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N-acyltransferases and their role in fatty acid amide biosynthesis

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Introduction:

Fatty acid amides are a family of cell signaling lipids with the general structure of R-CO-NH-Y. This structural simplicity belies a wealth of diversity amongst this lipid family as the R-group is derived from fatty acids (R-COOH) and the Y-group is derived from biogenic amines (H2N-Y). The fatty acid amide family is divided into classes, defined by parent amines. Examples include the N-acylethanolamines (NAEs, R-CO-NH-CH2-CH2OH) and the N-acylglycines (NAGs, R-CO-NH-CH2-COOH). Other classes of fatty acid amides are known. The best known fatty acid amide is N-arachidonoylethanolamine (anandamide), a fatty acid amide found in the human brain that binds to the cannabinoid receptors. We have a long interest in the enzymes of fatty acid amide biosynthesis. We identified an enzyme that oxidizes the NAGs to the primary fatty acid amides and showed that inhibiting this enzyme led to the cellular accumulation of the NAGs. We have characterized several insect N-acyltransferases (from D. melanogaster, B. mori, and T. castaneum) that catalyze the acyl-CoA-dependent formation of fatty acid amides from an amine acyl-acceptor substrate. Knock-out experiments in D. melanogaster validate our in vitro substrate specific studies demonstrating that one novel N-acyltransferases, arylalkyl N-acyltransferase-like 2 (AANATL2), does catalyze the formation of N-acyldopamines in vivo. We developed a straightforward platform technology to rapidly identify substrates for our panel of uncharacterized insect N-acyltransferases. Our application of this technology leads to identification of an enzyme in D. melanogaster, agmatine N-acetyltransferase (AgmNAT), which catalyzes the formation of N-acetylagmatine, a virtually unknown metabolite. We have determined the X-ray structure of AgmNAT. Our work on AgmNAT hints at an unknown reaction in arginine metabolism and points to a novel class on fatty acid amides, the N-acylagmatine. The presentation will also include our results on the kinetic and chemical mechanisms of the novel N-acyltransferases. Recent Publications 1. Dempsey D R et al. (2017) Structural and mechanistic analysis of Drosophila melanogaster agmatine N-acetyltransferase, an enzyme that catalyzes the formation of N-acetylagmatine. Sci. Rep. 7(1):13432. 2. Aboalroub A A et al. (2017) Acetyl group coordinated progression through the catalytic cycle of an arylalkylamine N-acetyltransferase. PLoS One. 12(5):e0177270. 3. Jeffries K A et al. (2016) Glycine N-acyltransferase-like 3 is responsible for long-chain N-acylglycine formation in N18TG2 cells. J. Lip. Res. 57(5):781-790. 4. Dempsey D R, Carpenter A M, Rodriguez Ospina S and Merkler D J (2015) Probing the chemical mechanism and critical regulatory amino acid residues in of Drosophila melanogaster arylalkylamine N-acyltransferase like 2. Insect Biochem. Mol. Biol. 66:1-12. 5. Dempsey D R et al. (2015) Mechanistic and structural analysis of a Drosophila melanogaster enzyme, arylalkylamine N-acetyltransferase like 7, an enzyme that catalyzes the formation of N-acetylarylalkylamides and N-acetylhistamine. Biochemistry. 54(16):2644-2658.

Biography

David J Merkler obtained a PhD in Biochemistry from Pennsylvania State University in 1985 and completed Postdoctoral Fellowships in Enzymology at Temple University School of Medicine (1985-1987) and the Albert Einstein College of Medicine (1987-1989). His next position was as Senior Scientist at Unigene Laboratories, Inc. involved in the in vitro production of a peptide hormone, calcitonin. In 1995, he moved back to academia as a Professor of Chemistry and Biochemistry first at Duquesne University (1995-1999) and then the University of South Florida (1999-present). His laboratory has been interested in the fatty amides: identification and characterization of the fatty acid amides (Lipidomics), identification and characterization of the enzymes of fatty acid amide biosynthesis (Enzymology and Structural Biology), and changes in the fatty acid amidome after targeted enzyme knock-out (subtraction lipidomics).