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Using Ionizing Radiation for Studying Radical Reactions with Nitroxides: Implications for their Biological Activity

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Radicals are part of the chemistry of life. The ever-increasing knowledge of the involvement of radicals in diverse pathological processes has expanded the search for more efficient antioxidants that can diminish radical-induced damage.Stable nitroxide radicals are receiving increased attention as potential therapeutic agents because of their pronounced antioxidative activity, low toxicity, and attenuation of oxidative and nitrosative damage in vitro and in animal models of inflammatory diseases.
We have used ionizing radiation for elucidating the kinetics and mechanisms of nitroxides reactions with radicals as well as with reduced metal ions and semiquinone radicals. Radicals which are neither good oxidants nor reductants such as carbon-centered radicals generally add to the nitroxyl group forming relatively stable adducts. The reactions of •NO2, HO2•and peroxyl and thiyl radicals with nitroxides proceed via an inner-sphere electron transfer mechanism. The reactivity of nitroxides towards most radicals, excluding HO2• and peroxyl radicals, hardly depend on their structure. In the case of HO2•(pKa = 4.8) the nitroxides reactivity decreases as the pH increases and, therefore, at physiological pH they are poor SOD-mimics.
The rate constant of nitroxides reaction with •NO2 is extremely high (7 x 108 M-1s-1), and nitroxides catalytically prevent protein nitration, which is involved in diverse pathological processes. This has been demonstrated in vitro during the peroxidative activity of heme proteins in the presence of H2O2 and nitrite and in vivo using a mouse model of allergic asthma, which is an inflammatory disease,reflected by increased production ofreactive oxygen and nitrogen species.The protective effects of nitroxides in suppressing the increase of main asthmatic inflammatory markers substantiate the key role played by reactive oxygen and nitrogen species in the molecular mechanism of asthma. Nitroxides are superior over common antioxidants, which their reaction with radicals always yields secondary radicals leading eventually to consumption of the antioxidant.Nitroxides act catalytically since their reactions with radicals form the respective oxoammonium cations, which are readily reduced back to the parent nitroxides by biological reductants.
The effects of the nitroxides are instrumental not only in protecting against oxidative and nitrosative damage, but also in elucidating the mechanisms underlying these processes.

Country/Organization invited to participate

Israel

Primary author: Ms GOLDSTEIN, Sara (Institute of Chemistry at the Hebrew University of Jerusalem, Israel)

Presenter: Ms GOLDSTEIN, Sara (Institute of Chemistry at the Hebrew University of Jerusalem, Israel)

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