Magnetic resonance imaging of organic contrast agents: applications to redox imaging and radioprotection

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Abstract

Nitroxides are a diverse class of organic small molecular weight (170-400 Da) paramagnetic radioprotectors. Nitroxide pharmacokinetics and reduction (metabolism) can be monitored directly with electron paramagnetic resonance (EPR) spectroscopy and indirectly with magnetic resonance imaging (MRI). In the current study, *in vitro* and *in vivo* studies using MRI and EPR have provided insights into: cancerous/healthy tissue redox status, possible causes of nitroxide toxicity, factors influencing nitroxide reduction, and the relationship between nitroxide pharmacokinetics and radioprotective potency. Such insights will be invaluable during the development of nitroxides as sensitive redox imaging probes and as radioprotectors.

All images were acquired in female nude or C3H mice using a 3 Tesla Philips clinical scanner with a custom made receive-only coil. During T_1 weighted gradient echo imaging, the nitroxides Tempol, 3-CP, 22c, and 23c were injected into the tail vein of the mouse, and the nitroxide concentration was calculated from T_1 maps and T_1 weighted images. Studies that tested the metabolic and environmental factors that contribute to nitroxide metabolism were performed in suspensions of SCCVII cells in a 300 MHz EPR spectrometer. Radioprotection studies of the nitroxides Tempol, 3-CP, 16c, 22c, and 23c were carried out in female C3H mice using 300kVp x-rays for a dose range of 6-12.5 Gy.

The pharmacokinetic, toxicological, and radioprotective properties of nitroxides varied remarkably between nitroxides. Except for a few tissues such as the brain and myocardium, the maximum nitroxide concentration did not vary substantially between the nitroxides studied. Also, the maximum nitroxide concentration achieved was usually higher for healthy tissues than for tumors. In terms of radioprotection, the potency was highly dependent on nitroxide structure: 23c (dose modification factor = 1.45) is markedly more radioprotective than 22c (no significant dose modification observed), but their molecular structure differs by only a methylene (-CH_2-) group. These data are an exciting step toward development of non-toxic and potent nitroxide radioprotectors.

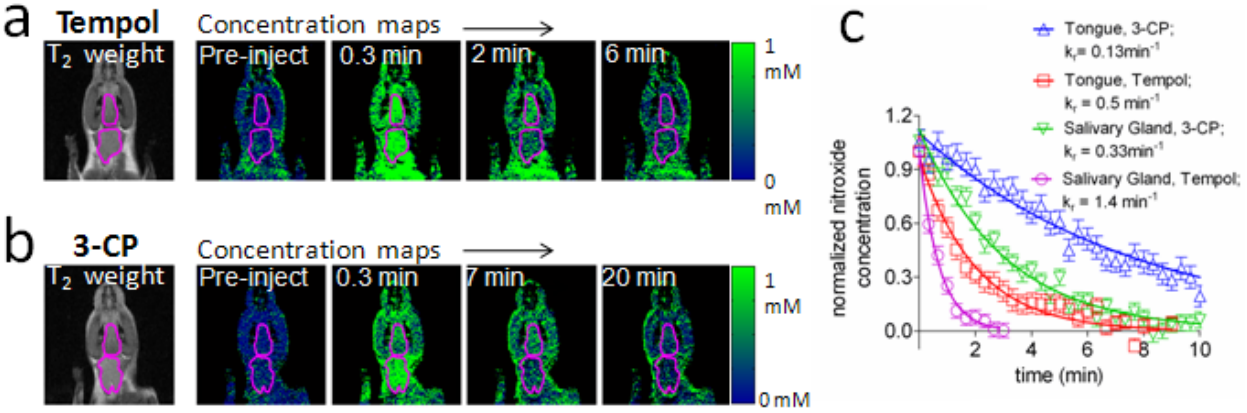

Figure 1: T_2 weighted images and concentration maps of Tempol (a) and 3-CP (b). Part c shows how Tempol tends to be reduced (metabolized) more rapidly than 3-CP, and how the salivary gland tends to metabolize nitroxides more rapidly than the tongue.