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Characterization of the catalytic antioxidants and probes for the detection of peroxynitrite

Reactive oxygen and nitrogen species (RONS) production is the normal process of cellular metabolism in all aerobic organisms, but desired only when RONS level is appropriate. RONS are involved in many enzymatic and signaling processes. They are also produced by phagocytic cells and used as antimicrobial agents. Disruption of cell's redox homeostasis, known as an oxidative stress, causes unspecified and irreversible cell oxidation and loss of cellular functions.

Peroxynitrite, formed *in vivo* in the diffusion-controlled reaction of the superoxide radical anion with nitric oxide, is an important biological oxidant, being also a precursor of highly oxidizing radicals: hydroxyl radical and nitrogen dioxide, and is able to oxidize proteins, DNA, lipids and other cell components.

Detection of reactive oxygen and nitrogen species, due to their high reactivity, short life-time and low concentration *in vivo*, is still a real challenge. The use of fluorescence techniques for the detection is very useful due to high sensibility and accessibility of these methods.

The scientific investigations described in my PhD thesis focused on two issues – the characteristics of fluorescent boronate probes dedicated for the detection of peroxynitrite in living cells and the characterization of the reactivity of catalytic antioxidants from the group of salen manganese complexes towards peroxynitrite.

The first part of my PhD thesis presents the results of my studies on the reactivity of two boronate probes designed for the detection of peroxynitrite, synthesized by 4-boronobenzylation of fluorescent compounds: 7-hydroxycoumarin (CBBE) and fluorescein methyl ester (FBBE). Oxidative conversion of those probes leads to release of the parent fluorescent compounds. The rate constants for the reaction of studied probes with peroxynitrite ($ONOO^-$), hypochlorite anion (OCl^-) and hydrogen peroxide (H_2O_2) were determined. The effect of glutathione, one of the main cellular antioxidants, on the oxidation of FBBE probe by H_2O_2, OCl^-, $ONOO^-$ was also studied. The FBBE probe was also used for the detection of peroxynitrite produced in endothelial cells incubated with doxorubicin.

The second part of my PhD thesis presents the characterization of catalytic antioxidants from the group of salen-manganese complexes. In the scientific literature salen-manganese complexes are described as SOD mimetics, also possessing catalase-like activity, but the reactivity of salen-manganese complexes towards peroxynitrite has not been characterized so far. The result of my research show that these complexes are able to decompose peroxynitrite in a catalytic manner. The catalytic rate constants of the peroxynitrite reaction with studied complexes were found. The SOD- and catalase-like activity of studied salen-manganese complexes was also determined. The results of my study show that there is a correlation between catalytic rate constants of H_2O_2 and $ONOO^-$ decomposition. Based on that observation the mechanism of the catalytic decomposition of peroxynitrite by salen-manganese complexes was proposed.

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