Direct tissue analyses of low molecular-weight drugs by Matrix Assisted Laser Desorption / Ionization and Ion Mobility Mass Spectrometry

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Abstract:

Conventional detection of drugs in tissues involves processing tissue homogenates for the subsequent chromatographic and/or mass spectrometric analyses. The homogenization procedure has precluded the possibility of acquiring detailed information for in situ drug distribution. Autoradiography, on the other hand, could compensate such deficits. However, it requires the use of custom-synthesized drugs containing radioisotopes. New methods were developed to directly detect low molecular-weight drugs in tissue using Matrix Assisted Laser Desorption/Ionization-Mass Spectrometer (MALDI-MS) and Matrix Assisted Laser Desorption/Ionization-Ion Mobility-Mass Spectrometer (MALDI-IM-MS). The new methods require minimal sample preparation, offer high detection sensitivity with low sample loss, shorten the sample turn-around time, and are devoid of radioisotope hazard.

Rat brains were rapidly collected and snap-frozen 20 minutes after intraperitoneal injection of cocaine (20 mg/kg freebase), and cut into 14 μm cryosections, then spotted with several matrices for directly analysis of cocaine by MALDI-MS and by MALDI-IM-MS. Another group of frozen rat brains collected 1 week after bilateral injection of chlorisondamine diiodide (CHL; 12.5 μg freebase per side) into nucleus accumbens. Similar tissue sectioning and handling methods, as well as mass spectrometric analyses were used to detect CHL in various brain regions. In a third study cholinesterase inhibitors neostigmine and physostigmine were added to normal brain sections, then directly analyzed in MALDI-MS.

Careful selection in matrices and cryosection methods, plus proper instrument tuning that minimize the background interference to the drug signals, would guarantee successful detections of all four drugs from the brain sections. Using optimized combinations, we were able to compare the relative abundance of cocaine and CHL against reference endogenous biological signals across various brain regions. We also detected the non-covalent interaction between neostigmine and lipids in the brain. Combine such mass spectrometric techniques with three-dimensional image reconstruction methods will extend the

applicability of our techniques, and further advance the current knowledge of drug distribution in organs and tissues. Optimization of such combined techniques will have profound impact in the imaging, pharmacokinetic, high-throughput proteomic, forensic, and toxicological applications.

MALDI-IM-MS spectrum of chlorisondamine from rat brain section: