

Mass Spectrometry Imaging Drives Research into Parkinson's Disease

Parkinson's disease is a progressive neurological disorder that affects movement in the body. With a study published in *Nature Medicine* indicating that more than 57 million people across the globe suffer from neurodegenerative disease, a figure expected to double every 20 years as the population ages, it is imperative to further our understanding of the causes of Parkinson's disease, as well as the conflicting side effects of a therapeutic drug used to alleviate its symptoms.¹

The capability of mass spectrometry imaging (MSI) to detect a range of neuroactive compounds and metabolites in a single tissue section has firmly established its potential in neuroscientific research. This article will explore the ground-breaking research by the Spatial Mass Spectrometry group at Uppsala University in Sweden, one of the largest centres for life sciences in Europe, into Parkinson's disease, specifically a specific stage of the disease, called levodopa (L-DOPA)-induced dyskinesia (LID), which develops in approximately 50 percent of patients after five to six years of L-DOPA treatment.

A Deeper Understanding of Parkinson's Disease

Parkinson's disease is an incurable neurodegenerative disease caused by the loss of dopamine-producing nerve cells in the brain. It is characterised by motor dysfunction, tremors, bradykinesia (or slowed movement), muscle rigidity, and postural instability including involuntary and unpredictable body movements.

L-3,4-dihydroxyphenylalanine (levodopa, or L-DOPA) administration is the primary treatment for Parkinson's. L-DOPA is a precursor to dopamine that crosses the blood-brain barrier where it is converted into dopamine, replenishing the brain's depleted supply of dopaminergic neurons in the substantia nigra pars compacta region that leads to reduced dopamine in the striatum, an area of the brain responsible for movement control in the body.

L-DOPA is highly effective in the early stages, but its long-term use is often accompanied

by the side-effect LID, a treatment-limiting complication which exhibits as involuntary, erratic, and uncontrollable tremors and whose pathophysiology is poorly understood.

LID has a significant negative impact on quality of life. What is not yet known is why only certain people are affected. Working with animal models, as well as human blood-cerebrospinal fluid (CSF) biobank samples supplied by collaborators at the Karolinska Institute, Stockholm, Bordeaux University, and Kings College London, researchers in the Department of Pharmaceutical Biosciences at Uppsala University are using MSI to investigate the elevated L-DOPA levels in the brain that are linked with LID.

The MSI Advantage

MSI is an advanced, label-free mass spectrometry tool that can be used to map the spatial distribution of molecules such as lipids, proteins and metabolites directly within thin tissue sections.

MSI can be integrated with microscopy or histology, and provides an additional parameter for identification over traditional MS by enabling the accurate simultaneous determination of multiple tissue distributions. This allows quantitative regional mapping, and high resolution visualisation of molecular change to support neurodegenerative disease research.

The research at Uppsala is focused on imaging the spatial distribution of neurotransmitters, or the signalling molecules in the brain, that are known to be affected in Parkinson's disease. The group has developed a method to image neurotransmitters in a specific brain region, at the same time providing a new view of the brain and the transmitters involved in current Parkinson's disease models. This method, using MALDI MSI, has enabled researchers to measure and quantify different neurotransmitters, and their metabolites and precursors, simultaneously.

MSI Supports Identification of Elevated Brain L-DOPA Levels

A study used ultrahigh mass resolution Fourier transform ion cyclotron resonance (FTICR) matrix-assisted laser desorption/ionisation (MALDI) MSI (7T solarix XR)

to map the distribution of L-DOPA and monoaminergic pathways in the brains of dyskinetic and nondyskinetic animal models.² Fourteen neurotransmitters and metabolites were simultaneously imaged and identified with accurate mass.

Elevated levels of L-DOPA and its metabolite 3-O-methyldopa were found in all measured brain regions of dyskinetic animals, and increases in dopamine and metabolites were noted in all regions analysed, except the striatum.

It was found that LID is linked to a dysregulation of L-DOPA metabolism throughout the brain: the inability of extrastriatal brain regions to regulate the formation of dopamine during L-DOPA treatment introduces the potential of dopamine, or L-DOPA itself, to modulate neuronal signalling widely across the brain, causing unwanted side effects.

Neuropeptides Demonstrate Link With LID

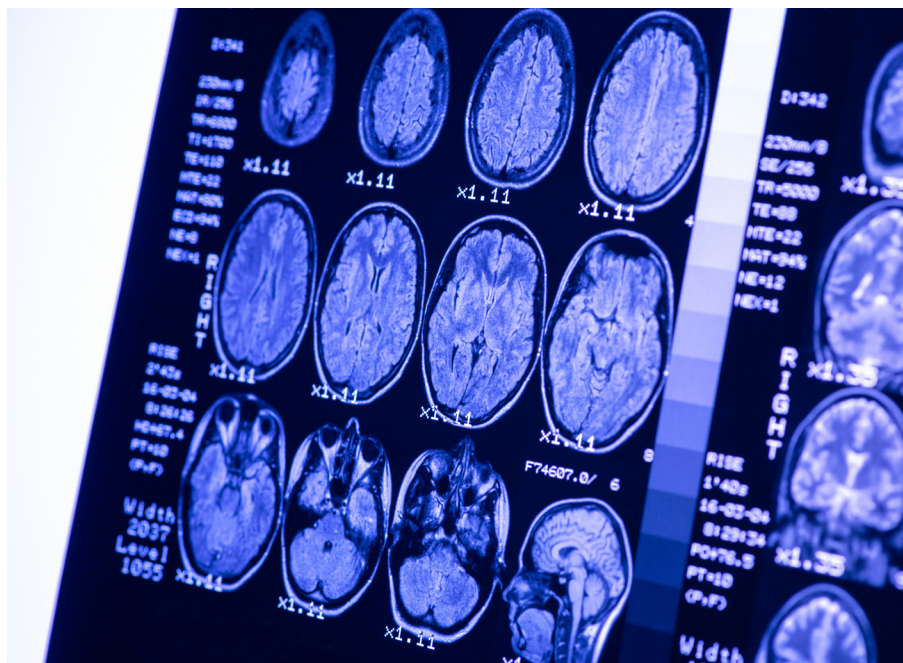
Parkinson's disease and LID have both been linked with altered expression of neuropeptide precursor messenger ribonucleic acids (mRNA).

An investigation into the basal ganglia neuropeptides that have been associated with LID development found that dyskinesia severity correlated with elevated levels of some abnormally processed peptides in multiple brain regions.³

Dynorphin, enkephalin and tachykinin neuropeptides of the basal ganglia have many effects, including regulation of neurotransmitter release, modulation of blood-brain barrier permeability and stimulation of neuro-inflammatory responses.

MALDI-MSI was used to characterise neuropeptide alterations in the same pre-existing cohort of samples from an animal model of Parkinson's disease during the peak LID behaviour period, targeting the depletion of catecholaminergic neurons to closely mimic symptoms of Parkinson's and LID.

In the study, MALDI-MSI was used to image and identify 23 neuropeptides, as



well as image and analyse the effect of LID on these neuropeptides in the brain. It was found that LID was associated with an increase in the multiple neuropeptide levels across the basal ganglia structures, while non-LID animals had low levels of these neuropeptides. The severity of LID correlated with the abundance of processed derivatives of the active neuropeptides in certain basal ganglia regions, and putaminal levels of L-DOPA correlated with the abundance of the active neuropeptides, but did not correlate with the levels of processed derivatives, suggesting that striatal L-DOPA itself may induce neuropeptide signalling, without first being converted to dopamine.

Lipid Dysregulation

As lipids are increasingly considered a prominent class of metabolites in neurodegenerative disease research, lipidomics has become an important metabolomics research pathway. Lipids are strongly linked to many aspects of Parkinson's disease, but there are few studies on their impact on LID-specific changes.

High resolution MSI was used in a study to map brain region-specific alterations of glycerophospholipids and sphingolipids in the same animal model of Parkinson's with and without LID following long term L-DOPA treatment.⁶ Spatial lipidomic analysis identified region-specific lipid dysregulation as a novel aspect of LID pathology, highlighting lipid pathways as potential targets for future research.

LID was associated with depletion of antioxidant ether phosphatidylcholines and

altered PUFA-containing glycerophospholipids in regions critical for motor function, which differed from similarly treated non-dyskinetic animals, suggesting lipid composition mediates differential susceptibility to LID. Lipid alterations correlated strongly with dyskinesia severity, dopamine and L-DOPA concentrations, supporting a mechanistic link between lipid metabolism, neurotransmitter dysregulation and LID.

Building a Better Understanding of LID

The new workflows for imaging neurotransmitters will continue to support neuroscience research using MSI.

Adopting an integrated spatial omics approach that combines MSI with spatial transcriptomics and spatial proteomics facilitates precise measurements of metabolites across brain tissue regions. These advances will continue to support fundamental research into the mechanisms underlying Parkinson's disease and treatment response.

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**Dr. Per
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Mass spectrometry veteran Dr. Per Andrén was a postdoc in the group of Professor Richard Caprioli, in the early days of electrospray ionisation, and became the world's first Professor of Mass Spectrometry Imaging, at the Department of Pharmaceutical Biosciences, Uppsala University, Sweden, having originally gained his MSc in Pharmacy and PhD in Medical Sciences (Psychiatry) at Uppsala University. Today, Dr. Andrén is interested in the use of MSI for the analysis of biological systems and focuses on MSI method development in applications for the brain and neurodegenerative diseases, with a particular emphasis on Parkinson's disease.



**Dr. Michael
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Dr. Michael Easterling is Vice President of MALDI Imaging at Bruker Daltonics. Following his PhD in Chemistry from The University of Georgia, Dr. Easterling has worked at Bruker Daltonics for almost 25 years, specialising in MALDI mass spectrometry. Dr. Easterling focuses on multimodal spatial analysis, more recently integrating mass spectrometry imaging with transcriptomics and proteomics to advance understanding of complex biological systems, including neurodegenerative disease.