

Myeloperoxidase - Expression And Activity During Neuroinflammatory Conditions

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Some neurodegenerative diseases are characterized by an inflammatory component. Subsequent disruption of the blood brain barrier (BBB) leads to extravasation of plasma proteins and infiltration of immune cells from the periphery, eg. macrophages, monocytes and neutrophil granulocytes. Together with brain-resident microglia (the immunocompetent cells of the brain) they migrate to the inflamed area and – upon chronic activation - produce cytokines and tissue-damaging substances. One of the enzymes, which lead to the generation of such compounds is myeloperoxidase (MPO). In cooperation with the NADPH oxidase complex and in the presence of physiological concentrations of chloride ions MPO generates the strong oxidant hypochlorous acid (HOCl). HOCl is capable of modifying proteins, nucleic acids, and lipids. Especially unsaturated CNS-lipids, present in high concentrations, are susceptible to modification by HOCl. As (unsaturated) lipids fulfill a variety of important functions in the brain, HOCl-mediated modification might have deleterious consequences to CNS function.

The aims of this study were to obtain in vivo evidence for MPO expression and formation of MPO-modified lipids in the central nervous system, to investigate consequences of neuroinflammation on brain lipid composition and to characterize global alterations in CNS gene expression during neuroinflammation.

The results show MPO expression under pathophysiological conditions in humans. Furthermore, peripheral administration of endotoxin leads to significantly elevated expression of MPO and other inflammatory markers on mRNA level in the brain of mice. The formation of 2-CIHDA, a lipid marker for MPO activity formed from plasmalogen modification, increases in a time dependent manner. Lipid analysis shows a pronounced time-dependent decrease of various sphingo- and phospholipid species in the brain. These changes are accompanied by decreased expression of pathway-relevant gene products.