Clinical Application of Magnetic Resonance Spectroscopy

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الملخص العربى

Abbreviations

AD Alexander disease
AD Alzheimer's disease
ADC apparent diffusion coefficient
ADEM acute disseminated encephalomyelitis
AIS Abbreviated Injury Scale
ALS amyotrophic lateral sclerosis
ATP adenosine triphosphate
CBD corticobasal degeneration
CBF cerebral blood flow
CIS clinically isolated syndrome
CRB Cramer–Rao bounds
CSD cortical spreading depression
CSF cerebrospinal fluid
CSI chemical shift imaging
CW continuous wave
DAI diffuse axonal injury
DLB dementia with Lewy bodies
DRN delayed radiation necrosis
DTI diffusion tensor imaging
DWI diffusion-weighted imaging
ECD Erdheim–Chester disease
EPSI echo-planar spectroscopic imaging
FFI fatal familial insomnia
FFT fast Fourier transformation
FID free induction decay
FOV field of view
FSE fast spin echo
FT Fourier transform
FTD frontotemporal dementia
GAMT guanidinoacetate methyl transferase
GCS Glasgow Coma Scale
GPC glycerophosphocholine
GSD Gerstmann–Straussler disease
HE hepatic encephalopathy
HGG high-grade glioma
HIE hypoxic–ischemic encephalopathy
HPD human prion disease(s)
ICA internal carotid artery
IVS inner volume suppression
LGG low-grade glioma
LOH loss of heterozygosity
MCA middle cerebral artery
MCD malformations of cortical development
MCI mild cognitive impairment
MEG magnetoencephalography
mI myo-inositol
MOA mixed oligoastrocytoma
MRI magnetic resonance imaging
MRS magnetic resonance spectroscopy
MRSI MR spectroscopic imagin

Introduction

Nuclear magneticresonance spectroscopy The history of magnetic resonance spectroscopy (MRS) can be traced back to the first, independent observations of a nuclear magnetic resonance (NMR) signal inbulk matterby Bloch andPurcell in1946.Whenatomicnuclei whichhave thepropertyof nuclear "spin" are placed in a static, strong magnetic field, their energy levels will vary depending on their orientation within the magnetic field. Due to the properties of quantummechanics, only limited nuclear orientations are allowed (e.g. either "up" or "down"for spin-half nuclei such as the proton(1H)). If an oscillating radiofrequency field is then applied at the so-called "resonant frequency" corresponding to the energy difference between the different spin orientations, an absorption of power occurs which corresponds to spins being exchanged between the upper and lower states, and a radiofrequency signal is emitted by the sample. This resonant phenomenon and the resulting emitted radiofrequency signal is the fundamental principle of NMR, which is now used worldwide for both magnetic resonance imaging (MRI) and in vivo MRS **(Bloch F et al.,2000).**

Although NMR was originally a somewhat obscure technology of interest only to physicists for the measurement of gyromagnetic ratios (γ) of different nuclei (see below), applications of NMR to chemistry became apparentafter thediscovery of chemical shift and spin–spin coupling effects in 1950 and 1951, respectively. These effects cause the resonant frequency of the NMR signal to change by small amounts (usually expressed in terms of parts per million (ppm) of the resonant frequency), because the local magnetic field surroundingeach nucleus depends on both the structure of its surrounding electrons (i.e. the chemical structure of the molecule that the nuclei occur in) and also on the magnetic

properties of neighboring nuclei. Thus, nuclei in different chemical environments will exhibit different resonant frequencies (or spectra in the case of molecules with multiple different nuclei), and NMR spectra can thereby be used to identify both the structure and relative concentrations of the molecules within the sample, informationthat can be of great value to chemists (**Gutowsky HS et al.,2000).**

In vivo MR spectroscopy

In vivo magnetic resonance spectroscopy (MRS) of the brain was first reported in the late 1970s in animal models. Previous studies of biological tissues by NMR spectroscopy had focused on isolated, perfused organ systems or cell suspensions, and had indicated the feasibility of obtaining biochemical information non-invasively using NMR. Most of these studies used the phosphorus-31nucleus, since there was interestin measuring metabolism relating to bioenergetics,which involved compounds such as adenosine tri-phosphate . 31p spectroscopy was relatively straight forward to preform,since the 31p nucleus is spin-1/2 and has a reasonably high gyromagnetic ratio and chemical shift range (~40ppm),and does not require any water suppression.it was also found that the resonance frequency of pi was sensitive to PH and .As interest in in vivo MRS and MRI increased .larger bore horizontal superconducting magnet system were developed for this purpose,for larger animal and humans ,although at lower field strengths than used for high resolution NMR(e.g.1.5-2.0 Tesla(T),64-85MHZ for 1H). An important technical advance was the introduction for local, surface RF coils that had high sensitivity ,and also limited signal production to only tissue that are proximal to the coil ,thereby eliminating signal from unwanted region or other organs. these advances enabled the first observation of in vivo MRS in humans and the detectionof birthasphyxia

in the brainof infants**(Cady EB et al.,2001).**

using31P MRS. In addition to 31P , there was also interest in the carbon-13 (13C) nucleus, which, like 31P , has some technical advantages, such as a wide chemical shift range (~200 ppm),spin-1/2, andnoneed for solvent suppression. However, both 31P, and 13C suffer from relatively low sensitivity. In the case of 13C, sensitivity is very low because of its low natural abundance (1%), although exogenously introduced isotopicenrichment can be used, which is in fact an important method for studying kinetics of metabolism **(Alger JR et al.,2002).**

It was recognized that proton(1H) spectroscopywould offer a large sensitivity advantage over these other nuclei, because the proton has the highest gyromagnetic ratio γ of non-radioactive nuclei, as well as a high natural abundance. Sensitivity is also enhanced compared to other nuclei because of favorable metabolite relaxation times, and also because several important brain metabolites have resonances resulting from functional groups with multiple protons (methyl groups with three protons). In order for protonMRS to be successful, however, water suppression techniques had to be developed for in vivo MRS, so as to remove the much larger water signal (compared to the metabolite signals), and magnetic field homogeneity and field strengths had to be suffcient to allow one to resolve the smaller chemicalshifts of protons(range~10 ppm) **(Behar KL et al .,2000).**

Nuclei for in vivo MRS

By far the most in vivo MRS studies have been performed using the proton (1H) nucleus, because of several reasons; the proton has high sensitivity because of its high γ and high natural abundance, as well as quite favorable relaxation times and spin half. In addition, the proton is

also the nucleus used for conventional MRI, so proton MRS can be performed usually with exactly the same hardware as is used for conventional MRI. However, there are other nuclei which can be used for in vivo MRS if appropriate RF coils, amplifiers, and electronics are available; some examples include carbon-13 (13C), nitrogen-15 (15N),or phosphorus-31 (31P): generally, these have lower sensitivity and natural abundance, which results in longer scan times and lower spatial resolution (increased voxel size). The properties of these nuclei are listed in Table 1. Since clinical applications of these nuclei arenot yet routinely available, the majority of this book will focus on the use of the proton nucleus for in vivo MRS. However, it should be mentioned that the use of these nuclei with hyperpolarization and/orisotropic enrichment can give large sensitivity increases, and are the subject of active research efforts at present (2008). If technical challenges and cost issues can be overcome, methods based on these nuclei may offer unprecedented opportunities to study dynamic metabolic processes in humans non-invasively **(Behar KL et al.,2000).**

Table 1. Properties of nuclei for in vivo MRS**(Behar KL.,2000).**

Nucleus	Frequency (MHz @1.5 T)	Spin	Natural abundance (%)
Proton (^{1}H)	63.9	1/2	99.98
Phosphorus (^{31}P)	25.9	1/2	100.00
Sodium (^{23}Na)	16.9	3/2	100.00
Carbon (^{13}C)	16.1	1/2	1.10
Deuterium (^{2}D)	9.8	1	0.02
Nitrogen (^{15}N)	6.5	1/2	0.37
Oxygen (^{17}O)	8.7	5/2	0.04
Fluorine (^{19}F)	59.8	1/2	100.00
Lithium (^{7}Li)	24.9	3/2	92.50

Information content of proton MR spectra of the brain

Because of therelatively low sensitivity of invivo MRS, in order for a compound to be detectable, generally its concentration must be in the millimolar range, and it must be a small, mobile molecule. Large and/or membrane-associated molecules are not usually detected, although they may exhibit broad resonances that contribute to the baseline of the spectrum **(Behar KL et al., 2000**).

The information content of a proton brain spectrum depends on quite a few factors, such as the field strength used, echo time, and type of pulse sequence. At the commonly used 1.5 T field strength, at long echotimes(e.g.140or280 msareoftenused; only signals from Cho, Cr, and NAA are observed in normal brain, while compounds such as lactate, alanine, or others may be detectable if their concentrations are elevated above normal levels due to pathological processes **(Lina DD et al.,2003).**

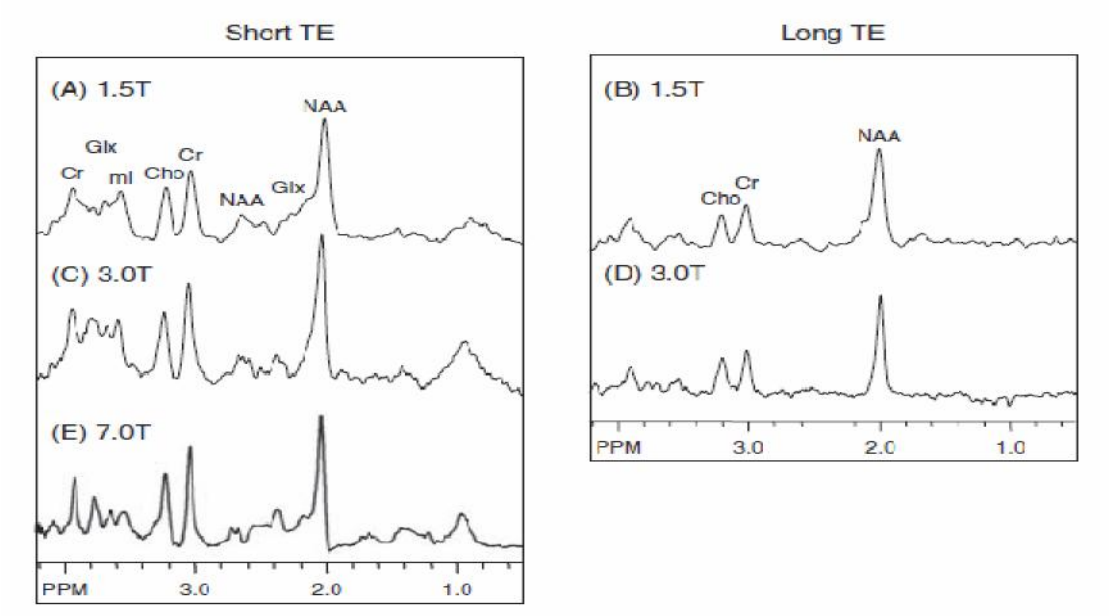

Figure 1. Single-voxel proton MRS of normal human brain white matter at different field strengths and echo times recorded using the STEAM pulse sequence (2 × 2 × 2 cm voxel size). 1.5 T: (A) TE 20 ms, (B) TE 136 ms; 3.0 T (C) TE 20 ms, (D) TE136 ms; and 7.0 T (E) TE 18 ms. Spectrum (E) provided by Dr James Murdoch, Philips Medical Systems. As field strength increases, spectral resolution improves, particularly for the strongly coupled resonances such as glutamate, glutamine, and myoinositol**(Lin DD.,2003).**

At short echo times (e.g. 35 ms or less) compounds with shorter T2 relaxation times (or multiplet resonances which become dephased at longer echo times) also become detectable. These include resonances from glutamate, glutamine, and GABA, which are not resolved from each other at1.5 T, myoinositol, as well as lipids and macromolecular resonances . Spectral appearance at 3.0 Tis generally similar to that at 1.5 T,although the coupling patterns of the multiplet resonances are somewhat different. Most of the multiplet(e.g. Glu,Gln,mI,taurine)are strongly coupled at these field strength,andGlu and Gln overlap slightly less at 3T than at 1.5T.As field strength increase further,to4.0 and7.0T,spectral resolution progressively increases(provided that magnetic field homogeneity can be maintained)and more compounds can be assigned with confidence, including separating N-actylaspartyl glutamate (NAAG) from NAA ,separating of Glu from Gln, and the detection of up to 14 different compounds at short echo times at 7T **(Tkac I et al.,2001).**

Table 2. Compounds detected by proton MRS in the human brain**(Tkac I.,2001).**

Compounds normally present	**Compounds which may be detected under pathological or other abnormal conditions**
Large signals at long TE	Long TE
N-acetylaspartate (NAA)	Lactate (Lac)
Creatine (Cr) and Phosphocreatine (PCr)	β-Hydroxy-butyrate, acetone
Cholines (Cho):	Succinate, pyruvate
Glycerophosphocholine (GPC)	Alanine
Phosphocholine (PC), free choline (Cho)	Glycine
Large signals at short TE	Short TE
Glutamate (Glu)	Lipids
Glutamine (Gln)	Macromolecules
myo-Inositol (mI)	Phenylalanine
	Galactitol
Small signals (short or long TE)	Exogenous compounds (short or long TE)
-acetyl-aspartyl-glutamate (NAAG), aspartate	NPropan-1,2-diol
Taurine, betaine, scyllo-inositol, ethanolamine	Mannitol
Threonine	Ethanol

Glucose, glycogen	Methylsulfonylmethane (MSM)
Purine nucleotides	
Histidine	
Small signals that can be detected with the use of two-dimensional and/or spectral editing techniques	
γ-Amino-butyric acid (GABA)	
Homocarnosine, pyrrolidinone	
Glutathione	
Threonine	
Vitamin C (ascorbic acid)	

NAA

The largest signal in the normal adult brain spectrum, theacetyl groupof N-acetyl aspartateresonates at2.01 ppm, with a usually unresolved (except at very high fields) contribution from N-acetyl aspartyl glutamate (NAAG) at 2.04 ppm. The aspartyl group also exhibits a pH-sensitive, strongly coupled resonance at approximately 2.6 ppm. Despite being one of the most abundant amino acids in the central nervous system, NAA was not discovered until 1956, and its function has been the subject of considerable debate **(Moffett JR et al.,2007).**

It has been speculated to be a source of acetyl groups for lipid synthesis, a regulator of protein synthesis, a storage form of acetyl-CoA or aspartate, a breakdown product of NAAG (which, unlike NAA, is a neurotransmitter),or an osmolyte. NAA is believed to be synthesized in neuronal mitochondria, from aspartate and acetyl-CoA . NAA is often referred to as a neuronal marker, based on several lines of evidence. For instance, immunocytochemical staining techniques have indicated that NAA is predominantlyrestricted toneurons,axons, anddendrites within the central nervous system, andstudies of diseases known to involve neuronal and/or axonal loss (for instance, infarcts, brain tumors,or multiple sclerosis (MS) plaques) have without exception found NAA to be decreased. In pathologies such as MS, good correlations between brain NAA levels and clinical measures of disability have been found,

suggesting that higher NAA levels may be associated with better neuronal function **(Destefano N et al.,2001).**

Animal models of chronic neuronal injury have also been shown to give good correlations between NAA levels (as measured by MRS) and in vitro measures of neuronal survival. All of these studies therefore suggest that MRS measurements of NAA may be useful for assessment of neuronal health or integrity in the central nervous systemHowever, other experiments suggest that caution should be used in interpreting NAA solely as a neuronal marker. For instance, it has also been reported that NAA may be found in non-neuronalcells, such as mast cells or isolated oligodendrocyte preparations, suggesting that NAA may not be specific for neuronal processes **(Bhakoo KK et al.,2000).**

Itisunclearifthesecells are present at high enough concentrations in the normal human brain to contribute significantly to the NAA signal, however. There are also some rare cases where NAA metabolism is perturbed, almost certainly independently of neuronal density or function. One example is the leukodystrophy, Canavan's disease, which is associated with a large elevation of intracellular NAA, owing to deficiency of aspartoacylase, the enzyme that degrades NAA to acetate and aspartate In addition, there has been a case report of a child, with mental retardation, with a complete absence of NAA . This case suggests that neurons can exist without the presence of NAA, and indeed that NAA is not necessary for neuronal function (**Martin E et al.,2001).**

While these observations indicate that there is evidence both for and against NAA as a measure of neuronaldensityandfunction,onbalance, NAA does appear to be one of the better surrogate neuronal markers that can be measured non-invasively in humans. Like all surrogate markers, there will be occasions when it does not reflect the true neuronal

status.Decreases inNAA insome diseases have beenshowntobereversible, suggesting thatlow NAAdoes not always indicate permanentneuronaldamage. Reversible NAA deficits (either spontaneous,or inresponsetotreatment) havebeen observed in diseases such as multiple sclerosis, mitochondrial diseases, AIDS, temporal lobe epilepsy, amyotrophic lateral sclerosis, or acute disseminated encephalomyelitis (ADEM).[Therefore, in individual patients, while a low NAA signal in some pathologies may indicate irreversible neuroaxonal damage (e.g. strokes, brain tumors), in others it may be due to dysfunction (perturbedNAA synthesis or degradation) that may be reversible with either treatmentrelated or spontaneous recovery **(Bizzi A etal.,2001).**

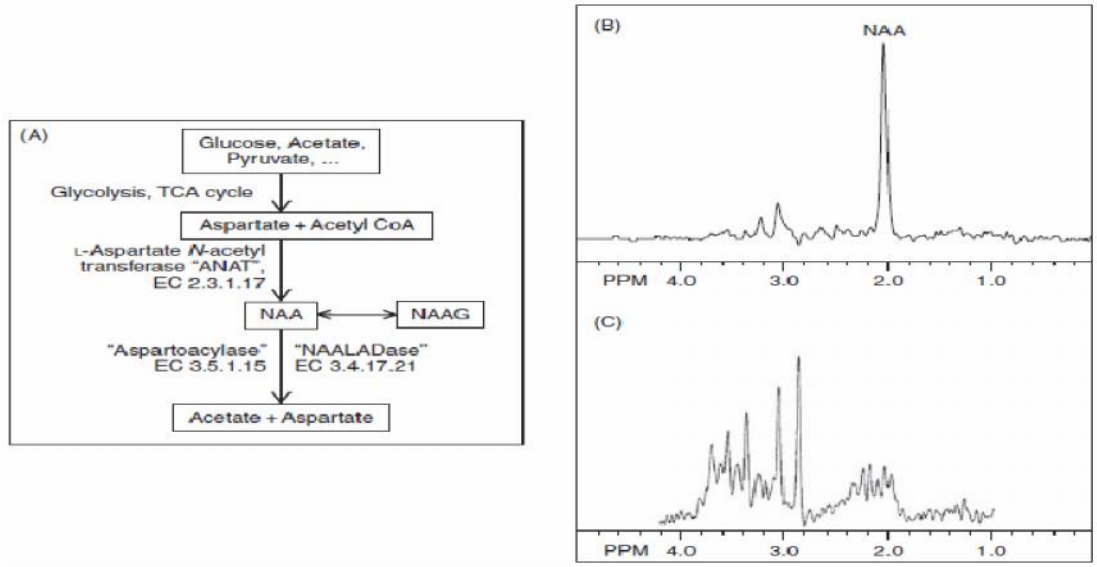

Figure 2. (A) Schematic of metabolism of NAA within the brain. NAA is synthesized from aspartate and acetyl CoA (generated from precursors such as glucose, acetate or pyruvate) and degraded to acetate and aspartate. There is also a pathway relating NAA and NAAG catalyzed by the enzyme NAALADase. (B) In Canavan's Disease, aspartoacylase is deficient, leading to large accumulations of NAA in the brain. (C) A case of NAA-deficiency, reproduced with permission from, resulting from a presumed deficit in the synthetic pathway of NAA. Normal signals from Cho, Cr, Glx, and mI are observed; however, NAA is absent. Spectra recorded at 1.5 T **(Marin E.,2001).**

Choline

The choline signal (Cho, 3.20 ppm)is a compositepeak consisting of contributionsfrom the trimethyl amine (–N(CH3)3) groups of glycerophosphocholine (GPC), phosphocholine (PC), and a small amount of free choline itself.These compounds are involved in membrane synthesis and degradation, and it has often been suggested that they are elevated in disease states where increased membrane turnover is involved (e.g. tumors). Glial cells have also been reported to have high levels of Cho. Otherpathological processes which lead toChoelevation include active demyelination,either resulting from the degradation of myelin phospholipids primarily to GPC, or perhaps due to inflammation (**Aboagye EO et al.,2000).**

Elevated Cholevels seem tobea characteristic of many types of neoplasms, including high-grade brain tumors (provided that they arenot necrotic), prostate, breast, head and neck, and other tumors. In particular, it would appear that malignant transformation of tumors involves an increase in PC relative to GPC.Low brain Cho has been observed in hepatic encephalopathy, and there is also some evidence to suggest that dietary intake of choline can modulate cerebral Cho levels.In bothcases, this may be due to altered (decreased or increased) systemic transport of Cho to the brain.Cho also shows quite strong regional variations in the brain, usually with somewhat higher levels in white matter than gray, although the thalamus, hypothalamus, and insular cortex also show high levels in the normal brain**(Stoll AL et al.,2000).**

Creatine

The creatine methyl resonance (Cr, 3.03 ppm)is a composite peak consisting of both creatine and phosphocreatine, compounds that are