Visualization of Intact protein for the study of lithium neuropharmacology in mouse brain with MALDI - Imaging Mass Spectroscopy

Yuki Yasui1; Kota Yamamoto2; Daiki Kameyama3; Takashi Nirasawa4; Ryo Kajita4; Nobuto Kakuda3; Takafumi Hirata2; Masaya Ikegawa3
1Doshisha University, Kyotanabe, Japan; 2Geophysical Research Center, The University of Tokyo, Japan; 3Doshisha University, Kyotanabe, Japan; 4Bruker Japan K.K., Yokohama, Japan

Introduction
Lithium (Li) is a well-established therapeutic drug for bipolar disorder and major depression. More recently, Li has also been regarded as a neuroprotective agent and a candidate drug for disease-modification in certain neurodegenerative disorders such as Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS), and Parkinson’s disease (PD). While the putative neuroprotective effects of Li are extensively studied through in vitro study, however, an exact pharmacokinetics and pharmacodynamics (PKPD) of Li was not clear. In a murine model of Li treatment, here we use MALDI Imaging mass spectrometry (IMS) to delineate Li administration effects of the brains at proteomic level. Li distribution in the brains was also monitored by LA-ICP-MS and TOF-SIMS.

Methods
Animals: C57BL/6 mice at 8 weeks of age were used for this study for 14 days. Experiments were performed using procedures approved by the Experimental Animal Research Committee at the Doshisha University. Mice had free access to Li containing water. Three different dose of Li were administered as 0 mM (Control), 4.72 mM (Lower Dose) and 14.2 mM (Higher Dose). Lithium in Tap Water were fed for 14 days. Mice were sacrificed by decapitation following isoflurane anesthesia at day 14. Brain was removed and stored by -80°C.

Tissue preparation: Frozen tissue sections were cut on a cryostat at a 10 mm thickness for MALDI-Imaging were obtained.

MALDI-Mass Imaging: Images were acquired using the rapiflex MALDI Tissuetyper, at a spatial resolution of 50 µm. Visualization and statistical analysis were performed by FlexImaging and SciLS Lab 2016a.

Results
• Segmentation map
• Single mass imaging

Visualization of Li in mouse brains

Conclusions
• In mouse brains, Lithium administration was monitored through LA-ICP-MS, which is detected mostly in olfactory bulb in a dose dependent manner.
• Brains from Li-treated mice were analyzed through MALDI-IMS at intact proteome level.
• Effects of Li-treatment on mouse brains were successfully visualized with segmentation map as well as single mass imaging of proteins morphologically and functionally detected.