Therapeutic effects of Mn porphyrins in radiation, cancer and central nervous system injuries

Ines Batinic-Haberle, PhD
Associate Professor

Department of Radiation Oncology, Duke University Medical School, Durham, NC 27710

Based on aqueous redox chemistry - which led to structure-activity relationships - and simple *in vivo* models of oxidative stress (aerobic growth of SOD-deficient *Escherichia coli* and *Streptomyces cerevisiae*) the cationic Mn(III) *N*-substituted pyridylporphyrins (MnPs) have been identified as the most potent mimics of superoxide dismutase family of enzymes – catalyzing the dismutation of superoxide, $O_2^{\cdot-}$. The equal ability to reduce and oxidize superoxide during the dismutation process, along with recently accumulated data, suggests that in addition to antioxidative, the pro-oxidative actions of MnPs may also contribute to their therapeutic effects. Based on our data, we have identified the superoxide dismutase (SOD)-like activity (estimated by log $k_{ca}(O_2^{\cdot-})$ as an excellent measure of MnPs reactivities and their therapeutic efficacy. Briefly, SOD-like activity parallels their ability to reduce peroxynitrite, carbonate anion radical ($CO_3^{\cdot-}$), hypochlorous acid (HClO), nitric oxide (NO), lipid peroxyl and alkoxyl radicals, thus suppressing the primary oxidative event. While doing so, MnPs could couple with cellular reductants and redox-active proteins (protein thiols). Reactive species are widely accepted as regulators of cellular transcriptional activity: minute, nanomolar levels are essential for normal cell function, while submicromolar or micromolar levels impose oxidative stress, which is evidenced in increased inflammatory and immune responses. By interfering with reactive species and redox-active signaling proteins, MnPs modulate redox-based cellular transcriptional activity and consequently secondary oxidative stress, and inflammatory processes. Their accumulation in mitochondria and their ability to cross the blood brain barrier contribute to their remarkable efficacy in cancer, radiation injuries, central nervous system injuries, diabetes, etc. The pharmacokinetic studies demonstrated ~20% oral availability of most frequently studied and most potent SOD mimics: MnTE-2-PyP^{5+}, MnTDE-2-ImP^{5+}, MnTnHex-2-PyP^{5+} and MnTnBuOE-2-PyP^{5+}.

The most remarkable recent effects were demonstrated in rat spinal cord injury model, rat stroke middle cerebral occlusion (MCAO) model, mouse prostate radiation and lymphoma chemo-sensitization. The 1 mg/kg/day sc injections starting immediately post T10 spinal cord injury for a period of 7 days, resulted in near normal function or rat limbs. One-week sc injections of 2 x 225 μg/kg/day of MnTnHex-2-PyP^{5+} and MnTnBuOE-2-PyP^{5+}, starting 6 hours after 90-min MCAO, resulted in a major reduction of infarct volume and improvement in neurologic score. Mice irradiated for 5 days at 7.5 Gy/day in a lower pelvic region were injected ip with MnTE-2-PyP^{5+} at 5 mg/kg 24 hours before radiation, followed first by 2.5 mg/kg every other day for 2 weeks and then by 5 mg/kg once a week for 12 weeks, have fully reversed erectile dysfunction observed in control non-treated but radiated mice. Shrinkage of testes, damage of prostate tissue and hair loss was prevented. In a lymphoma cellular model MnTE-2-PyP^{5+} and MnTnBuOE-2-PyP^{5+} enhanced dexamethasone treatment *via* pro-oxidative mechanism - glutathionylation and inactivation of major cellular proteins. MnTE-2-PyP^{5+}, MnTDE-2-ImP^{5+}, MnTnHex-2-PyP^{5+} and MnTnBuOE-2-PyP^{5+} are presently under preclinical and clinical development.