



Visualizing neurodegenerative diseases with multiple layers of biochemical detail

Prof. Per Andrén

Ph.D., Medical Mass Spectrometry, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

MALDI-mass spectrometry imaging (MSI) is a powerful technique that provides spatial information about multiple molecular species in diverse biological tissues. Recent technological advances in instrumentation, software, and chemical tools^{1,2} have allowed its use in quantitative spatial omics. It now enables visualization of distributions of diverse molecules at high lateral resolution in studies of drugs' pharmacokinetic and pharmacodynamic effects on functional biomolecules.

We have used MALDI-MSI to study multiple layers of biomolecular changes in postmortem brains from humans and animal models with neurodegeneration, and particularly Parkinson's disease (PD)³. L-DOPA administration is the primary treatment for PD but long-term administration is usually accompanied by hyperkinetic side-effects called L-DOPA-induced dyskinesia (LID) in about 50% of patients after 5 years of treatment. LID significantly impair the patient's quality of life. Here, we exploited the advantages of MALDI-MSI to perform on-tissue mapping of a large number of neurochemical species for investigating their changes associated with LID.

Excessive amounts of L-dopa and its metabolite 3-O-methyldopa were detected in the brain of dyskinetic animals and higher levels of dopamine and metabolites in all regions (except the striatum) than in the non-dyskinetic animals under similar treatment³. Furthermore, signaling neuropeptides of the basal ganglia are affected in LID and changes in the expression of neuropeptide precursors have been described, but the final products formed from these precursors have not been well defined and regionally mapped. We found that LID severity correlated with the levels of some abnormally processed peptides, and that the abundance of selected active neuropeptides is associated with L-DOPA concentrations in the brain, emphasizing their sensitivity to L-DOPA⁴. LID animals exhibited reduced levels of various metabolites important for brain homeostasis, including S-adenosylmethionine, glutathione, adenosine monophosphate, and acylcarnitines. These results provide new insights into pathological metabolic changes in PD and LID.

MALDI-MSI has become a versatile technique with a multitude of applications that have transformed neuropharmacological research and enabled research into brain physiology at unprecedented resolution.

1. Shariatgorji, M., et al. Comprehensive mapping of neurotransmitter networks by MALDI-MS imaging. *Nat Methods* 16, 1021-1028 (2019).
2. Shariatgorji, R., et al. Spatial visualization of comprehensive brain neurotransmitter systems and neuroactive substances by selective in situ chemical derivatization mass spectrometry imaging. *Nat Protoc* 16, 3298-3321 (2021).
3. Fridjonsdottir, E., et al. Mass spectrometry imaging identifies abnormally elevated brain L-DOPA levels and extrastriatal monoaminergic dysregulation in L-DOPA-induced dyskinesia. *Sci Adv* 7, eabe5948 (2021).
4. Hulme, H., et al. Basal ganglia neuropeptides show abnormal processing associated with L-DOPA-induced dyskinesia. *NPJ Parkinsons Dis* 8, 41 (2022).

Biography:

Dr. Per Andrén is a Professor of Mass Spectrometry Imaging at the Dept. of Pharmaceutical Biosciences, Uppsala University, Sweden. He received his MSc in Pharmacy in 1984 and his PhD in 1989 in Medical Sciences (Psychiatry) at Uppsala University. He did a postdoctoral fellowship at University of Texas Medical School, Houston, USA (1989-1995) before he returned to Uppsala University as an Associate Professor. He has also worked at GE Healthcare R&D (2000-2009).

Dr. Andrén is interested in the use of mass spectrometry imaging (MSI) for the analysis of biological systems and focus on MSI method developments and applications of the brain and neurodegenerative diseases, with particular emphasis on Parkinson's disease. His laboratory (Spatial Mass Spectrometry) is a Swedish national facility for MSI within the Science for Life Laboratory, is an institution for the advancement of molecular biosciences in Sweden.