Overhauser MRI of free radicals

David J. Lurie
School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, AB25 2ZD, Scotland, UK
d.lurie@abdn.ac.uk

It is almost 30 years since the Overhauser effect was first employed as a method of imaging the spatial distribution of free radicals [1]. The basic method is known as Proton-Electron Double-Resonance Imaging (PEDRI) or, equivalently, as Overhauser MRI (OMRI). The sample's EPR is irradiated during the acquisition of a proton NMR image; parts of the sample containing unpaired electrons exhibit altered image intensity due to the Overhauser transfer of polarisation from electron to proton spins, revealing the location of the free radical. Low magnetic fields are usually employed in order to achieve adequate penetration of the EPR irradiation and to avoid overheating the sample through non-resonant absorption; for example, *in vivo* PEDRI experiments have been performed on rats at 10 mT (237 MHz) [2] and on mice at 20 mT (564 MHz) [3]. Nevertheless, Massot *et al.* have demonstrated *in vivo* experiments at significantly higher fields and frequencies (194 mT, 5.43 GHz), apparently without adverse effects [4].

The disadvantage of using ultra-low magnetic fields is the inherently low signal-to-noise ratio (SNR) of the NMR experiment. Fortunately, magnetic field-cycling can be employed to improve SNR. In Field-Cycled PEDRI (FC-PEDRI) the magnetic field is switched between a low value (the evolution field, B_0^E) and a high value (the detection field, B_0^D) during the pulse sequence [5]. EPR irradiation takes place at B_0^E (~4 mT) at low frequency (~100 MHz) and lasts for $\sim 3\times T_1 \approx 500$ ms. The field is then switched to B_0^D and the NMR detection pulse(s) and magnetic field gradients for imaging are applied.

In our laboratory we constructed two FC-PEDRI systems, both of which employed dual, coaxial magnets. In the first system a large (60 cm bore) permanent magnet provided a vertically-oriented detection field of 59 mT [6]. An internal, resistive, field-offset coil generated an opposing field, so that the value of B_0^E could be selected. The second system used a 450 mT superconducting primary magnet, with a coaxial resistive, actively-shielded field-offset coil (12 cm bore) [7]. An interesting, alternative approach to field-cycled PEDRI has been demonstrated by Utsumi and colleagues, which involves rotating the sample through low-field (20 mT) and high-field (1.5 T) regions for EPR irradiation and signal detection, respectively [8].

Applications of Overhauser techniques to date have included the study of exogenous free radicals as contrast agents [2,3], the use of probes of pH [9,10] and for monitoring redox status [11] or tissue oxygen concentration [12]. The main advantage of Overhauser methods over "direct" EPR imaging is that the spatial resolution is independent of the linewidth of the free radical. Furthermore, a spatially-registered proton MR image comes "for free" with OMRI/PEDRI and can be used to display anatomy.

[1] Lurie D.J. *et al.*, J. Magn. Reson. **76**, 366-370 (1988).
[2] Seimenis I. *et al.*, Magn. Reson. Med. **37**, 552-558 (1997).
[3] Lurie D.J. *et al.*, Magn. Reson. Med., **47**, 181-186 (2002).
[4] Massot P. *et al.*, Contr. Media Mol. Imaging **7**, 45-50 (2012).
[5] Lurie D.J. *et al.*, J. Magn. Reson. **84**, 431-437 (1989).
[6] Lurie D.J. *et al.*, Phys. Med. Biol. **43**, 1877-1886 (1998).
[7] Lurie D.J. *et al.*, Magn. Reson. Imaging **23**, 175-181 (2005).
[8] Naganuma T. *et al.*, Yakugaku Zasshi **135**, 733-738 (2015).
[9] Khramtsov V.V. *et al.*, Spectroscopy **18**, 213-225 (2004).
[10] Samouilov A. *et al.*, Anal. Chem. **86**, 1045-1052 (2014).
[11] Eto H. *et al.*, Free Rad. Biol. Med. **89**, 1097-1104 (2015).
[12] Matsumoto *et al.*, Proc. Natl. Acad. Sci. USA **106**, 17898-17903 (2009).