Omar Islam <omarislam9902@gmail.com>

# MRS

1 message

**Omar <omarislam70@gmail.com>** **Thu, Aug 19, 2010 at 1:42 PM**
To: Omar <omarislam9902@gmail.com>

**MRS (Magnetic Resonance Spectroscopy)**

Magnetic resonance spectroscopy (MRS) is a non-invasive means for the characterization of tissue. While MRI uses the signal from hydrogen protons to form anatomic images, proton MRS uses this information to determine the concentration of metabolites (such as lipids, lactate, N-acetylaspartate (NAA), glutamate/glutamine (Glx), creatine (Cr), choline (Cho), and myo-inositol (mI), see figure 1 below) in the tissue examined. With MRS, we are able to study the metabolism and biochemistry of the brain in action and to observe gene expressions or the activity of a particular membrane receptor, using molecular imaging with targeted MR contrast agents.

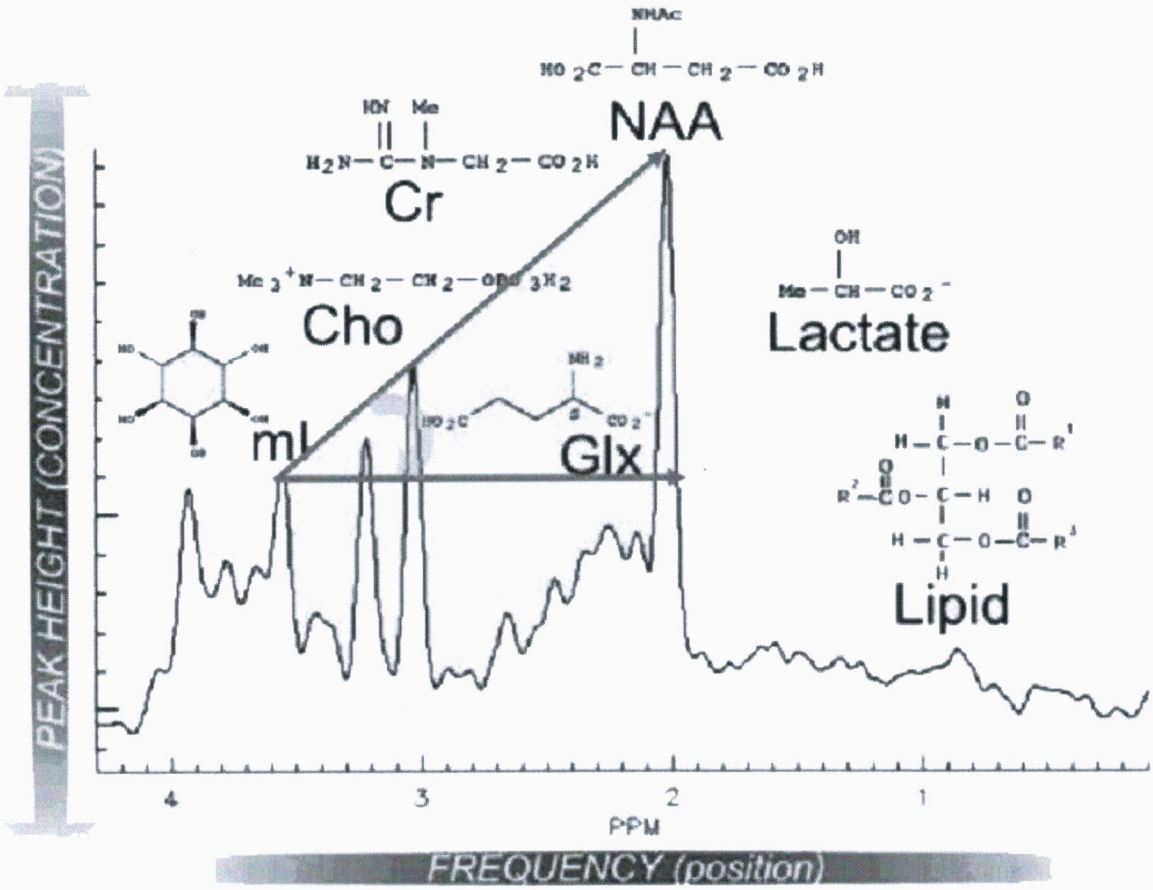


FIG. 1.

Representative spectrum of the human brain in vivo. Each peak is labeled with the molecule and its structure (SciFinder). Note that lipid and lactate are not observed in healthy brain (as shown here), and therefore their absorptions are not visible. The curved arrow represents Hunter's Angle, which is drawn starting from mI to NAA.

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**Interpretation or MRS:**

*Lipids*

Lipids are broad peaks that occur at 0.9 and 1.2 parts per million (ppm). In healthy tissues, there should be very little lipid in the spectrum unless the area includes subcutaneous fat from the skull. The presence of lipid can have diagnostic value in brain tumor where lipid indicates necrosis.5 In this extreme setting, a third lipid peak, at 2 ppm may displace or mask the normal NAA resonance.

*Lactate*

Lactate is generally seen as a doublet (two peaks close together) that has a frequency of exactly 1.33 ppm. Healthy tissue does not have sufficient lactate to be detectable with MRS. CSF contains lactate at about 1 mm so that if the voxel is placed entirely in the ventricle, lactate will appear in the spectrum (a potential source of error when examining patients with hydrocephalus). Lactate as a product of anaerobic glycolysis is detected in diseased brain, which is oxygen starved in stroke, mitochondrial myopathy, encephalopathy, lactacidosis, and stroke, recovery from cardiac arrest, neonatal hypoxia, etc. It is of greatest diagnostic value in cases of brain injury or trauma where hypoxia is part of the differential. It is also a nonspecific marker of tumor aggressiveness and is found in cysts and abscesses of all types.

*N-acetyl aspartate*

At 2.0 ppm, NAA is an amino acid derivative synthesized in neurons and transported down axons. It is therefore an almost 100%-specific marker of viable neurons, axons, and dendrites. The diagnostic value of NAA lies in the ability to quantify neuronal injury or loss on a regional basis.

*Glutamate-glutamine*

A mixture of closely related amino acids, amines and derivatives closely involved in excitatory and inhibitory neurotransmission that lies between 2.1 and 2.4 ppm. Because these are also integral products of intact TCA (Krebs) cycle activity and mitochondrial redox systems, Glx offers a vital marker(s) in MRS of stroke, lymphoma, hypoxia, and many metabolic brain disorders.

*Creatine*

The primary resonance of creatine lies at 3.0 ppm. As phosphocreatine, it is the central energy marker of both neurons and astrocytes. A "constant" in the normal brain spectrum, the Cr peak intensity thereby standardizes its interpretation. Metabolite/Cr peak height ratios are astonishingly reproducible and a visual pattern described by **Hunter's angle (HA)** (see below), can be relied upon for radiological interpretation of almost all pathological spectra.

*Choline*

Cho [sometimes designated trimethylamine (TMA)] is an umbrella term for several soluble components of brain myelin and fluid-cell membranes that resonate at 3.2 ppm. Because by far the majority of choline-containing brain constituents are not normally soluble, pathological alterations in membrane turnover (tumor, leukodystrophy, multiple sclerosis) result in a massive increase in MRS-visible Cho, providing a diagnostic gold mine.

*Myo-inositol*

A previously little-known polyol (sugar-like molecules) that resonates at 3.6 ppm, ml is the missing osmolyte of the early neurological literature for brain volume regulation. In neurospectroscopy, ml is mostly a diagnostic modifier in those diseases that affect Cho (tumor, multiple sclerosis, etc). As an astrocyte marker and osmolyte, ml contributes specificity in dementia diagnosis and adds specificity to monitoring hepatic encephalopathy and hyponatremic brain syndromes.

*Additional resonance peaks*

MRS is a "spectrum" of normal and abnormal brain constituents. Lots of "odd" things turn up in the brain after ingestion: alcohol, methylsulphonylmethane (a common health food supplement),6 mannitol and propylene glycol, common medications, glucose, acetate, acetone, succinate, phenyl-alanine, all defined by their chemical shift (ppm) and adding spice and diagnostic specificity to the clinical practice of neurospectroscopy. Every metabolite has a normal concentration that generates a pattern of peaks that is the same from person to person unless there is an underlying pathology. Diagnosis with MRS can therefore be made by either comparing the numeric values of metabolite concentrations or by recognizing abnormal patterns of peaks in the spectra such as in electrocardiogram interpretations.

*Hunter's angle*

Named for an eminent neurosurgeon who applied a pocket comb to the task of recognizing the 45-degree angle formed by the peaks ml, Cr, Cho, and NAA, when they are present in normal proportions, viz: NAA/Cr :1.5, Cho/Cr :0.75; ml/Cr: 0.5, thus, a very rough-and-ready approach for short-echo-stimulated echo acquisition mode (STEAM on GE MR systems or Stimulated-Echo on Siemens) spectroscopy. Like all rules, exceptions abound—moving from STEAM to point resolved

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|---|---|---|---|---|
| | Detectable >~1mM | May be energetic substrate of much brain metabolism. Thought to be elevated in foamy macrophages. | respiratory chain defects, tumors (all grade)), abscesses, inflammation. | |
| Lipids<br>Mobile liquid moieties | 0.9 and 1.3 ppm (short TE unless (↑↑)) | Not seen in normal brain. Membrane breakdown/lipid droplet formation. May preced histological necrosis. Products of bacterial metabolism. | High-grade tumors, abscesses, acute inflammation, acute stroke. | |

Table 1. Summary of assignment and significance of each resonance in the MR spectrum. (Ref: Barker, P. (2005). Fundamentals of MR Spectroscopy. Gillard J, Waldman A and Barker P. Cambridge, Cambridge University Press: 7-26.)

spectroscopy (PRESS on GE MR systems or Spin-Echo on Siemens), from short to long echo time (TE) and repetition time (TR), from cortex to midbrain, all change HA. Nevertheless, it is rather convincing when applied to such common MRS diagnoses as tumor (HA < −50°), stroke, AD (HA = 15°), neonatal hypoxia (HA = −45°) or acquired immune deficiency syndrome (AIDS)-related progressive multifocal leukomalacia (HA = 0°).

References:

Danielsen E, Ross BD. Magnetic resonance spectroscopy diagnosis of neurological diseases. New York: Marcel-Dekker, 1999.

Lin A, B.D. Ross, et al. (2005). "Efficacy of proton magnetic resonance spectroscopy in neurological diagnosis and neurotherapeutic decision making." NeuroRx 2(2): 197-214.

| **Metabolite** | **Chemical shift Normal concentration Median (range)** | **Physiological significance** | **Increased** | **Decreased** |
|---|---|---|---|---|
| NAA (NAA, other N-acetyl moieties) | 2.02 ppm 7.8 mM (6.5-9.7) | Health neuronal cell marker. Only seen in nervous tissue. Exact physiological role uncertain. | v. rarely Canavan's disease | Commonly: non-specific neuronal loss or dysfunction due to range of insults. Incl. Ischaemia, trauma, inflammation, infection, tumors, dementia, gliosis. |
| Cho Cho-containing compounds | 3.2 ppm 1.3 mM (0.8-1.6) | Detectable resonance is predominantly free Cho and derivative. Marker of membrane turnover. Higher in W.M. than G.M. Increase with age. | Tumors, inflammation, chronic hypoxia | Stroke, encephalopathy (hepatic human immunodeficiency virus (HIV)/liver disease |
| Cr Creatine/ phosphocreatine | 3.0 ppm 4.5 mM (3.4-5.5) | Compounds related to energy storage; thought to be marker of energetic status of cells. Other metabolites are frequently expressed as ration to Cr. Low in infants. Increase with age. | Trauma, hyperosmolar states | Hypoxia, stroke, tumors |
| Myo Myo-inositol (mI) (other inositols) | 3.56 ppm (short TE only) 3.8 mM (2.2-6.8) | Pentose sugar. Involved in inositol triphosphate intra-cellular second messenger cycle, osmolyte, glial cell marker. High in infants. | Neonates, Alzheimer's disease, diabetes, recovered encephalopathy, low grade glioma, hyperosmolar | Malignant tumors, Chronic hepatic encephalopathy, stoke |
| Glx Glutamate (Glu)/ Glutamine (Gln) | 2.1-2.4 ppm (short TE only) Glu ~ 10 mM Glm ~ 5mM | Complex overlapping J-coupled resonance difficult to separate and quantify at clinical field strengths (1.5 – 3T). Amino acid neurotransmitters Glu excitatory, Gln inhibitory. | Hepatic encephalopathy, severe hypoxia, OTC deficiency | Possibly Alzheimer's disease |
| Lactate | 1.35 ppm (doublet, 7 ppm separation) | Not seen in normal brain. End product of anaerobic respiration. | Ischaemia, inborn errors of metabolism (especially | |