4th Department of Pediatrics of the Aristotle University of Thessaloniki

Athanasios Evangeliou MD
4th Dept of Pediatrics
of the Aristotle University of Thessaloniki
Papageorgiou Hospital

PAPAGEORGIOU GENERAL HOSPITAL

Athanasios E Evangeliou
Prof. of Pediatrics and Child Neurology

4th Department of Pediatrics of the Aristotle University of Thessaloniki.


© Cavallo Summer 2006 - Kavala Port Panoramic

Greece

- population is about 11.5 million people
- area of 132 000 km²
- Greece features a vast number of islands, between 1,200 and 6,000, depending on the definition, **227** of which are inhabited

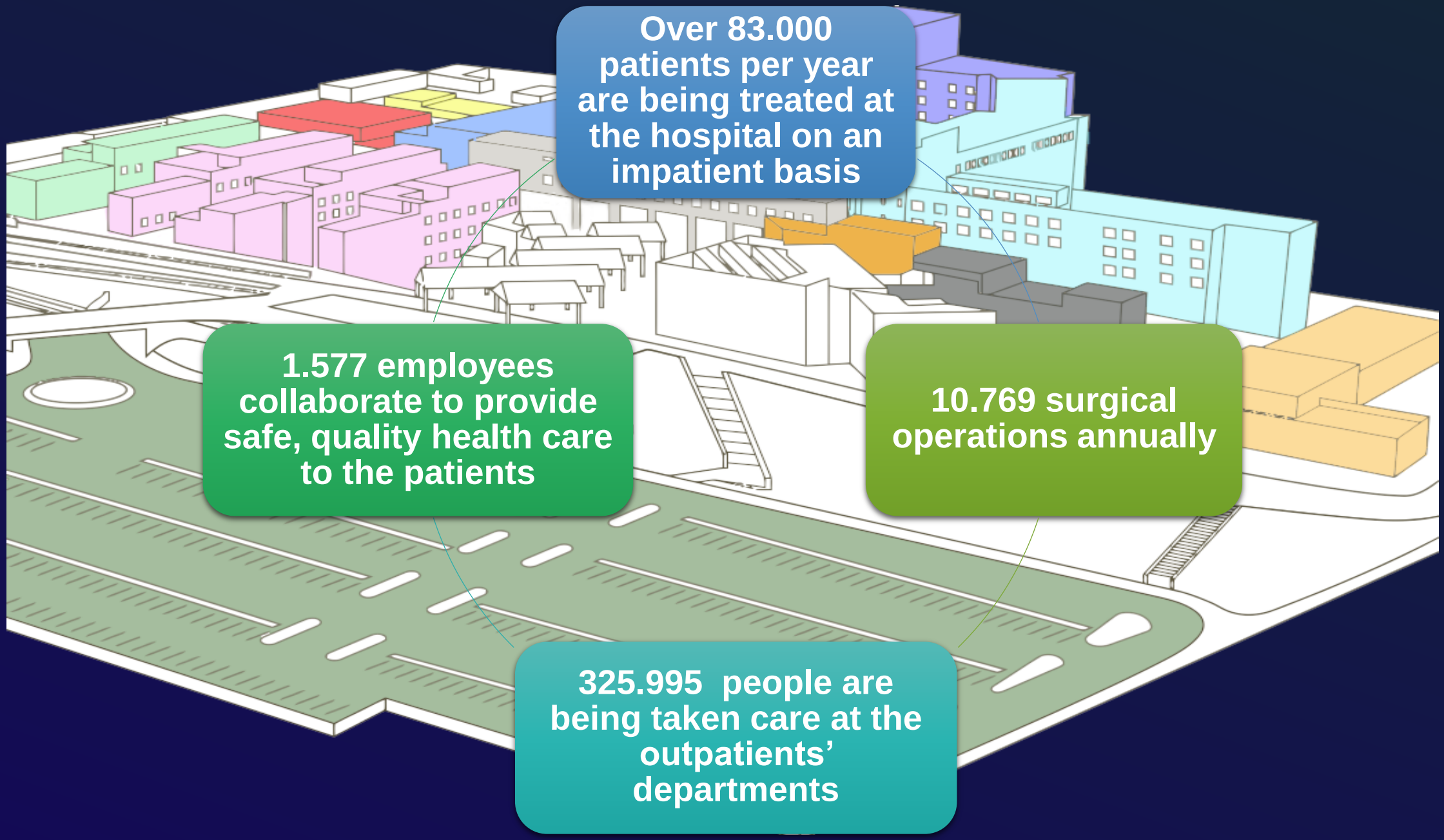

Thessaloniki
Papageorgiou General Hospital
Larissa
Ioannina
Patras
Athens
Heraklion
Capital
Major cities
Erasmus+

PAPAGEORGIOU GENERAL HOSPITAL

The Hospital is a Legal Entity Governed by Private Law, of a non-profit nature, which offers prevention, diagnosis, treatment and rehabilitation services.

It's completely integrated to the National Health System, under the supervision of the Ministry of Health and is run by a Board of 7 Directors.

PAPAGEORGIOU GENERAL HOSPITAL



PAPAGEORGIOU GENERAL HOSPITAL

DEPARTMENT OF PEDIATRICS

BEDS 40

DIVISIONS

Child Neurology

Endocrinology

Gastroenterology

Immunology

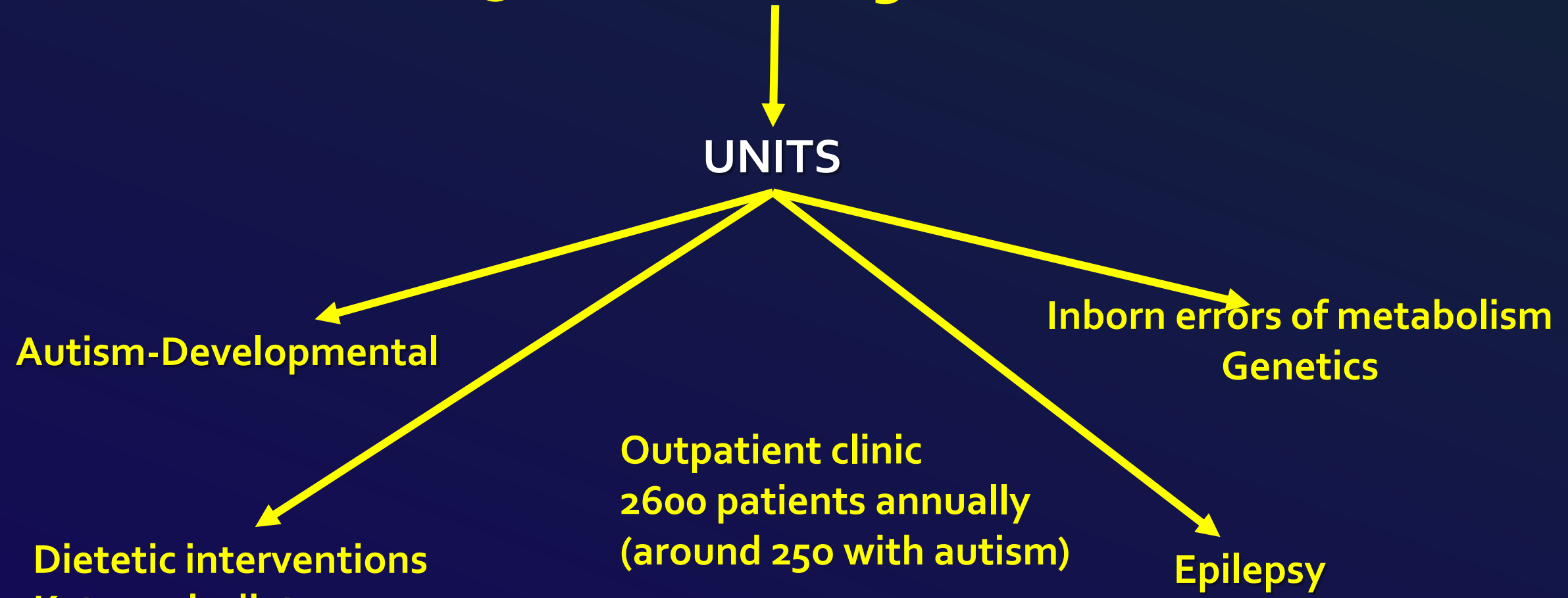
Nephrology

Cardiology

General Pediatrics

DIVISION OF CHILD NEUROGY

15 BEDS(waiting list 6-12 months)



AUTISM-DEVELOPMENTAL UNIT

Research interest

Autism

Metabolism, Genetics
Neurochemistry, Dietetic interventions

AUTISM – BASIC PRINCIPLES

- Autism is a collection of problems that many of them can be improved, especially for some may be a radical solution.

- Many of the disorders that exist in autism coexist in many other clinical entities.

AUTISM – BASIC PRINCIPLES

- There is no treatment that alone will cure autism.

- Autism is multifactorial.

CAUSES OF AUTISTIC BEHAVIOR

- Fetal infections (rubella, CMV, toxoplasmosis)
- Bacterial meningitis
- Neonatal asphyxia
- Environmental factors
- Fragile X syndrome
- Rett Syndrome
- Tuberous sclerosis
- Several gene mutations
- Inborn errors of metabolism.

- **AUTISM – SOME BASIC PRINCIPLES**

- **KEEP ON MIND!**

- Genes can be the causes of autistic behavior while some of them are of high risk for developing an autistic behavior.

- The environment may be implicated in the appearance of autistic behavior and some environmental stimuli are at high risk of developing such a symptoms.

- Our daily choices can modulate the expression of our genes.

- Our daily choices can cause or prevent genetic damage.

GENES- MYTH AND REALITY

- The genes are not a blueprint on what we become.
- Genes are a living document that in the course of our lives changes made up on several things like the air we breathe, the food we receive, the experiences we have and the environmental reports we have.
- We can not change our genetic code, but you can change many harmful stimuli that our genes are accepting.

GENES- MYTH AND REALITY

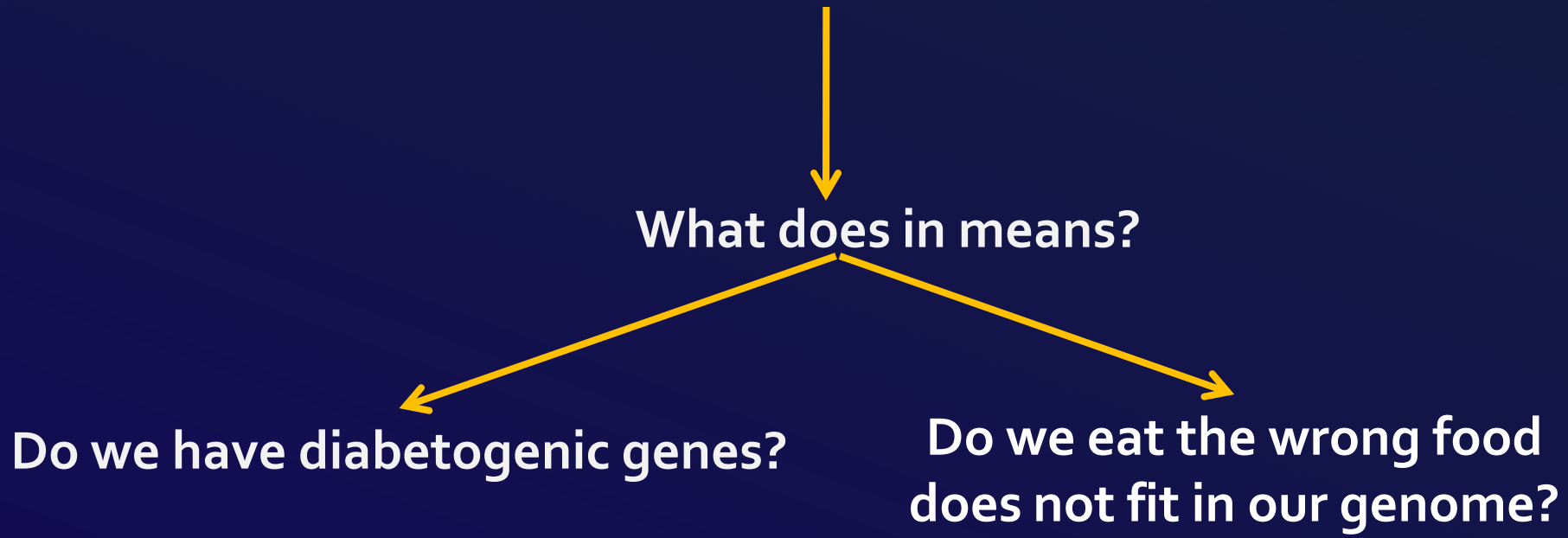
- Changes in genes are occurring from generation to generation through mutations.
- The mutations are not always pathogenic.
- Most of the mutations are occuring in pregnancy and in the elderly.

GENES-
IS THERE ANY RELATION WITH AUTISM?

- Some children with autism have mutations that do not have their parents.
- Sometimes genes who are not pathogenic for parents can be for children who grew up under different conditions.
- Even from recent research we know that some genes, does not need to be mutated in order to act differently.

ENVIRONMENT CAN CHANGE THE GENES EXPRESSION

In the last years our children become overweight and the incidence of diabetes has been increased.



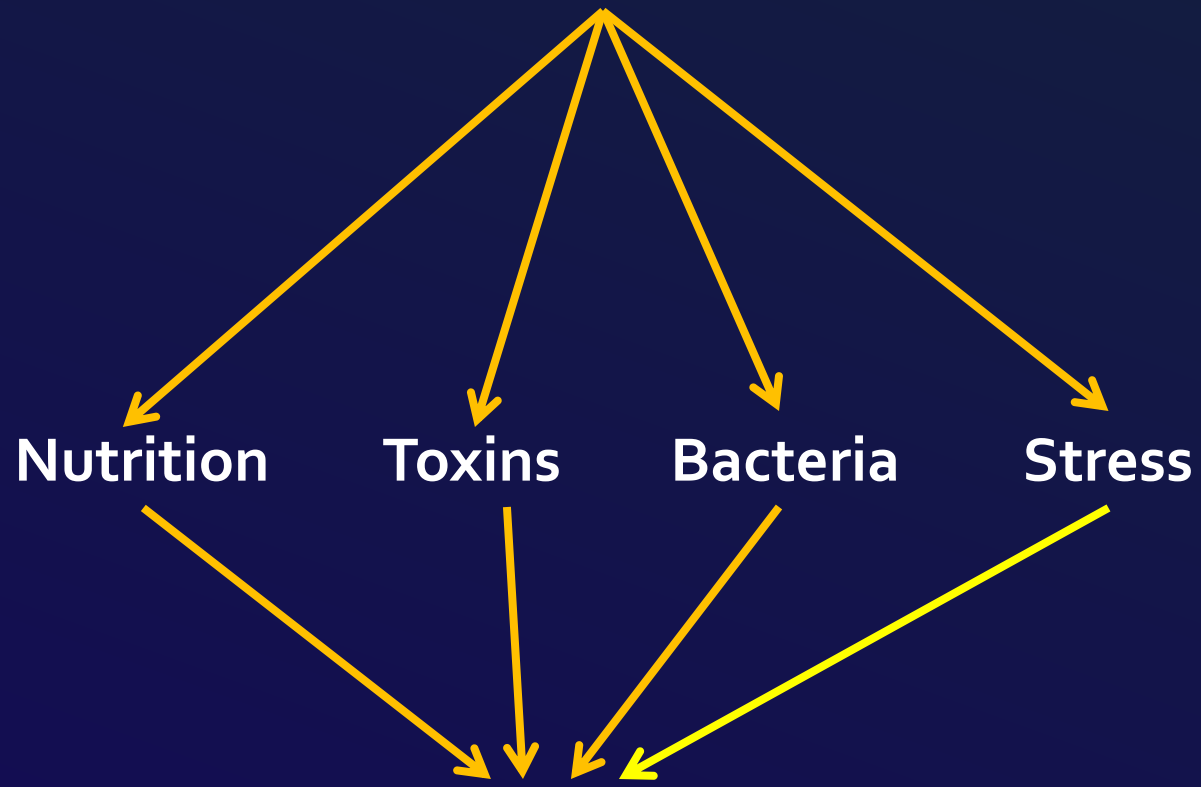
NOBODY HAS THE PERFECT GENOME!

The environment can force the genes
towards difficult energy processes that are stressful
for organism and sometimes are
predisposing factors for morbidity

It is well known that children with autism are
particularly sensitive to
environmental changes

CHILDREN WITH AUTISM

What can we change in order to reduce the harmful environmental stimuli

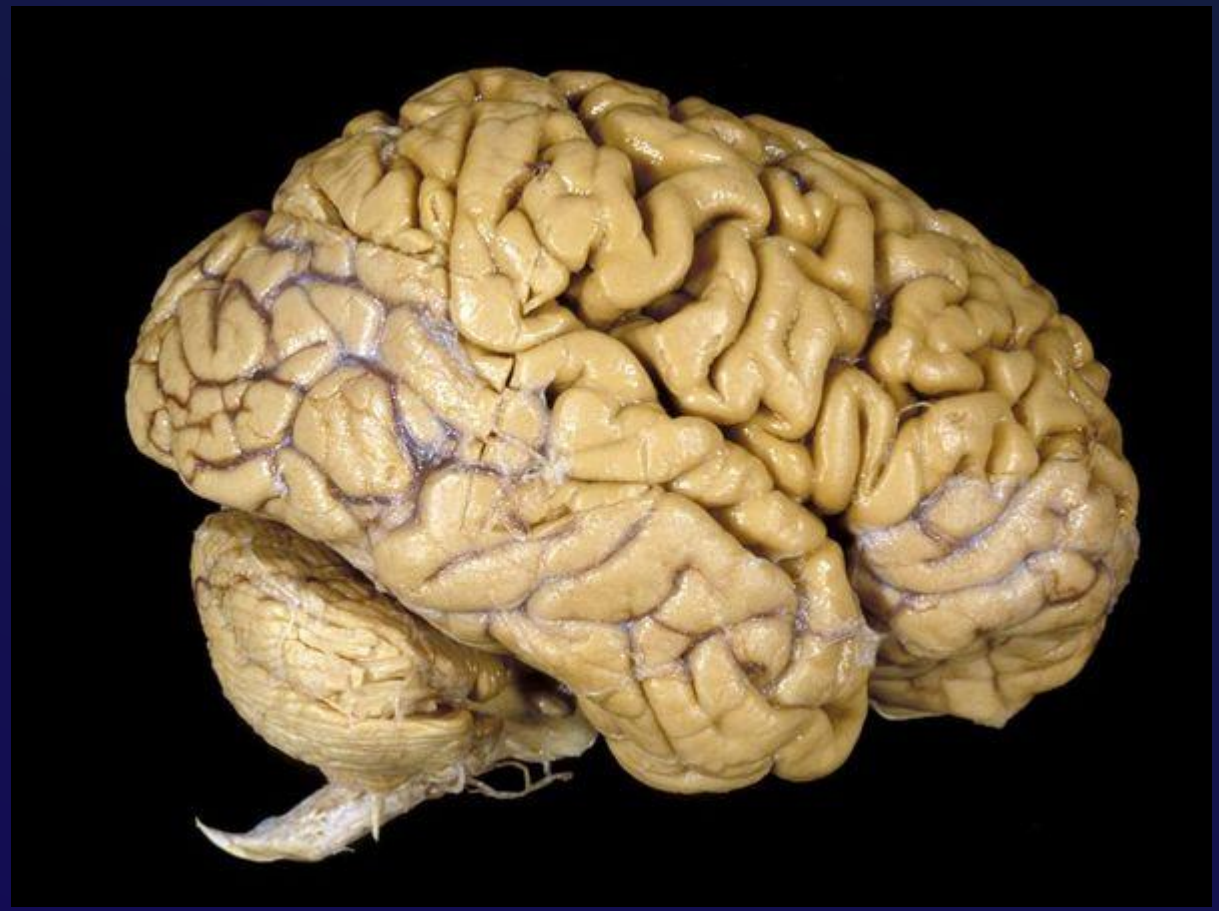


All the above can be limited if we take the appropriate actions

GENES

REST OF THE BODY

ENVIRONMENT



KETOGENIC DIET IN AUTISM-WHY?

- Clinical experience of older colleagues that glucose worsens the autism symptoms
- The implementation of the ketogenic diet in epilepsy had a positive effect on patient behavior.
- Studies with PET and NMR showing defective glucose combustion inside the brain.
- Biochemical investigations of our clinic suggesting disturbed glucose entry inside the mitochondria.

KETOGENIC DIET EFFECT ON THE INTERMEDIARY METABOLISM OF AUTISTIC BRAIN

Increase of energy brain reserves.

↓

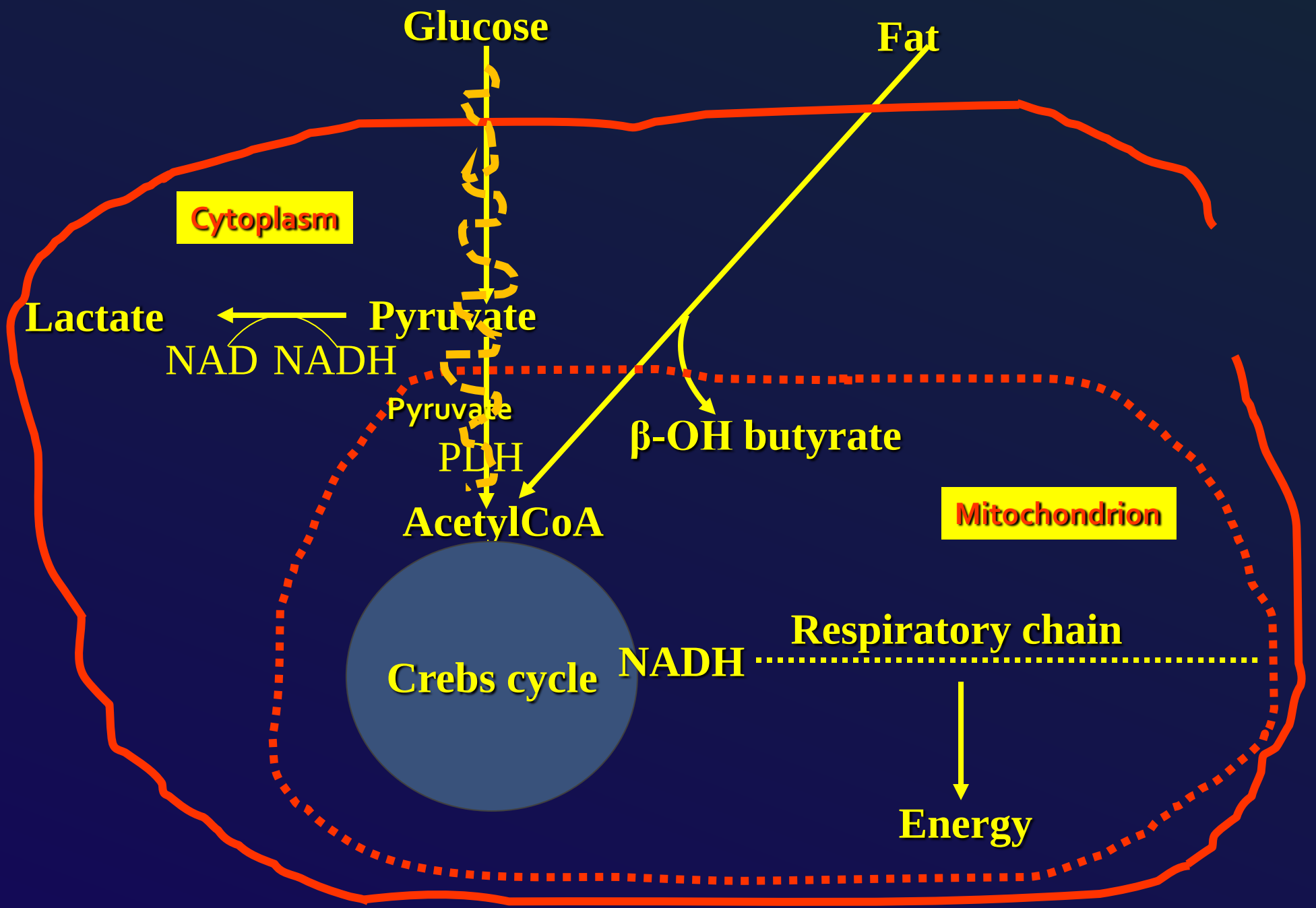
Improving behavior

↓

How?

↓

By passing energy consuming glycolytic pathways,
increasing this way the energy production from Crebs


Glucose
Fat
Cytoplasm
Lactate
Pyruvate
NAD NADH
Pyruvate
PDH
β-OH butyrate
AcetylCoA
Mitochondrion
Crebs cycle
NADH
Respiratory chain
Energy

- MCT 30% of total calories
- Milk 30%
- Saturated fats 11%
- Carbohydrates 19%
- Proteins 10%

- Vitamins and mineral supplements

JOHN RADCLIFFE KETOGENIC DIET

J Child Neurol. 2003 Feb;18(2):113-8.

Application of a ketogenic diet in children with autistic behavior: pilot study.

Evangeliou et al

Patients With Pathologic Increased β-Hydroxybutyrate After GLT Values in mmol/L

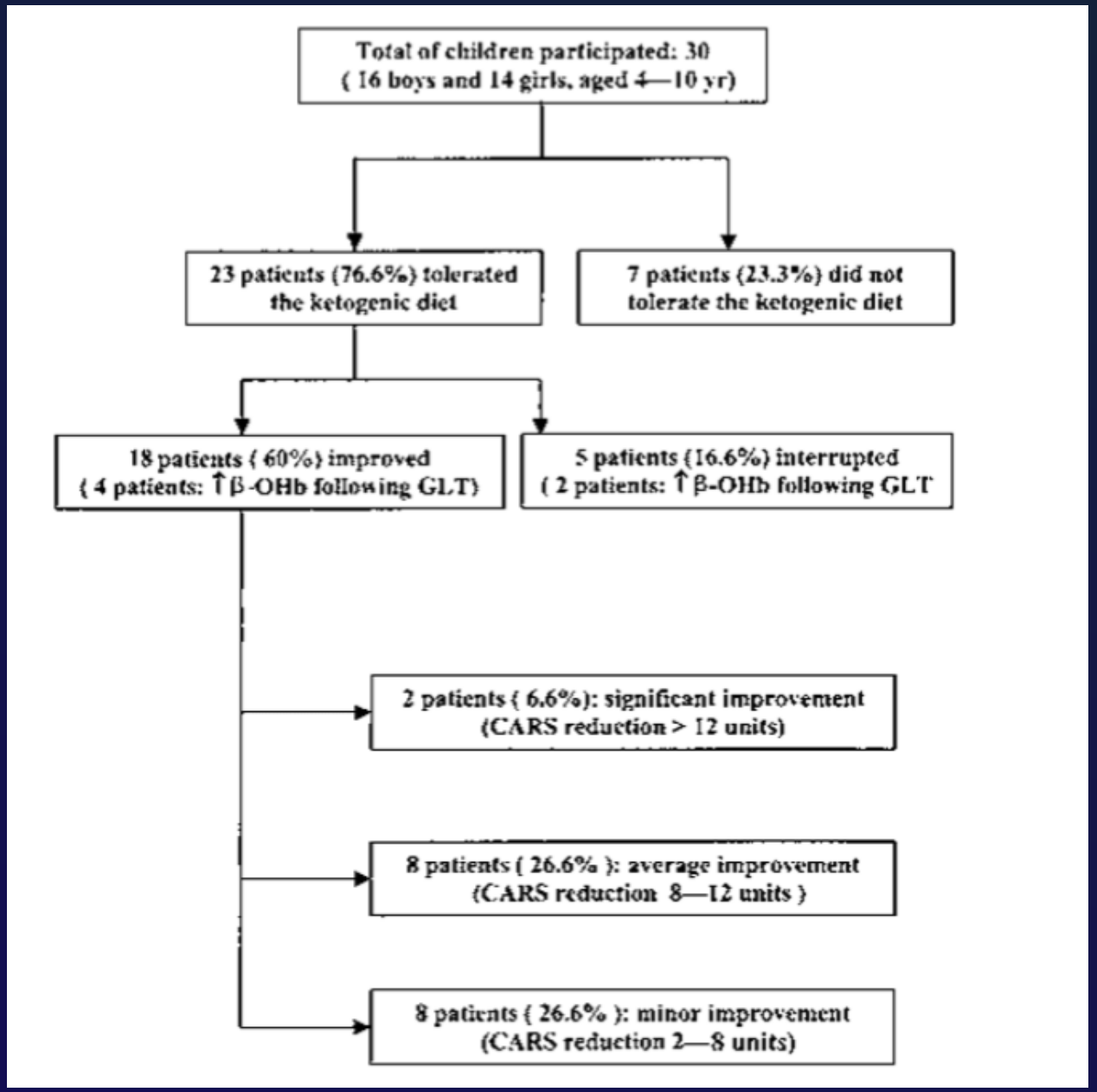
Patient	*β-Hydroxybutyrate Before GLT*	*β-Hydroxybutyrate After GLT*
1	1.45	1.82
2	1.05	1.49
3	1.23	1.65
4	1.45	1.88
5	1.30	1.45
6	1.15	1.34

GLT = glucose loading test.

Patients With Improvement after a Ketogenic Diet

Significant improvement	(CARS: > 12 units)	2: Pre-CARS: 35.00 ± 1.41 (mean ± SD)
Average improvement	(CARS: > 8–12 units)	8: Pre-CARS: 41.88 ± 3.14(mean ± SD)
Minor improvement	(CARS: 2–8 units)	8: Pre-CARS: 45.25 ± 2.76(mean ± SD)

CARS = Childhood Autism Rating Scale.


Total of children participated: 30
(16 boys and 14 girls, aged 4—10 yr)
23 patients (76.6%) tolerated the ketogenic diet
7 patients (23.3%) did not tolerate the ketogenic diet
18 patients (60%) improved
(4 patients: ↑β-OHb following GLT)
5 patients (16.6%) interrupted
(2 patients: ↑β-OHb following GLT
2 patients (6.6%): significant improvement
(CARS reduction > 12 units)
8 patients (26.6%): average improvement
(CARS reduction 8—12 units)
8 patients (26.6%): minor improvement
(CARS reduction 2—8 units)

- Tolerance 23
- Non tolerance 7

PATIENTS ON KETOGENIC DIET

Patients With Improvement after a Ketogenic Diet

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Average improvement	(CARS: > 8–12 units)	8: Pre-CARS: 41.88 ± 3.14(mean ± SD)
Minor improvement	(CARS: 2–8 units)	8: Pre-CARS: 45.25 ± 2.76(mean ± SD)

CARS = Childhood Autism Rating Scale.

PATIENTS ON KETOGENIC DIET

Improvement	Number of patients	% of total number	Improvement on CARS scale
Significant	2	6.6	>12
Moderate	8	26.6	8-12
Minor	8	26.6	2-8
No	5	16.6	

CONCLUSION

- Ketogenic diet may be useful in children with autism.
- The whole issue needs further study.

KETOGENIC DIET – AUTISM FURTHER EFFORTS

Efforts to improving ketogenic diet

- **Modified Atkins diet**

  (Kossoff et al. Neurology. 2003;61(12):1789-1791)

- **Low-glycemic-index diet**

  (Pfeifer et al. Neurology. 2005;65(11):1810-1812)

- **Branched chain aminoacids as adjunctive therapy to the ketogenic diet**

  (Evangeliou et al.J Child Neurol. 2009 ;24(10):1268-72.)

BCAA AND KETOGENIC DIET

- **WHY?**

- Shimomura Y, Harris RA.

  J Nutr. 2006;136(1 suppl):232S-233S.

- Yudkoff M, Daikhin Y, Nissim I, et al.

  J Nutr. 2005;135(6 suppl):1531S-1538S.

Experimental data relating to the antiepileptic action of branched chain amino acids

BCAA- Effect on autistic brain

- BCAA buffer excessive amounts of Glutamate by converting it to Glutamine.

- It is well known that increase glutamate levels may be the cause of autistic behavior

AUTISM -GLUTAMATE

Excitatory neurotransmitter signaling through glutamate receptors modulates cognitive functions such as memory and learning, which are usually impaired in autism spectrum disorders (ASD).

Autistic children had higher plasma levels of glutamate and elevated plasma glutamate levels may play an important role in the pathogenesis of autism.

Cai J, et al. Elevated plasma levels of glutamate in children with autism spectrum disorders. Neuroreport. 2016 Mar 2;27(4):272-6.

Bonnet-Brilhault F, et al. GABA/Glutamate synaptic pathways targeted by integrative genomic and electrophysiological explorations distinguish autism from intellectual disability. Mol Psychiatry. 2016 Mar;21(3):411-8.

Tebartz van Elst L, et al. Disturbed cingulateglutamate metabolism in adults with high-functioning autism spectrum disorder:evidence in support of the excitatory/inhibitory imbalance hypothesis. Mol Psychiatry. 2014 Dec;19(12):1314-25.

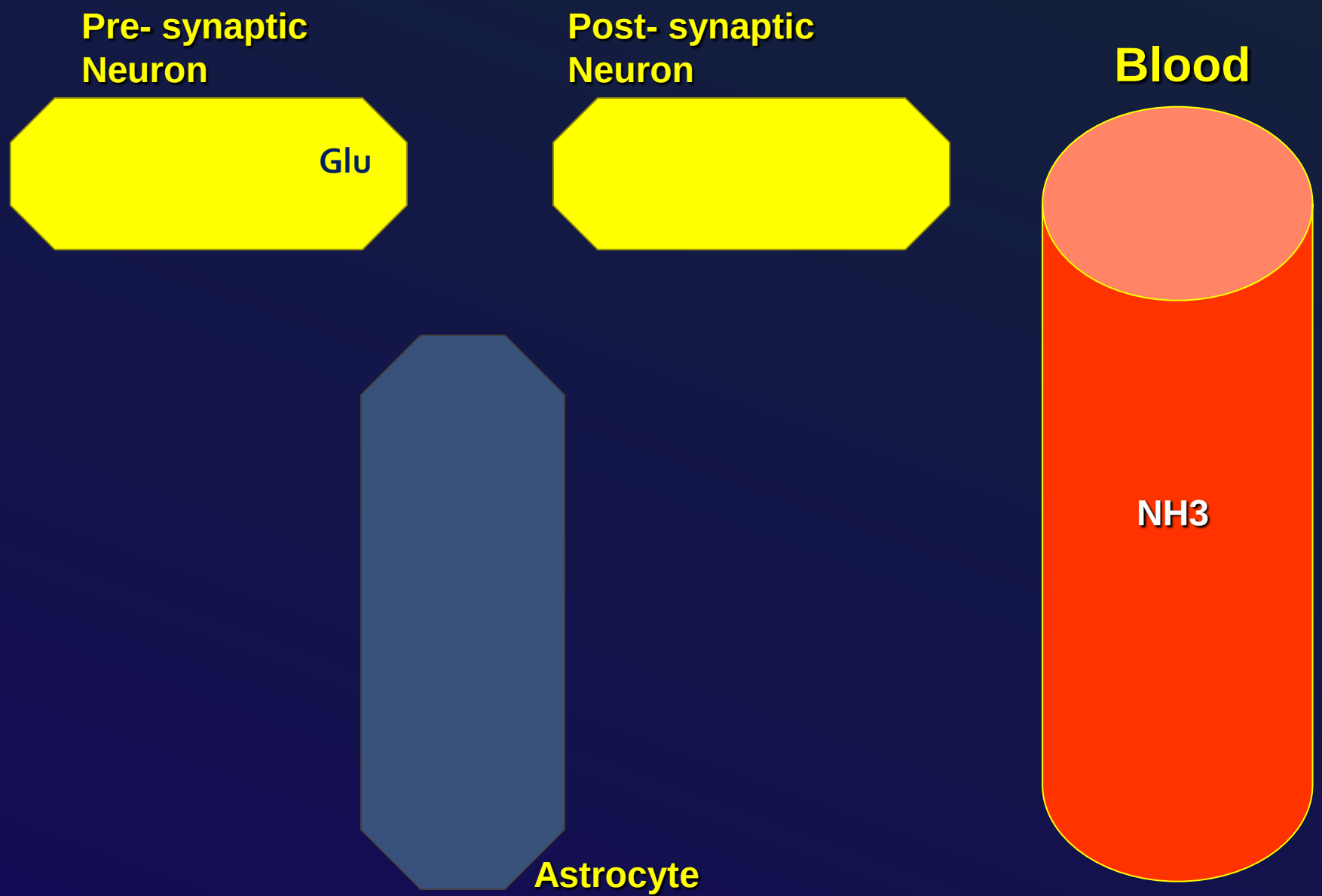
Hadley D, et al. The impact of the metabotropic glutamate receptor and other gene family interaction networks on autism. Nat Commun. 2014 Jun 13;5:4074.

Rojas DC. The role of glutamate and its receptors in autism and the use of glutamate receptor antagonists in treatment. J Neural Transm (Vienna). 2014 Aug;121(8):891-905.

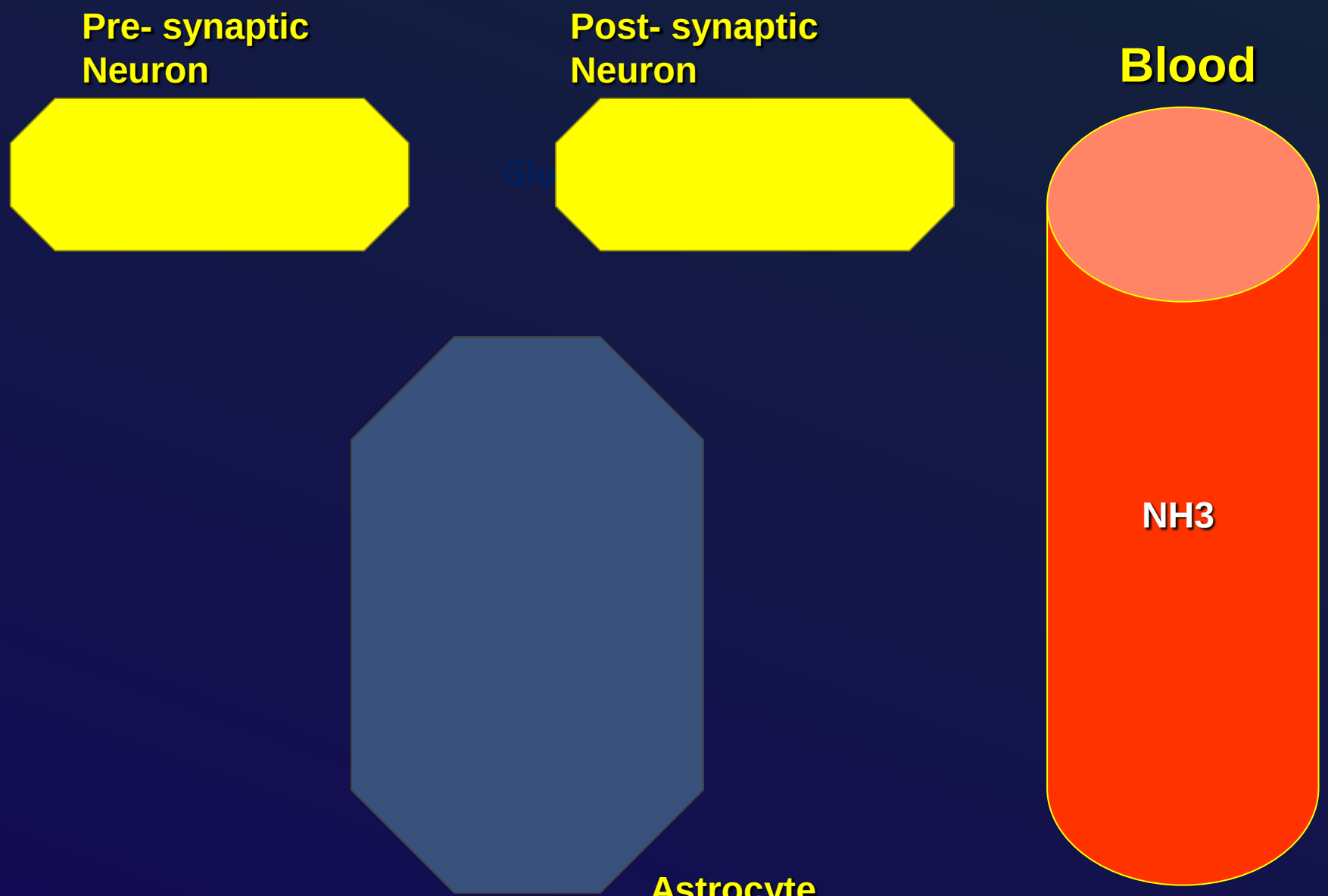
Uzunova G, et al. The role of ionotropic glutamate receptors in childhood neurodevelopmental disorders: autism spectrum disorders and fragile x syndrome. Curr Neuropharmacol. 2014 Jan;12(1):71-98.

Yang P, Chang CL. Glutamate-mediated signaling and autism spectrum disorders:emerging treatment targets. Curr Pharm Des. 2014;20(32):5186-93

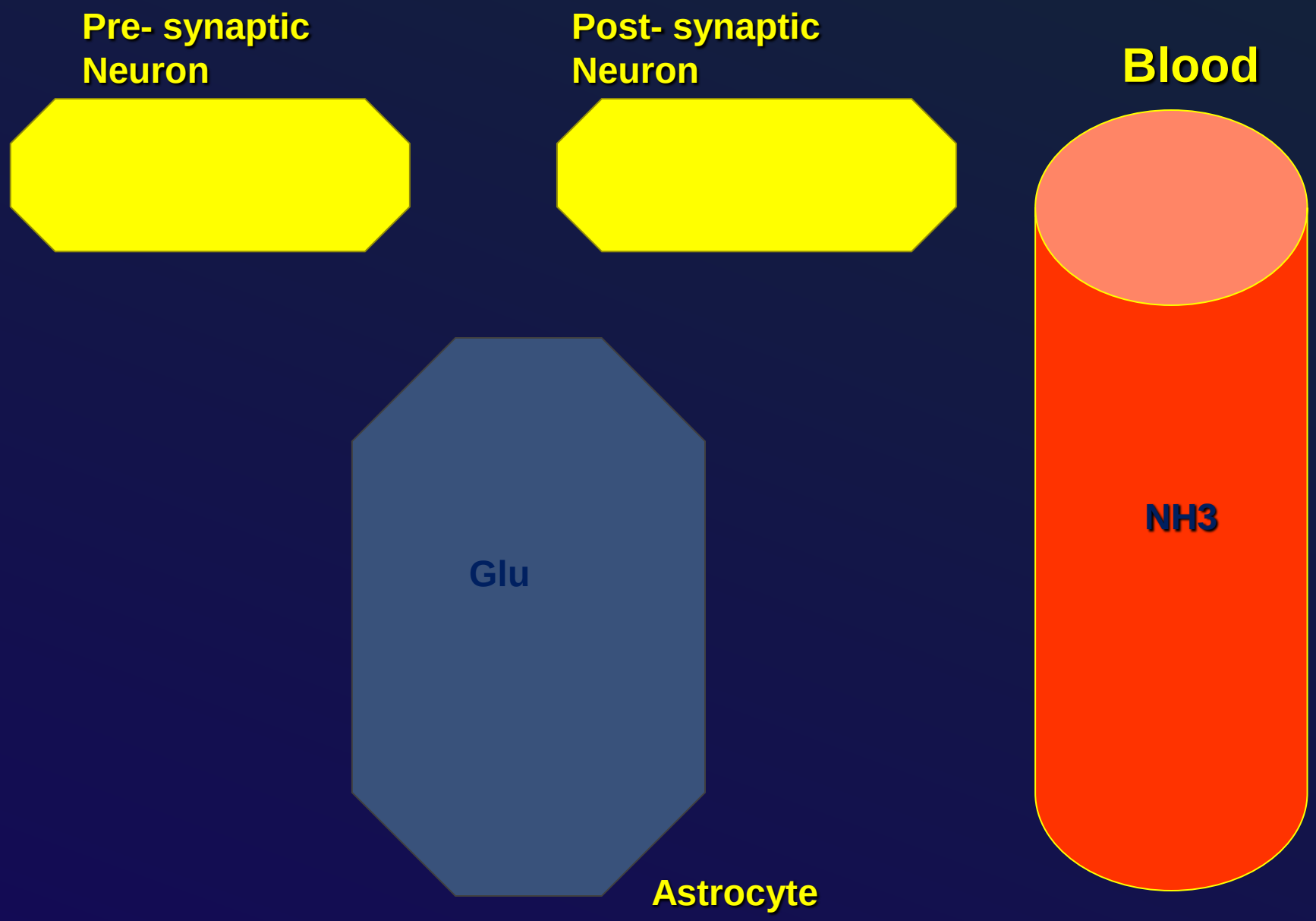
Glutamine-glutamate cycle



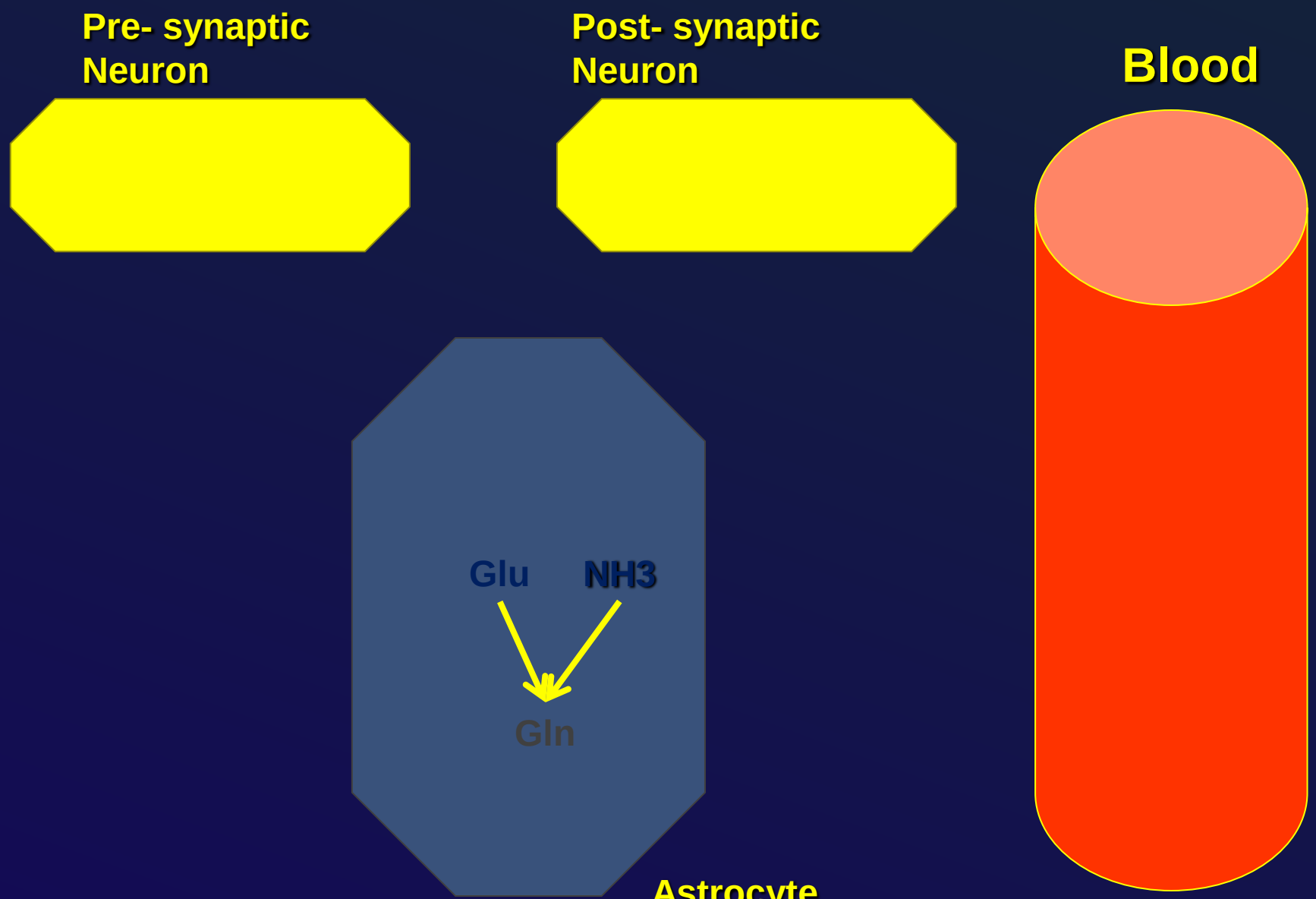
Glutamine-glutamate cycle



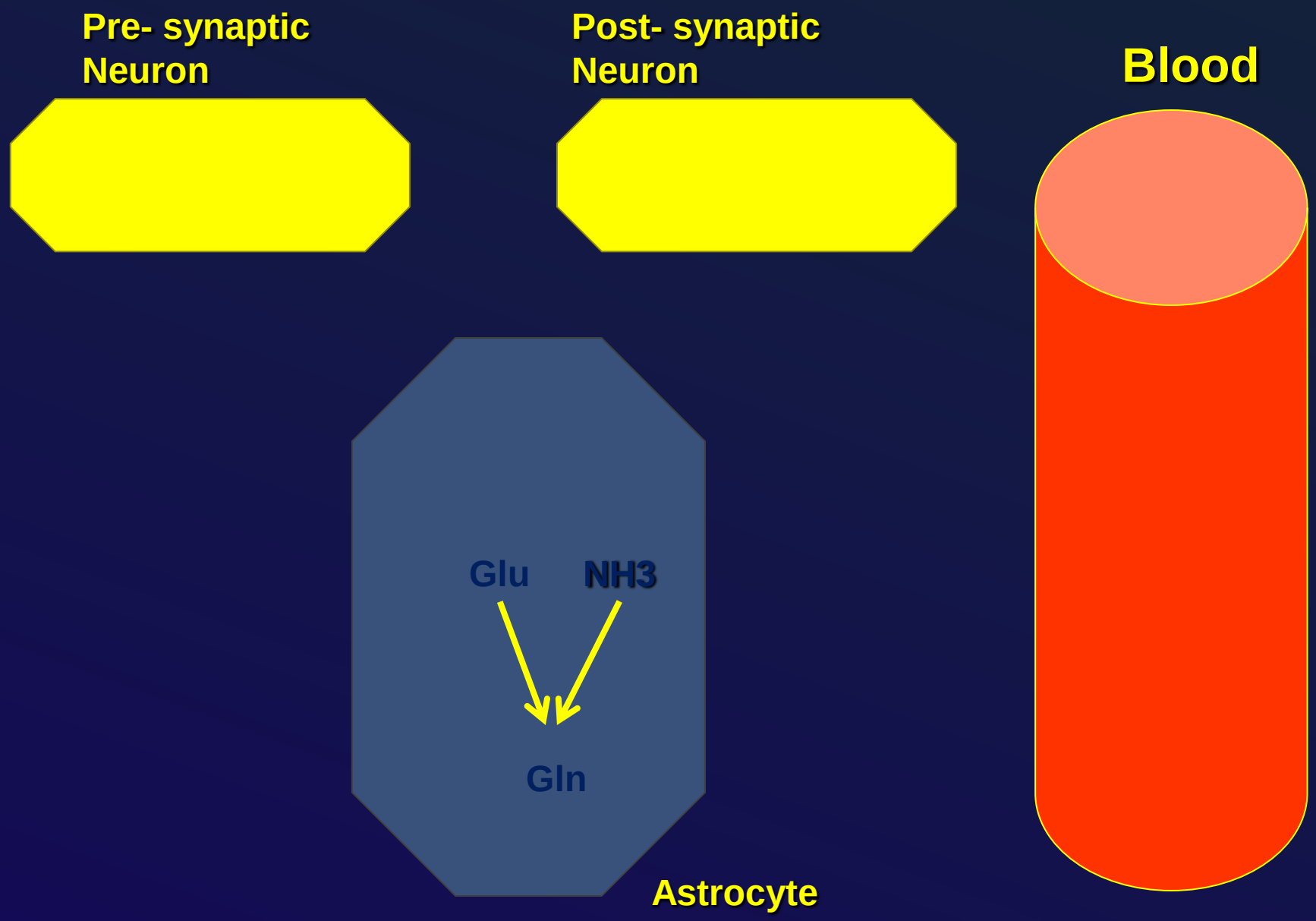
Glutamine-glutamate cycle



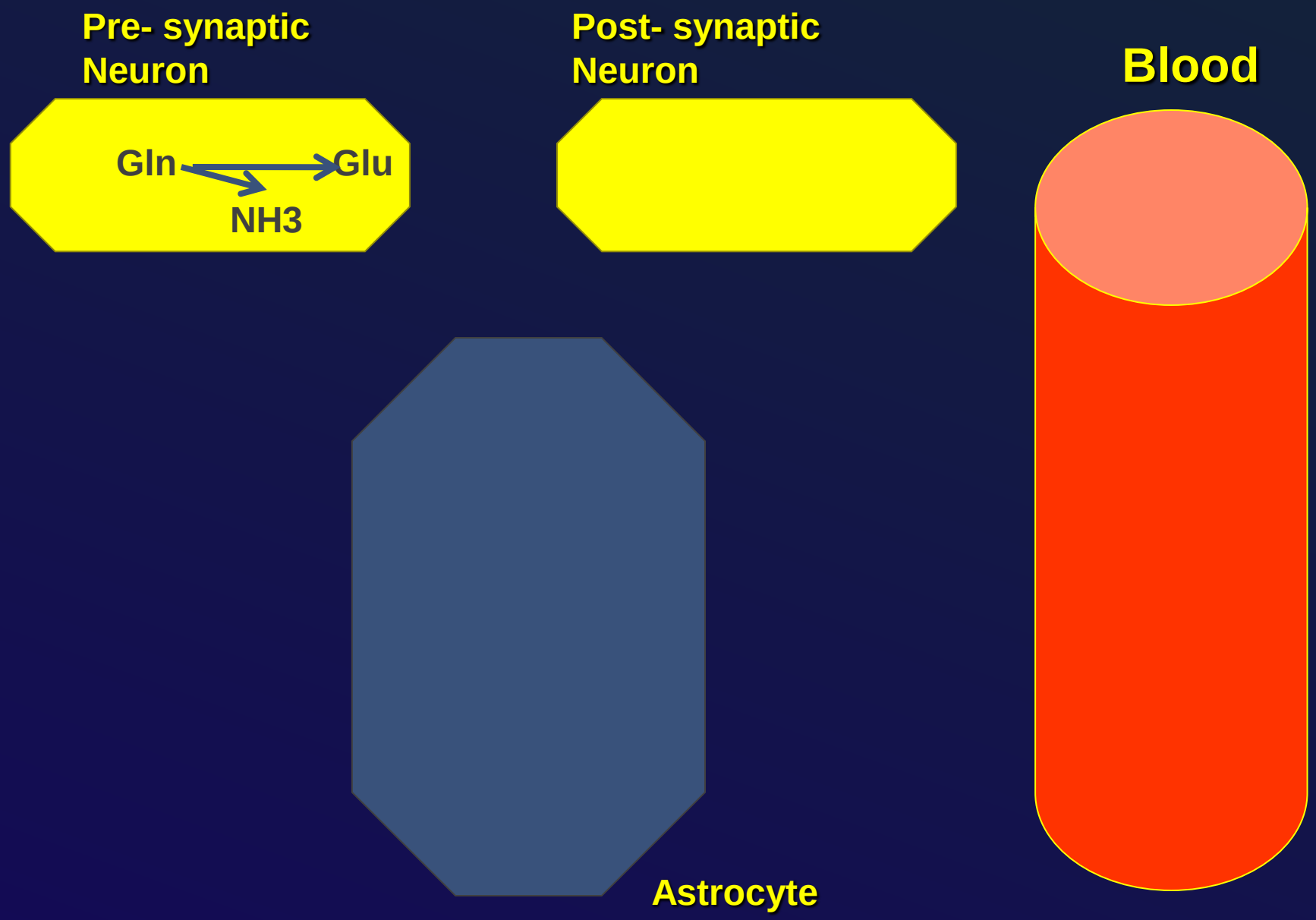
Glutamine-glutamate cycle



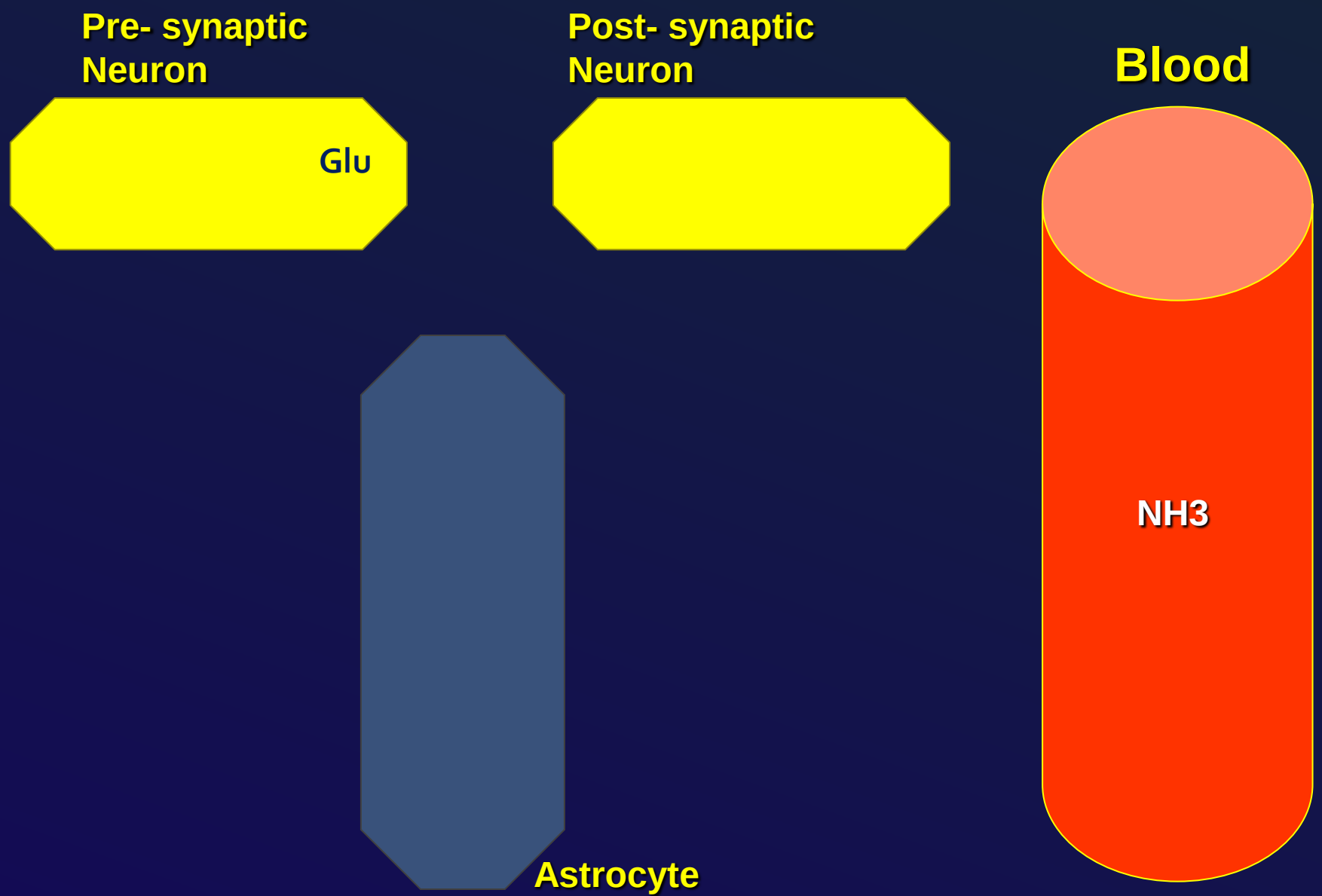
Glutamine-glutamate cycle



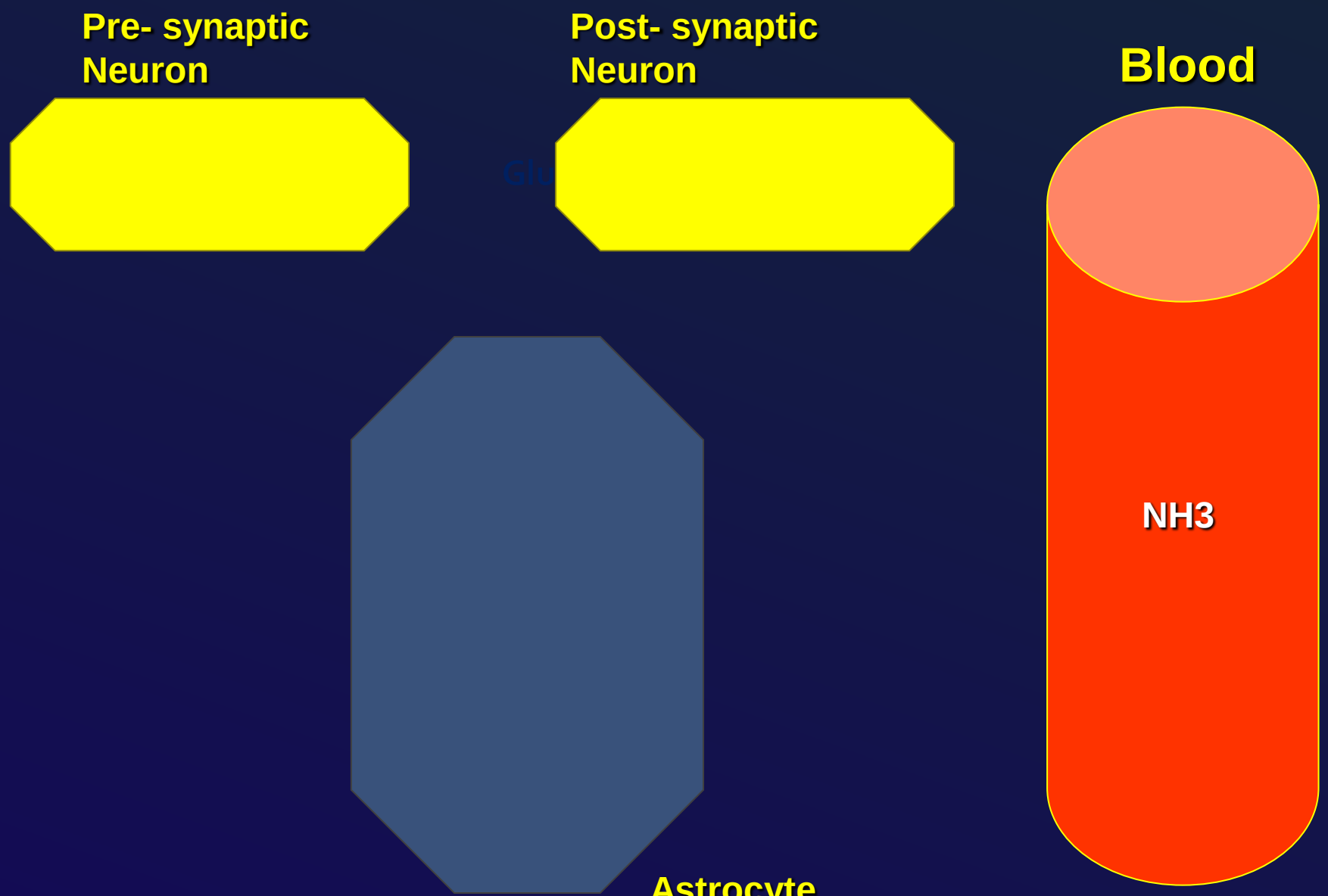
Glutamine-glutamate cycle



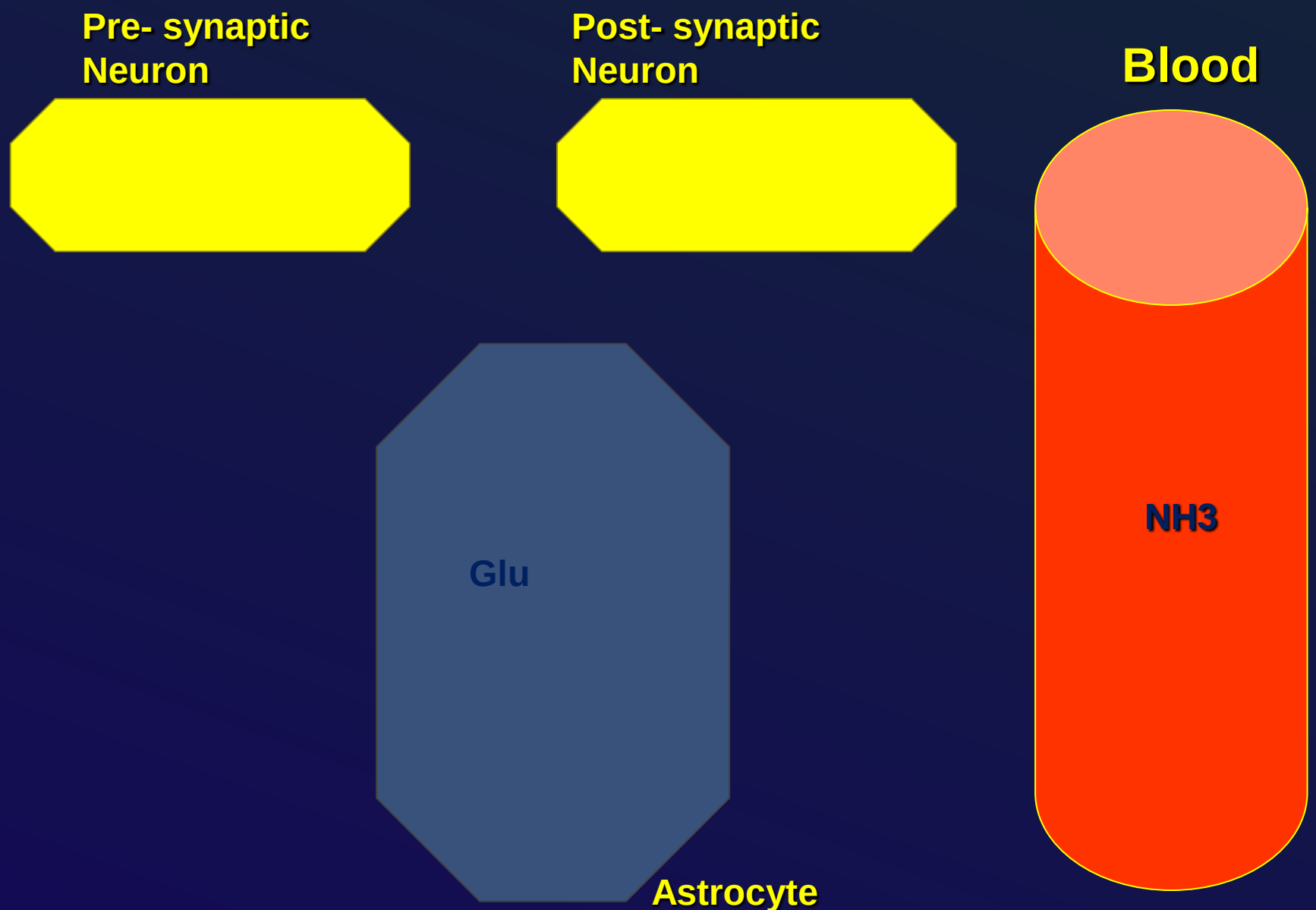
Glutamine-glutamate cycle in autistic brain



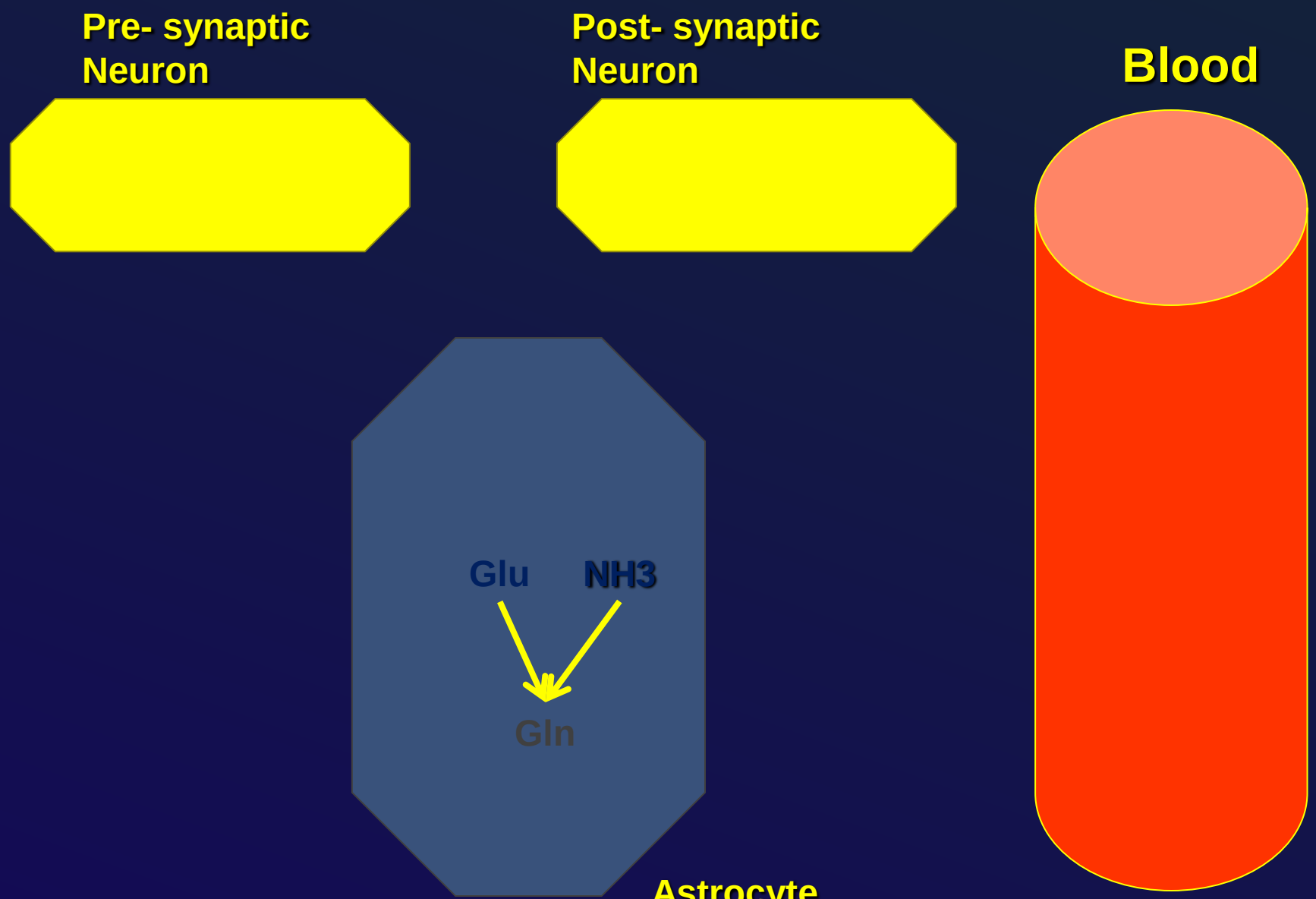
Glutamine-glutamate cycle



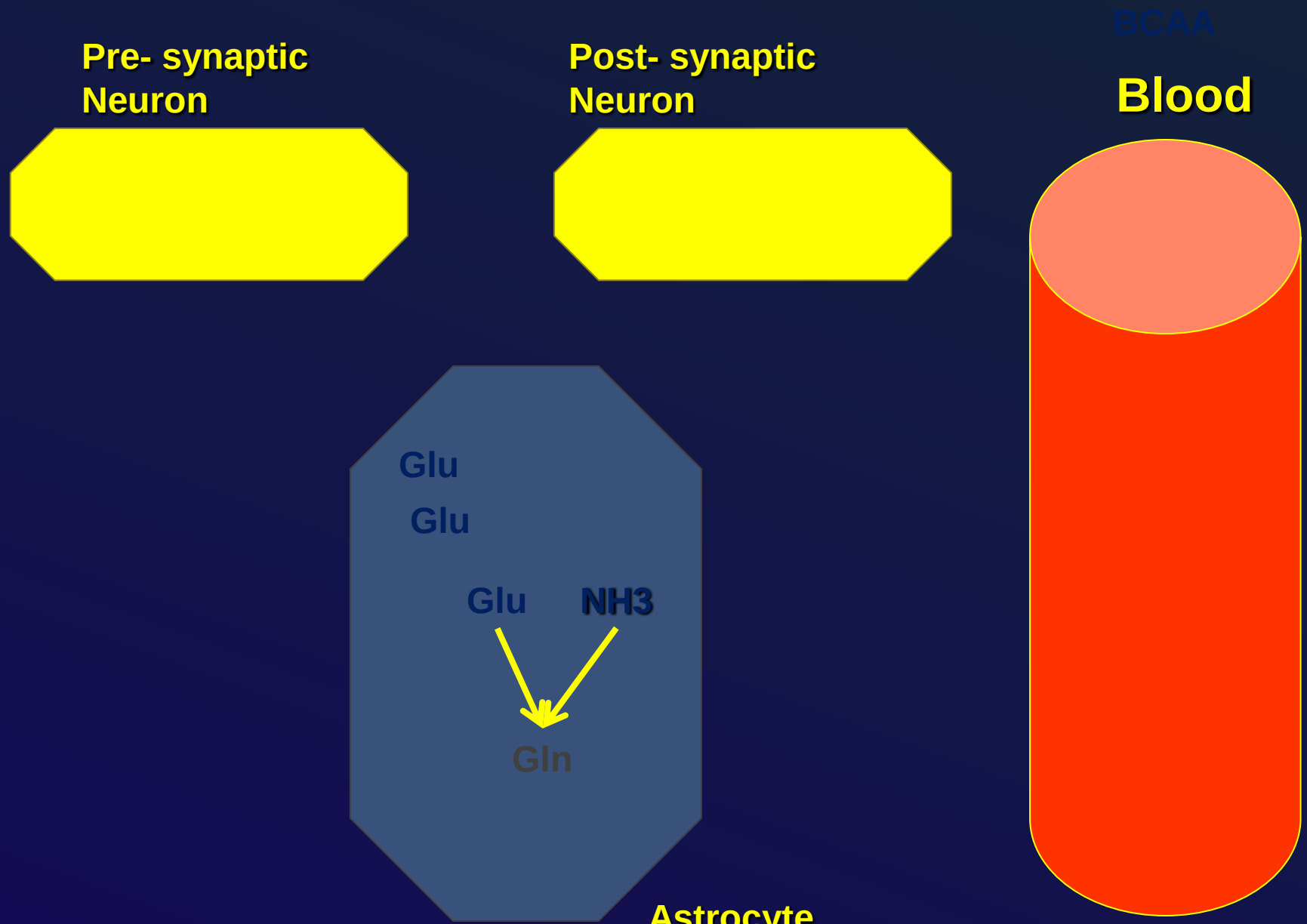
Glutamine-glutamate cycle



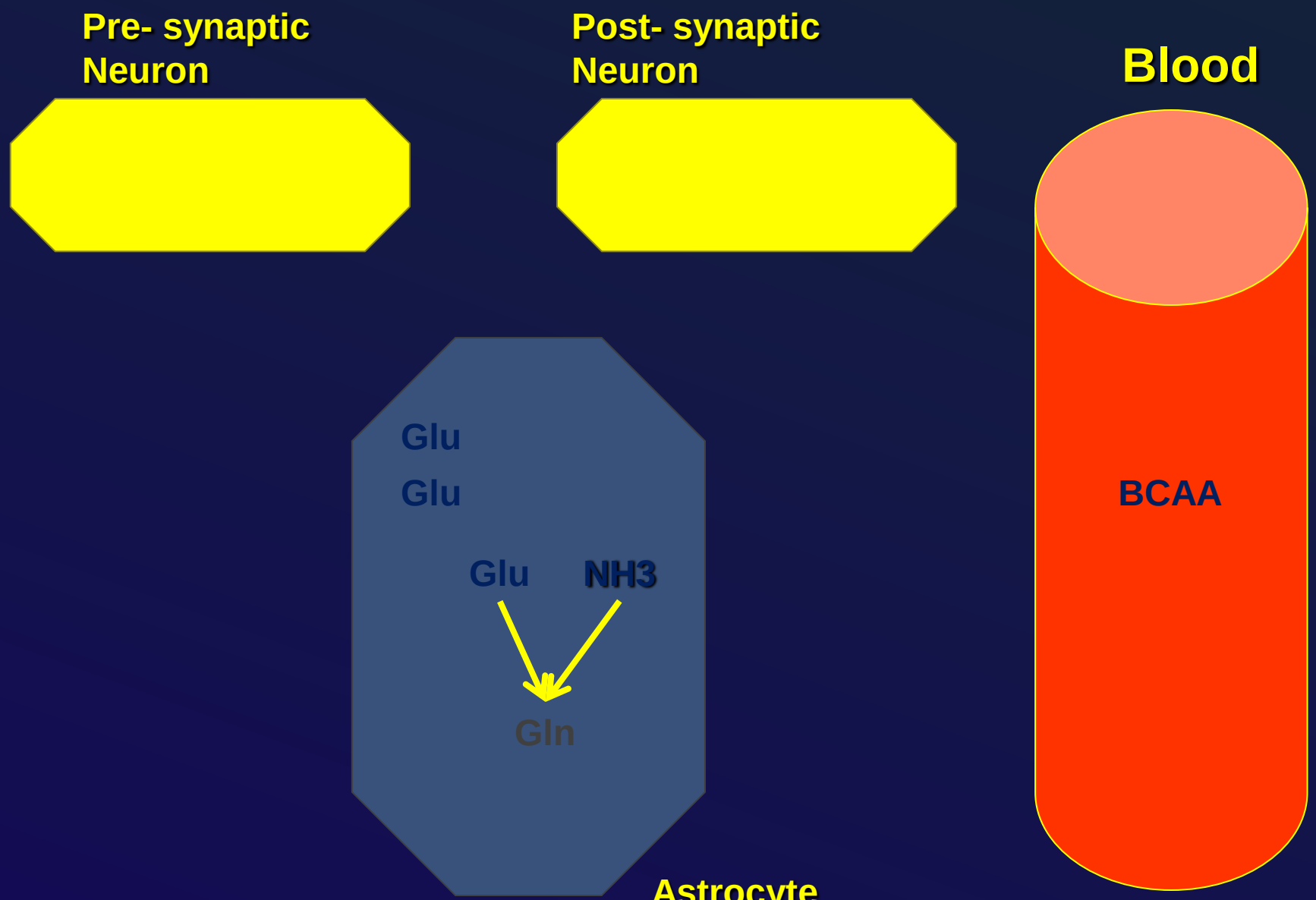
Glutamine-glutamate cycle



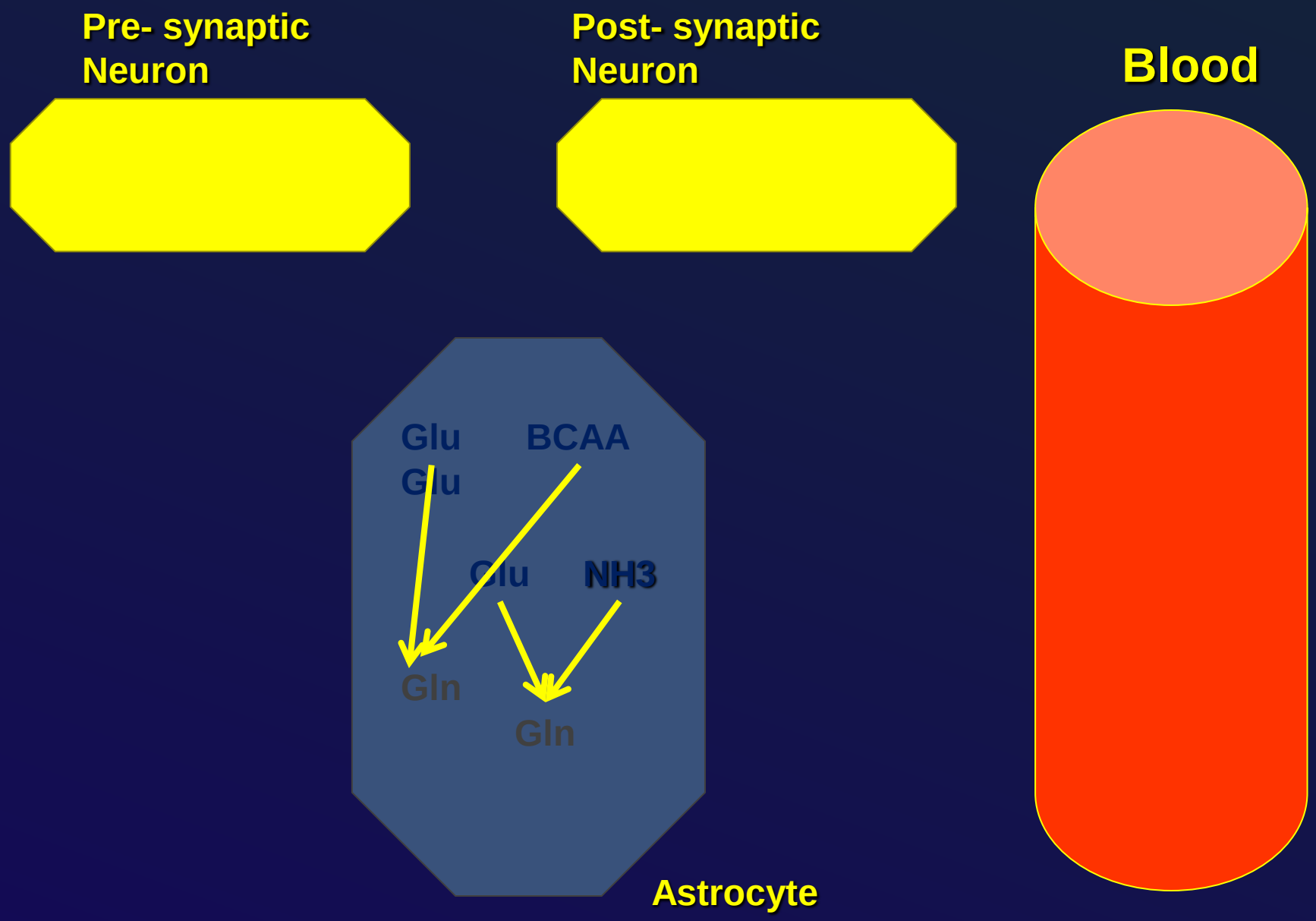
Glutamine-glutamate cycle



Glutamine-glutamate cycle

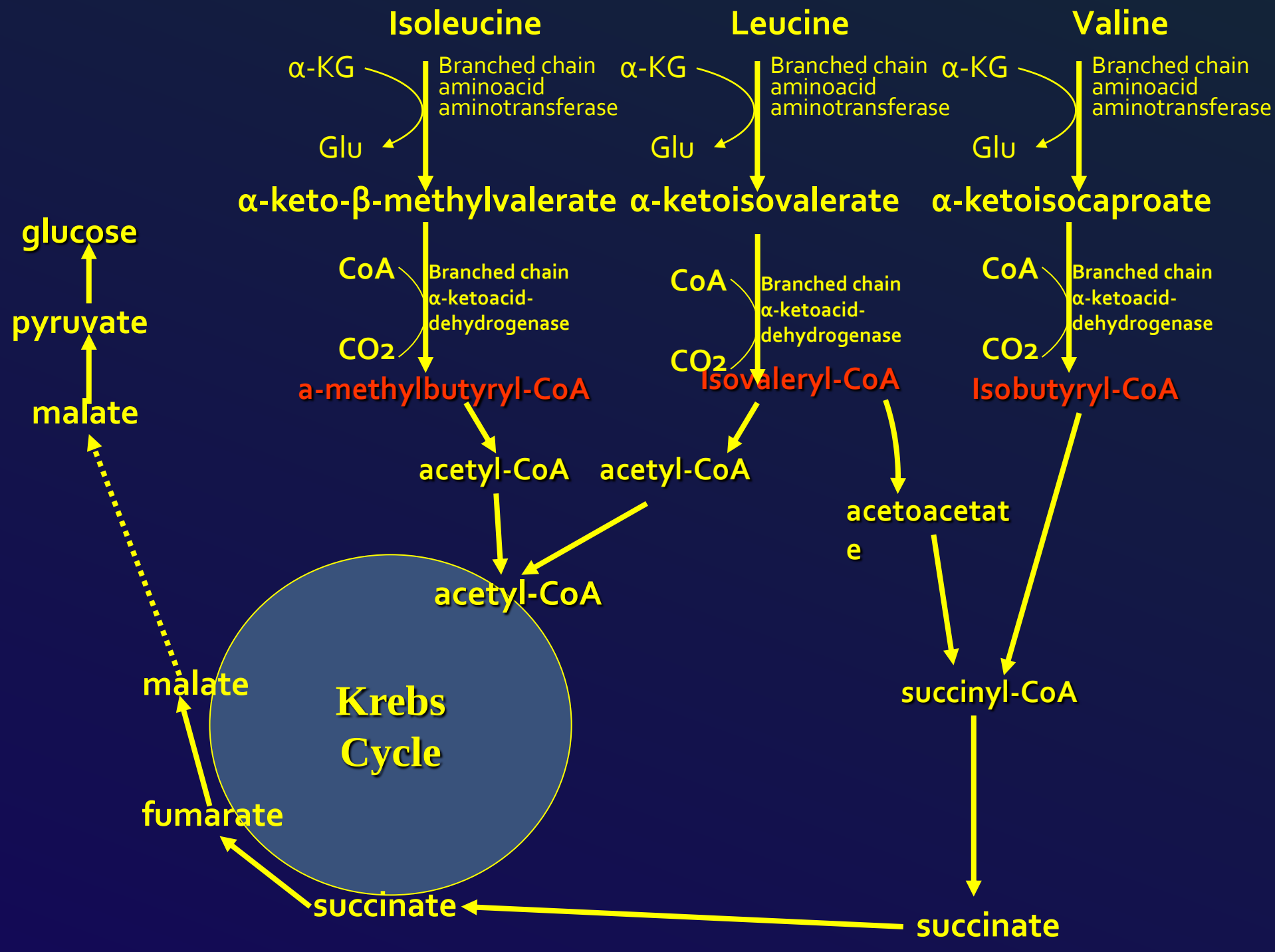


Glutamine-glutamate cycle



- Leucine: ketotic & glycogenic
- Isoleucine: ketotic
- Valine: glycogenic

Why as adjunctive to ketogenic diet?


Isoleucine
Leucine
Valine
α-KG
Glu
Branched chain aminoacid aminotransferase
α-keto-β-methylvalerate
α-ketoisovalerate
α-ketoisocaproate
CoA
CO2
Branched chain α-ketoacid-dehydrogenase
a-methylbutyryl-CoA
Isovaleryl-CoA
Isobutyryl-CoA
glucose
pyruvate
malate
acetyl-CoA
acetoacetate
Krebs Cycle
fumarate
succinyl-CoA
succinate

KETOGENIC DIET+BCAA patient example

- Patient K ….

- Initial diet: 1095 Kcal
- 22,875 g N = 91,5 Kcal
- 4,5 g CHO = 18 Kcal
- 109,5 g F = 985,5 Kcal

4:1 F+P/CHO

- BCAA containing:
- L-Valine……1,44 g
- L-Leucine ….2,175 g
- L-Isoleucine..1,2 g

Patient example (cont.)

- Adding 20g BCAA (SHS)
- (L-Valine 4,9 g, L-Leucine 9,1 g, L-Isoleucine 6 g)

- Total amount of BCAA i.e. BCAA(SHS) + BCAA (Ketocal)
- L-Valine 6,34 g, L-Leucine 11,275 g, L-Isoleucine 7,2 g

- Since 20 gr, additional BCAA are equivalent to 13,74 net protein we have a change in the ratio F/P+CHO from 4:1 as follows:
- 22,875 g N from BCAA Ketocal + 13,74 g N from BCAA SHS= 36,615 g= 146,46 Kcal
- 4,5 g CHO = 18 Kcal, 109,5 g F = 985,5 Kcal
- F = 109,5
- N + CHO = 41,11

- New ratio F / P+CHO = 2,66 / 1 (To 4:1 2,66 : 1), total calories 1149,96

COMPLICATIONS

- In 3 patients, a slight increase in heart rate was reported at the initiation of treatment, which returned to normal without a reduction in the dose of BCAA

- No other side effects were recorded during the BCAA administration period.

BCAA +Ketogenic Diet:Ketosis

- **By adding the BCAA, the fat/protein ratio of the diet changed from 4:1 to ~ 2.5:1 (depending on the patient's BW) without causing any alteration in degree of ketosis**

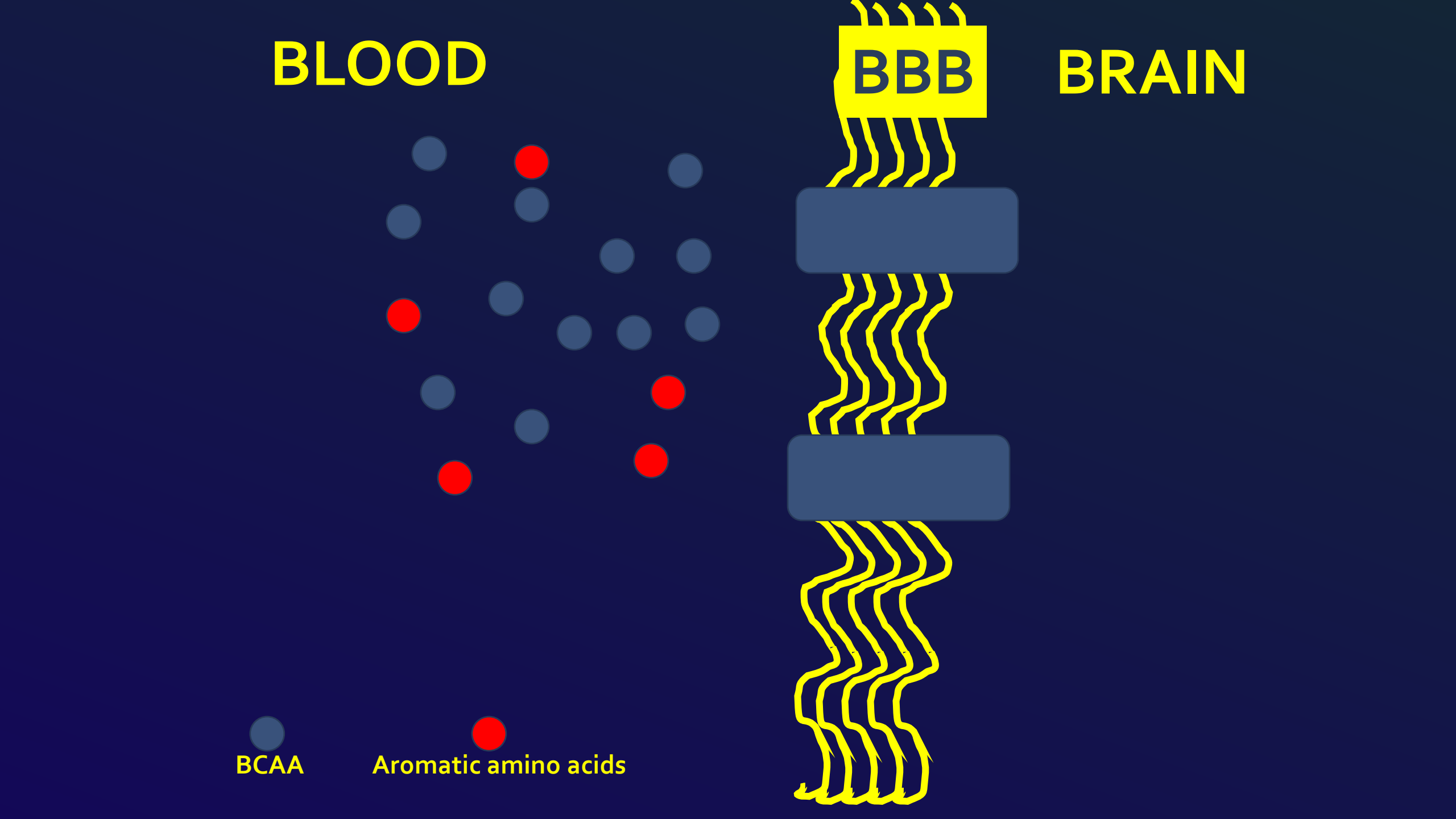
Branched Chain Amino Acids as Adjunctive Therapy to Ketogenic Diet in Epilepsy: Pilot Study and Hypothesis

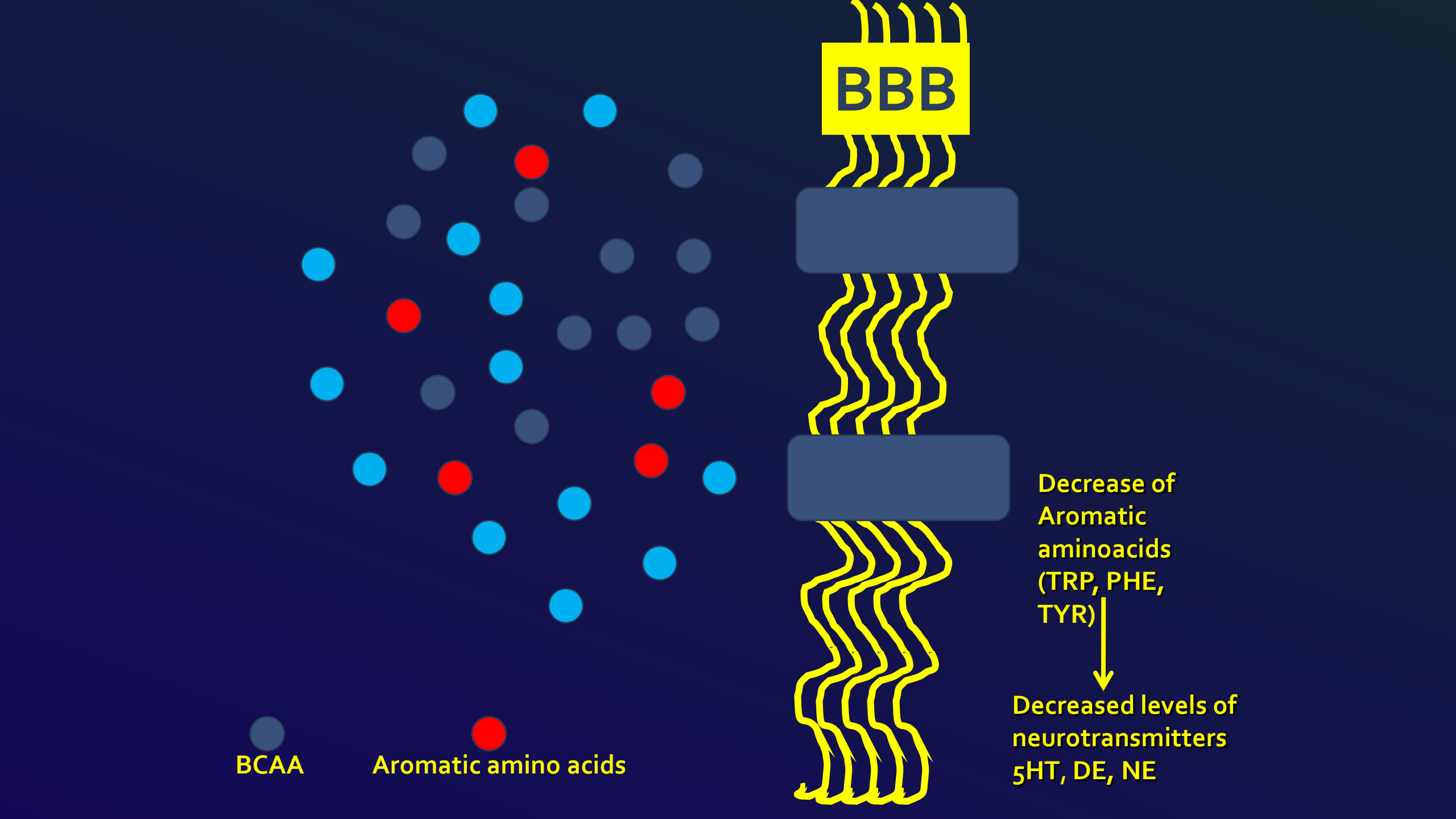
Evangeliou A, Doulioglou et al.

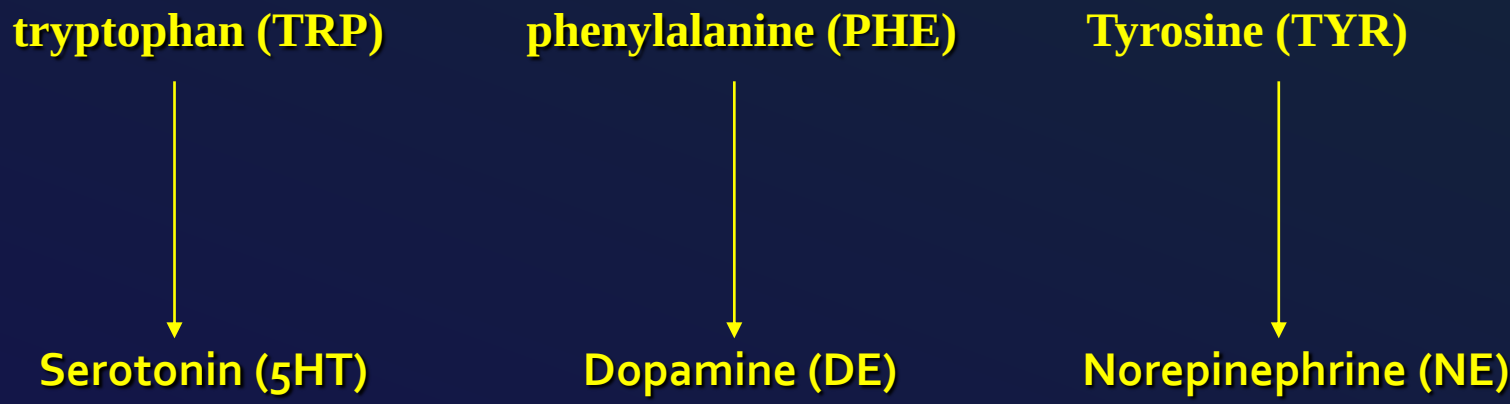
J Child Neurol. 2009;24:1268-1272.

COGNITIVE FUNCTION

- **According to the reports of parents and teachers, improvement was noted regarding behavior and cognitive functions in 9 of 17 patients, particularly in the areas of concentration, learning ability, and communication skills with other children.**


BLOOD
BBB
BRAIN
BCAA
Aromatic amino acids


BBB
Decrease of Aromatic aminoacids (TRP, PHE, TYR)
Decreased levels of neurotransmitters 5HT, DE, NE
BCAA
Aromatic amino acids


tryptophan (TRP)
phenylalanine (PHE)
Tyrosine (TYR)
Serotonin (5HT)
Dopamine (DE)
Norepinephrine (NE)

Branched chain aminoacids in the treatment of autism.

Asprangathou D, Spilioti M, Papadimitriou I, Evangeliou A.

At the beginning of the study, the pediatric psychiatric evaluation according to the Childhood Autism Rating Scale yielded **26 (47.27%)** patients with scores of 30 and 36, or mild to moderate autistic condition, whereas **29 (52.73%)** patients had scores between 37 and 54, that is, more severe cases.

32 (58.18 %) received BCAAt beyond 4 weeks, whereas the remaining 23 patients (41.82 %) didn’t. The reason they stopped the BCCA for 10 patients was the disagreeable testing, while in 13 patients was the high BCAA cost.

Branched chain aminoacids in the treatment of autism

(55 patients).*Asprangathou D, Spilioti M, Papadimitriou I, Evangeliou A.*

Patients receiving the BCAA was 58.18.%, significantly higher than the set target of 50% (Z = 1.391; P <.001).

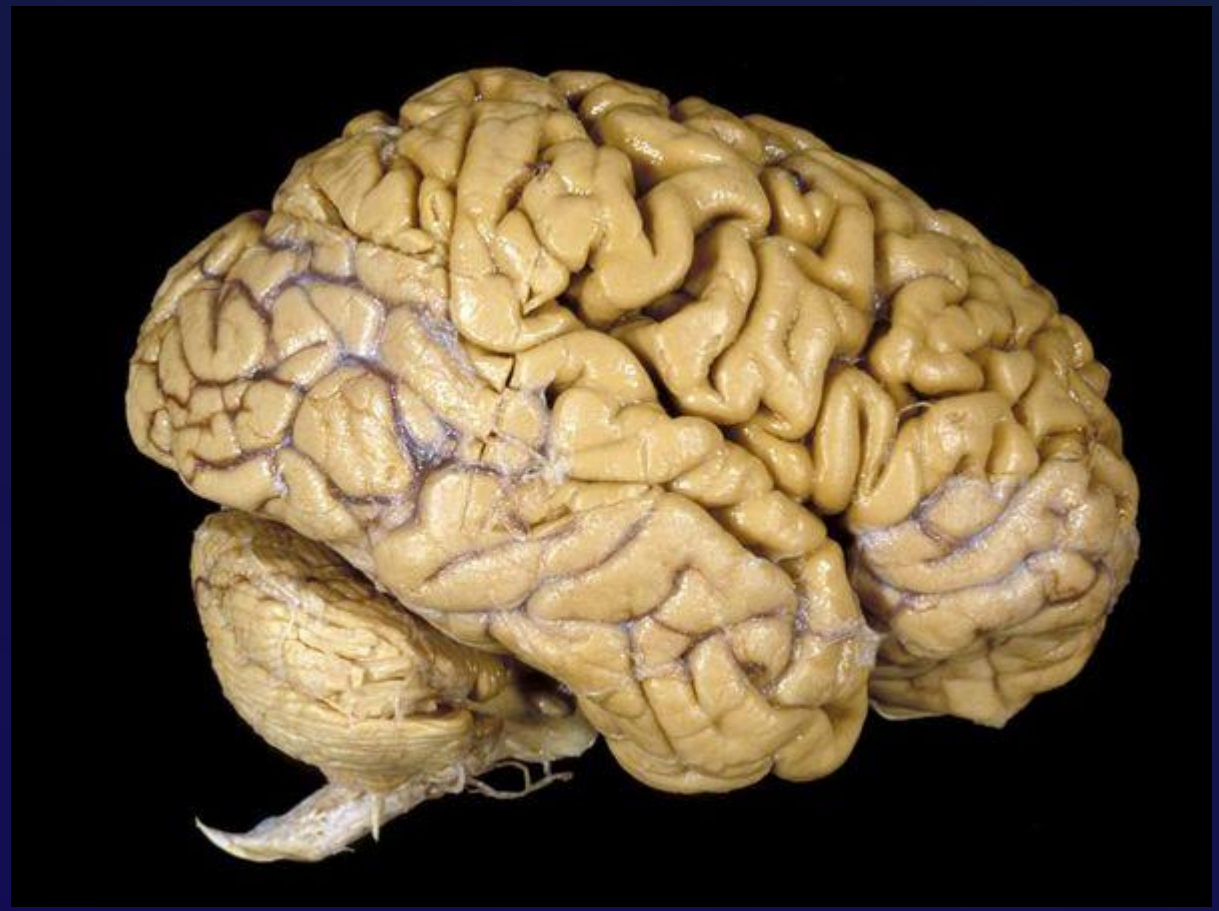
32 (58.18 %) received BCAAt beyond 4 weeks, whereas the remaining 23 patients (41.82 %) didn't. The reason they stopped the BCCA for 10 patients was the disagreeable testing, while in 13 patients was the high BCAA cost.

Of these 32 patients, 6(10.9%)discontinued application after 4 to 10 weeks owing to lack of improvement. The remaining 26 patients (47.27%), who concluded the BCAA ingestion for more than 10 weeks period, presented with improvements in their social behavior and interactions, speech, cooperation, stereotypy, and, principally, hyperactivity, which contributed significantly to their improvement in learning.

GENES

REST OF THE BODY

ENVIRONMENT



SOCIAL ROBOT

VIDEO-EEG RECORDING

3T MRI +MRS+ TRACTOGRAPHY

PET-SCAN

AFFILIATED METABOLIC LAB

GC/MS
Tandem MS/MS
HPLC
Whole exome sequencing

PAPAGEORGIOU GENERAL HOSPITAL

PROJECT MANAGEMENT OFFICE
PROJECT PORTFOLIO

The PMO was established in 2017 in order to coordinate a portfolio of several national and international projects and to ensure projects are meeting strategic objectives, staying on budget and sticking to their original goals

PAPAGEORGIOU GENERAL HOSPITAL

PROJECT MANAGEMENT OFFICE
PROJECT PORTFOLIO

INTERREG V-A
GREECE - BULGARIA
2014-2020
COOPERATION PROGRAMME

IMPROVING QUALITY AND ACCESSIBILITY OF SOCIAL HEALTH CARE SERVICES IN CROSS-BORDER REGIONS / HEALTH CARE CENTER

Interreg
Greece-Bulgaria
EUROPEAN UNION

PAPAGEORGIOU GENERAL HOSPITAL

PROJECT MANAGEMENT OFFICE
PROJECT PORTFOLIO

Atlantis - Hospital Observation Program

Cooperation Program between Papageorgiou General Hospital and St. Mary´s Institute for Educational Excellence, LLC,

ATLANTIS PROJECT
Experience European Healthcare

PAPAGEORGIOU GENERAL HOSPITAL

PROJECT MANAGEMENT OFFICE
PROJECT PORTFOLIO

Erasmus + Programme

Early care training programme for health care professionals working with children born with orofacial clefts and/or craniofacial conditions.

Health Innovation, implementation and Impact (HI3) - A functional training program on how to implement sustainable change in the health care system on a clinical level.

Act Now - A training program development for healthcare professionals to use the principles of acceptance and commitment therapy (ACT) to facilitate patient adjustment to the challenges of living with a visible difference

PAPAGEORGIOU GENERAL HOSPITAL

PROJECT MANAGEMENT OFFICE
PROJECT PORTFOLIO

3rd Health Programme / HP-JOINT ACTION

Facilitating the Authorisation of Preparation Process for blood and tissues and cells - GAPP

eHAction

3rd Health Programme

GAPP

European Commission

PAPAGEORGIOU GENERAL HOSPITAL

PROJECT MANAGEMENT OFFICE
PROJECT PORTFOLIO

ESPA 2014-2020

- Social Robots as Tools in Special Education
- 3DLIVER
- PVClinical

ΕΣΠΑ 2014-2020
ανάπτυξη - εργασία - αλληλεγγύη
Partnership Agreement 2014 - 2020

EPAnEK 2014–2020
OPERATIONAL PROGRAMME
COMPETITIVENESS
ENTREPRENEURSHIP
INNOVATION

PAPAGEORGIOU GENERAL HOSPITAL

PROJECT MANAGEMENT OFFICE
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EUROPEAN CLEFT AND CRANIOFACIAL INITIATIVE FOR EQUALITY IN CARE

COST ACTION 16234

cost
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY
COST is supported by the Framework Programme Horizon 2020

PAPAGEORGIOU GENERAL HOSPITAL

Contact Us

aeevange@auth.gr

+30-2313-323916

+30-6942868720