebral Folate Transport Deficiency: A Treatable Neurodegenerative Disorder Associated with Disturbed Myelin Metabolism

Robert Steinfeld,[1,5,*] Marcel Grapp,[1,5] Ralph Kraetzner,[1] Steffi Dreha-Kulaczewski,[1] Gunther Helms,[2] Peter Dechent,[2] Ron Wevers,[3] Salvatore Grosso,[4] and Jutta Gärtner[1]

354 The American Journal of Human Genetics *85*, 354–363, September 11, 2009

- Leads to brain specific folate deficiency
- Loss of function mutations in the FOLR1.
- Gene coding for the FR$\alpha$
- AR disorder manifests in late infancy with Severe developmental regression, movement disturbances,epilepsy and leukodystrophy
- Beneficial effect of *folinic acid*.

# CSF 5-MTHF Deficiency & Mitochondrial Disorders

| Sex | Age (years) | 5-MTHF | Ref Range (nmol/L) |
|---|---|---|---|
| F | 15 | 29 | 46 - 160 |
| M | 9 | 5 | 72 - 172 |
| M | 8 | 44 | 72 - 172 |
| F | 2 | 17 | 52 - 178 |
| F | 6 | 7 | 72 - 172 |

No correlation between CSF 5-MTHF status and severity of respiratory chain defect in muscle

Hyland, Shoffner, Heales, *J. Inherit Metab Dis* (2010) 33, 63-570

# Secondary Causes

- HIE
- Neurodegeneration
- Seizures
- Lysosomal
- Mitochondrial
- Molybdenum cofactor
- Drugs – L-dopa
- Sample Processing

Molecular Genetics and Metabolism 117 (2016) 42–48

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

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

Secondary neurotransmitter deficiencies in epilepsy caused by voltage-gated sodium channelopathies: A potential treatment target?

Gabriella A. Horvath [a], Michelle Demos [b], Casper Shyr [c,d], Allison Matthews [c,d], Linhua Zhang [c], Simone Race [a], Sylvia Stockler-Ipsiroglu [a], Margot I. Van Allen [d], Ogan Mancarci [e], Lilah Toker [e], Paul Pavlidis [e], Colin J. Ross [d], Wyeth W. Wasserman [c,d], Natalie Trump [f], Simon Heales [g,h], Simon Pope [g], J. Helen Cross [i], Clara D.M. van Karnebeek [a,c,*]

Available online at www.sciencedirect.com

ScienceDirect

Mitochondrion 8 (2008) 273–278

Mitochondrion

www.elsevier.com/locate/mito

Mitochondrial diseases mimicking neurotransmitter defects

Angels Garcia-Cazorla [a,b,*,1], Sofia Duarte [a,b,1], Mercedes Serrano [a,b], Andres Nascimento [a,b], Aida Ormazabal [a,b], Ines Carrilho [c], Paz Briones [d], Julio Montoya [e], Rafael Garesse [f], Pere Sala-Castellvi [g], Mercedes Pineda [a,b], Rafael Artuch [a,b]

JIMD Reports
DOI 10.1007/8904_2015_421

RESEARCH REPORT

**Coenzyme $Q_{10}$ and Pyridoxal Phosphate Deficiency Is a Common Feature in Mucopolysaccharidosis Type III**

Dèlia Yubero • Raquel Montero • Mar O'Callaghan • Mercè Pineda • Silvia Meavilla • Veronica Delgadillo • Cristina Sierra • Laura Altimira • Plácido Navas • Simon Pope • Marcus Oppenheim • Viruna Neergheen • Arunabha Ghosh • Phillipa Mills • Peter Clayton • Emma Footitt • Maureen Cleary • Iain Hargreaves • Simon A. Jones • Simon Heales • Rafael Artuch