We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

# Mass Spectrometry Imaging of Neurotransmitters

Katherine A. Stumpo

Abstract

Mass spectrometry imaging (MSI) is a powerful analytical method for the simultaneous analysis of hundreds of compounds within a biological sample. Despite the broad applicability of this technique, there is a critical need for advancements in methods for small molecule detection. Some molecular classes of small molecules are more difficult than others to ionize, e.g., neurotransmitters (NTs). The chemical structure of NTs (i.e., primary, secondary, and tertiary amines) affects ionization and has been a noted difficulty in the literature. In order to achieve detection of NTs using MSI, strategies must focus on either changing the chemistry of target molecules to aid in detection or focus on new methods of ionization. Additionally, even with new strategies, the issues of delocalization, chemical background noise, and ability to achieve high throughput (HTP) must be considered. This chapter will explore previous and up-and-coming techniques for maximizing the detection of NTs.

Keywords: mass spectrometry imaging, neurotransmitters, gold nanoparticles, derivatization, sample preparation

1. Introduction

Mass Spectrometry Imaging (MSI) is an incredibly powerful label-free technique that can determine qualitative and quantitative information of hundreds of compounds in a tissue section in one experiment [1, 2]. Small molecule detection, especially of neurotransmitters (NTs), currently relies heavily on histochemical, immunohistochemical, and ligand-based assays. Antibody-based methods suffer from limitations in cost and availability of antibodies, lack of specificity for target molecules of interest, and low throughput [3, 4]. The development of MSI has overcome many of these challenges and will be discussed throughout. The basic methodology of MSI is to section tissue using a cryostat to approximately 10-20 μm thickness; tissues may or may not be embedded in a cryomatrix such as Shandon™ M-1 (ThermoFisher Scientific). Next, matrix must be deposited on the tissue section, which is most often done by spray-coating the tissue using a pneumatic sprayer. Variations on typical organic matrices, such as inorganic nanoparticles (NPs), have been explored by numerous researchers and will be commented on here. Mass spectral data is collected at discrete locations on the sample surface via a raster pattern, which can then be assembled into a heat-map image of molecule location. **Figure 1** depicts the typical MSI scheme [5]. A number of overall reviews of MSI have appeared in recent years [6] that address broad topics like ionization of small molecules [7], clinical applications [2], and high-resolution analyses [5].
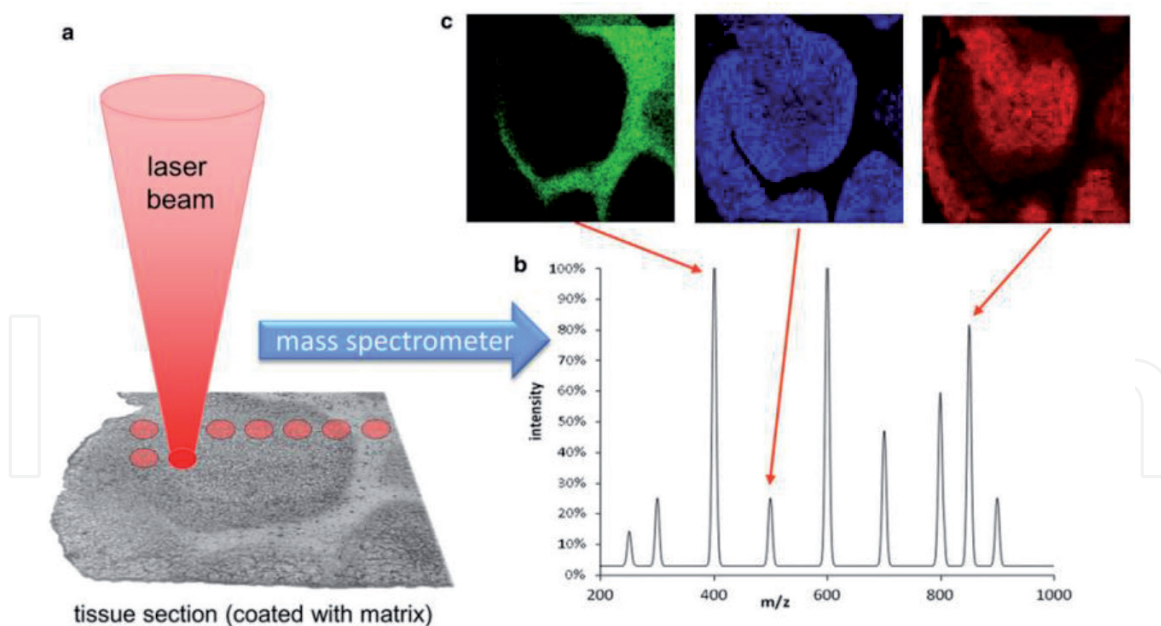
Figure 1.
General scheme of the mass spectrometry imaging process. (a) The tissue section is covered with matrix and irradiated by a pulsed laser beam. (b) Mass spectrum acquired from one spatial location on the tissue section. (c) MS images of different m/z peaks compiled from all spatial locations. Reprinted with permission from Ref. [5]. Copyright 2013 Springer.

The broader scientific community is not yet fully utilizing MSI as there are still challenges to be overcome [7, 8], including: (i) low ionization efficiency for small molecules, (ii) chemical noise interferents/overlapping signals of small molecules with traditional matrices [9], (iii) reproducibility issues across laboratories which limits universal procedures for MSI in pre-/clinical research, (iv) limits to lateral spatial resolution inherent to the matrix crystallization process which affects the ability to clearly define tissue margins, and (v) delocalization of analyte molecules during sample preparation. This chapter will focus on the analysis of small molecules, specifically neurotransmitters (NTs), due to the complex biological processes that occur in the brain and have broad implications in disease states and overall health. This chapter is broken down in two main categories, as strategies to improve ionization must either focus on (i) the chemical nature of the analyte and changing its properties to better facilitate ionization, or (ii) on utilizing a different mechanism of ionization to favor small molecules of interest.

2. Small molecule basics for MSI

Small molecule NTs are the chemical messengers of the central nervous system. Having a complete picture of NT location and abundance will aid in understanding of many different disease states and developmental processes. NTs are difficult to detect *in situ* via mass spectrometry due to their low physiological abundance (e.g., nM to pM concentration) within a complex biological tissue with many different classes of biomolecules, and overlapping low molecular mass range with most traditional matrices. Prior to the analyses discussed here, NTs were localized based on their protein-receptors or transporters, which does not always give an accurate accounting of present location.

Instrumentation used for MSI can vary widely, but most laser-based work is performed by time-of-flight (TOF) instruments. The other common setup is using desorption electrospray ionization (DESI) as an ion source, which is not the focus here, but is another option gaining in popularity [10, 11]. Other hardware
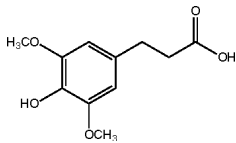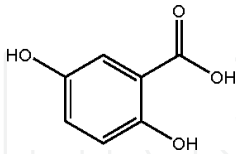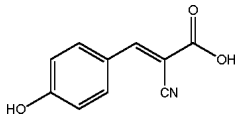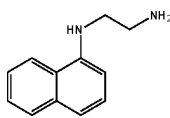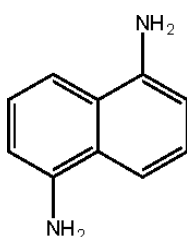
configurations can favor small molecules (e.g., ion mobility, triple quadrupole instruments, Fourier transform – ion cyclotron resonance) and so there is no one-size-fits-all set-up for small molecule MSI experiments. In contrast to instrument choice, sample preparation/derivatization and ionization conditions are areas that can be standardized in order to achieve similar results across different platforms. The focus here is not on the many instrument combinations as other reviews have adequately explored this topic [6, 7].

Sample handling and preparation of tissue sections are integral to maintaining sample integrity; after cryo-sectioning, tissue is typically thaw mounted onto a solid surface. The surface must be conductive in order to apply a potential to the sample and accelerate ions out of the instrument source. Common materials include coated metal targets (expensive, cannot be archived, and not histology compatible) or indium-tin oxide (ITO) coated glass slides. Matrix application to the tissue section is ideally a homogenous coating of small crystals that provide optimum extraction conditions of analyte. After application, the key process is the co-crystallization that must occur between matrix and analyte. Spraying parameters affect the "wet-ness" of the surface of the tissue and are a balance between molecular diffusion and effective extraction. Crystal size is one of the more critical factors for a successful MSI experiment and multiple studies determined the parameters important for optimum crystallization.

Commonly used organic acid matrices for MSI are shown in **Table 1** and include sinapinic acid (SA), 2,5-dihydroxybenzoic acid (DHB), and α-cyano-4-hydroxycinnamic acid (CHCA). These matrices work for a broad variety of biomolecules including peptides and lipids, but do not always translate well to small molecule detection. The introduction of N-(1-napthyl)ethylenediamine dihydrochloride (NEDC) and 1,5-diaminonapthalene (DAN) have improved the detection of small molecules, though these matrices have different preparation needs (e.g., sublimation and recrystallization) which increases the time required for sample processing [12, 19]. DAN and NEDC matrices have not been fully explored yet in the literature. Moreover, the propensity for organic matrices to self-ionize and create chemical noise in the low mass range prevents effective analysis of most metabolites. Recently, this has led toward the rational design [35] or selection [36] of matrices that can address this, but the lack of consistency in performance can still be an issue. Matrix applications are notorious for behaving differently across laboratories, and significant research in the past 25 years has been devoted to identifying preparation methods that result in the most consistent data [37–39].

Sublimation procedures, mentioned *vida supra*, require that matrix and sample are placed in a vacuum chamber which is evacuated [32]. The sample is cooled while the matrix is heated, resulting in sublimation of the matrix which will condense on the cool sample surface. Recrystallization of the matrix is often coupled with this technique. There are advantages and disadvantages to all of the aforementioned matrix application techniques, which have been discussed thoroughly in the literature [40–42]. Automated sprayers have become increasingly popular and help with consistency of matrix application, though the size and spacing of the matrix droplets will ultimately affect spatial resolution of the experiment. This topic has been frequently discussed and reviewed in the literature [2, 6], so only a basic introduction is given here.

Despite these challenges, there are a few examples of successful metabolomics imaging experiments, though they have utilized purposefully designed matrices that do not generate interfering signals [35] or have used high-resolution instruments that have the high mass accuracy to distinguish between isobaric signals [43, 44]. These approaches are not an all-encompassing solution, and the next sections explore other strategies to achieve broader success with MSI of small molecules, specifically NTs.

Matrix and structure	Common analytes
Sinapinic acid (SA)	Proteins [12–15]
2,5-dihydroxybenzoic acid (DHB)	Peptides [16–18], lipids [19, 20], some small molecules [4, 21, 22]
α-cyano-4-hydroxycinnamic acid (CHCA)	Neuropeptides [23], peptides [24], proteins [25], lipids [26, 27], drugs [28]
N-(1-napthyl)ethylenediamine dihydrochloride (NEDC)• 2HCl	Small molecule metabolites [29], lipids [30]
1,5-diaminonapthalene (DAN)	Lipids [31–33], small molecule metabolites [34]

Table 1.
Common MSI organic acid matrices and their applications.

3. Alternative matrix materials

As an alternative to the traditional organic acid matrices, contemporary studies have returned to the inorganic materials that were originally proposed for MALDI-MS by Tanaka *et al*. [45]. Nanoparticles (NPs) made of gold [46–49], silver [50–53], carbon based substrates [54–57], and silicon surfaces [58, 59] have been demonstrated on the target plate as materials that facilitate ionization of biomolecules. In particular, gold NPs (AuNPs) have the potential to be a more universal material to help facilitate ionization of small molecules and seem to have fewer reproducibility issues across multiple instrument platforms, locations, and organisms/biofluids [46, 60, 61]. Specific advantages for ionization of small molecules using AuNPs on the target plate include: (i) less chemical noise in the range where small molecules are found (below *m/z* 300), (ii) flexible analyte solution preparation conditions, including tolerances for salts, surfactants, and pH, and (iii) broad applicability across chemical classes [46, 48, 57, 60, 62].

The general success, though not broad usage, of these materials on the target plate have led to several different approaches for using alternative inorganic

materials for MSI, such as sputtering of metals or the use of metallic NPs, both of which are described in the paragraphs below.

Sputtering of metals over tissue sections has produced a number of quality articles that have utilized silver [50], platinum [63], and gold [64]. Sputtering deposits highly pure and homogeneous metal or metal oxide nanolayers onto biological tissue sections. Magnetron sputtering systems utilize a plasma gun under high- or ultra-high vacuum and deposits layers of metal onto the substrate of interest. Deposition times range from under a minute to several minutes, with total sample preparation time at least several minutes long because of the need for a vacuum-based system. Sputtered layers of silver or gold are typically reported in the 20-50 nm range [49, 50, 65], which is a narrower size distribution than solution-based NPs. The biggest disadvantages of sputtering are the need for expert users, the time involved for sample preparation, and the equipment cost (e.g., sputtering apparatuses are up to tenfold more expensive than pneumatic sprayers).

Molecules that have been successfully detected using Ag or Au sputtering experiments are largely neutral lipids, with cholesterol being of high interest [49, 50, 52, 66]. Pt sputtering has been demonstrated on lipids in tissue [67] and in leaves where metabolites of interest were detected, including many with molecular features similar to NTs, such as acetamiprid [63]. Rafols *et al.* showed an Au sputtering MSI experiment that resulted in the potential detection of 25 different compounds, but only 1 of which could be called a small molecule metabolite (i.e., citrulline) [64]. A significant advantage that sputtering demonstrates, compared to organic acid matrices [22], is the lack of analyte delocalization [64]. The largest survey of sputtering materials was done by Hansen *et al.,* where Ag, Au, Cu, Ni, Pt, and Ti were sputtered for varying times on plant tissues [68]. Noble metals (e.g., Ag, Au, Pt) were found to be more effective than transition metals (e.g., Cu, Ni, Ti) for overall ionization in positive- and negative-ion modes. While lipids were the most prevalent biomolecule class examined, this is a rare demonstration of the detection of amine-based structures, including choline, asparagine, glutamic acid, and leucine. DHB was used for comparison in positive-ion mode and DAN in negative-ion mode, with primarily insoluble lipids being effectively ionized with organic matrices. A summary of the molecules detected is shown in **Figure 2**.

Nanomaterials in suspension form, such as colloidal NPs, could potentially be deposited or sprayed onto tissue sections for analysis, yet there are only select demonstrations of this application for MSI, which are described herein. This area of research has again been applied primarily to lipidomics, with successful detection of fatty acids and their derivatives, sterols, phospholipids (e.g., phosphatidyletha-nolamine, phosphatidylcholine, phosphatidylinositol, etc.), sphingomyelins, and ceramides. Silver NPs (AgNPs), including those that have been surface-derivatized are most popular. Polyvinylpyrrolidone-capped AgNPs have been utilized for analysis of brain [69], and AuNPs with alkylamine surface modifications have been used for imaging of glycosphingolipids in the brain [70]. Fluorinated AuNPs have been shown to detect carbohydrates, lipids, bile acids, sulfur metabolites, amino acids, nucleotide precursors, and more in mouse colon [71].

Small molecule examples, specifically NTs, are notably lacking in the MSI literature. We have been developing a method for the detection of endogenous NTs from biological samples using citrate-capped AuNPs that are pneumatically sprayed on tissue sections [47]. Successful detection of acetylcholine, dopamine/octopa-mine, epinephrine, glutamine, GABA, norepinephrine, and serotonin was achieved in rabbit brain tissue sections, zebrafish embryos, and neuroblastoma cells [61, 72]. See **Figure 3** for an image of seven different NTs in 5 day-post fertilization zebrafish embryos.
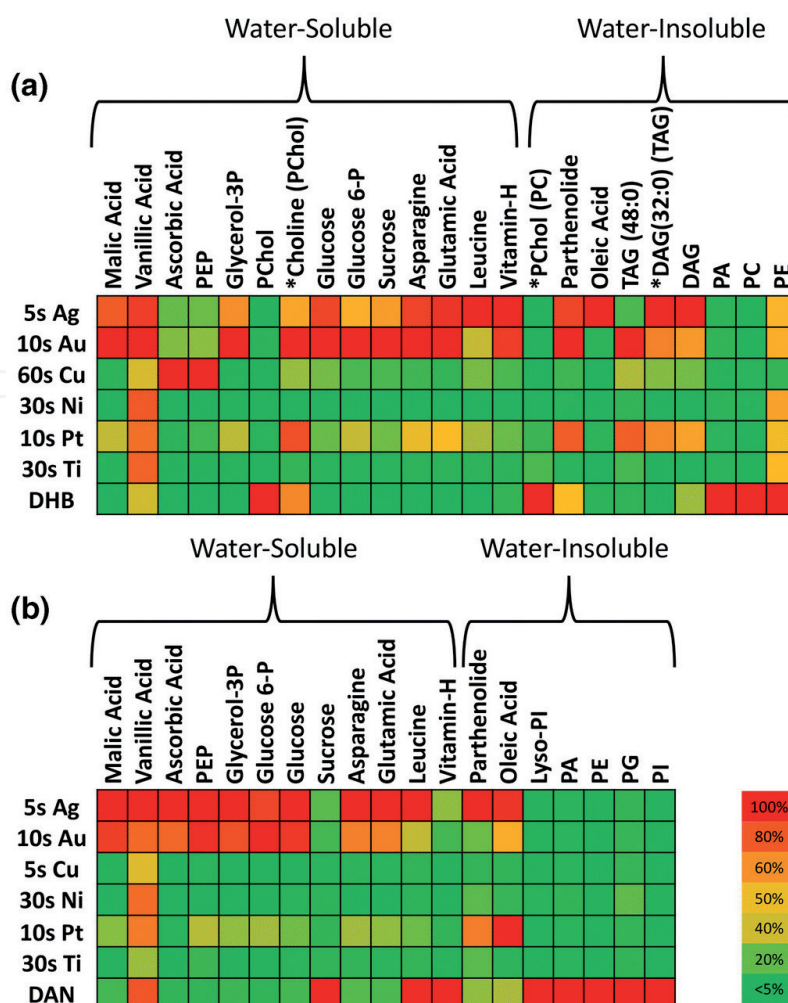
Figure 2.
Summary of sputter-coated metal screening for small metabolite analysis in (a) positive and (b) negative ion mode. Asterisks indicate a fragment ion was detected. Reprinted with permission from Ref. [68]. Copyright 2018 American Society for Mass Spectrometry.

With the intention of demonstrating the flexibility of AuNPs in terms of sample preparation, spraying parameters have been explored, including matrix concentration, solvent composition, spray temperature, and linear flow rate (which determines overall spray density of material). Early data and statistical analysis by principal component analysis (PCA) suggests that: (i) AuNP concentration can be varied over 4 orders of magnitude, (ii) a variety of organic:aqueous solvent mixes are possible, and (iii) temperatures from 30 to 60°C can be utilized [73, 74]. The flexibility in spray parameters means that less-experienced users with varying spraying capabilities can still get optimum data from their tissue sections, opening the application of MSI to more areas of study.

As previously mentioned, delocalization is an issue with organic acid matrices, often because of a "wet" matrix spray that results in true molecular diffusion instead of analyte extraction from the tissue. A standard literature method for CHCA has been compared with AuNPs, where CHCA gives only extreme delocalization outside of the tissue margins, and the AuNPs result in distinct anatomical visualization, as well as the ability to see subtle differences in analyte concentration [61]. Another advantage of AuNPs that we have discovered is flexibility in sample storage. For example, AuNP-sprayed tissue sections on slides were stored overnight at −20°C and imaging runs were repeated after 24 hours. Nearly identical data resulted and up to 8 imaging runs were completed on the same tissue section without loss of signal or the need to reapply AuNPs. The ability to archive slides for later
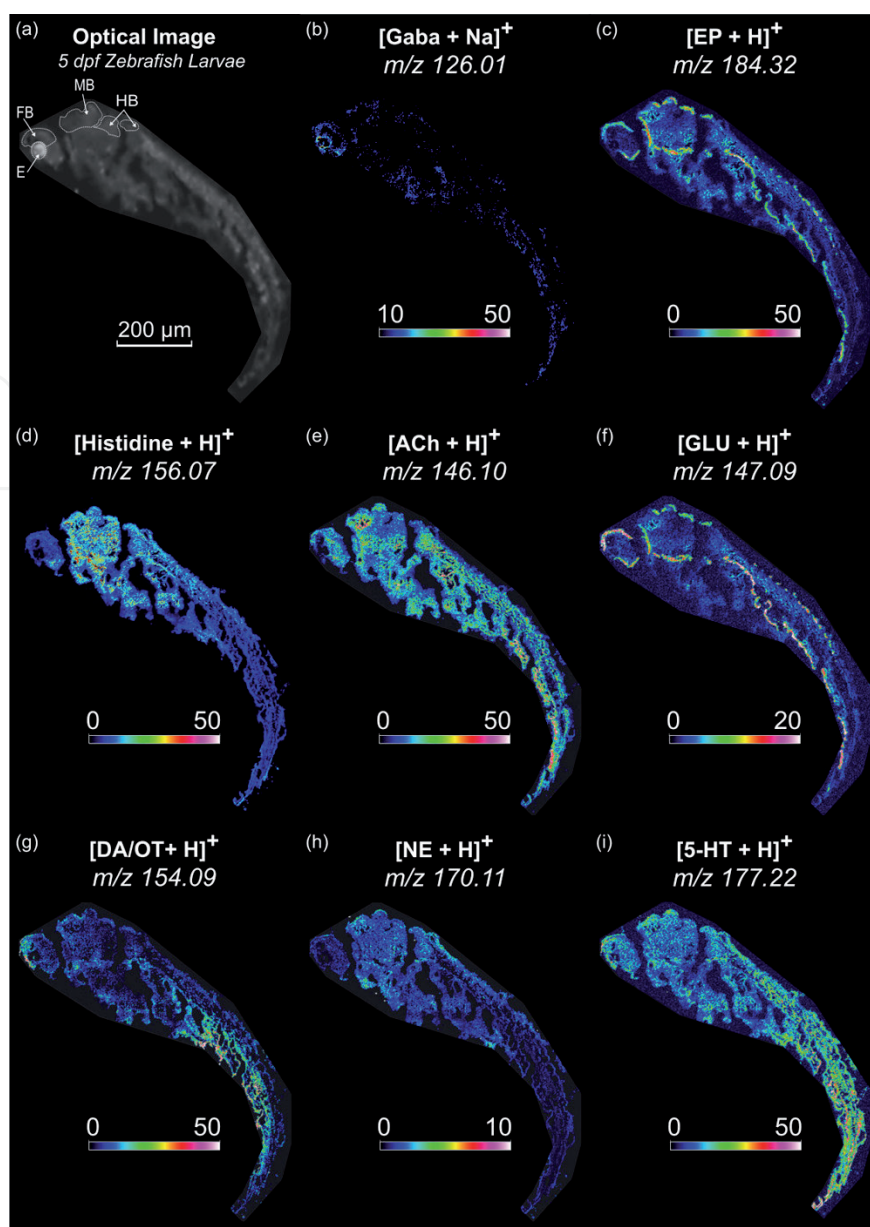
Figure 3.
MSI of a sagittal zebrafish tissue section at 5 μm lateral spatial resolution with eye (E), forebrain (FB), midbrain (MB), and hindbrain (HB) indicated in (a), (b) is the [GABA + Na]⁺ image, (c) is the epinephrine image, (d) is the histidine image, (e) is the acetylcholine image, (f) is the glutamine image, (g) is the dopamine/octopamine image, (h) is the norepinephrine image, and (i) is the serotonin image. Reprinted with permission from Ref. [61]. Copyright 2020 American Chemical Society.

examination could allow for follow-up data to be collected as well as the potential to reduce the number of organisms needed in a given research project.

The improvements in delocalization, reproducibility, and long-term stability from pneumatically-sprayed AuNPs warrant further investigation of this method. Finally, the quick and low-cost preparation may enable a broad range of new applications in neuroscience, pharmacology, drug discovery, and pathology.

4. Derivatization strategies

Chemical derivatization of functional groups is a common strategy to improve detection in MS techniques for a variety of molecular classes. On-tissue derivatization has been explored for many different purposes, including tryptic digestion [75, 76], phospholipid digestion [77], N-terminal peptide derivatization [78], and

derivatization of various metabolites/drugs of interest [79–82]. One particularly attractive advantage of derivatization is that small mass species typically have a change in molecular weight which avoids interferences from low mass matrix peaks.

Some of the aforementioned studies were on small molecular weight species, but derivatization was typically for only one analyte of interest. Examples of NT derivatization have met with varied success in terms of how many different molecular classes are accessible. Coniferyl aldehyde has been used to derivatize primary amines in pig adrenal glands and rat brains [83]. Methods included pre-coating target plates and then incubating after tissue was affixed for several minutes. Spray-coating with an organic matrix followed.

Specific reactions focused on NTs have utilized pyrylium salts (e.g., 2,4-diphenyl pyranylium (DPP)) that are reactive toward primary amines. The reaction scheme with a common NT, dopamine, is shown in **Figure 4a**. The reaction can proceed at room temperature but requires 30-80 spray passes of the derivatizing agent, followed by drying time, and then application of an organic matrix [84]. Additionally, preparation of the derivatizing agent is required and can be a multi-day process. While smaller crystals than typical organic matrix preparations have been reported, there are still limitations on overall spatial resolution. **Figure 4b** shows dopamine derivatized with 3 different pyrylium salts and the resulting images that are generated; without derivatization no dopamine was observed.

Derivatization with DPP has been demonstrated in multiple instances, with the generation a 3D mouse brain atlas of dopamine, norepinephrine and serotonin [85] as well as detection of up to 23 amino metabolites [86].

Additional derivatization methods have been developed since the initial report on primary amines only. For example, fluoromethylpyridinium-based materials
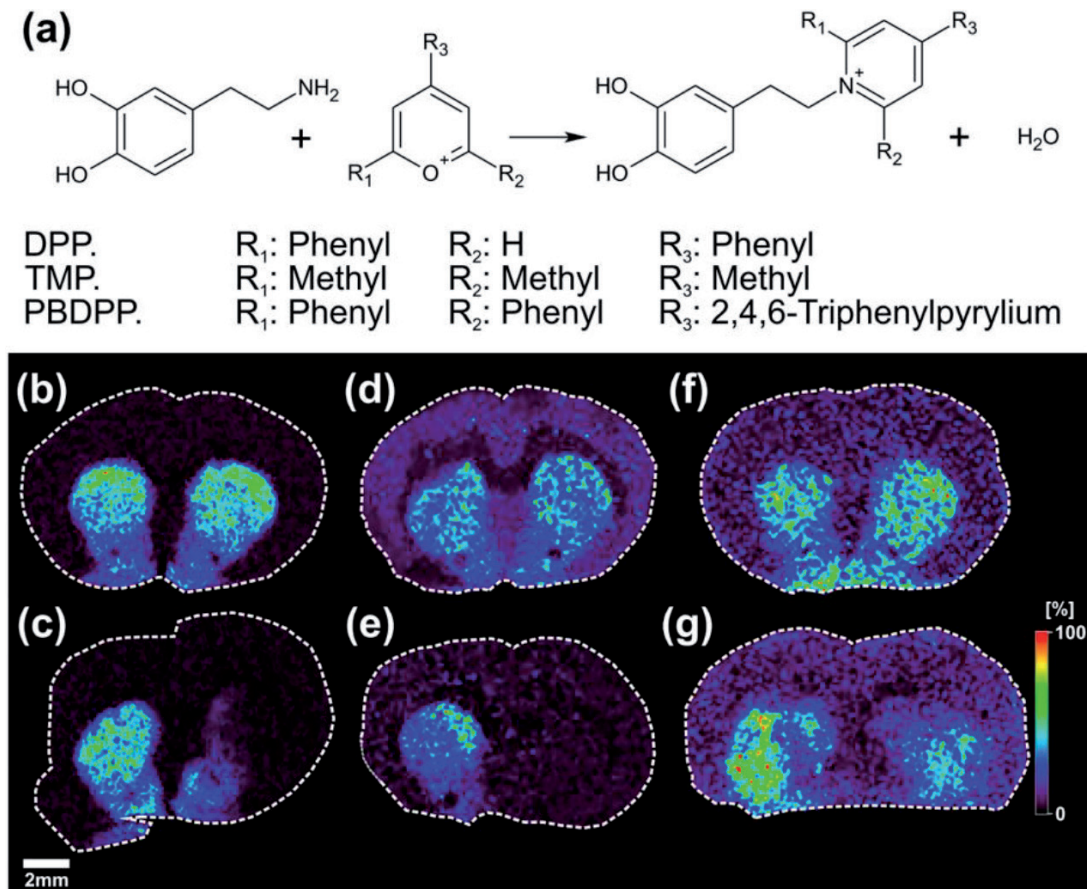
Figure 4.
(a) Reaction of dopamine with pyrylium salts. MALDI-MSI images of dopamine derivatized with DPP (b, c), PBDPP (d, e) or TMP (f, g). Signal intensity is indicated using a rainbow scale. Reprinted with permission from Ref. [84]. Copyright 2015 American Society for Mass Spectrometry.
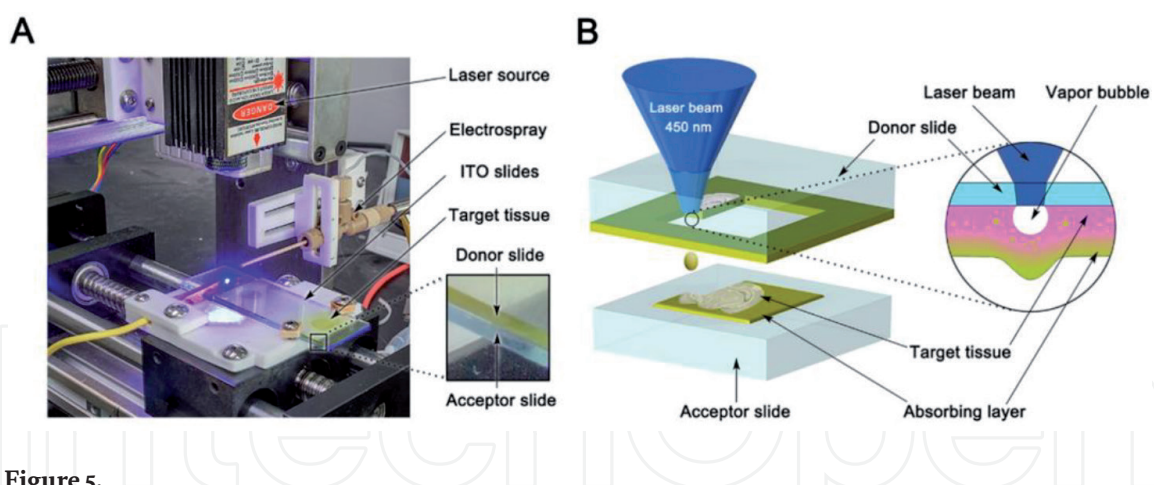
Figure 5.
*(A) LATT setup and (B) schematic diagram of the system. Reprinted with permission from Ref. [89].
Copyright 2020 American Chemical Society.*

are reactive with phenolic hydroxyl and/or primary or secondary amines, which expand the potential range of NTs that can be detected [87]. Charge-tagging using 2-(4-bromophenyl)-4,6- diphenylpyranylium (Br-TPP) results in distinctive isotopic distributions in the mass spectrum, making it easier to identify derivatized species from other potential species [88].

The last example here is a laser-induced tissue transfer (LATT) system that enhances on-tissue derivatization of small molecules [89]. An electrosprayer applies the derivatization reagent and matrix solution on tissue and is then irradiated with a 450 nm laser beam in transmission mode, which results in transfer of a thin film of tissue to a second slide. **Figure 5** shows the setup and diagram of the LATT system. Chemicals used for derivatization include coniferyl acetate or Girard's T reagent. Preparation time requires multiple hours (overnight) and additional matrix application. Multiple classes of biomolecules were analyzed, including amino acids, NTs, polyamines, dipeptides, and others. The issue of analyte delocalization is improved in LATT as compared to other derivatization techniques.

5. Quantitation

MSI has been applied to quantitative analysis of drugs [90, 91], metabolites [92], and biomarkers in tissue [93] using pneumatic sprayers and sublimation techniques described in this chapter. Nearly all of these demonstrations have utilized organic acid matrices such as DHB, CHCA, and trihydroxyacetophenone (THAP), with one research group utilizing TiO_2 NPs [94, 95]. Methods of quantitation are still being investigated [96], as many of the consistency issues with MALDI-MSI that have been discussed in this chapter are even more relevant with quantitative MSI (qMSI). **Figure 6** shows a summary of two of the more common methods used for generation of a calibration curve for qMSI, on-tissue spotting and tissue mimetic models which feature spiking of tissue homogenates [96].

On-tissue spotting uses either a standard molecule that is chemically similar to the analyte or a stable isotope of the analyte for making the calibration curve. Ion intensities between the analyte and standard are used to estimate the drug concentration in dosed tissue. Disadvantages include difficulty in maintaining uniform application of standards and differences in ionization for sprayed on standards vs. analyte molecules embedded within tissue. Advantages are that this method is fast and straightforward. The tissue mimetic model uses a surrogate tissue that is homogenized and spiked with the analyte of interest, frozen, sectioned, then prepared with matrix. The advantage of this method is that there is
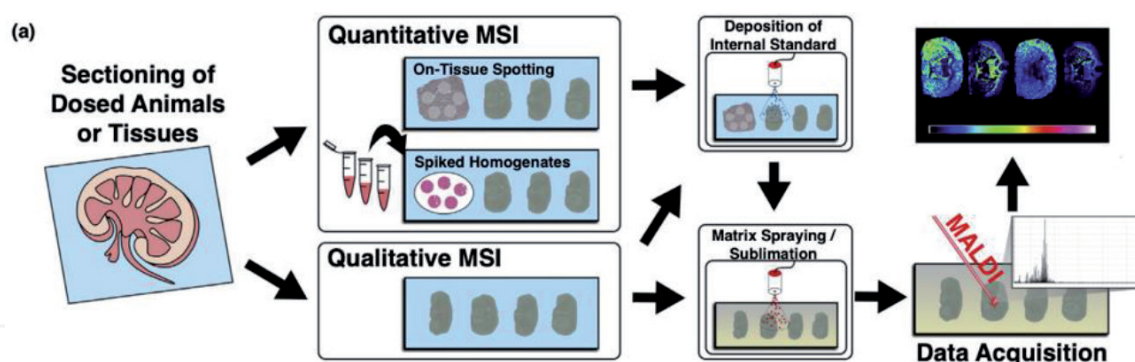
Figure 6.
Description of qMSI experiments where on-tissue spotting and homogenate spiking are two popular methods. Reprinted with permission from Ref. [94]. Copyright 2019 Elsevier Ltd.

better representation of the ionization process for analyte embedded within tissue. However, it is more time consuming, labor intensive, and requires more tissue for the calibration curve. Each method has been correlated with LC-MS data, the current primary method used for quantification [97].

Specific examples with clinical relevancy are briefly described here. First, epertinib and lapatinib were quantified in a metastatic brain cancer mouse model using stable isotope labeling, and with liquid chromatography (LC)-MS validation [91]. The topical drugs roflumilast, tofacitinib, ruxolitinib, and LEO 29102 were examined in human skin explants to determine drug penetration and evaluate lipid markers [90]. qMSI data had a much lower quantitation range than LC-MS data of individual skin layers. Rifampicin in mouse liver tissue was quantified via a fragment ion of the intact molecule. The method used an in-house synthesized stable isotope and correlated the results with LC-MS/MS [98]. Lastly, there is one example that specifically focused on comprehensive mapping of NTs in Parkinson's disease lesioned mouse brain and demonstrated quantitation of dopamine using a stable isotope [87]. All of the drug molecules listed in this paragraph are above the general size range that NTs and metabolites fall within, ranging from 400 to 800 Da, but present possible future avenues of research for the NT-focused methods discussed in this chapter.

The tissue mimetic model first gained popularity with examination of lapatinib and nevirapine in mouse liver by Groseclose and Castellino [99]. In addition to demonstrating high spatial resolution, they examined reproducibility and drug distribution within the homogenate. Fewer applications of the tissue mimetic model have been done, especially with small molecules as opposed to lipids [100]. A notable example includes the determination of the spatial distribution of gemcitabine, a chemotherapeutic agent, and its metabolites in mouse model pancreatic tumors using AuNPs and a traditional matrix as comparison [101]. Further experiments also work on the computational side of MSI and determining the best ways to normalize spectra [102, 103].

6. Concluding remarks

This chapter has introduced the utility of mass spectrometry imaging (MSI) for small molecules, with a specific focus on neurotransmitters (NTs). Methods that have resulted in enhanced signals of NTs were highlighted, with alternative matrix materials and chemical derivatization of analytes the two main points of discussion. Future research is needed in both of these areas to determine optimum conditions and applications, as well as establishing standard procedures so that broad application of MSI can continue. Finally, an area not discussed here that is relevant to these

techniques and that will likely be explored in the future is the quantitative determination of small molecules.

Acknowledgements

Conflict of interest

The author declares no conflict of interest.

Nomenclature

DAG	diacylglycerol
DAN	1,5-diaminonapthalene
DESI	desorption electrospray ionization
DHB	2,5-dihydroxybenzoic acid
DPP	2,4-diphenyl pyranylium
CHCA	α-cyano-4-hydroxy cinnamic acid
Glucose 6-P	glαucose 6-phosphate
HTP	high throughput
ITO	indium tin oxide
LATT	laser-assisted tissue transfer
LC-MS	liquid chromatography mass spectrometry
MALDI	matrix-assisted laser desorption ionization
MSI	mass spectrometry imaging
qMSI	quantitative mass spectrometry imaging
NEDC	N-(1-napthyl)ethylenediamine dihydrochloride
NT	neurotransmitter
NP	nanoparticle
PA	phosphatidic acid
PCA	principal component analysis
PChol	phosphocholine
PE	phospatidylethanolamine
PEP	phosphoenolpyruvic acid
PG	phosphatidylglycerol
PI	phosphatidylinositol
PC	phosphatidylcholine
SA	sinapic (or sinapinic) acid
TAG	triacylglycerol
THAP	trihydroxyacetophenone

Author details

Katherine A. Stumpo
University of Scranton, Scranton, PA, USA

*Address all correspondence to: katherine.stumpo@scranton.edu

IntechOpen

References

[1] Caprioli, R.M., Farmer, T.B., Gile, J.: Molecular Imaging of Biological Samples: Localization of Peptides and Proteins Using MALDI-TOF MS. Anal. Chem. 69, 4751-4760 (1997). https://doi.org/10.1021/ac970888i

[2] Norris, J.L., Caprioli, R.M.: Analysis of tissue specimens by matrix-assisted laser desorption/ionization imaging mass spectrometry in biological and clinical research. Chem. Rev. 113, 2309-2342 (2013). https://doi.org/10.1021/cr3004295

[3] Danbolt, N.C., Zhou, Y., Furness, D.N., Holmseth, S.: Strategies for immunohistochemical protein localization using antibodies: What did we learn from neurotransmitter transporters in glial cells and neurons. Glia. 64, 2045-2064 (2016). https://doi.org/10.1002/glia.23027

[4] Ye, H., Wang, J., Greer, T., Strupat, K., Li, L.: Visualizing Neurotransmitters and Metabolites in the Central Nervous System by High Resolution and High Accuracy Mass Spectrometric Imaging. ACS Chem. Neurosci. 4, 1049-1056 (2013). https://doi.org/10.1021/cn400065k

[5] Römpp, A., Spengler, B.: Mass spectrometry imaging with high resolution in mass and space, (2013)

[6] Buchberger, A.R., DeLaney, K., Johnson, J., Li, L.: Mass Spectrometry Imaging: A Review of Emerging Advancements and Future Insights, (2018)

[7] Trim, P.J., Snel, M.F.: Small molecule MALDI MS imaging: Current technologies and future challenges. Methods. 104, 127-141 (2016). https://doi.org/10.1016/j.ymeth.2016.01.011

[8] Seeley, E.H., Caprioli, R.M.: MALDI imaging mass spectrometry of human tissue: method challenges and clinical perspectives. Trends Biotechnol. 29, 136-143 (2011). https://doi.org/10.1016/j.tibtech.2010.12.002

[9] Smirnov, I.P., Zhu, X., Taylor, T., Huang, Y., Ross, P., Papayanopoulos, I.A., Martin, S.A., Pappin, D.J.: Suppression of α-Cyano-4-hydroxycinnamic Acid Matrix Clusters and Reduction of Chemical Noise in MALDI-TOF Mass Spectrometry. Anal. Chem. 76, 2958-2965 (2004). https://doi.org/10.1021/ac035331j

[10] Manicke, N.E., Dill, A.L., Ifa, D.R., Cooks, R.G.: High-resolution tissue imaging on an orbitrap mass spectrometer by desorption electrospray ionization mass spectrometry. J. Mass Spectrom. 45, 223-226 (2010). https://doi.org/10.1002/jms.1707

[11] Wiseman, J., Ifa, D.R., Song, Q., Cooks, R.G.: Tissue Imaging at Atmospheric Pressure Using Desorption Electrospray Ionization (DESI) Mass Spectrometry. Angew. Chemie Int. Ed. 45, 7188-7192 (20016). https://doi.org/10.1002/anie.200602449

[12] Yang, J., Caprioli, R.M.: Matrix sublimation/recrystallization for imaging proteins by mass spectrometry at high spatial resolution. Anal. Chem. 83, 5728-5734 (2011). https://doi.org/10.1021/ac200998a

[13] Leinweber, B.D., Tsaprailis, G., Monks, T.J., Lau, S.S.: Improved MALDI-TOF Imaging Yields Increased Protein Signals at High Molecular Mass. J. Am. Soc. Mass Spectrom. 20, 89-95 (2009). https://doi.org/10.1016/j.jasms.2008.09.008

[14] Mainini, V., Bovo, G., Chinello, C., Gianazza, E., Grasso, M., Cattoretti, G., Magni, F.: Detection of high molecular weight proteins by MALDI imaging mass spectrometry. Mol. Biosyst. 9, 1101-1107 (2013). https://doi.org/10.1039/c2mb25296a

[15] Grey, A.C., Chaurand, P., Caprioli, R.M., Schey, K.L.: MALDI imaging mass spectrometry of integral membrane proteins from ocular lens and retinal tissue. J. Proteome Res. 8, 3278-3283 (2009). https://doi.org/10.1021/pr800956y

[16] Andersson, M., Groseclose, M.R., Deutch, A.Y., Caprioli, R.M.: Imaging mass spectrometry of proteins and peptides: 3D volume reconstruction. Nat. Methods. 5, 101-108 (2008). https://doi.org/10.1038/nmeth1145

[17] Groseclose, M.R., Andersson, M., Hardesty, W.M., Caprioli, R.M.: Identification of proteins directly from tissue: In situ tryptic digestions coupled with imaging mass spectrometry. J. Mass Spectrom. 42, 254-262 (2007). https://doi.org/10.1002/jms.1177

[18] Altelaar, A.F.M., Taban, I.M., McDonnell, L.A., Verhaert, P.D.E.M., de Lange, R.P.J., Adan, R.A.H., Mooi, W.J., Heeren, R.M.A., Piersma, S.R.: High-resolution MALDI imaging mass spectrometry allows localization of peptide distributions at cellular length scales in pituitary tissue sections. Int. J. Mass Spectrom. 260, 203-211 (2007). https://doi.org/10.1016/j.ijms.2006.09.028

[19] Dufresne, M., Patterson, N.H., Norris, J.L., Caprioli, R.M.: Combining Salt Doping and Matrix Sublimation for High Spatial Resolution MALDI Imaging Mass Spectrometry of Neutral Lipids. Anal. Chem. 91, 12928-12934 (2019). https://doi.org/10.1021/acs.analchem.9b02974

[20] Schiller, J., Arnhold, J., Benard, S., Müller, M., Reichl, S., Arnold, K.: Lipid analysis by matrix-assisted laser desorption and ionization mass spectrometry: A methodological approach. Anal. Biochem. 267, 46-56 (1999). https://doi.org/10.1006/abio.1998.3001

[21] Dekker, L.J.M., van Kampen, J.J.A., Reedijk, M.L., Burgers, P.C., Gruters, R.A., Osterhaus, A.D.M.E., Luider, T.M.: A mass spectrometry based imaging method developed for the intracellular detection of HIV protease inhibitors. Rapid Commun. Mass Spectrom. 23, 1183-1188 (2009). https://doi.org/10.1002/rcm.3981

[22] Li, B., Zhang, Y., Ge, J., Liu, K., Li, P.: Sample preparation for mass spectrometry imaging of leaf tissues: a case study on analyte delocalization. Anal Bioanal Chem. 410, 7449-7456 (2018)

[23] Ly, A., Ragionieri, L., Liessem, S., Becker, M., Deininger, S.O., Neupert, S., Predel, R.: Enhanced Coverage of Insect Neuropeptides in Tissue Sections by an Optimized Mass-Spectrometry-Imaging Protocol. Anal. Chem. 91, 1980-1988 (2019). https://doi.org/10.1021/acs.analchem.8b04304

[24] Gemperline, E., Keller, C., Jayaraman, D., Maeda, J., Sussman, M.R., Ané, J.M., Li, L.: Examination of Endogenous Peptides in *Medicago truncatula* Using Mass Spectrometry Imaging. J. Proteome Res. 15, 4403-4411 (2016). https://doi.org/10.1021/acs.jproteome.6b00471

[25] Goodwin, R.J.A., Pennington, S.R., Pitt, A.R.: Protein and peptides in pictures: Imaging with MALDI mass spectrometry. Proteomics. 8, 3785-3800 (2008). https://doi.org/10.1002/pmic.200800320

[26] Hart, P.J., Francese, S., Claude, E., Woodroofe, M.N., Clench, M.R.: MALDI-MS imaging of lipids in ex vivo human skin. Anal. Bioanal. Chem. 401, 115-125 (2011). https://doi.org/10.1007/s00216-011-5090-4

[27] Kompauer, M., Heiles, S., Spengler, B.: Atmospheric pressure MALDI mass spectrometry imaging of tissues and cells at 1.4-μm lateral resolution. Nat. Methods. 14, 90-96 (2016). https://doi.org/10.1038/nmeth.4071

[28] Marko-Varga, G., Fehniger, T.E., Rezeli, M., Döme, B., Laurell, T., Végvári, Á.: Drug localization in different lung cancer phenotypes by MALDI mass spectrometry imaging. J. Proteomics. 74, 982-992 (2011). https://doi.org/10.1016/j.jprot.2011.03.019

[29] Wang, J., Qiu, S., Chen, S., Xiong, C., Liu, H., Wang, J., Zhang, N., Hou, J., He, Q., Nie, Z.: MALDI-TOF MS imaging of metabolites with a N -(1-Naphthyl) ethylenediamine dihydrochloride matrix and its application to colorectal cancer liver metastasis. Anal. Chem. 87, 422-430 (2015). https://doi.org/10.1021/ac504294s

[30] Wang, J., Wang, C., Han, X.: Enhanced coverage of lipid analysis and imaging by matrix-assisted laser desorption/ionization mass spectrometry via a strategy with an optimized mixture of matrices. Anal. Chim. Acta. 1000, 155-162 (2018). https://doi.org/10.1016/j.aca.2017.09.046

[31] Thomas, A., Charbonneau, J.L., Fournaise, E., Chaurand, P.: Sublimation of new matrix candidates for high spatial resolution imaging mass spectrometry of lipids: Enhanced information in both positive and negative polarities after 1,5-diaminonapthalene deposition. Anal. Chem. 84, 2048-2054 (2012). https://doi.org/10.1021/ac2033547

[32] Fernández, R., Garate, J., Martín-Saiz, L., Galetich, I., Fernández, J.A.: Matrix Sublimation Device for MALDI Mass Spectrometry Imaging. Anal. Chem. 91, 803-807 (2019). https://doi.org/10.1021/acs.analchem.8b04765

[33] Kaya, I., Jennische, E., Dunevall, J., Lange, S., Ewing, A.G., Malmberg, P., Baykal, A.T., Fletcher, J.S.: Spatial Lipidomics Reveals Region and Long Chain Base Specific Accumulations of Monosialogangliosides in Amyloid Plaques in Familial Alzheimer's Disease Mice (5xFAD) Brain. ACS Chem.

Neurosci. 11, 14-24 (2020). https://doi.org/10.1021/acschemneuro.9b00532

[34] Korte, A.R., Lee, Y.J.: MALDI-MS analysis and imaging of small molecule metabolites with 1,5-diaminonaphthalene (DAN). J. Mass Spectrom. 49, 737-741 (2014). https://doi.org/10.1002/jms.3400

[35] Weißflog, J., Svatoš, A.: 1,8-Di(piperidinyl)-naphthalene-rationally designed MAILD/MALDI matrix for metabolomics and imaging mass spectrometry. RSC Adv. 6, 75073-75081 (2016). https://doi.org/10.1039/c6ra17237g

[36] Demeure, K., Quinton, L., Gabelica, V., De Pauw, E.: Rational Selection of the Optimum MALDI Matrix for Top-Down Proteomics by In-Source Decay. Anal. Chem. 79, 8678-8685 (2007). https://doi.org/10.1021/ac070849z

[37] Gusev, A.I., Wilkinson, W.R., Proctor, A., Hercules, D.M.: Improvement of signal reproducibility and matrix/comatrix effects in MALDI analysis. Anal. Chem. 67, 1034-1041 (1995). https://doi.org/10.1021/ac00102a003

[38] O'Rourke, M.B., Djordjevic, S.P., Padula, M.P.: The quest for improved reproducibility in MALDI mass spectrometry. Mass Spectrom. Rev. 37, 217-228 (2018). https://doi.org/10.1002/mas.21515

[39] Calvano, C.D., Monopoli, A., Cataldi, T.R.I., Palmisano, F.: MALDI matrices for low molecular weight compounds: an endless story? Anal. Bioanal. Chem. 410, 4015-4038 (2018). https://doi.org/10.1007/s00216-018-1014-x

[40] Gemperline, E., Rawson, S., Li, L.: Optimization and comparison of multiple MALDI matrix application methods for small molecule mass spectrometric imaging. Anal. Chem. 86, 10030-10035 (2014). https://doi.org/10.1021/ac5028534

[41] Tucker, L.H., Conde-González, A., Cobice, D., Hamm, G.R., Goodwin, R.J.A., Campbell, C.J., Clarke, D.J., Mackay, C.L.: MALDI Matrix Application Utilizing a Modified 3D Printer for Accessible High Resolution Mass Spectrometry Imaging. Anal. Chem. 90, 8742-8749 (2018). https://doi.org/10.1021/acs.analchem.8b00670

[42] Goodwin, R.J.A.: Sample preparation for mass spectrometry imaging: Small mistakes can lead to big consequences. J. Proteomics. (2012). https://doi.org/10.1016/j.jprot.2012.04.012

[43] Kreutzer, L., Aichler, M., Walch, A.K.: In situ metabolomics in cancer tissue by high-resolution mass spectrometry imaging. In: Fundamentals and Applications of Fourier Transform Mass Spectrometry. pp. 253-279. Elsevier (2019)

[44] Ly, A., Buck, A., Balluff, B., Sun, N., Gorzolka, K., Feuchtinger, A., Janssen, K.P., Kuppen, P.J.K., Van De Velde, C.J.H., Weirich, G., Erlmeier, F., Langer, R., Aubele, M., Zitzelsberger, H., McDonnell, L., Aichler, M., Walch, A.: High-mass-resolution MALDI mass spectrometry imaging of metabolites from formalin-fixed paraffin-embedded tissue. Nat. Protoc. 11, 1428-1443 (2016). https://doi.org/10.1038/nprot.2016.081

[45] Tanaka, K., Waki, H., Ido, Y., Akita, S., Yoshida, Y., Yoshida, T., Matsuo, T.: Protein and polymer analyses up to m/z 100 000 by laser ionization time-of-flight mass spectrometry. Rapid Commun. Mass Spectrom. 2, 151-153 (1988). https://doi.org/10.1002/rcm.1290020802

[46] McLean, J.A., Stumpo, K.A., Russell, D.H.: Size-Selected (2-10 nm) Gold Nanoparticles for Matrix Assisted Laser Desorption Ionization of Peptides. J. Am. Chem. Soc. 127, 5304-5305 (2005). https://doi.org/10.1021/ja043907w

[47] Stumpo, K.A., McLaughlin, N.: Method of Comprehensive Neurotransmitter Detection using citrate-capped AuNPs for Imaging Mass Spectrometry. Proceedings of the 67th American Society for Mass Spectrometry National Meeting (2019)

[48] Wu, H.-P., Yu, C.-J., Lin, C.-Y., Lin, Y.-H., Tseng, W.-L.: Gold nanoparticles as assisted matrices for the detection of biomolecules in a high-salt solution through laser desorption/ionization mass spectrometry. J. Am. Soc. Mass Spectrom. 20, 875-882 (2009). https://doi.org/10.1016/j.jasms.2009.01.002

[49] Dufresne, M., Masson, J.-F., Chaurand, P.: Sodium-Doped Gold-Assisted Laser Desorption Ionization for Enhanced Imaging Mass Spectrometry of Triacylglycerols from Thin Tissue Sections. Anal. Chem. 88, 6018-6025 (2016). https://doi.org/10.1021/acs.analchem.6b01141

[50] Dufresne, M., Thomas, A., Breault-Turcot, J., Masson, J.F., Chaurand, P.: Silver-assisted laser desorption ionization for high spatial resolution imaging mass spectrometry of olefins from thin tissue sections. Anal. Chem. 85, 3318-3324 (2013). https://doi.org/10.1021/ac3037415

[51] Sherrod, S.D., Diaz, A.J., Russell, W.K., Cremer, P.S., Russell, D.H.: Silver Nanoparticles as Selective Ionization Probes for Analysis of Olefins by Mass Spectrometry. Anal. Chem. 80, 6796-6799 (2008). https://doi.org/10.1021/ac800904g

[52] Muller, L., Kailas, A., Jackson, S.N., Roux, A., Barbacci, D.C., Albert Schultz, J., Balaban, C.D., Woods, A.S., Schultz, J.A., Balaban, C.D., Woods, A.S., Albert Schultz, J., Balaban, C.D., Woods, A.S.: Lipid imaging within the normal rat kidney using silver nanoparticles by matrix-assisted laser desorption/ionization mass

spectrometry. Kidney Int. 88, 186-192 (2015). https://doi.org/10.1038/ki.2015.3

[53] Hua, L., Chen, J., Ge, L., Tan, S.N.: Silver nanoparticles as matrix for laser desorption/ionization mass spectrometry of peptides. J. Nanoparticle Res. 9, 1133-1138 (2007). https://doi.org/10.1007/s11051-007-9244-4

[54] Pan, C., Xu, S., Hu, L., Su, X., Ou, J., Zou, H., Guo, Z., Zhang, Y., Guo, B.: Using Oxidized Carbon Nanotubes as Matrix for Analysis of Small Molecules by MALDI-TOF MS. J. Am. Soc. Mass Spectrom. 16, 883-892 (2005). https://doi.org/10.1016/j.jasms.2005.03.009

[55] Ren, S., Zhang, L., Cheng, Z., Guo, Y.: Immobilized carbon nanotubes as matrix for MALDI-TOF-MS analysis: Applications to neutral small carbohydrates. J. Am. Soc. Mass Spectrom. 16, 333-339 (2005). https://doi.org/10.1016/j.jasms.2004.11.017

[56] Han, M., Sunner, J.: An activated carbon substrate surface for laser desorption mass spectrometry. J. Am. Soc. Mass Spectrom. 11, 644-649 (2000). https://doi.org/10.1016/S1044-0305(00)00129-X

[57] Tang, H.-W., Ng, K.-M., Lu, W., Che, C.-M.: Ion Desorption Efficiency and Internal Energy Transfer in Carbon-Based Surface-Assisted Laser Desorption/Ionization Mass Spectrometry: Desorption Mechanism(s) and the Design of SALDI Substrates. Anal. Chem. 81, 4720-4729 (2009). https://doi.org/10.1021/ac8026367

[58] Wei, J., Buriak, J.M., Siuzdak, G.: Desorption–ionization mass spectrometry on porous silicon. Nature. 399, 243-246 (1999). https://doi.org/10.1038/20400

[59] Wen, X., Dagan, S., Wysocki, V.H.: Small-Molecule Analysis with Silicon-Nanoparticle-Assisted Laser Desorption/Ionization Mass Spectrometry. Anal. Chem. 79, 434-444 (2007). https://doi.org/10.1021/ac061154l

[60] Sacks, C., Stumpo, K.A.: Gold Nanoparticles for Enhanced Ionization and Fragmentation of Biomolecules using LDI-MS. J. Mass. Spectrom. 53, 1070-1077 (2018). https://doi.org/10.1002/jms.4282

[61] McLaughlin, N., Bielinski, T., Tressler, C., Barton, E., Glunde, K., Stumpo, K.A.: Pneumatically Sprayed Gold Nanoparticles for Mass Spectrometry Imaging of Neurotransmitters. J. Am. Soc. Mass Spectrom. ASAP Article, DOI: 10.1021/jasms.0c00156

[62] Chiu, T., Chang, L., Chiang, C., Chang, H.: Determining Estrogens Using Surface-Assisted Laser Desorption/Ionization Mass Spectrometry with Silver Nanoparticles as the Matrix. J. Am. Soc. Mass Spectrom. 19, 1343-1346 (2008). https://doi.org/10.1016/j.jasms.2008.06.006

[63] Ozawa, T., Osaka, I., Hamada, S., Murakami, T., Miyazato, A., Kawasaki, H., Arakawa, R.: Direct Imaging Mass Spectrometry of Plant Leaves Using Surface-assisted Laser Desorption/Ionization with Sputter-deposited Platinum Film. Anal. Sci. 32, 587-591 (2016). https://doi.org/10.2116/analsci.32.587

[64] Ràfols, P., Vilalta, D., Torres, S., Calavia, R., Heijs, B., McDonnell, L.A., Brezmes, J., del Castillo, E., Yanes, O., Ramírez, N., Correig, X.: Assessing the potential of sputtered gold nanolayers in mass spectrometry imaging for metabolomics applications. PLoS One. 13, (2018). https://doi.org/10.1371/journal.pone.0208908

[65] Xu, L., Kliman, M., Forsythe, J.G., Korade, Z., Hmelo, A.B., Porter, N.A., McLean, J.A.: Profiling and Imaging Ion

Mobility-Mass Spectrometry Analysis of Cholesterol and 7-Dehydrocholesterol in Cells Via Sputtered Silver MALDI. J. Am. Soc. Mass Spectrom. 26, 924-933 (2015). https://doi.org/10.1007/s13361-015-1131-0

[66] Tang, H.-W., Lu, W., Che, C.-M., Ng, K.-M.: Gold Nanoparticles and Imaging Mass Spectrometry: Double Imaging of Latent Fingerprints. Anal. Chem. 82, 1589-1593 (2010). https://doi.org/10.1021/ac9026077

[67] Ozawa, T., Osaka, I., Ihozaki, T., Hamada, S., Kuroda, Y., Murakami, T., Miyazato, A., Kawasaki, H., Arakawa, R.: Simultaneous detection of phosphatidylcholines and glycerolipids using matrix-enhanced surface-assisted laser desorption/ionization-mass spectrometry with sputter-deposited platinum film. J. Mass. Spectrom. 50, 1264-1269 (2015)

[68] Hansen, R.L., Duenas, M.E., Lee, Y.J.: Sputter-Coated Metal Screening for Small Molecule Analysis and High-Spatial Resolution Imaging in Laser Desorption Ionization Mass Spectrometry | Journal of the American Society for Mass Spectrometry. J. Am. Soc. Mass Spectrom. 30, 299-308 (2019)

[69] Guan, M., Zhang, Z., Li, S., Liu, J., Liu, L., Yang, H., Zhang, Y., Wang, T., Zhao, Z.: Silver nanoparticles as matrix for MALDI FTICR MS profiling and imaging of diverse lipids in brain. Talanta. 179, 624-631 (2018)

[70] Goto-Inoue, N., Hayasaka, T., Zaima, N., Kashiwagi, Y., Yamamoto, M., Nakamoto, M., Setou, M.: The detection of glycosphingolipids in brain tissue sections by imaging mass spectrometry using gold nanoparticles. J. Am. Soc. Mass Spectrom. 21, 1940-1943 (2010). https://doi.org/10.1016/j.jasms.2010.08.002

[71] Palermo, A., Forsberg, E.M., Warth, B., Aisporna, A.E., Billings, E., Kuang, E., Benton, H.P., Berry, D., Siuzdak, G.: Fluorinated Gold Nanoparticles for Nanostructure Imaging Mass Spectrometry. ACS Nano. 12, 6938-6948 (2018). https://doi.org/10.1021/acsnano.8b02376

[72] McLaughlin, N., Bielinski, T., Stumpo, K.A.: The new gold standard for mass spectrometry imaging. In: Proceedings of the 68th American Society for Mass Spectrometry National Meeting (2020)

[73] Bielinski, T.: Optimization and Method Development of Pneumatically Sprayed AuNPs for Laser-Desorption Ionization Mass Spectrometry Imaging. Proceedings of the 68th American Society for Mass Spectrometry National Meeting (2020)

[74] Shedlock, C., Gianello, M., Bielinski, T., McLaughlin, N., Graham, J., Stumpo, K.A.: Computational Analysis of MSI Preparation Conditions using AuNPs. Proceedings of the 68th American Society for Mass Spectrometry National Meeting. Current Opinion in Biotechnology. (2020), 51-59. DOI: 10.1016/j.copbio.2018.08.003

[75] Beine, B., Diehl, H.C., Meyer, H.E., Henkel, C.: Tissue maldi mass spectrometry imaging (MALDI MSI) of peptides. In: Methods in Molecular Biology. pp. 129-150. Humana Press Inc. (2016)

[76] Diehl, H.C., Beine, B., Elm, J., Trede, D., Ahrens, M., Eisenacher, M., Marcus, K., Meyer, H., Henkel, C.: The challenge of on-tissue digestion for MALDI MSI— a comparison of different protocols to improve imaging experiments. Anal Bioanal Chem. 407, 2223-2243 (2015)

[77] Vens-Cappell, S., U. Kouzel, I., Kettling, H., Soltwisch, J., Bauwens, A., Porubsky, S., Müthing, J., Dreisewerd, K.: On-Tissue Phospholipase C Digestion for Enhanced MALDI-MS Imaging

of Neutral Glycosphingolipids. Anal. Chem. 88, 5595-5599 (2016). https://doi.org/10.1021/acs.analchem.6b01084

[78] Franck, J., El Ayed, M., Wisztorski, M., Salzet, M., Fournier, I.: On-Tissue N-Terminal Peptide Derivatizations for Enhancing Protein Identification in MALDI Mass Spectrometric Imaging Strategies. Anal. Chem. 81, 8305-8317 (2009). https://doi.org/10.1021/ac901043n

[79] Flinders, B., Morrell, J., Marshall, P.S., Ranshaw, L.E., Clench, M.R.: The use of hydrazine-based derivatization reagents for improved sensitivity and detection of carbonyl containing compounds using MALDI-MSI. Anal Bioanal Chem. 407, 2085-2094 (2015)

[80] Fülöp, A., Bausbacher, T., Rizzo, S., Zhou, Q., Gillandt, H., Hopf, C., Rittner, M.: New Derivatization Reagent for Detection of free Thiol-groups in Metabolites and Proteins in Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry Imaging. Anal. Chem. 92, 6224-6228 (2020). https://doi.org/10.1021/acs.analchem.9b05630

[81] Shimma, S., Kumada, H.-O., Taniguchi, H., Konna, A., Yao, I., Furata, K., Matsuda, T., Ito, S.: Microscopic visualization of testosterone in mouse testis by use of imaging mass spectrometry. Anal Bioanal Chem. 408, 7607-7615 (2016)

[82] P. Y. Barré, F., Flinders, B., P. Garcia, J., Jansen, I., R. S. Huizing, L., Porta, T., B. Creemers, L., M. A. Heeren, R., Cillero-Pastor, B.: Derivatization Strategies for the Detection of Triamcinolone Acetonide in Cartilage by Using Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry Imaging. Anal. Chem. 88, 12051-12059 (2016). https://doi.org/10.1021/acs.analchem.6b02491

[83] Manier, M.L., Spraggins, J.M., Reyzer, M.L., Norris, J.L., Caprioli, R.M.: A derivatization and validation strategy for determining the spatial localization of endogenous amine metabolites in tissues using MALDI imaging mass spectrometry: Endogenous amine metabolites in tissue. J. Mass Spectrom. 49, 665-673 (2014). https://doi.org/10.1002/jms.3411

[84] Shariatgorji, M., Nilsson, A., Källback, P., Karlsson, O., Zhang, X., Svenningsson, P., Andren, P.E.: Pyrylium Salts as Reactive Matrices for MALDI-MS Imaging of Biologically Active Primary Amines. J. Am. Soc. Mass Spectrom. 26, 934-939 (2015). https://doi.org/10.1007/s13361-015-1119-9

[85] Sugiyama, E., Guerrini, M.M., Honda, K., Hattori, Y., Abe, M., Källback, P., Andrén, P.E., Tanaka, K.F., Setou, M., Fagarasan, S., Suematsu, M., Sugiura, Y.: Detection of a high turnover serotonin circuit in the mouse brain using mass spectrometry imaging. iScience. (2019). https://doi.org/10.1016/j.isci.2019.09.036

[86] Esteve, C., Tolner, E.A., Shyti, R., van den Maagdenberg, A.M.J.M., McDonnell, L.A.: Mass spectrometry imaging of amino neurotransmitters: a comparison of derivatization methods and application in mouse brain tissue. Metabolomics. 12, 1-9 (2016). https://doi.org/10.1007/s11306-015-0926-0

[87] Shariatgorji, M., Nilsson, A., Fridjonsdottir, E., Vallianatou, T., Källback, P., Katan, L., Sävmarker, J., Mantas, I., Zhang, X., Bezard, E., Svenningsson, P., Odell, L.R., Andrén, P.E.: Comprehensive mapping of neurotransmitter networks by MALDI–MS imaging. Nat. Methods. 16, 1021-1028 (2019). https://doi.org/10.1038/s41592-019-0551-3

[88] Shariatgorji, R., Nilsson, A., Strittmatter, N., Vallianatou, T., Zhang, X., Svenningsson, P., Goodwin, R.J.A., Andrén, P.E.: Bromopyrylium Derivatization Facilitates Identification

by Mass Spectrometry Imaging of Monoamine Neurotransmitters and Small Molecule Neuroactive Compounds. J. Am. Soc. Mass Spectrom. 16, 18 (2020). https://doi.org/10.1021/jasms.0c00166

[89] Guo, S., Tang, W., Hu, Y., Chen, Y., Gordon, A., Li, B., Li, P.: Enhancement of On-tissue Chemical Derivatization by LaserAssisted Tissue Transfer for MALDI MS Imaging. Anal. Chem. 92, 1431-1438 (2020)

[90] Bonnel, D., Legouffe, R., Eriksson, A.H., Mortensen, R.W., Pamelard, F., Stauber, J., Nielsen, K.T.: MALDI imaging facilitates new topical drug development process by determining quantitative skin distribution profiles. Anal. Bioanal. Chem. 410, 2815-2828 (2018). https://doi.org/10.1007/s00216-018-0964-3

[91] Tanaka, Y., Hirata, M., Shinonome, S., Torii, M., Nezasa, K.I., Tanaka, H.: Distribution analysis of epertinib in brain metastasis of HER2-positive breast cancer by imaging mass spectrometry and prospect for antitumor activity. Sci. Rep. 8, 1-12 (2018). https://doi.org/10.1038/s41598-017-18702-2

[92] Goodwin, R.J.A., Nilsson, A., Mackay, C.L., Swales, J.G., Johansson, M.K., Billger, M., Andrén, P.E., Iverson, S.L.: Exemplifying the Screening Power of Mass Spectrometry Imaging over Label-Based Technologies for Simultaneous Monitoring of Drug and Metabolite Distributions in Tissue Sections. J. Biomol. Screen. 21, 187-193 (2016). https://doi.org/10.1177/1087057115623740

[93] Hulme, H., Fridjonsdottir, E., Gunnarsdottir, H., Vallianatou, T., Zhang, X., Wadensten, H., Shariatgorji, R., Nilsson, A., Bezard, E., Svenningsson, P., Andrén, P.E.: Simultaneous mass spectrometry imaging of multiple neuropeptides in the brain and alterations induced by experimental parkinsonism and L-DOPA therapy. Neurobiol. Dis. 137, 104738 (2020). https://doi.org/10.1016/j.nbd.2020.104738

[94] Giordano, S., Zucchetti, M., Decio, A., Cesca, M., Fuso Nerini, I., Maiezza, M., Ferrari, M., Licandro, S.A., Frapolli, R., Giavazzi, R., Maurizio, D., Davoli, E., Morosi, L.: Heterogeneity of paclitaxel distribution in different tumor models assessed by MALDI mass spectrometry imaging. Sci. Rep. 6, 1-12 (2016). https://doi.org/10.1038/srep39284

[95] Giordano, S., Morosi, L., Veglianese, P., Licandro, S.A., Frapolli, R., Zucchetti, M., Cappelletti, G., Falciola, L., Pifferi, V., Visentin, S., D'Incalci, M., Davoli, E.: 3D Mass Spectrometry Imaging Reveals a Very Heterogeneous Drug Distribution in Tumors. Sci. Rep. 6, 1-8 (2016). https://doi.org/10.1038/srep37027

[96] Schulz, S., Becker, M., Groseclose, M.R., Schadt, S., Hopf, C.: Advanced MALDI mass spectrometry imaging in pharmaceutical research and drug development, (2019)

[97] Sun, N., Fernandez, I.E., Wei, M., Wu, Y., Aichler, M., Eickelberg, O., Walch, A.: Pharmacokinetic and pharmacometabolomic study of pirfenidone in normal mouse tissues using high mass resolution MALDI-FTICR-mass spectrometry imaging. Histochem. Cell Biol. 145, 201-211 (2016). https://doi.org/10.1007/s00418-015-1382-7

[98] W. Chumbley, C., L. Reyzer, M., L. Allen, J., A. Marriner, G., E. Via, L., E. Barry, C., M. Caprioli, R.: Absolute Quantitative MALDI Imaging Mass Spectrometry: A Case of Rifampicin in Liver Tissues. Anal. Chem. 88, 2392-2398 (2016). https://doi.org/10.1021/acs.analchem.5b04409

[99] Reid Groseclose, M., Castellino, S.: A Mimetic Tissue Model for the Quantification of Drug Distributions by MALDI Imaging Mass Spectrometry.

Anal. Chem. 85, 10099-10106 (2013). https://doi.org/10.1021/ac400892z

[100] Jadoul, L., Longuespée, R., Noël, A., De Pauw, E.: A spiked tissue-based approach for quantification of phosphatidylcholines in brain section by MALDI mass spectrometry imaging. Anal. Bioanal. Chem. 407, 2095-2106 (2015). https://doi.org/10.1007/s00216-014-8232-7

[101] Tressler, C., Liang, H., Eshleman, J.R., Stumpo, K.A., Glunde, K.: MALDI Mass Spectrometry Imaging of Gemcitabine Treatment in Pancreatic Cancer: Exploring Multiple Matrices to See the Whole Picture. In: Proceedings of the 68th American Society for Mass Spectrometry National Meeting (2020)

[102] Källback, P., Shariatgorji, M., Nilsson, A., Andrén, P.E.: Novel mass spectrometry imaging software assisting labeled normalization and quantitation of drugs and neuropeptides directly in tissue sections. J. Proteomics. 75, 4941-4951 (2012). https://doi.org/10.1016/j.jprot.2012.07.034

[103] Hamm, G., Bonnel, D., Legouffe, R., Pamelard, F., Delbos, J.M., Bouzom, F., Stauber, J.: Quantitative mass spectrometry imaging of propranolol and olanzapine using tissue extinction calculation as normalization factor. J. Proteomics. 75, 4952-4961 (2012). https://doi.org/10.1016/j.jprot.2012.07.035