Chem 412 Seminar
26. March, 2001

Hilary Preis

Maple Syrup Urine Disease

Abstract: Maple Syrup Urine Disease is an autosomal recessive disorder caused by decreased function of branched-chain alpha-ketoacid dehydrogenase complex (BCKD). This disease is characterized by urine that has an odor of maple syrup. The maple syrup smell is attributed to the elevated levels of branched-chain amino acids and ketoacids in the body fluids. The elevated levels are caused by a metabolic block in the catabolism of these compounds. Amino acids such as leucine, isoleucine, and valine are not broken down into their proper intermediates for the Krebs Cycle. People who are afflicted with this disease can suffer from ketoacidosis, neurological disorders, and mental retardation, if not treated. The treatment consists of a diet restricted from branched-chain amino acids. There are other vitamin specific treatments that correlate to the specific type of MSUD the patient has. The three types of MSUD are classified by the subunit of the BCKD complex that is defective. Type 1a correlates to the E1-alpha subunit that is responsible for binding TPP to create the active site for the ketoacid substrate and decarboxylation. Type 1b correlates to the E1-beta subunit that aids in transferring the acyl group to E2. The third type, Type II, is a result of decreased function in the core subunit of the BCKD complex, E2. The E2 subunit forms the acceptor site for the branched-chain acyl group that is created by the decarboxylation. Defects in these subunits occur from point mutations or deletions in the gene that result in faulty protein products. The BCKD complex is essential for the decarboxylation of amino acids and is similar to two other important decarboxylase complexes in metabolism. These closely related complexes, alpha-ketoglutarate and pyruvate, are also structurally similar. The seminar discussion will focus on the structure BCKD complex, metabolism of branched-chain amino acids, and the genetic problems that cause decreased function of the complex.

Keywords: BCKD, leucine, isoleucine, valine, and maple syrup

References:

1. Chuang, J. L.; Cox, R. P.; Chuang, D. T.: **E2 transacylase-deficient (Type II) maple syrup urine disease: aberrant splicing of E2 mRNA caused by internal intronic deletions and associations with thiamine-responsive phenotype**, *J. Clin. Invest.* 100:736-744, 1997
2. Herring, W. J.; Litwer, S.; Weber, J. L.; Danner, D. J.: **Molecular genetic basis of maple syrup urine disease in a family with two defective alleles for branched chain acyltransferase and localization of the gene to human chromosome 1**. *Am. J. Hum. Genet.* 48: 342-350, 1991.
3. Lau, K. S.; Herring, W. J.; Chuang, J. L.; Mckean, M.; Danner, D. J.; Cox, R. P.; Chuang, D. T.: **Structure of the gene encoding dihydrolipoyl transacylase (E2) component of human branched chain alpha-keto acid dehydrogenase and characterization of an E2 pseudogene**. *J. Biol. Chem.* 267: 24090-24096,1992.
4. Mitsubuchi, H.; Nobukuni, Y.; Akaboshi, I.; Indo, Y.; Endo, F.; Matsuda, I.: **Maple syrup urine disease caused by a partial deletion in the inner E2 core domain of the branched chain alpha-keto acid dehydrogenase complex due to aberrant splicing: a single base deletion at a 5-prime-splice donor site of an intron of the E2 gene disrupts the consensus sequence in this region**. *J. Clin. Invest.* 87: 1207-1211, 1991.
5. Montgomery; Conway; Spector; Chappell: **Biochemistry: a case oriented approach**. Ed. Underdown. St. Louis: Mosby-Year Book, Inc. 6th ed., 1996.
6. Peinemann, F.; Danner, D. J.: **Maple syrup urine disease 1954 to 1993**. *J. Inher. Metab. Dis.* 17: 3-15, 1994.
7. Turchany, J. M.; Leung, P. S. C.; Iwayama, L. T.; Jefferson, D. M; Ishida, J.; Yamaguchi, M.; Munoz, S.; Danner, D. J.; Dickson, E. R.; Gershwin, M. E.: **Comparative metabolism and structure of BCKD-E2 in primary biliary cirrhosis**. *J. Autoim.* 6 (4) : 459-466, 1993.

8.*http://www.ncbi.nlm.nih.gov:80/entrez/que...ed&tmpl=dispomimTemplate&list_uids=248610*

9. *http://www.ncbi.nlm.nih.gov/cgi-bin/Entre...A3976.00],gene[1p31.3%A1p31.3]&Zoom*

10. http://medlineplus.adam.com/ency/article/000373.htm

11. http://www.vtmednet.org/~m145037/vhgi_mem/nbsman/msud.htm