

## Branched Chain Amino Acids as Adjunctive Therapy to Ketogenic Diet

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## Ketogenic diet

- Over the last decades the ketogenic diet has become a valuable weapon in the management of intractable seizures.
- However, not all patients have truly benefited from this therapy.
- In addition, the application of this diet is limited by the fact that many patients cannot tolerate it while others present with side effects.

## 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

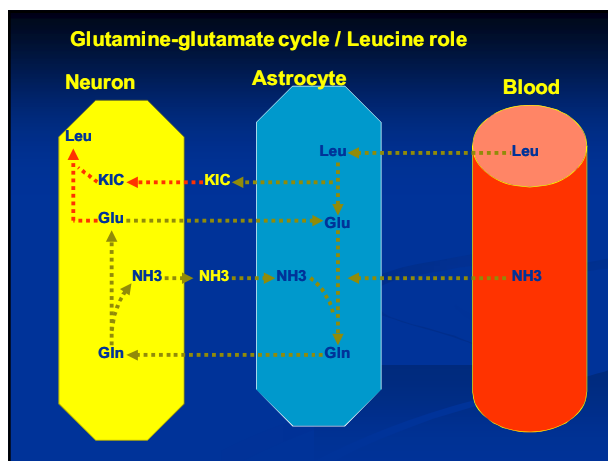
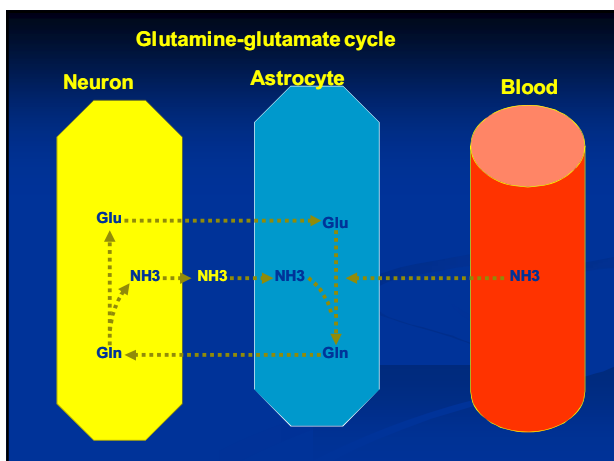
■ WHY?

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

- 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.

## BCAA-Antiepileptic action

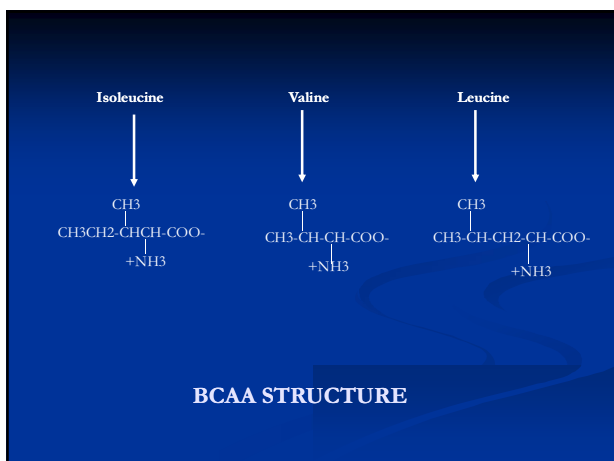
- BCAA buffer excessive amounts of Glutamate by converting it to Glutamine.



### Why as adjunctive to ketogenic diet?

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

## BCAA BIOCHEMISTRY

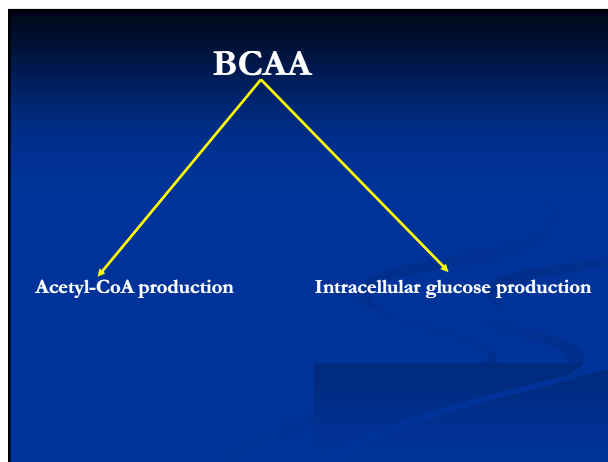
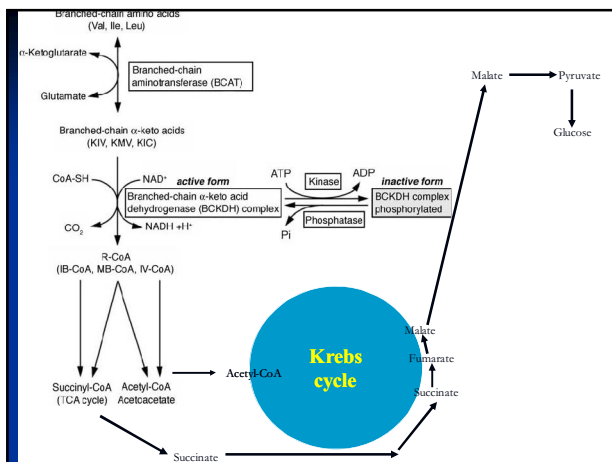
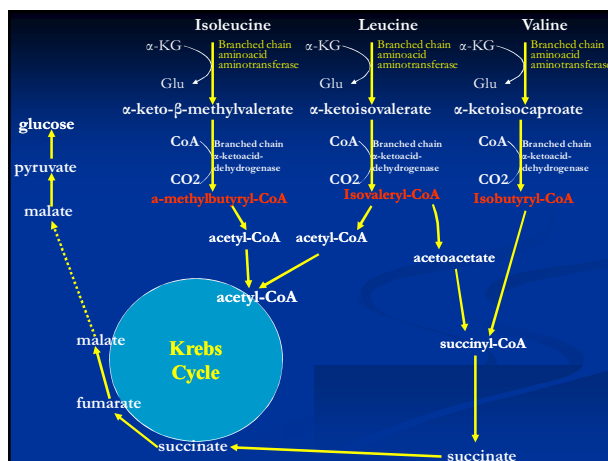


### BCAA PROPERTIES (1)

- BCAA commonly account for ~20–25% of most dietary proteins.
- Dietary BCAA largely escape first-pass splanchnic metabolism.
- The first steps in their catabolism are common to all three, involving the BCAA aminotransferase (BCAT) and branched chain a-keto acid dehydrogenase (BCKD).
- Their further metabolism employs distinct pathways to different endproducts (glucose and/or ketone bodies).

## BCAA PROPERTIES (2)

- Their circulating concentrations can influence the brain uptake of precursor amino acids for neurotransmitter synthesis, and they can regulate protein synthesis in a variety of tissues.
- They play crucial roles in determining the structures of globular proteins as well as the interaction of the transmembrane domains of membranous proteins with phospholipid bilayers.
- The fact that the flux-generating step for the catabolism of the three BCAAs occurs at one of the common steps indicates that the production of these downstream products are not individually regulated and, hence, may not play important individual roles.



J.B.M. Vianna et al.  
 The oral glucose tolerance test is frequently abnormal in patients with uncontrolled epilepsy  
 Epilepsy & Behavior 9 (2006) 140–144

## OGTT IN EPILEPTIC CHILDREN

Unpublished data  
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## OGTT IN EPILEPTIC CHILDREN

Patients were divided in 3 groups.

- **Group A:** 20 children (7 males, 13 females) with medically refractory epilepsy, which can be defined as inadequate seizure control despite appropriate medical therapy with at least 2 anti-epileptic drugs (AEDs) in maximally tolerated doses for 18 months – 2 years. These children were not good candidates for surgery.
- **Group B:** 22 children (16 males, 6 females) with well-controlled epilepsy with 1 AED or a combination of AEDs.
- **Group C:** 33 children (17 males, 16 females) who developed seizures for the first time in their lives and did not receive treatment with AEDs.

## OGTT IN EPILEPTIC CHILDREN

EARLY RESULTS

### OGTT CURVES

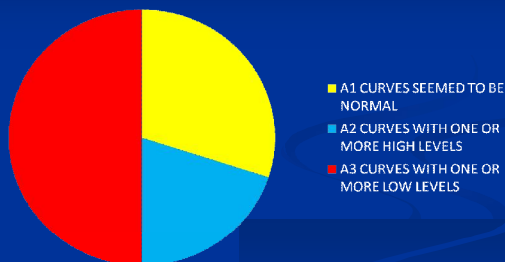
Patients with intractable seizures (Group A)

**Group A1:** 6 children (6/20, 30% of Group A), whose OGTT curve seemed to be normal (neither high nor low levels at any time of the OGTT).

- **Group A2:** 4 children (4/20, 20% of Group A), whose OGTT curve had one or more high levels at some time.
- **Group A3:** 10 children (10/20, 50% of Group A), whose OGTT curve had one or more low levels at some time.

## OGTT IN EPILEPTIC CHILDREN

GROUP A (PATIENTS WITH INTRACTABLE EPILEPSY)



## BCAA and ketogenic diet

### PATIENT SELECTION (1)

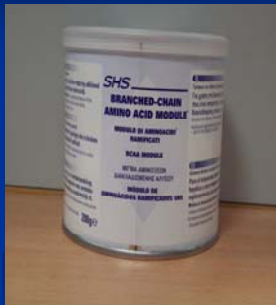
- 17 children aged 2 to 7 years, with intractable epilepsy, who were administered a ketogenic diet for a period of 6 to 24 months.
- 13/17 patients had a seizure reduction of 40% to 90%, while 4 of them had no improvement at all.

### REQUIREMENT FOR INCLUSION IN THE STUDY

- Observation period of 3-months before the administration of branched chain amino acids.
- No change in the number of seizures during this period
- Patients with an any inborn error of metabolism

## METHODS (1)

- A carbohydrate-free branched chain amino acids powdered mixture containing 45.5 g of leucine, 30 g of isoleucine, and 24.5 g of valine was administered to all participants.



## METHODS (2)

- Initially a daily dose of 5g and weekly increments of 5 g, up to a maximum of 20 g/d, until we reached the final 2.5:1 fat-to-protein ratio.
- We measured daily urine ketones throughout the study.

## METHODS (2)

### EEG

- Before BCAA supplementation.
- 4 weeks, 3 and 6 months after achieving the final dosage.

## 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 = 41,31
- ↓
- 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

Results of BCAA supplementation to the KD on seizure decrease and number of AEDs

aa	Diagnosis	Diet onset (Age years)	Follow-up (months) Only KD	Follow-up (months) KD+BCAA	Seizure decreasing Only KD (%)	Seizure decreasing KD+BCAA (%)	AED Pre	AED Only KD	AED KD+BCAA
1	PR	2	24	6	90	100	3	1	-
2	PR	7	9	6	60	100	3	2	1
3	L-G		9	6	60	100	2	1	1
4	E	3	15	12	70	90	3	2	1
5	E	2	9	6	70	90	3	2	1
6	L-G	4	9	6	60	90	3	3	2
7	FL	7	12	12	50	80	4	3	3
8	I	2	18	2	20	50	2	2	2
9	L-G	4	6	6	50	-	2	2	2
10	L-G	5	12	12	50	-	3	3	3
11	L-G	4	9	6	40	-	3	3	3
12	West	2	9	6	40	-	4	4	4
13	I	3	10	6	40	-	3	3	3
14	I	4	6	6	-	-	4	4	4
15	West	2	6	6	-	-	4	4	4
16	I	5	6	6	-	-	3	3	3
17	P	3	6	6	-	-	4	4	4

Abbreviations: BCAA branched chain aminoacids, KD=ketogenic diet, AED=antilepileptic drugs, PR: psychomotor retardation L-G: Lennox-Gastaut, E: encephalitis, F-L: frontal lobe, I: Idiopathic, P: pachygyria.

Seizure decreasing Only KD (%)	Seizure decreasing KD+BCAA (%)	AED Pre	AED Only KD	AED KD+BCAA
90	100	3	1	-
60	100	3	2	1
60	100	2	1	1
70	90	3	2	1
70	90	3	2	1
60	90	3	3	2
50	80	4	3	3
20	50	2	2	2
50	-	2	2	2
50	-	3	3	3
40	-	3	3	3
40	-	4	4	4
40	-	3	3	3
-	-	4	4	4
-	-	4	4	4
-	-	3	3	3
-	-	4	4	4

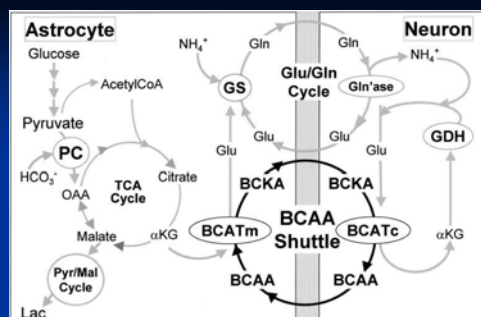
## KETOGENIC DIET AND BCAA

### HOW DOES IT WORK ?

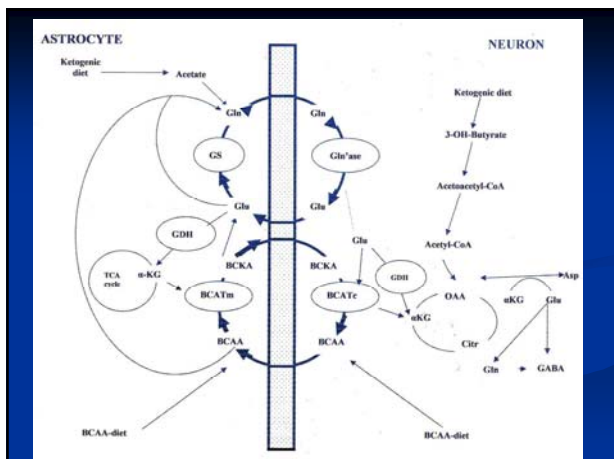
#### Synergy KD & BCAA?

All 8 patients who benefited from the BCAA, also benefited from the ketogenic diet.

This strengthens the hypothesis that BCAA and ketogenic diet act in a synergistic way.

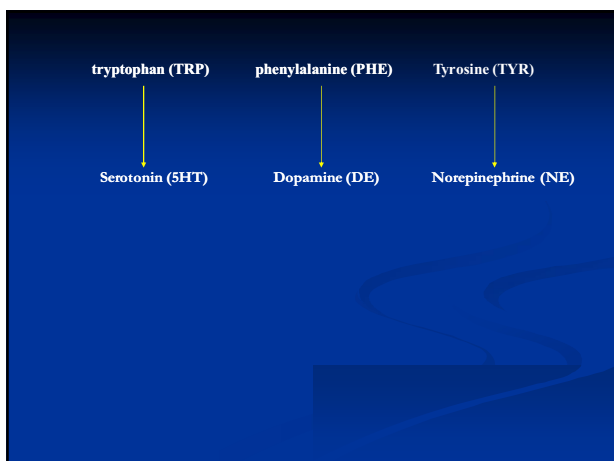
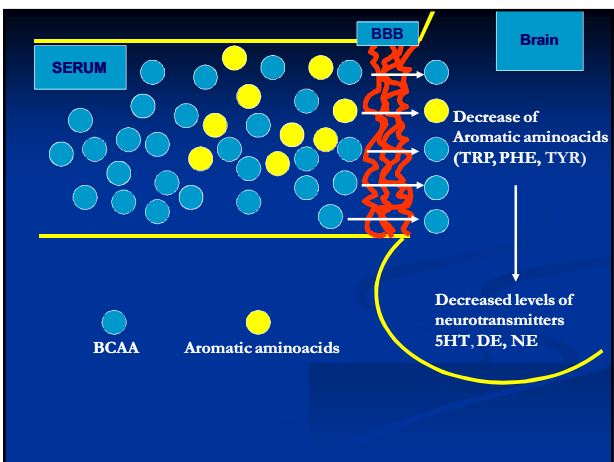
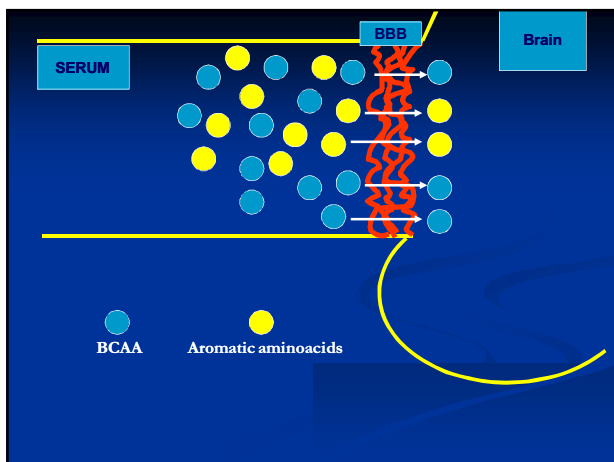


BCAA shuttle and brain glutamate metabolism. Abbreviations are: BCAA, branched-chain amino acids; BCKA, branched-chain a-keto acids; Gln'ase, glutaminase; GDH, glutamate dehydrogenase; a-KG, a-ketoglutarate; OAA, oxaloacetate; PC, pyruvate carboxylase; TCA Cycle, tricarboxylic acid cycle (Hutson et al).



## 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.



## CONCLUSIONS (1)

- By adding the branched chain amino acids, we have a change to the fat-to-protein ratio without causing any alteration in ketosis.
- BCAA may increase the effectiveness of ketogenic diet acting with a possible synergistic way.

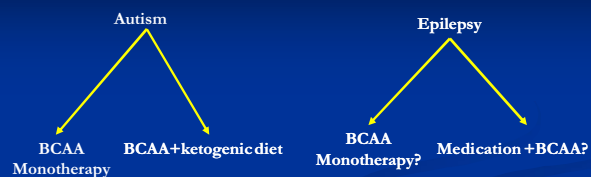
## CONCLUSIONS (2)

- BCAA may increase the effectiveness of ketogenic diet.
- Possible mechanisms.
  - Ammoniac donors to Glutamate.
  - Improved energy balance.
  - Increased GDH effectiveness.
  - Increased flux through the Krebs cycle, facilitating GABA formation
- May improve the cognitive functions by decreasing the levels of aromatic aminoacids

### Unresolved issues

- Ideal dosage?
- BCAA-monotherapy?

## FUTURE PERSPECTIVES



## OTHER THERAPEUTICAL IMPLICATIONS OF BCAA

- Liver diseases
- Reducing central fatigue
- Exercise and sports
- Burn, Trauma, and Sepsis
- Diabetes
- Mania

