Lecture #14
In Vivo MRS-detectable Metabolites

• Topics
  – $^1$H-MRS
  – $^{31}$P-MRS
  – $^{13}$C-MRS
  – Other nuclei

• Handouts and Reading assignments
  – de Graaf, Chapter 2.
  – de Graaf, Chapter 3, 158-171.
Introduction

MRI: anatomy and structure

MRS: metabolism and function
MR of the Brain

- Conventional MRI
- Microvasculature
- Microstructure
- Cellular function and metabolism
- Perfusion imaging
- DWI/DTI
- MRS

Anatomy
Cells

General cellular functions

- Turn glucose into energy
- Maintain cellular integrity
  - Ionic balance
  - Osmotic balance
  - Membrane structure
- Perform cell specific functions, e.g. neurons send/receive electrical signals
Some general rules of thumb

• In vivo MRS does not see everything! Maudsley paper is rather optimistic.
• Concentration limit (of protons) around 1 mM for NMR-detection
• Macromolecules are non-detectable ($T_2$s too short)
$^1$H Brain Spectroscopy

1.5T (in vivo)

11T (extract)

In vivo

GE MRS phantom

In vitro solutions

- glutamate
- glutamine
- myo-inositol
- glucose
- taurine
We’ll start with “late” echo spectra
N-acetyl Aspartate (NAA)

Biochemical role?

- Largest peak in a $^1$H-MRS brain spectrum
- Neuronal marker
- 2.0 ppm
- Approx 10 mM
Creatine (Cre)

“Cre” peak from both creatine and phosphocreatine (often called referred to as total creatine peak)

PCr

\[
\text{HO-PO-N-C-N-C-C-O} \\
\text{HO} \quad \text{CH}_3 \quad \text{H}
\]

Biochemical role

- Reflects cellular energetics
- 3.0 ppm
- Cre+PCr=“tCr”
- Approx 5-10 mM

Fast reaction to buffer energy levels while glucose is metabolized
Choline (Cho)

Biochemical role

- Largely reflects cell membrane repair and synthesis (acetylcholine component very small)
- 3.2 ppm
- Approx 1-2.5 mM

“Cho” peak from several choline containing compounds: phosphocholine, glycerophosphocholine, etc.

9 protons!
Example: Brain Tumor

52 y.o male: MRI #1 - rule out stroke, MRI # - tumor?

- NAA
- creatine
- choline
- TE = 144 ms
- post-contrast T<sub>1</sub>
- T<sub>2</sub>
- NAA
- choline
- creatine
- TE = 144 ms
Lactate (Lac)

Biochemical role

- Indicator of anaerobic metabolism
- Doublet at 1.3 ppm
- Approx 0.4 mM (normal brain tissue)

Short TE $^1$H-MRS Brain Spectra

1.5T $^1$H-MRS In Vivo Brain Spectrum
TE = 35 ms

some new peaks
myo-Inositol (mI)

1.5 T In vivo $^1$H Brain Spectrum (TE=35ms)

Biochemical role?

- Suggested as a glial marker.
- Glial cells provide structural support for neurons in addition to involvement in neurotransmitter processes.
- Largest peak at 3.6 ppm
- Approx 4-8 mM
Neurotransmitters

Glutamate is the major excitatory neurotransmitter in the brain.
Glutamate (Glu) and Glutamine (Gln)

1.5 T In vivo $^1$H Brain Spectrum (TE=35ms)

In vivo concentrations

- Glu: 8-10 mM
- Gln: 2-3 mM
γ-aminobutyric acid (GABA)

GABA is the major inhibitory neurotransmitter in the brain (conc: 1-2 mM)

Example In vivo GABA (3T)

A real neural net
Muscle and Fat
Prostate

Normal prostate (1.5 T)

Prostate cancer (1.5 T)
Breast cancer

Noncancerous lesion

2D-J spectrum
## Sensitivity

### Table 1.1. NMR properties of commonly encountered nuclei in *in vivo* NMR

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Spin</th>
<th>Gyromagnetic ratio (\left(10^7 \text{ rads}^{-1}\text{T}^{-1}\right))</th>
<th>NMR frequency at 2.35 T (MHz)</th>
<th>Natural abundance (%)</th>
<th>Relative sensitivity(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^1\text{H})</td>
<td>1/2</td>
<td>26.752</td>
<td>100.000</td>
<td>99.985</td>
<td>1.00</td>
</tr>
<tr>
<td>(^2\text{H})</td>
<td>1</td>
<td>4.107</td>
<td>15.351</td>
<td>0.015</td>
<td>(1.45 \times 10^{-6})</td>
</tr>
<tr>
<td>(^{13}\text{C})</td>
<td>1/2</td>
<td>6.728</td>
<td>25.145</td>
<td>1.108</td>
<td>(1.76 \times 10^{-4})</td>
</tr>
<tr>
<td>(^{14}\text{N})</td>
<td>1</td>
<td>1.934</td>
<td>7.228</td>
<td>99.630</td>
<td>(1.01 \times 10^{-3})</td>
</tr>
<tr>
<td>(^{15}\text{N})</td>
<td>1/2</td>
<td>-2.712</td>
<td>10.137</td>
<td>0.370</td>
<td>(3.85 \times 10^{-6})</td>
</tr>
<tr>
<td>(^{19}\text{F})</td>
<td>1/2</td>
<td>25.181</td>
<td>94.094</td>
<td>100.000</td>
<td>0.833</td>
</tr>
<tr>
<td>(^{23}\text{Na})</td>
<td>3/2</td>
<td>7.080</td>
<td>26.466</td>
<td>100.000</td>
<td>(9.27 \times 10^{-2})</td>
</tr>
<tr>
<td>(^{31}\text{P})</td>
<td>1/2</td>
<td>10.841</td>
<td>40.481</td>
<td>100.000</td>
<td>(6.65 \times 10^{-2})</td>
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<tr>
<td>(^{39}\text{K})</td>
<td>3/2</td>
<td>1.250</td>
<td>4.672</td>
<td>93.100</td>
<td>(4.75 \times 10^{-4})</td>
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</tbody>
</table>

\(^1\text{Relative sensitivity is calculated as the product of NMR sensitivity (proportional to } \gamma ^3\text{I}(I + 1)) \text{ and the natural abundance.}

\[ \text{in vivo SNR} \propto \rho \gamma^2 \frac{\hbar^2 B_0}{4kT} \]
$^{31}$P Spectroscopy

muscle

brain

liver
$^{13}$C Spectroscopy

Table 2.3. Chemical shifts of biological relevant $^{13}$C containing metabolites

<table>
<thead>
<tr>
<th>Compound</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
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<tr>
<td>Acetate</td>
<td>182.6</td>
<td>24.5</td>
<td>17.1</td>
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<tr>
<td>Alanine</td>
<td>176.6</td>
<td>51.5</td>
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<tr>
<td>Aspartate</td>
<td>175.1</td>
<td>53.0</td>
<td>37.4</td>
<td>178.4</td>
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<td></td>
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<tr>
<td>Citrate</td>
<td>179.7</td>
<td>46.8</td>
<td>76.0</td>
<td>46.8</td>
<td>179.7</td>
<td>182.3</td>
</tr>
<tr>
<td>Creatine</td>
<td>175.4</td>
<td>37.8</td>
<td>158.0</td>
<td>54.7</td>
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<td></td>
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<tr>
<td>GABA</td>
<td>182.3</td>
<td>35.2</td>
<td>24.6</td>
<td>40.2</td>
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<td></td>
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<tr>
<td>Glycerol</td>
<td>63.6</td>
<td>73.3</td>
<td>63.6</td>
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<tr>
<td>β-hydroxy butyrate</td>
<td>181.2</td>
<td>47.6</td>
<td>66.8</td>
<td>22.9</td>
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<tr>
<td>Glucose α</td>
<td>92.7</td>
<td>72.1</td>
<td>73.5</td>
<td>70.4</td>
<td>72.1</td>
<td>61.4</td>
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<tr>
<td>Glucose β</td>
<td>96.6</td>
<td>79.9</td>
<td>76.5</td>
<td>70.4</td>
<td>76.5</td>
<td>61.4</td>
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<tr>
<td>Glutamate</td>
<td>175.3</td>
<td>55.5</td>
<td>27.8</td>
<td>34.2</td>
<td>182.0</td>
<td></td>
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<tr>
<td>Glutamine</td>
<td>174.8</td>
<td>55.0</td>
<td>27.1</td>
<td>31.7</td>
<td>178.4</td>
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<tr>
<td>Glycine</td>
<td>173.3</td>
<td>42.5</td>
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<tr>
<td>Glycogen</td>
<td>100.5</td>
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<td>74.0</td>
<td>78.1</td>
<td>72.1</td>
<td>61.4</td>
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<tr>
<td>Inositol</td>
<td>73.3</td>
<td>73.1</td>
<td>73.3</td>
<td>71.9</td>
<td>75.1</td>
<td>71.9</td>
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<tr>
<td>Lactate</td>
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<td>69.3</td>
<td>21.0</td>
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<tr>
<td>Malate</td>
<td>182.1</td>
<td>71.7</td>
<td>43.9</td>
<td>180.9</td>
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<tr>
<td>NAA</td>
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<td>54.0</td>
<td>40.3</td>
<td>179.7</td>
<td>174.3</td>
<td>22.8</td>
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<td>Succinate</td>
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<td>35.3</td>
<td>35.3</td>
<td>183.4</td>
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<td>Taurine</td>
<td>48.4</td>
<td>36.2</td>
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</tbody>
</table>

All chemical shifts are referenced relative to 3-(trimethylsilyl)-1-propanesulfonic acid at 0.00 ppm.

$^{13}$C natural abundance is low, but $^{13}$C-labeled glucose or acetate infusions can yield important information regarding metabolic fluxes.

Note: very wide chemical shift range
Example: $^{13}$C-glucose Infusion

Other Nuclei

• Sodium ($^{23}\text{Na}$, spin=3/2)
  – Intracellular 10 mM
  – Extracellular 150 mM

  Involved in ionic balances, generation of action potentials, regulations of cell volume.

• Fluorine ($^{19}\text{F}$)
  – No endogenous $^{19}\text{F}$ compounds in biological tissue
  – Lots of fluorinated drugs!
Next Lecture: $^{1}$H MRS Methods