1H MR Spectroscopy Outside the Brain

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Introduction

The majority of clinical applications of 1H-MR spectroscopy (MRS) concern diseases of the human brain. This is caused by two main reasons:

1) The main clinical reason is that the brain is poorly accessible for biopsies, whereas other organs are more suitable for invasive biopsy investigations.

2) The technical reasons involve lipids, motion and general experience. First, in most organs lipid deposits are not so clearly separated from the tissue of interest as in brain and, hence lipid suppression may become an issue. Second, all of the inner organs and even some of the muscles and the spine reflect cardiac and/or breathing and/or gastric motion that can lead to artifacts and bad spectra. Third, very few MRS research groups only apply their skills to solve these technical issues, such that neurologic applications seem more enticing for many clinicians or physiologists, too.

This overview deals with both, the technical challenges and solutions to overcome potential problems related to motion artifacts and overwhelming lipid signals, as well as with some applications of large interest for the clinician and the physiologist.

Prostate

The largest clinical interest for 1H-MRS outside the brain currently concerns the prostate. Metabolites that are observable in vivo in the human prostate are citrate (Cit), trimethyl-ammonium compounds (TMA), creatine (Cr) and phosphocreatine (PCr, Cr\text{tot}=Cr+PCr), and spermine (or - more generally – polyamines). Citrate features a strongly coupled AB spin system, that has been the focus of interest for optimization of acquisition parameters (1-5). The main resonance of spermine coincides with TMA and the detection of spermine requires the use of 2D MRS (6). A further difficulty for prostate MRS is the proximity of lipid containing tissues, which...
often leads to signal bleed. Inversion recovery lipid suppression, spectrally selective excitation schemes, as well as specific outer volume suppression methods have been devised for improved spectral quality (7,8). Furthermore, the size and heterogeneity of the prostate and the required clinical voxel size necessitate the use of local coil detection, implemented by endorectal coils. The main application of MRS in the prostate is the identification of prostate cancer in treatment naïve patients and after different therapies (Refs (9-18) and refs therein).

Mamma
A further field of topical interest is the detection and differential diagnosis of breast tumors. This application is particularly challenging because of the very high lipid content in the female breast and the fact that tumor detection appears to rely solely on the presence or absence of a choline signal. Ascertaining the spectral quality, and hence making a diagnosis based on a single peak is challenging and special care will have to be used (19-23).

Kidney
Normal short TE spectra of the kidney characterizing its content of osmotically active metabolites (betaine, cholines, myo-inositol) have been recorded close to ten years ago (24), but have hardly ever been followed up by clinical studies (25). One reason may be that good spectral quality can only be obtained if the organ motion is taken care of by use of respiratory, possibly respiratory/cardiac triggering.

Liver
Similarly for the liver, organ motion makes MRS cumbersome. Respiratory triggering or the use of navigator scans (26) is mandatory for meaningful results. As for the breast, TMA (26) and lipids seem to be the only reliably identified metabolites for the liver. The origin of the broad resonance at 3.5-3.9 ppm (see Figure) is unclear, but may well be due to myo-inositol and other carbohydrates. The assignments in Ref (27) do not seem to be tenable given the signal to noise in these spectra. In animal liver (28), glycogen has been shown to contribute to the $^{1}$H-MR spectrum. Clinical applications of $^{1}$H-MRS have mostly concerned the quantification of lipids in the liver (29,30).
Brain Muscle: M.Tib.Ant

Muscle: M.Soleus

Liver

Kidney

Heart

Figure: Localized, semi-quantitative $^1$H MR spectra recorded in vivo from different parts of the human body. A) Brain (occipital cortex, 10cm$^3$ of mostly gray matter); B) Kidney (8.4 cm$^3$); C) Liver (48 cm$^3$); D) Skeletal muscle (M. tibialis anterior with muscle fibers parallel B$_0$, 6 cm$^3$); E) Skeletal muscle (M. soleus with muscle fibers at ~50° off B$_0$, 4.5 cm$^3$); F) Cardiac muscle (4 cm$^3$ in septum). All spectra recorded on a clinical MRI scanner at 1.5T (GE Signa) in Berne using a PRESS sequence with water presaturation, outer volume saturation, echo time of 20ms and 3s repetition time (except spectrum from heart which was cardiac and respiratory gated). The spectra were scaled using the unsaturated and T$_2$ corrected tissue water signal yielding a molal comparison. Some of the spectral features are still unassigned. The dashed line indicates the resonance position of the methyl group protons of total creatine. (Modified from (31). Contains unpublished material recorded in collaboration with Drs. C.Boesch, J.Felblinger, C.Fusch, R.Gruetter, and P.Maloca)

Other organs

Lipid quantification by use of $^1$H-MRS has been performed in other instances. The characterization of vertebral bodies is a fairly abundant application (32-39). And also whole body composition (40,41) has been assessed by $^1$H-MRS and compared to other techniques ($^2$D dilution, dual-energy X-ray absorptiometry)

Furthermore, pelvic (42,43) and rectal (44) tumors have recently been assessed by $^1$H-MRS, where however at least some of the results are highly questionable for lack of signal to noise and
potential artifacts from the surrounding tissue. Lymph node metastasis of primary squamous cell carcinomas have been studied in Ref (45), where it appears to have been possible to detect TMA, Cr, and even lactate in places that do not favor good spectral quality. Finally, as proven in Ref. (46), $^1$H-MR spectra of reasonable quality can also be obtained from the spinal cord. With a prominent peak from N-acetyl components, they resemble spectra from the brain.

**Skeletal muscle**

$^1$H-MRS of muscle (47,48) has been booming, ever since it had been realized that this provides a tool to quantitate intramyocellular lipids (i.e. lipid droplets within the muscle cell, which are directly available for energy production), and even more so after it had become clear that IMCL content was linked to insulin sensitivity. After the basic observation of the fact that two lipid compartments are observable by $^1$H-MRS (49), it needed the unequivocal identification of one of them as IMCL (50), and the link to insulin resistance (51-54) to get the field started. The current activity encompasses mainly work with regards to diabetes and sports physiology (55-67). Besides lipids, there are a number of other MRS-detectable metabolites in human muscle (47): Cr and PCr (68,69), TMA, which in muscle includes carnitines (70,71), acetylcarnitine (72), carnosine (73), lactate(73-75), deoxymyoglobin (75-87), and tentatively taurine. Some of these metabolites are only visible after exercise or in ischemia.

Finally, basic NMR phenomena that are important to understand $^1$H-MR spectra of muscle tissue (48), but presently appear not to be relevant for brain spectra are addressed. They include anisotropic susceptibility (50), dipolar splitting (88-93), chemical shift anisotropy, orientation-dependence of relaxation rates (94), and associated phenomena of MR visibility (95).

**Heart**

The heart is probably the most challenging target for *in vivo* $^1$H-MR spectroscopy, because its spatial form and position depends on cardiac and respiratory motion, and also because the outer heart wall suffers from large susceptibility anisotropies. Furthermore, it is likely that the cardiac spectrum is orientation dependent, just like the spectrum of skeletal muscle.

The same metabolites as in skeletal muscle are of potential interest in cardiac $^1$H-MRS, in particular the lipids, because the cardiac metabolism mostly relies on lipids as energy supply.
The distinction of lipid deposits from outside and within the myocardium is very challenging. Lipids have been the first target for cardiac $^1$H-MRS (96). Later studies focused on the creatines (97) and the methodology of double triggered MRS (98-100).

References


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