MR Spectroscopy: The promise

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Despite important progresses in the last decades, the development of Magnetic Resonance Spectroscopy (MRS) approaches in the Clinic remains significantly slower than the widespread clinical applications of its imaging counterpart (MRI). Probably the most fundamental advantage of MRS is its chemical specificity, allowing for the non-invasive characterization of metabolite profiles and their changes with time, in normal and diseased tissues of animals and humans. The clinical implementation of this important advantage has been, however, hampered by important limitations in sensitivity and resolution demanding, progressively, drastic technological advances as higher field magnets, improved field homogeneity, advanced volume localization techniques and sophisticated spectral acquisition and processing algorithms. Many of these developments are not presently accessible in most clinical imaging centers, making it difficult to implement successfully the MRS approach widespread in the clinic. These limitations have not hampered, however, the impressive development of MRS approaches in preclinical research, where very high field magnets, specialized personnel and powerful software packages have endowed MRS with a prominent role in the evaluation of animal models of disease, drug development and therapy design.

Probably the most general landmark in the development and outcome of any pathology is the appearance of energy limitations, leading eventually to energy failure and death of the diseased tissues. These circumstances result always in important adaptive metabolic responses that constitute the metabolic fingerprints of the pathological development, as well as of its response to therapy. In the following, we shall support that MRS from different nuclei, is well endowed to detect these metabolic alterations, many times, much earlier than the morphological alterations observable later by MRI.

^{1}H MRS

Taking the brain as an example, ^{1}H MRS provides a robust fingerprint of metabolites revealing healthy or diseased metabolism in animal models and humans [1-6]. Relative decreases in N-acetyl-aspartic acid (NAA) are thought to reveal neuronal loss, increases in lactate (Lac) are associated to hypoxia and enhanced glycolitic contribution, lipid resonance (Lip) increases are normally observed in hypoxic tumor areas, alterations in the total creatine resonance (tCr) are thought to represent alterations in energy metabolism, changes the total Choline resonance (tCho) reflect changes in phospholipid metabolism, and alterations in the myo-inositol (Ino) content reveal inflammatory responses and osmolite volume regulation. In the prostate, alterations in the citrate levels have been correlated with malignity of the lesions [7, 8]. In addition to these metabolites, easily detectable even in low field clinical scanners (1,5T), up to fourteen cerebral metabolites may become detectable in higher field scanners, including the amino acids glutamate, glutamine, gaba and taurine among other metabolites. ^{1}H MRS provides thus, the most comprehensive, non invasive, metabolic profiling method available to date, useful in the diagnosis and prognosis of cancer, neurodegenerative diseases and ischemic episodes.

^{31}P MRS

^{31}P NMR was the earliest MRS implemented providing direct information on the bioenergetics of skeletal and cardiac muscle, brain and tumors, because of the direct detection of ATP, PCr, Pi, Phosphomonester (PME) and Phosphodiester (PDE) resonances. ^{31}P NMR was mainly used to investigate cerebral energetics in the healthy brain, as well as in cerebral tumors [9-11]. In the latter sense, ^{31}P NMR pioneered the development of the pattern recognition algorithms implemented for the intelligent diagnosis of tumors [12-15]. An important clinical multicenter study merits special mention here, illustrating the diagnostic potential of ^{31}P NMR in oncology [16, 17].

^{13}C NMR (and hyperpolarization)

^{13}C NMR has been probably the slowest MRS approach to be incorporated to the clinic. The low natural abundance of ^{13}C required the use of relatively expensive ^{13}C enriched isotopes, specialized volume localization and proton decoupling techniques and sophisticated mathematical modeling approaches. Despite its drawbacks, ^{13}C NMR provides unique information on cerebral metabolism and its compartmentation, the neuronal and glial tricarboxylic acid cycle rates, and the transcellular glutamate-glutamine or gaba cycles and in vivo neurotransmission [18-22]. Nevertheless, the clinical applications of ^{13}C MRS remained limited by the inherently low sensitivity of the technique [23].

The recent advent of ^{13}C hyperpolarization strategies has improved spectacularly the previous signal to noise limitations, at the expense of very fast technologies for ^{13}C acquisition, observing only the longest relaxation time hyperpolarized ^{13}C carboxylic carbons [24-29]. Although mainly implemented in preclinical ^{13}C NMR laboratories, the future impact of this technique in the clinic is considered feasible [30], providing information on tumor pH, pyruvate dehydrogenase flux and redox state, with comparable spatial resolution to the nuclear medicine PET or SPECT techniques.

Finally, other nuclei are conveniently available for MRS approaches including mainly ^{19}F NMR [31] and ^{17}O NMR [32]

Conclusion

The advance of clinical MRS approaches in the last decades cannot be underscored, but probably remains still insufficient for wide spread, routine, clinical applications except in frontier clinical research centers. The current limitations of clinical MRS appear to be mostly due to economic constrains and educational or translational difficulties, rather than to an insufficient supply of a wealth of relevant diagnostic and prognostic information. On these grounds, the main promise of MRS as the most powerful, specific, non-invasive tool, for personalized diagnosis and treatment remains intact.

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Proc. Intl. Soc. Mag. Reson. Med. 22 (2014)   1027.