Molecular Mechanisms of Nutrient Amino Acid Absorption in Diseases Vector Insects.

Dmitri Y. Boudko. The Whitney Laboratory for Marine Bioscience, University of Florida, Florida, USA.

The biosynthesis of proteins, monoamine neurotransmitters, and signaling peptides, depends upon intracellular concentration of amino acids, which is regulated through the systems for intracellular synthesis and amino acid-specific plasma membrane transporters. While plants retain pathways for the biosynthesis of an entire set of proteinogenic amino acids, metazoan organisms substitute the slow and thermodynamically expensive synthesis of several of those amino acids by acquiring them from the environment. Such a strategy provides new opportunities for adaptation and diversification, but makes uptake and redistribution of essential amino acids crucial for development and survival of metazoan organisms. Since we expect that transmembrane carriers of essential amino acids diverge under pressure of nutrient adaptations we anticipate that essential amino acid uptake mechanisms provide potent and environmentally safe targets for population management of vector and pest insects.

Our laboratory studies molecular and physiological mechanisms which mediate uptake and distribution of nutrient amino acids in a comparative framework of two tropical diseases vectors, *An. gambiae* and *Ae. aegypti* and a genetic model, *D. melanogaster*. We have cloned several new members of the Sodium Neurotransmitter symporter Family (SNF/SSN/SLC6) and identified a new population of Nutrient Amino Acid transporters (NATs). NATs properties correspond to a B^0 system, which mediate sodium driven uptake of neutral amino acids in mammals. Using comparative phylogenetic analyses we first identified a lineage-specific diversification of NATs in a framework of several genomic invertebrates and vertebrate organisms. In invertebrates NATs comprise 4-7 genes which share similar patterns of spatial and temporal expression in absorptive/secretory epithelia and neuronal tissues but differ dramatically in substrate preferences. For example, we have cloned and characterized two new NATs from the primary malaria vector mosquito, *Anopheles gambiae* (NCBI CAF25029 and AAN40409), which both transport essential aromatic amino acids, but one strongly prefers tyrosine/phenylalanine while the other prefers tryptophan (both substrates are precursors in the synthesis of monoamine neurotransmitters). The first *Drosophila* NAT cloned in our laboratory displayed the strongest affinity for methionine; however, it showed a broader substrate spectrum than its mosquito relatives. Despite notable trans- and intra- specific variations in transport properties, a comparison of normalized substrate profiles revealed strong amplification of NAT efficiencies for a subset of essential amino acids that is unified among metazoans. Based on this preliminary data we anticipate that NAT populations comprise a core part of transport systems for absorption and redistribution of essential amino acids which cooperate with amino acid transporters of other types. Pharmacological analysis of heterologously expressed NATs showed that these transporters can be selectively blocked by pharmacological agents or transcript silencing which would mimic critical starvation and impact development in mosquito larvae. Supported by NIH/NIAID research grant 2R01AI030464