COMMENT

Magic angle spinning magnetic resonance: a novel method opening up translational research into NAFLD?

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ABSTRACT

NAFLD (non-alcoholic fatty liver disease) and NASH (non-alcoholic steatohepatitis) are of increasing importance, both in connection with insulin resistance and with the development of liver cirrhosis. Histological samples are still the ‘gold standard’ for diagnosis; however, because of the risks of a liver biopsy, non-invasive methods are needed. MAS (magic angle spinning) is a special type of NMR which allows characterization of intact excised tissue without need for additional extraction steps. Because clinical MRI (magnetic resonance imaging) and MRS (magnetic resonance spectroscopy) are based on the same physical principle as NMR, translational research is feasible from excised tissue to non-invasive examinations in humans. In the present issue of Clinical Science, Cobbold and co-workers report a study in three animal strains suffering from different degrees of NAFLD showing that MAS results are able to distinguish controls, fatty infiltration and steatohepatitis in cohorts.

In vivo MRS methods in humans are not obtainable at the same spectral resolution; however, know-how from MAS studies may help to identify characteristic changes in crowded regions of the magnetic resonance spectrum.

NAFLD (non-alcoholic fatty liver disease) generates major interest because it is associated with the epidemic development of obesity, insulin resistance and the so-called ‘metabolic syndrome’ in almost all parts of the world. It encompasses several histological stages, ranging from a reversible increase in the lipid/water ratio to NASH (non-alcoholic steatohepatitis), that can lead to liver cirrhosis with severe and life-threatening complications. Currently, only liver biopsy followed by histological assessment can provide that critical diagnosis [1]. Owing to the potential complications of liver biopsies, non-invasive methods are needed that would allow for a safe, reliable and repeatable diagnosis of NASH and related diseases in the fatty liver.

In the present issue of Clinical Science, Cobbold et al. [2] report a study that has the potential to launch translational research on NAFLD, ranging from mouse models to humans. They use MAS (magic angle spinning) [3], which is a special type of NMR where signals from material in a strong magnetic field are analysed. In medicine, NMR is better known as MRI (magnetic resonance imaging) or MRS (magnetic resonance spectroscopy); nevertheless, all of the special types of NMR have in common that either the spatial distribution and/or chemical identity of the examined tissue/solution can be determined. The strength of MRI/MRS in humans is the organ selectivity, which is not the case for tests that are using, for example, blood plasma. MRS can be used to study lipid metabolism in specific organs, including skeletal muscle [4], liver [5] or heart [6]. Since NMR is the basis for MAS, as well as for MRI and MRS, it is reasonable to assume that in vivo MRS in humans can benefit from the findings as reported in the study by Cobbold et al. [2]; however, because MAS spectra of intact, but excised, tissue are much more resolved than in vivo spectra, it makes sense to analyse the potential

Key words: diabetes, magnetic resonance spectroscopy, non-alcoholic fatty liver disease (NAFLD), NMR, steatohepatitis.

Abbreviations: MAS, magic angle spinning; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

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of the present study for the translation to in vivo applications.

High-resolution NMR spectra of water-soluble extracts and MAS spectra of intact tissue both require excised material and thus suffer from the same disadvantage as the gold standard histology; however, in contrast with histological images, findings in the NMR/MAS spectra can be translated to in vivo spectra obtained by the same physical principle, yet at a much lower resolution. MAS spectra are acquired from tissue that is rotated at a very high speed at a 'magic' angle relative to the applied magnetic field, a technique that drastically improves the spectral resolution. It has the advantage over NMR spectra from extracts that the chemical environment and the structure of the tissue are altered much less, even if blood flow, oxygenation and the energetic status of tissue are no longer comparable with the in vivo situation. Although MAS and in vivo MRS observe, at least in principle, the same resonances, several limitations have to be considered in vivo: (i) the magnetic field in whole-body magnets is weaker, leading to less-resolved resonances and reduced sensitivity; (ii) interactions in the tissue are not cancelled as in MAS and thus broaden the lines; (iii) motion of the liver during examination reduces the resolution further; and (iv) the living patient cannot be examined for hours, which is necessary for some sophisticated experiments that can reveal multi-dimensional high-resolution spectra.

Do the many limitations of in vivo MRS as compared with MAS invalidate the translational character of the study? This conclusion would be too pessimistic and inappropriate. When Cobbold et al. [2] observe an increase in lipid resonances, the same can be found in humans since the CH$_2$ and CH$_3$ resonances are clearly visible in vivo. The same is true for the total choline resonance as soon as motion artefacts are avoided in vivo and a reasonable signal-to-noise-ratio can be achieved. A decrease in the polyunsaturated indices may be less visible in vivo because the C=O resonances are close to the suppressed water resonance and the 1.5–2.9 p.p.m. region is much more crowded. Nevertheless, exactly these problems in vivo make a study such as the one by Cobbold et al. [2] valuable. Modern fitting algorithms can separate resonances in crowded regions when prior knowledge is available. Such prior knowledge can be based on such an exploratory MAS study, where potential candidates are identified based on a principal component analysis. In addition, suppression of the water signal can be further improved when it is known that the C=O resonance is relevant to a study and should be observed specifically.

Nevertheless, some inherent limitations of the study by Cobbold et al. [2] need to be addressed. The most significant discrimination is found between controls and steatosis, not between steatosis and steatohepatitis; however, in order to prevent life-threatening complications, the latter would be specifically relevant. The overlap between the groups is relatively large and one must expect that results in humans are even more scattered, e.g. while Cobbold et al. [2] find an impressive relationship between body mass and the lipid/water ratio in well-standardized animals, the analogous data from the Dallas Heart Study in humans [5] scatter to a much larger degree. One must expect that the distinction between NASH and steatosis based on other parameters than the lipid/water ratio would scatter in a similar manner in humans, simply because much more co-founding influences are present in humans; however, these limitations are inherent if animals studies are compared with results in humans and do not reduce the value of the study by Cobbold et al. [2].

The analysis above deals mainly with the translational character of the study by Cobbold et al. [2]. It should be emphasized that NMR of various mouse models would keep its own value for phenotyping even without the translational aspect. The wealth of information in a highly resolved NMR spectrum can lead to additional information that is not visible in a histological slice. In addition, if MAS leads to in vivo MRS in animals, repeated and longitudinal measurements in the same animal become possible. That reduces inter-individual variations in the study and saves animals.

To conclude, the exploratory data from Cobbold et al. [2] have a great potential to initiate translational studies on NAFLD and NASH.

REFERENCES

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