2-Chlorohexadecanal, a Product of HOCl-mediated Plasmalogen Oxidation, Induces Barrier Dysfunction of Brain Microvascular Endothelial Cells

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Central nervous system (CNS) related diseases, such as brain stroke, Alzheimer's disease (AD) and multiple sclerosis (MS) are in general accompanied by blood-brain barrier (BBB) dysfunction. Within the last few years several studies have implicated that myeloperoxidase (MPO) plays an important role in pathophysiological sequelae of neurodegenerative diseases with an inflammatory component. A unique property of MPO is its ability to form the extremely potent oxidant hypochlorite/hypochlorous acid (HOCl). One of the major lipid targets for HOCl is the plasmalogen fraction, a quantitatively important lipid subclass in the CNS. This reaction targets the vinylether bond leading to the formation of reactive chlorinated aldehydes, e.g. 2-chlorohexadecanal (2-ClHDA).

Results of the current study provide evidence that 2-ClHDA is formed *in vitro* and *in vivo.* Moreover, we have investigated the impact of 2-ClHDA on physiological properties of primary porcine brain microvascular endothelial cells (pBMVECs), which are a major constituent of the neurovascular unit and form the physical basis of the BBB. Most importantly, 2-ClHDA induced severe BBB dysfunction as analyzed by transendothelial electrical resistance measurements and *in situ* brain perfusion technique. This observation was accompanied by pronounced intercellular gap formation most likely due to cell death and significant alterations in intracellular signalling events, like e.g. induction of the MAPK pathways in response to 2-ClHDA.

In summary the present study demonstrates 2-ClHDA formation *in vitro* and *in vivo* and indicates an extremely high lipotoxic potential of 2-ClHDA indicating that this chlorinated aldehyde might be a key player contributing to BBB dysfunction in neurodegenerative diseases.