UNDERSTANDING THE EFFECTS OF MSUD AND IMPROVING TREATMENT OPTIONS: THE WORK CONTINUES

Details

Written by Dr. Susan Hutson
Published: 11 August 2009

Our work with mouse models is directed towards developing a clearer understanding of the molecular basis for the effects of MSUD on the central nervous system and body metabolism. It is our hope that such an understanding will lead to better treatment options for MSUD.

We are generating an animal that is genetically engineered so that a key part of the E1_ subunit of the E1 decarboxylase enzyme can be deleted when this animal is bred with a line of mice containing an enzyme that clips out a specific piece of DNA in the E1_ gene. The founder mice, which are scheduled for shipment in October, will be bred and the colony expanded here. Once this colony is ready we will breed them with appropriate mice carrying Cre-recombinase, the enzyme that makes the targeted gene deletion, to make the following animals:

1. A mouse animal model of Classic MSUD in which branched chain amino acid (BCAA) breakdown at the branched chain a-keto acid dehydrogenase step is severely impaired in all body tissues (global E1 knockout). The complete knock out can be generated in utero or after weaning so the animal can be managed and will mimic classic MSUD. The heterozygotes (50% of normal enzyme levels) will provide a model of intermittent MSUD using diet to challenge the animal.
2. An animal where BCAA breakdown is impaired only in the brain (central nervous system only). As the primary effects of MSUD are neurological, this animal will allow us to determine if impaired metabolism of BCAAs in the brain is sufficient to manifest the neurological pathology, and to test our theory of how BCAAs and their a-keto acid metabolites produce the pathological effects in brain.
3. Animals where BCAA breakdown is impaired in a specific tissue outside the central nervous system. These animals will be used to answer specific questions about the role of BCAAs in body energy metabolism.

In an exciting development, my longtime collaborator Dr. Kathryn LaNoue at Penn State College of Medicine and I at Wake Forest University Health Sciences, have recently established collaboration with Dr. William Zinnanti also at Penn State. We will work together

on the E2 animal that was obtained from Dr. Gregg Homanics at the University of Pittsburgh, using the E2 knockout mouse he developed with Dr. Paul. Dr. Zinnanti has found biochemical and pathologic changes that give us immediate targets to look at in the new E1 mice and E2 mice. Additionally, we will be testing a newly developed treatment in these mice based on reducing brain leucine accumulation using non protein amino acid analogs. This treatment concept has been developed in another disorder of essential amino acid metabolism with promising results. We plan to submit an NIH grant to support our project once we have enough data on the new E1_ KO mouse.

Recently, we have generated a mouse containing a global knockout (KO) of the mitochondrial branched chain aminotransferase (BCATm). In this animal BCAA metabolism is blocked at the first step in all tissues outside the central nervous system. The cytosolic BCAT is found in brain neurons whereas BCATm is found in brain astroglia. This BCATm KO has elevated levels of BCAAs in plasma and body tissues. This KO mouse does not exhibit the neurologic symptoms found in MSUD but it does show increased protein turnover, changes in insulin sensitivity, hypermetabolism, and resistance to diet induced obesity. This animal provides evidence that BCAAs have profound effects on body metabolism, independent of their effects in brain and suggests the branched chain keto acids are the primary toxic metabolite in MSUD. Our manuscript describing the animal that we generated has just been published in Cell Metabolism and is also a collaborative project with scientists working in the obesity/diabetes field.

Those of us in the field of branched chain amino acid metabolism are very excited about the future as we work together to understand the molecular basis of MSUD and the role of branched chain amino acids in the body, and to develop improved treatments for people with MSUD. We appreciate the support of the MSUD Family Support Group.