UNIVERSITY OF GOTHENBURG

Mass spectrometry based analysis of drugs, neurotransmitters and lipids in invertebrate model systems

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ABSTRACT

Mass spectrometry (MS) is one of the most universal analytical techniques due to its label-free detection principle and high chemical specificity, high selectivity, and sensitivity. MS is diverse with many different types of systems to meet different analytical demands from various research areas. MS can be used for bulk analysis, in particular when coupled with a separation tools such as capillary electrophoresis or liquid chromatography, provides highly accurate qualitative and quantitative information of sample compositions. Imaging mass spectrometry (IMS), on the other hand, allows imaging chemical structures in intact samples with impressive spatial resolution. In this thesis, MS is used for two main objectives. First, MS is used to investigate the concentration at the site of action of methylphenidate (MPH), and its neurological effects on the nervous system of *Drosophila melanogaster* (fruit fly). MPH has a stimulant action similar to cocaine as it also binds to the dopamine transporter protein and thereby increases the concentration of extracellular dopamine, a neurotransmitter, in the mammalian nervous system. *Drosophila* is a good model to study the effects of MPH on the brain. It has a short life cycle to facilitate genetic manipulation, prolific reproduction, and highly conserved physiological effects with humans, especially drug addiction. The second main objective of the thesis is to develop MSI methods for biomolecular imaging of tissue samples including *Drosophila* brain and *C. elegans*. Multimodal imaging with secondary ion mass spectrometry (SIMS) and laser desorption ionization mass spectrometry (LDI MS) of the fly brain provide complementary biomolecular information of the brain structure. The molecular signature of *C. elegans*, another primary biological model used today, is very useful for studies of cellular processes and worm behavior.

In paper I, the in vivo concentration of MPH in *Drosophila* brain after oral administration was determined by capillary electrophoresis mass spectrometry (CE-MS). The information was applied to study the effects of methylphenidate treatment on the action of cocaine on dopamine uptake in vivo in *Drosophila*. In paper II, capillary electrophoresis mass spectrometry was used for qualitative and quantitative analysis of orally administrated methylphenidate and metabolites, and neurotransmitter concentrations in the fly brain. In paper III, an imaging protocol for *Drosophila* brain with SIMS, including sample preparation, data treatment with image-based principle components analysis, and continuous imaging was developed. The imaging protocol was applied in paper IV to investigate lipid structural effects of MPH on *Drosophila* brain using a combination of SIMS and SEM imaging. The oral administration of MPH significantly altered the distribution and abundance of various brain lipids. Paper V presents a multimodal imaging approach to *Drosophila* brain for lipid detection using matrix assisted laser desorption ionization (MALDI). Different surface modifications, including matrix sublimation and nanoparticle deposition, were used in a complementary fashion to profile biological samples. In paper VI, the chemical anatomy of *C. elegans* was studied using 2D and 3D SIMS imaging.

KEYWORDS: Imaging mass spectrometry, CE-MS, drug, lipids, neurotransmitters, Drosophila, C. elegans

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