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**BC368 - Biochemistry of the Cell II**
**Case Study #8**

## Background:

A 26-year-old, natural, amateur bodybuilder is rushed to the hospital after vomiting and experiencing confusion before collapsing at his local gym. The patient's trainer mentions that there is a bodybuilding competition coming up, and that the patient has been on a low-calorie and strictly high-protein diet for the past few days. Doctors believe that the patient is unconscious due to a lack of carbohydrates. Additionally, it is hypothesized that the patient's blood may have high levels of ammonia due to their high-protein diet. The patient's blood is drawn to test for hypoglycemia, lactic acidosis, and hyperammonemia. These findings are depicted in **Table 1**.[1]

## Initial Lab Findings:

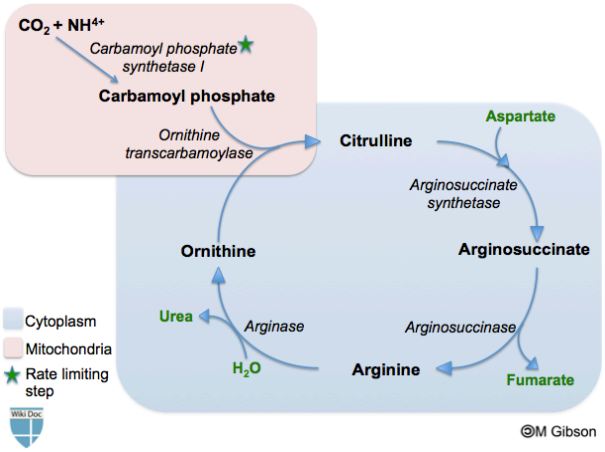
**Table 1**. The patient's initial blood testing results after admittance to the hospital.

| Compound | Reading | Normal Range |
|---|---|---|
| Blood Glucose | 2.5mM | 3.9-5.5mM |
| Blood Lactate | 4.1mM | 0.5-2.2mM |
| Plasma Ammonia | 218 µmol/L | 11–32µmol/L |

**Question 1.** What factors might account for these changes in the patient's blood composition? Disruptions in which pathway would explain their plasma ammonia level?

## Biochemistry:

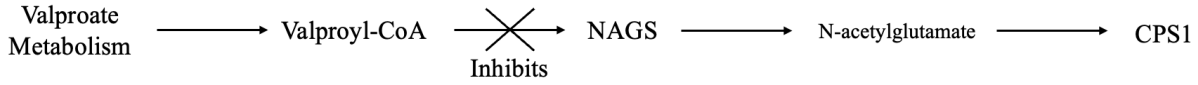
The urea cycle is a five-step pathway that helps process the excess ammonia produced by amino acid breakdown. This pathway leads to the production of urea, which can be excreted through urine. Buildup of ammonia is toxic to the liver, and the inability to remove it can lead to hyperammonemia and death. The urea cycle is active when glutamate levels are high in the blood, which indicates high levels of protein breakdown. The process is energy-intensive and uses ATP to power its reactions.



**Question 2.** Based on the patient's initial lab findings in Table 1, explain the biochemical mechanisms that account for each of the three abnormal readings (hyperammonemia, hypoglycemia, and lactic acidosis). Additionally, how do these findings relate to the patient's presenting symptoms of vomiting, confusion, and loss of consciousness?

**Further Developments:**

The patient wakes up and reveals he has a history of bipolar disorder, and he has been taking a drug called valproate for the past few days, since he thought it would reduce the anxiety that he has for his show. Valproate metabolism results in an intermediate, valproyl-CoA, which inhibits N-acetylglutamate synthase (NAGS).[2] This enzyme synthesizes N-acetylglutamate, which is an allosteric activator of carbamoyl phosphate synthetase (CPS1).[2] With this information, the clinical team decided to run more tests for urea cycle intermediates.




**Mechanism 1.** Inhibition of NAGS by valproyl-CoA leads to decreased N-acetylglutamate and CPS1 activity.

**Question 3.** How might the presence of these species lead to the patient's symptoms? Which urea cycle intermediates would you expect to find in a blood sample?

**Question 4.** Why might this patient be affected by valproate more than the average person?

References:


1. Tarafdar, S.; Slee, M.; Ameer, F.; Doogue, M. A Case of Valproate Induced Hyperammonemic Encephalopathy. *Case Reports in Medicine* **2011**, *2011* (1), 969505. https://doi.org/10.1155/2011/969505.
2. Aires, C. C. P.; van Cruchten, A.; IJlst, L.; de Almeida, I. T.; Duran, M.; Wanders, R. J. A.; Silva, M. F. B. New Insights on the Mechanisms of Valproate-Induced Hyperammonemia: Inhibition of Hepatic N-Acetylglutamate Synthase Activity by Valproyl-CoA. *Journal of Hepatology* **2011**, *55* (2), 426–434. https://doi.org/10.1016/j.jhep.2010.11.031.