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A deep, combined omics exploration of the FAAH knockout brain lipidome

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Fatty acid amide hydrolase (FAAH) is a serine protease, which hydrolyzes bioactive endocannabinoids (ECs). ECs are lipid mediators that bind to and activate cannabinoid receptors CB1 and CB2. Upon binding ECs initiate a number of signaling pathways which control diverse set of biological functions including memory, learning, social behavior, appetite and inflammation. Modulating the metabolism of ECs by inhibiting FAAH holds therapeutic promise in a wide range of neurological diseases. Since the discovery of FAAH, it has been a very good target for pharmacological studies, many natural and synthetic analogues have been designed to target this enzyme. Given its large number of biological functions, a deeper understanding of its lipidome and proteome could generate useful information for future pharmacological strategies to combat neurological disorders. The aim of our work is to investigate the difference in lipidome of FAAH knockout mice brain compared to its wild type using ion mobility based mass spectrometry, difference in proteome using TMT labeled quantitative proteomics and a deeper targeted lipidomics of all the biosynthetic intermediates of anandamide pathway which is the most important signaling lipid in the brain. By using ion-mobility assisted, untargeted mass spectrometry, we discovered the up-regulation of pro-apoptotic ceramides, besides previously known fatty acid ethanolamides and acyl taurines. Further we extended our study to TMT labeled quantitative proteomics to explore the effect of upregulated bioactive lipids on the proteome of FAAH knockout brain. The experiment generated relative expression data on various mouse proteins, out of which the majority of significantly upregulated proteins are related to cell growth, apoptosis, transport processes, cell to cell adhesion and RNA splicing. Our targeted lipidomic analysis of anandamide pathway showed a down-regulation of its metabolic precursors, which could be a possible feedback inhibition to fine tune the levels of anandamide. Overall our study gives a deeper understanding of the lipidome and proteome of FAAH knockout mice brain. In this seminar, I will discuss how to perform different omics techniques like untargeted lipidomics, untargeted proteomics and targeted lipidomics from a single experimental set of samples and how to predict different metabolic precursors of an unknown pathway and develop a reliable targeted LCMS method.

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Bimodal anesthetic modulation revealed by structure, function studies in a pentameric ligand gated ion channel

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Allosteric modulation by general anesthetics, such as propofol, is a key pharmacological property of many pentameric ligand-gated ion channels (pLGICs) with critical implications for receptor biophysics and drug development. Functional studies have revealed conserved sites of both positive and negative modulation by anesthetics in this channel family, but mechanistic interpretations have been limited by the scope and resolution of structural data. The prokaryotic homolog GLIC has been shown a useful model system that recapitulates functional modulation of human ion channels, and enables structure determination both in apparent conducting and non-conducting states. Here, we provide crystallographic and electrophysiological evidence that anesthetics either inhibit or potentiate GLIC function by binding in the ion pore or in several sub regions of a key transmembrane cavity, respectively. Binding to each region evidently stabilizes a different functional state of the receptor, thus offering an integrated, multiple site allosteric model of pLGIC modulation by general anaesthetics.

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