Mediator Lipidomics in Translational Neurosciences

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The application of mass spectrometry (MS) in biology has increased dramatically since the advent of “soft” ionization techniques such as electrospray ionization (ESI) and matrix assisted laser desorption/ionization (MALDI). The field of neurolipidomics has advanced radically as a result of these developments. These techniques allow delivery of target compounds to a mass spectrometer without the need for prior fragmentation or derivatization. Thus, a huge diversity of target lipid molecules in complex matrices (e.g., serum, cerebrospinal fluid, brain interstitial fluid obtained by microdialysis; brain tissue itself or neural cells) can be analyzed with only minimal sample preparation. Typical components of an HPLC-ESI-MS/MS-based system, operated in “product ion” mode, are illustrated in the schematic diagram. A sample extract is loaded onto a high performance liquid chromatography (HPLC) analytical column and eluted by flowing mobile phase solvent, which is interfaced with the mass spectrometer via an ESI source. The ESI source desolvates the target compounds as they elute from the column, and the target compounds enter the mass spectrometer in the form of gaseous ions. A popular format for mass spectrometers is the triple quadrapole design. Tandem quadrapolar electromagnetic fields are used to separate target compounds from matrix on the basis of mass-to-charge ratio (*m/z*). In this example, the first quadrapole (Q1) selects compounds with a specific *m/z* value and these compounds enter the collision cell (q2), where they undergo collision-induced dissociation (CID) as a result of interaction with an inert gas. The resulting product ions produce a characteristic mass spectrum, which can be used in combination HPLC retention time matching and auxiliary on-line tools such as UV spectroscopy to confirm the identity of a target compound and to quantify its abundance (Figure 1). HPLC-ESI-MS/MS–based lipidomic analysis in

combination with other technologies is used to characterize novel lipids in the nervous system and other tissues. Analysis of lipid oxidation products holds particular promise for uncovering early markers of the initiation and progression of neurodegenerative diseases as well as in mechanistic studies designed to reveal new therapeutic targets in brain disease. For instance, DHA autoperoxidation products (neuroprostanes) are increased in the brains of Alzheimer's disease patients (Reich et al., 2001), whereas the stereospecific DHA-derived mediator neuroprotectin D1 (NPD1) is decreased 2 (Lukiw et al., 2005). Moreover, recently mediator lipidomic–identified NPD1 and its precursor enhanced in the penumbra of a middle cerebral artery occlusion (MCAo) model of ischemic stroke upon intravenous DHA injection (Belayev et al., 2011). The selective oxidation of a mitochondria-specific phospholipid, cardiolipin, has been analyzed in clinical traumatic brain injury and is thought to be a marker of neuronal injury as well as a target for prevention of neuronal apoptosis (Sparvero et al., 2010).

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