New mass spectrometric tools in brain research

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BrainMet (Bioimaging of Metals in Brain and Metallomics) at Forschungszentrum Jülich, Germany, provides mass spectrometric technology that enables quantitative imaging of metal distributions in brain tissue slices in combination with other medical imaging techniques (such as histochemistry, immunostaining, positron emission tomography, magnetic resonance tomography, and autoradiography).

The aim of this article is to demonstrate the capability of established BrainMet techniques by investigating thin cryosections of native rat brain and to illustrate the benefits of analytical strategies with examples of tumor, stroke and haematoma in rat brain.

The development and future trends in novel mass spectrometric instrumentation of two different laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) techniques with spatial resolution at the low µm and nm scale are discussed:

(1) using the near-field effect on the thin tip of a thin silver needle; and

(2) coupling a laser microdissection apparatus to ICP-MS.

Both these nanotechniques provide improved spatial resolution for the detection of essential and toxic metals in small sample sizes, so that new structural information about the metallo-architecture of diseased brain compared to control brain can be obtained down to the single cell level.

Keywords: Bioimaging; Brain stroke; Brain tissue; Hematoma; Laser ablation inductively coupled plasma mass spectrometry; Laser microdissection inductively coupled mass spectrometry; Metal distribution; Metallomics; Nano-LA-ICP-MS; Tumor

Abbreviations: ALS, Amyotrophic lateral sclerosis; AD, Alzheimer's disease; BBB, Blood-brain barrier; BCB, Blood-cerebrospinal fluid barrier; BrainMet, Bioimaging of Metals in Brain and Metallomics; CSF, Cerebrospinal fluid; ESI-MS, Electrospray ionization mass spectrometry; LA-ICP-MS, Laser ablation inductively coupled plasma mass spectrometry; LMD, Laser microdissection; MALDI-MS, Matrix-assisted laser desorption/ionization mass spectrometry; MRI, Magnetic resonance imaging; MS, Mass spectrometry; PD, Parkinson's disease; PET, Positron-emission tomography; PIXE, Proton-induced X-ray emission; SEM-EDX, Scanning electron microscopy with energy-dispersive X-ray analysis; SIMS, Secondary ion mass spectrometry; SOD, Superoxide dismutase

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1. Introduction

Trace metals (e.g., zinc, copper and iron) are involved in cellular processes (e.g., proliferation, myelinization and signaling) and are essential for growth and functioning of the brain. Metal ions are a vital component in the chemistry of life. Approximately one-third of all proteins are believed to require metal cations as cofactors with catalytical functions [1]. It is known that metal accumulations in the brain (e.g., in amyloid plaques) appear to be directly linked to neurodegenerative processes (e.g., Alzheimer's, Parkinson's or Wilson's disease, ageing and ischemia) [2–6].

Bioimaging of metals in thin tissue sections of brain is a novel, challenging topic in analytical chemistry and can be established as a new emerging field in brain research that provides information on the pathophysiology, pharmacology and toxicology of elements of interest [3,4,6,7]. To date, different analytical approaches {e.g., X-ray spectroscopic techniques for biological tissues [8,9], scanning electron microscopy with energy-dispersive X-ray analysis (SEM-EDX) [10], X-ray fluorescence analysis using the Synchrotron Radiation Facility (SRXRF) [11,12], X-ray photoelectron spectroscopy (XPS) [13], proton-induced X-ray emission (PIXE) [14], laser ablation inductively coupled mass spectrometry (LA-ICP-MS) and secondary ion MS (SIMS) [15–17]} are important analytical techniques in the life sciences for direct imaging (mapping) of metals in biological samples [18]. Table 1 compares LA-ICP-MS with other

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Table 1. Comparison of analytical techniques for elemental imaging of tissue

Method	Primary process	Particle/ray analyzed	Depth resolution	Spatial resolution	Imaging capability	Detection limits	Strengths of technique	Limitations of technique	Ref.
SIMS	ions ions  ions neutrals	Sputtered ions	>1 nm	50 nm	+++	>ng/g	High depth resolution imaging of elements, biomolecules (<2000 Da)	Strong matrix effects, intense molecular ions, quantitation of images	[17]
SNMS		Neutrals post-ionized by e-beam or laser	>3 nm	100 nm	(+)	µg/g	High depth resolution, elemental information	Poor sensitivity	[19]
LA-ICP-MS	photons neutrals 	Neutrals post-ionized in ICP	>100 nm	>10 µm	+++	>ng/g	High sensitivity, isotope ratios, quantitation via laboratory standards	Spatial resolution (required nano-LA-ICP-MS)	[7]
SEM-EDX	e^- X-ray 	X-ray	none	~5 nm	+++	0.1%	High spatial resolution (Na – U)	Low sensitivity	[10]
XPS	X-ray e^- 	Photo electrons	4–8 mono-layers	~100 µm	+	0.1%	Chemical species (Li – U)	Low sensitivity	[13]
SRXRF	X-ray fluores-cence 	Fluorescent X-ray	10 µm	~100 nm	+++	0.1 µg/g	High spatial resolution, single-cell imaging	Needs very expensive synchrotron facility, quantitation of images	[11]
MALDI-MS	photons ions 	Ions	>µm	>20 µm	+++	–	Large biomolecules (<100 000 Da)	Quantitation of images	[20]