^{1}H-NMR Chemical Shifts and Coupling Constants for Brain Metabolites

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A detailed compilation of ^{1}H-NMR chemical shift (δ) and coupling constant (J) values of 38 low-molecular-weight metabolites, found in mammalian brain at physiological or pathological conditions, is presented. These metabolites are detectable using in vivo ^{1}H magnetic resonance spectroscopy techniques and include energy metabolites (sources, intermediaries, and products), essential and nonessential amino acids, excitatory and inhibitory neurotransmitters, neuro-modulators, and phospholipid membrane precursors and break-down products. The values of δ and J were measured from high-field NMR data of aqueous solutions of each metabolite acquired at typical physiological temperature and pH conditions. The spectral parameter values (δ, J) may be used to identify metabolites from their resonances in in vivo spectra, to simulate metabolite spectra or to generate basis functions (i.e., amplitude, frequency, and phase) for spectral fitting, and to optimize parameters in data acquisition sequences in order to improve metabolite quantitation or selectively edit different spectral components.

Keywords: ^{1}H magnetic resonance spectroscopy, chemical shifts, coupling constants, metabolites, brain, hydrogen, proton, in vivo

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Introduction

Metabolites are the intermediates and products of life-sustaining catabolic and anabolic chemical reactions that occur within the cells of living organisms. Quantification of metabolite concentrations, therefore, helps us to understand their functional role in reactions in physiologically normal and pathological conditions. In vivo hydrogen (^{1}H) NMR spectroscopy (MRS) is well suited to noninvasively obtain concentrations of low-molecular-weight metabolites in the brain.[1–6]

Brain metabolites give rise to singlet and/or multiplet ^{1}H NMR spectral patterns (including doublet, triplet, and quartet) in vivo, depending on the number of scalar coupled hydrogen atoms in their molecular structures. The spectral patterns of metabolites overlap considerably within the range 0–5 ppm, which is particularly severe at the lower field strengths ($B_0 \leq 3$ T) that are commonly available for studies in humans. Analysis of these overlapping spectra benefits greatly from prior knowledge of the number of metabolites that could potentially contribute to the data and by incorporating their spectral information (chemical shift or frequency position, amplitude and phase of all resonances in each metabolite) in parametric modeling approaches (see ***Time-Domain Methods for Quantifying MR Spectra***, ***Quantifying Spectra in the Frequency Domain***, ***Advanced Spectral Quantification: Parameter Handling, Nonparametric Pattern Modeling, and Multidimensional Fitting***).[7–11]

In this article, a literature compilation of ^{1}H NMR chemical shift (δ) and coupling constant (J) values of 38 low-molecular-weight metabolites, found in mammalian brain at physiological or pathological conditions, is presented. These metabolites are reported as being detectable in the brain using in vivo MRS techniques.[5] The spectral parameter values (δ, J) of these metabolites were obtained from high-field NMR spectra of each metabolite in aqueous solution at typical physiological temperature and pH conditions,[5,12–17] unless stated otherwise. Knowledge of these NMR spectral parameters is important for the identification of metabolites from their resonances in vivo, for the simulation of metabolite spectra and the development of basis functions (i.e., amplitude, frequency, and phase) for use in spectral fitting methods, for optimizing parameters in data acquisition sequences to minimize signal loss due to dephasing of coupled spins;, and for tuning selective editing techniques (such as homonuclear decoupling and chemically selective excitation methods) to select and quantify specific metabolites (see ***Spectral Editing***).

Experimental Conditions

Solutions of 33 metabolites listed in Table1, excluding adenine triphosphate (ATP), ascorbate (Asc), citrate (Cit), glucose (Glc), 2-hydroxyglutarate (2-HG), and *N*-acetyl aspartylglutamate (NAAG), were prepared individually both in deuterated (^{2}H) water (D_2O) at pH = 6.6 and in H_2O at pH =7.0 (for details, see Ref. 5). A trace amount of sodium salt of 2, 2-dimethyl-2-silapentane-5-sulfonate (DSS) was added to the solutions as a chemical shift reference. ^{1}H NMR spectra of the solutions were acquired at 37 °C using either a 500 or 600 MHz NMR spectrometer.[5] Chemical shifts and coupling constants

Table 1. Chemical shifts (δ) and coupling constant (J) values of 38 low-molecular-weight metabolites that are detectable in the mammalian brain by ^{1}H NMR spectroscopic techniques

Compound	Group	δ (ppm) in H_2O	δ (ppm) in D_2O	Multiplicity	J (Hz)	Connectivity
Acetate	$^2CH_3{}^*$	1.9040	1.9030	s	None	
N-Acetyl aspartate						
Acetyl moiety	$^2CH_3$	2.0080	2.0050	s		
Aspartate moiety	^2CH	4.3817	4.3823	dd	3.861	2–3
	$^3CH_2$	2.6727	2.6759	dd	9.821	2–3′
		2.4863	2.4866	dd	−15.592	3–3′
	NH	7.8205	7.8155	d	6.400	NH-2
N-Acetyl aspartylglutamate[a]	^2CH	4.14 (±0.02)		dd	4.61 (±0.02)	2–3
	$^3CH_2$	2.06 (±0.03)		m	8.42 (±0.04)	2–3′
		1.90 (±0.02)		m	7.46 (±0.01)	2–6
	$^4CH_2$	2.20 (±0.01)		m	−14.28 (±0.03)	3–3′
		2.21 (±0.01)		m	10.56 (±0.03)	3–4
	^6NH	7.95 (±0.04)			6.09 (±0.02)	3–4′
	^8CH	4.63 (±0.04)		dd	4.90 (±0.01)	3′–4
	$^9CH_2$	2.54 (±0.02)		dd	11.11 (±0.03)	3′–4′
		2.74 (±0.02)		dd	−15.28	4–4′
	^{11}NH	8.26 (±0.03)			9.62 (±0.02)	8–9
	$^{13}CH_3$		2.042[b]	s	4.38 (±0.01)	8–9′
					7.32 (±0.03)	8–11
					−15.97 (±0.01)	9–9′
ATP[c]						
Ribose moiety	1′CH	6.126[d]	6.129	d	5.7	1′–2′
	2′CH		4.796	t	5.3	2′–3′
	3′CH		4.616	dd	3.8	3′–4′
	4′CH		4.396	qu	3	4′–5′
	5′,5″CH_2		4.295	m	3.1	4′–5″
			4.206	m	−11.8	5′–5″
					1.9	4′-P
					6.5	5′-P
					4.9	5″-P
Adenosine moiety	^2CH	8.224[d]	8.234	s		
	^8CH	8.514[d]	8.522	s		
	NH_2	6.755[d]		s		
Alanine	^2CH	3.7746	3.768	q	7.234	2–3
	$^3CH_3$	1.4667	1.4655	d	−14.366	3–3′, 3″
					−14.366	3′–3″
GABA[e]	$^2CH_2$	2.2840			7.678	2–3
					6.980	2–3′
	$^3CH_2$	1.8880			6.980	2′–3
					7.678	2′–3′
	$^4CH_2$	3.0130			8.510	3–4
					6.503	3–4′
					6.503	3′–4
					8.510	3′–4′
					−15.938	2–2′
					−15.000	3–3′
					−14.062	4–4′
Ascorbate[f]	^4CH	4.5		d		
	^5CH	4.01		m		
	$^6CH_2$	3.73		m		
Aspartate	^2CH	3.8914	3.8867	dd	3.647	2–3
	$^3CH_2$	2.8011	2.8021	dd	9.107	2–3′
		2.6533	2.6508	dd	−17.426	3–3′

Table 1. Continued

Compound	Group	δ (ppm) in H_2O	δ (ppm) in D_2O	Multiplicity	J (Hz)	Connectivity
Choline	$N(CH_3)_3$	3.1850	3.1890	s	None	
	$^{1}CH_2$	4.0540	4.0500	m	3.140	1–2
	$^{2}CH_2$	3.5010	3.5060	m	6.979	1–2′
					3.168	1′–2′
					7.011	1′–2
					2.572	1-N
					2.681	1′-N
					0.57	N-CH_3
					−14.100	1–1′
					−14.070	2–2′
Citrate[g]	$^{1}CH_2^{*}$	2.54		dd	−15.1	1–1′
		2.65				
	$^{3}CH_2^{*}$	2.54		dd	−15.1	3–3′
		2.65				
Creatine	$N(CH_3)$	3.0270	3.0260	s	None	
	$^{2}CH_2$	3.9130	3.9110	s	None	
	NH	6.6490		s	None	
Ethanolamine	$^{1}CH_2$	3.8184		m	3.897	1–2
	$^{2}CH_2$	3.1467		m	6.794	1–2′
					6.694	1′–2
					3.798	1′–2′
					0.657	1-N
					0.142	1′-N
					−10.640	1–1′
					−11.710	2–2′
D-Glucose[h]						
α-Anomer	^{1}CH		5.216	d	3.8	1–2
	^{2}CH		3.519	dd	9.6	2–3
	^{3}CH		3.698	t	9.4	3–4
	^{4}CH		3.395	t	9.9	4–5
	^{5}CH		3.822	m	1.5	5–6
	^{6}CH		3.826	dd	6.0	5–6′
	$^{6'}CH$		3.749	dd	−12.1	6–6′
β-Anomer	^{1}CH		4.63	d	8.0	1–2
	^{2}CH		3.23	dd	9.1	2–3
	^{3}CH		3.473	t	9.4	3–4
	^{4}CH		3.387	t	8.9	4–5
	^{5}CH		3.45	m	1.6	5–6
	^{6}CH		3.882	dd	5.4	5–6′
	$^{6'}CH$		3.707	dd	−12.3	6–6′
Glutamate	^{2}CH	3.7433	3.7444	dd	7.331	2–3
	$^{3}CH_2$	2.0375	2.0424	m	4.651	2–3′
		2.1200	2.1206		−14.849	3–3′
	$^{4}CH_2$	2.3378	2.3354	m	8.406	3–4′
		2.3520	2.3507		6.875	3′–4′
					6.413	3–4
					8.478	3′–4
					−15.915	4–4′
Glutamine	^{2}CH	3.7530	3.7625	t	5.847	2–3
	$^{3}CH_2$	2.1290	2.1360	m	6.500	2–3′
		2.1090	2.1180		−14.504	3–3′
	$^{4}CH_2$	2.4320	2.4350	m	9.165	3–4
		2.4540	2.4570		6.347	3–4′
					6.324	3′–4
					9.209	3′–4′
					−15.371	4–4′
	NH_2	6.8160		s		
		7.5290		s		

(*continued overleaf*)

Table 1. Continued

Compound	Group	δ (ppm) in H_2O	δ (ppm) in D_2O	Multiplicity	J (Hz)	Connectivity
Glutathione[i]						
Glycine moiety	$^{10}CH_2$	3.769		s		
	^{9}NH	7.154		t		
Cysteine moiety	^{7}CH	4.5608		dd	7.09	7–7′
	$7'CH_2$	2.9264		dd	4.71	7–7″
		2.9747		dd	−14.06	7′–7″
	^{6}NH	8.1770		d		
Glutamate moiety[j]	^{2}CH	3.769		t	6.34	2–3
	$^{3}CH_2$	2.159		m	6.36	2–3′
		2.146		m	−15.48	3–3′
	$^{4}CH_2$	2.510		m	6.7	3–4
		2.560		m	7.6	3–4′
					7.6	3′–4
					6.7	3′–4′
					−15.92	4–4′
Glycerol	$^{1}CH_2$	3.5522	3.5486	dd	−11.715	1–1′, 3–3′
		3.6402	3.6364	dd	4.427	1–2, 2–3
	^{2}CH	3.7704	3.7680	m	6.485	1′–2, 2–3′
	$^{3}CH_2$	3.5522	3.5486	dd		
		3.6402	3.6363	dd		
Glycero-phosphocholine[k]						
Glycerol moiety	$^{1}CH_2$	3.605		dd	5.77	1–2, 2–3
		3.672		dd	4.53	1′–2, 2–3′
	^{2}CH	3.903		m		
	$^{3}CH_2$	3.871		m	−14.78	1–1′, 3–3′
		3.946		m	−9.32	7–7′, 8–8′
Choline moiety	$^{7}CH_2$	4.312		m	3.10	7–8, 7′–8′
					2.67	7,7′-N
	$^{8}CH_2$	3.659		m	5.90	7–8′, 7′–8
	$N(CH_3)_3$	3.212		s	6.03	3,3′-P; 7,7′-P
Glycine	$^{2}CH_2$	3.548	3.545	s	None	
Histamine	$^{\alpha}CH_2$	2.9813	3.0320	m	−16.120	α–α'
		2.9897	3.0420		6.270	α'–β'
	$^{\beta}CH_2$	3.2916	3.3148	t	8.147	α–β'
					7.001	α'–β
					6.868	α–β
					−14.145	β–β'
Imidazole ring	$^{2}CH^{*}$	7.8520	8.0250	d	1.07	2-^{1}NH
	$^{5}CH^{*}$	7.0940	7.1620	m	1.19	5-^{1}NH
					0.73	5-β,β'
Histidine	$^{\alpha}CH$	3.9752	3.9959	dd	7.959	α–β
	$^{\beta}CH_2$	3.1195	3.1866	dd	4.812	α–β'
		3.2212	3.2644	dd	−15.513	β–β'
Imidazole ring	$^{2}CH^{*}$	7.791	7.901	d	1.07	2-^{1}NH
	$^{5}CH^{*}$	7.058	7.103	m	1.2	5-^{1}NH
					0.72	5-β,β'
Homocarnosine[k]	$^{\alpha}CH$	4.472		m	6.88	α-NH
	$^{\beta}CH_2$	3.185		dd		
		3.003		dd		
Imidazole ring	$^{2}CH^{*}$	7.075		s		
	$^{5}CH^{*}$	8.081		d		
GABA moiety	$^{2}CH_2$	2.962		m		
	$^{3}CH_2$	1.891		m		
	$^{4}CH_2$	2.367		m		
		7.899		d		
	NH_3	6.397		s		

Table 1. Continued

Compound	Group	δ (ppm) in H_2O	δ (ppm) in D_2O	Multiplicity	J (Hz)	Connectivity
2-Hydroxyglutarate[l]	^{2}CH	4.022		m	7.6	2–3
	$^{3}CH_2$	1.825		m	4.1	2–3′
		1.977		m	5.3	3–4
	$^{4}CH_2$	2.221		m	10.4	3–4′
		2.272		m	10.6	3′–4
					6.0	3′–4′
					−14.0	3–3′
					−15.0	4–4′
myo-Inositol	^{1}CH	3.5217	3.5177	dd	2.889	1–2
	^{2}CH	4.0538	4.0488	t	9.998	1–6
	^{3}CH	3.5217	3.5177	dd	3.006	2–3
	^{4}CH	3.6144	3.6114	t	9.997	3–4
	^{5}CH	3.2690	3.2652	t	9.485	4–5
	^{6}CH	3.6144	3.6114	t	9.482	5–6
scyllo-Inositol	$^{1–6}$CH	3.3400	3.3340	s	None	
Lactate	^{2}CH	4.0974	4.0908	q	6.933	2–3
	$^{3}CH_3$	1.3142	1.3125	d		
Phenylalanine	$^{\alpha}$CH	3.9753	3.9829	dd	5.209	α–β
	$^{\beta}CH_2$	3.2734	3.2827	dd	8.013	α–β'
		3.1049	3.1132	dd	−14.573	β–β'
Phenyl ring	^{2}CH	7.3223	7.3223	m	7.909	2–3
	^{3}CH	7.4201	7.4201	m	1.592	2–4
	^{4}CH	7.3693	7.3693	m	7.204	3–4
	^{5}CH	7.4201	7.4201	m	0.493	2–5
	^{6}CH	7.3223	7.3223	m	0.994	3–5
					7.534	4–5
					1.419	2–6
					0.462	3–6
					0.970	4–6
					7.350	5–6
Phosphocreatine[m]	$N(CH_3)$	3.029	3.0280	s	None	
	$^{2}CH_2$	3.93	3.9260	s	None	
	NH	6.5810[m]		s	None	
	NH	7.2960[m]		s	None	
Phosphocholine	$^{1}CH_2$	4.2805	4.2851	m	2.284	1–2
					7.231	1–2′
					2.235	1′–2′
					7.326	1′–2
	$^{2}CH_2$	3.6410	3.6440	m	2.680	1-N
					2.772	1′-N
					6.298	1-P
					−14.89	1–1′
					−14.19	2–2′
	$N(CH_3)_3$	3.2080	3.2100	s	6.249	1′-P
Phospho-ethanolamine	$^{1}CH_2$	3.9765	3.9825	m	3.182	1–2
					7.204	1′–2
					6.716	1–2′
					2.980	1′–2′
	$^{2}CH_2$	3.2160	3.2150	m	7.288	1-P
					7.088	1′-P
					0.464	1-N
					0.588	1′-N
					−14.560	1–1′
					−14.710	2–2′
Pyruvate	$^{3}CH_3$	2.359	2.355	s	None	

(*continued overleaf*)

Table 1. Continued

Compound	Group	δ (ppm) in H_2O	δ (ppm) in D_2O	Multiplicity	J (Hz)	Connectivity
Serine	^{2}CH	3.8347	3.8349	dd	5.979	2–3
	$^{3}CH_2$	3.9379	3.9352	dd	3.561	2–3′
		3.9764	3.9764	dd	−12.254	3–3′
Succinate	$^{2}CH_2$	2.3920	2.3970	s	None	
	$^{3}CH_2$	2.3920	2.3970	s	None	
Taurine	$^{1}CH_2$	3.4206	3.4190	t	6.742	1–2
					6.403	1′–2
	$^{2}CH_2$	3.2459	3.2473	t	6.464	1–2′
					6.792	1′–2′
					−12.438	1–1′
					−12.930	2–2′
Threonine	^{2}CH	3.5785	3.5784	d	4.917	2–3
	^{3}CH	4.2464	4.2444	m	6.350	3–4
	$^{4}CH_3$	1.3158	1.3169	d		
Tryptophan	$^{\alpha}CH$	4.0468	4.0483	dd	4.851	α–β
	$^{\beta}CH_2$	3.4739	3.4787	dd	8.145	α–β'
		3.2892	3.2949	dd	−15.368	β–β'
Indole ring	^{2}CH	7.3120	7.3112	s	None	
	^{4}CH	7.7260	7.7255	d	7.6	4–5
	^{5}CH	7.2788	7.2759	t	1.0	4–6
	^{6}CH	7.1970	7.1934	t	7.507	5–6
	^{7}CH	7.5360	7.5315	d	0.945	4–7
					1.2	5–7
					7.677	6–7
Tyrosine	$^{\alpha}CH$	3.9281	3.9299	dd	5.147	α–β
	$^{\beta}CH_2$	3.1908	3.1965	dd	7.877	α–β'
		3.0370	3.0434	dd	−14.726	β–β'
Phenyl ring	^{2}CH	7.1852	7.1880	m	7.981	2–3
	^{3}CH	6.8895	6.8916	m	0.311	2–5
	^{5}CH	6.8895	6.8916	m	2.445	3–5
	^{6}CH	7.1852	7.1880	m	2.538	2–6
					0.460	3–6
					8.649	5–6
Valine	^{2}CH	3.5953	3.5954	d	4.405	2–3
	^{3}CH	2.2577	2.2622	m	6.971	3–4
	$^{4}CH_3$	1.0271	1.0290	d	7.071	3–4′
	$4'CH_3$	0.9764	0.9793	d		

Chemical shifts are reported with reference to DSS trimethyl singlet resonance at 0.0000 ppm, unless stated otherwise. The multiplicity given here was observed in conventional one-dimensional (1-D) ^{1}H NMR spectra recorded at 500 or 600 MHz, unless stated otherwise. Abbreviations used for multiplicity are: s, singlet; d, doublet; t, triplet; q, quartet; qu, quintet; and m, other multiplet. Multiplet groups with pH-dependent chemical shifts in the physiological range are indicated by asterisks. Superscript numbers, Greek characters, and primes designate the locations of carbon atoms on moieties and molecules as indicated in Figure 1.

[a]From Krawczyk *et al.*[12]; pH: 6.75, temperature: 30 °C; chemical shift values with reference to TSP.

[b]From Govindaraju *et al.*[5]

[c]From Son and Chachaty[13]; pH: between 7 and 8, temperature: 35 °C; multiplicity given here was observed at 250 MHz proton frequency.

[d]From Govindaraju *et al.*[5]; data acquired at 600 MHz ^{1}H NMR.

[e]From Near *et al.*[53].

[f]From Fan[15]; pH: neutral, temperature: not reported; chemical shift values with reference to DSS or TSP.

[g]From Choi *et al.*[16]; pH: 7.0, temperature: not reported; 3 T data.

[h]From Perkins *et al.*[14]; pH: not reported, temperature: 25 °C; multiplicity given here was observed at 270 MHz ^{1}H NMR.

[i]Coupling constants for glutathione were measured from 2-D ECOSY spectra acquired at 500 MHz, and these values were optimized only for the cysteine moiety.

[j]Refined values for the glutamate moiety were reported by Choi. *et al.*[97].

[k]Chemical shifts and coupling constants for these metabolites were measured from the conventional 1-D ^{1}H NMR spectra, and the values were not optimized.

[l]From Bal and Greff-Keller[17]; pH: 7.0, temperature: 30 °C; data acquired at 400 MHz.

[m]These two NH resonances of phosphocreatine are from —C=NH— and —NH—P— hydrogens; however, no specific assignments have been made.

of the metabolites were obtained using a spectral optimization program.[5]

ATP, Asc, Cit, Glc, 2-HG, and NAAG ^{1}H NMR spectra were acquired as follows. An Asc solution in D_2O at pH = 7.0 containing DSS as a chemical shift reference was used.[15] ATP was prepared in D_2O at a pH of 7–8 and spectra acquired at 250 MHz.[13] Phantom solutions containing Cit at pH = 7.0 were used for acquisition of spectral data at 3 T.[16] A Glc solution in D_2O (pH not known) was used to acquire ^{1}H NMR spectral data at 25 °C using a 270-MHz spectrometer.[14] A 2-HG solution in H_2O at pH = 7.0 with DSS as a chemical shift reference was used to acquire ^{1}H NMR data at 400 MHz and 30 °C.[17] An NAAG solution in H_2O at pH = 6.75 with 3-trimethylsilyl-2,2′,3,3′-tetradeuteropropionic acid sodium salt (sodium salt of TSP-d4) was used for recording NAAG data at 30 °C, utilizing an 11.7 T spectrometer.[12]

Spectral Parameters of Brain Metabolites

The chemical shifts and coupling constants of 38 in-vivo NMR-detectable brain metabolites are listed in Table 1. Their molecular structures are shown in Figure 1. A brief description of the molecular groups, ^{1}H-MRS spin system at high-magnetic fields ($B_0 \geq 11.7$ T), and known functions of each metabolite together with its cellular localization is provided in the following sections.

Acetate (Ace)

Acetate is an essential building block for the synthesis of a number of compounds in the body. It has been observed in high-resolution NMR studies of neural cell cultures,[18] brain tissue extracts,[19] and the brain in vivo in pathological conditions.[20,21] Its concentration in human brain varies in both directions in pathological conditions relative to healthy brain (for example, it is increased in brain tumors[22] and decreased in multiple sclerosis[23,24]). Acetate has a single CH_3 group that provides a singlet at 1.90 ppm, which overlaps with a multiplet from GABA.

N-Acetyl Aspartate (NAA)

NAA is the second most concentrated amino acid derivatives (after glutamate) in the central nervous system (CNS). It is localized predominantly in neurons,[25] although it has also been reported to be present in oligodentrocytes[26] and in trace amounts outside the CNS.[27,28] Its exact physiological functions are not completely understood (see ***N-Acetyl Aspartate***). However, it is reported to be involved in at least four possible functions: as an organic osmolite,[29] a source for acetate,[30,31] an energy source in neurons,[32] and a precursor of NAAG.[33] NAA has seven hydrogens that provide NMR signals between 2.0 and 8.0 ppm. It provides the most prominent resonance in the brain spectrum: a singlet at 2.01 ppm, originating from the three hydrogens of an *N*-acetyl CH_3 group. In one-dimensional (1-D) in vivo NMR spectra at $B_0 \leq 3$ T, this resonance may also contain smaller contributions from NAAG, although this can be separated at higher field strengths or using two-dimensional (2-D) NMR methods.[34] NAA also has three doublet-of-doublets centered at 2.49, 2.67, and 4.38 ppm that correspond to the hydrogens of aspartate CH_2 and CH groups. These three hydrogens form an ABX spin system with eight resonance lines for the CH_2 group and four resonance lines for the CH group. The amide NH hydrogen, which is exchangeable with water hydrogens, gives a broad doublet at 7.82 ppm that is known to be temperature dependent.[35]

The high abundance of NAA in the CNS and the source for a prominent singlet resonance at 2.01 ppm greatly facilitate its ^{1}H-MRS observation in vivo. Brain NAA is variously described in the literature as a marker of neuronal density,[36,37] neuronal viability,[38,39] neuronal integrity,[40] neuronal loss,[36] or neuronal health.[38] However, this is not fully substantiated as NAA concentrations vary among neuron types[41]; it has been found in other cell types[42]; and dynamic changes of neuronal NAA concentrations have been observed. The latter suggests that declining NAA levels may also reflect reversible neuronal dysfunction rather than loss.[34,38,43] NAA concentration is reported to be reduced in all pathological conditions[38] except two: Canavan's disease[44] and sickle cell disease[45,46] in children.

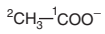
N-Acetyl Aspartylglutamate (NAAG)

NAAG is a dipeptide that is reported to be unevenly distributed within the brain.[36] It is possibly involved in excitatory neurotransmission as well as serving as a source of glutamate,[47] although its function remains to be clearly established. The NAAG molecule consists of acetyl, aspartyl, and glutamate moieties, with 11 nonexchangeable hydrogens and three water-exchangeable hydrogens. As NAAG is structurally similar to NAA and glutamate, many of their resonance multiplets overlap. For in-vivo studies at lower field strengths, it is primarily detected via the acetyl-CH_3 hydrogens that give a singlet resonance at 2.04 ppm[5] and which therefore appears as a shoulder of the CH_3 resonance of NAA. Another published report[12] provides the coupling constants and chemical shifts of hydrogens in the aspartyl and glutamate moieties of NAAG, measured at 11.7 T and at 30 °C and 6.75 pH. The chemical shifts and the coupling constants reported in Table 1 include data from two publications.[5,12]

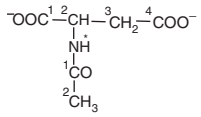
Adenosine Triphosphate (ATP)

ATP is a nucleotide and a high-energy phosphate compound that is comprised adenine, ribose, and triphosphate units. The analysis of spin–spin coupling patterns of ATP is complex. As its signal contributions upfield from the water resonance are small, our measurements are limited to only the down-field region where in-vivo ^{1}H-MRS detection is possible.[48] The chemical shifts and coupling constants presented in Table 1 represent a combination of our measurements for the down-field region, and those from the report of Son and Chachaty,[13] which were for an ATP solution in D_2O at 7–8 pH and acquired at 250 MHz. However, differences between these previously reported literature values[13] and ours were noted, typically in the second decimal place, which are probably due to slightly different experimental conditions of temperature and pH. In the ATP adenine ring, the ^{2}CH and ^{8}CH hydrogens resonate as singlets at 8.22 and 8.51 ppm, respectively. These ring-CH

Acetate



N-acetyl aspartate



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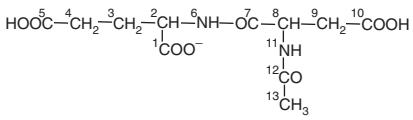
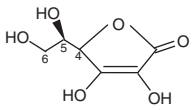
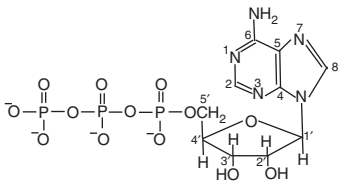


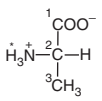
Ascorbate



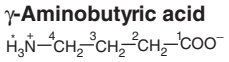
Adenine Triphosphate



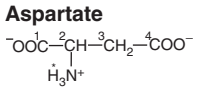
Alanine



γ-Aminobutyric acid



Aspartate



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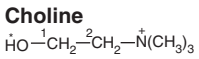

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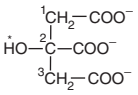
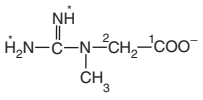
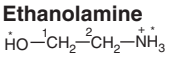


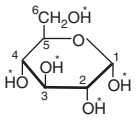
Creatine



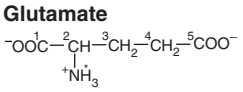
Ethanolamine



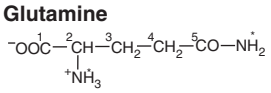
Glucose



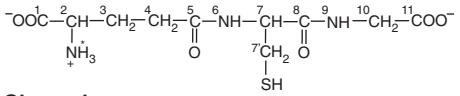
Glutamate



Glutamine



Glutathione



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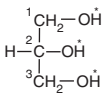

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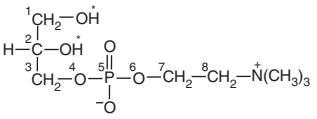

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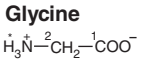

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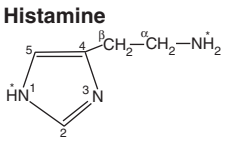

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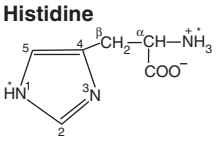
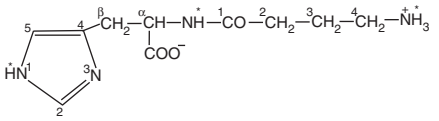
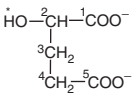


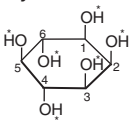
Homocarnosine



2-Hydroxyglutarate



***Myo*-Inositol**



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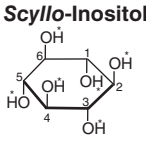

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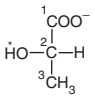

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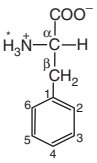
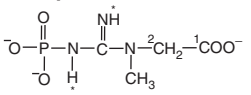
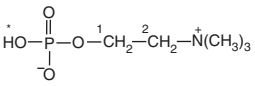


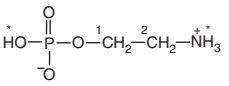
Phosphocreatine



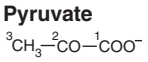
Phosphocholine



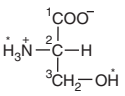
Phosphoethanolamine



Pyruvate



Serine



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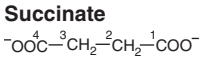

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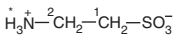
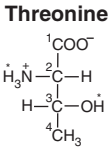
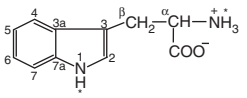


Threonine



Tryptophan



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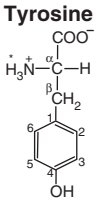

Valine

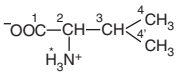

Figure 1. Molecular structures of 38 metabolites detectable by ^{1}H NMR in mammalian brain are shown. Hydrogen atoms of the metabolites that are exchangeable with the hydrogen atoms of water molecules are indicated by asterisks. Superscript numbers, Greek characters, and primes designate the locations of carbon atoms on moieties and molecules as listed in Table 1. (Reproduced with permission from Ref. 5. © John Wiley & Sons Ltd., 2000.)

hydrogens exchange slowly with water, and although two separate peaks are seen in solution, only one peak is observed at 8.22 ppm in vivo.[48] These resonances are also pH dependent. The NH_2 hydrogens give a broad line at 6.75 ppm and the ribose-$1'$CH hydrogen gives a doublet centered at 6.13 ppm. The remaining resonances occur in several multiplets in the range 4.2–4.8 ppm.

Alanine (Ala)

Ala is a nonessential amino acid (meaning that the body can synthesize it) that has four hydrogens. The $^{3}CH_3$ and ^{2}CH hydrogens of Ala form a weakly coupled AX_3 system with a doublet at 1.47 ppm and a quartet at 3.77 ppm. Its chemical shifts exhibit pH dependence, although this falls outside the physiological range.

γ-Aminobutyric Acid (GABA)

GABA is the primary inhibitory neurotransmitter in the brain. Its altered concentrations are associated with several neurological, psychiatric, and developmental disorders. ^{1}H-MRS permits quantification of GABA in the brain in vivo[49] and the monitoring of changes during therapy.[50] GABA has three methylene groups, forming an $A_2M_2X_2$ spin system, with their resonance multiplets centered at 1.89, 2.28, and 3.01 ppm. Few publications have reported the chemical shifts and coupling constants of GABA.[5,51–53] Although we have obtained updated values,[54] use of either further optimized values[51] or a new set of published values (shown in Table 1)[53] is recommended. As these resonances overlap considerably with contributions from other more abundant metabolites, selective measurements of GABA are usually performed using spectral editing techniques (see ***Spectral Editing***).[55–59]

Ascorbate (Asc)

Asc (i.e., vitamin C) is an antioxidant,[60] an enzymatic cofactor,[61] and a neuromodulator[62] in the CNS. Asc has three hydrogen-containing groups, $^{6}CH_2$, ^{5}CH, and ^{4}CH, that give rise to two multiplets and a doublet at 3.73, 4.01, and 4.50 ppm, respectively.[15] Detection of the resonances of Asc in the brain in vivo using conventional 1-D ^{1}H NMR is difficult (although it has been reported[63]) owing to their overlap with resonances of *myo*-inositol (m-Ins), Glc, glutamate (Glu), and glutamine (Gln)[64] as well as the close proximity of some of its resonance patterns to the dominating water resonance at approximately 4.8 ppm. Hence, spectral editing methods have been utilized to improve the accuracy of detection of Asc in the brain in vivo.[64–66]

Aspartate (Asp)

Asp is an excitatory amino acid. It has $^{3}CH_2$ and ^{2}CH groups, forming an ABX spin system that gives a doublet-of-doublets from the CH group at 3.89 ppm and a pair of doublet-of-doublets from the hydrogens of the $^{3}CH_2$ group at 2.65 and 2.80 ppm.

Choline (Cho), Glycerophosphocholine (GPC), and Phosphocholine (PC)

Cho is an essential nutrient for the normal function of cells, which is mainly obtained in the form of phospholipids from the diet. The MRS-observed choline signal has a prominent singlet at 3.2 ppm that originates from glycerophosphocholine (GPC), phosphocholine (PC), and free choline. Thus, this singlet is often referred to as *total choline* (tCho). Free choline actually contributes little to the normal brain tCho signal, although it is reported to be significantly increased in pathological conditions such as brain tumors.[67] Although phosphatidylcholine is also present in the brain at larger concentrations, no signal is observed from this component due to its very short spin–spin relaxation times (T_2).[68]

Cho has 13 nonexchangeable hydrogens, nine from a trimethylamine group and four from two methylene groups. The nine hydrogens of the trimethylamine group are magnetically equivalent and give rise to the 3.19 ppm peak. The multiplets from the hydrogens of the two $^{1,2}CH_2$ groups appear at 3.50 and 4.05 ppm. The ^{14}N–H couplings between the hydrogens of the $^{1}CH_2$ and the ^{14}N atom[69] were measured to be approximately 2.6 Hz.

GPC has a total of 18 hydrogens from its glycerol (Gro) and choline moieties. The trimethyl hydrogens resonate at 3.21 ppm as a singlet. Hydrogens of the choline moiety $^{7}CH_2$ and $^{8}CH_2$ groups give a multiplet at 4.31 ppm and a pseudo-triplet at 3.66 ppm that overlaps with resonances of the glycerol ^{1}CH hydrogen, respectively. The resonances from the Gro-moiety $^{1}CH_2$ hydrogens appear at 3.61 and 3.67 ppm as a doublet-of-doublets. The remaining ^{2}CH and $^{3}CH_2$ hydrogens resonate at 3.90, 3.87, and 3.95 ppm as multiplets. The observed ^{14}N–H couplings between $^{7}CH_2$ hydrogens and ^{14}N have been measured as 2.67 Hz, and the ^{31}P–H couplings between the $^{3,7}CH_2$ hydrogens and the ^{31}P are 6.03 Hz. However, owing to the complex spectral patterns of this metabolite, the optimization procedure failed to converge and the values presented in Table 1 were derived from experimental data only.

PC, like choline, also has 13 hydrogens. A singlet seen at 3.21 ppm arises from the trimethylamine hydrogens. The hydrogens of the $^{1}CH_2$ group resonate at 4.28 ppm as a multiplet, arising from their couplings with $^{2}CH_2$ hydrogens, ^{31}P and ^{14}N. These ^{14}N–H and ^{31}P–H couplings were determined and have values of 2.7 and 6.3 Hz, respectively. The $^{2}CH_2$ hydrogens generate a pseudo-triplet at 3.64 ppm.

Citrate (Cit)

Cit is an intermediary in the citric acid or Krebs cycle and is necessary for lipid synthesis. Cit in healthy brain is not detectable by MRS methods[16] owing to its oxidation in the Krebs cycle. However, its concentration may be increased in brain tumors.[16,70–72] Cit has two magnetically equivalent CH_2 groups. Each group forms a strongly J-coupled AB spin system that gives rise to a doublet-of-doublets pattern with a second-order intensity perturbation.[15,73] The doublets are centered at 2.54 and 2.65 ppm with a scalar coupling of −15.1 Hz.[16]

Creatine (Cr) and Phosphocreatine (PCr)

Cr and PCr are compounds present in brain and muscle. Cr is also present in blood. These compounds contribute to normal cellular energy metabolism and also act as a buffer for generating ATP (see ***Cardiac MRS Studies in Rodents and Other Animals***, ***MRS in the Failing Heart: From Mice to Humans***, ***Muscle Studies by*** ^{31}***P MRS***). Both compounds contribute to the prominent 3.02 ppm singlet peak observed at ≤3 T, but contributions from these two compounds may be resolved at high magnetic fields (e.g., $B_0 = 9.4$ T[74]). The spectra of Cr and PCr are very similar, with their prominent singlet resonances from the methyl-hydrogens at 3.02 ppm differing by only 0.002 ppm and those from their methylene-hydrogens at 3.9 ppm differing by only 0.02 ppm. In addition, their NH hydrogen resonances at 6.6 ppm differ by 0.07 ppm. While PCr also has a second NH resonance at 7.3 ppm, these resonances are difficult to observe in vivo owing to their short T_2, exchange with water, and strong overlap with other resonances. Accordingly, the 3.0 and 3.9 ppm resonances detectable in vivo are typically assigned as 'total creatine'.

Ethanolamine and Phosphoethanolamine (PE)

Ethanolamine is a common alcohol moiety of phosphoglycerides, and a precursor of PE. It has two methylene groups, and these give a pair of pseudo-triplets at 3.15 and 3.82 ppm, indicating an A_2B_2 coupling network among the methylene hydrogens. Because several other phospholipids with similar structures are also present in brain, accurate characterization of these spectral regions may be difficult.

D-Glucose (Glc)

Glc is essential as a source of energy in the brain and as a precursor for a number of compounds. Glc contains seven nonexchangeable hydrogens. The ^{1}CH hydrogen exists in two different orientations relative to the ring, (axial and equatorial) resulting in α- and β-anomers. These anomers coexist in aqueous solutions, with an equilibrium concentration of 36% for the α-anomer and 64% for the β-anomer.[75] The signal from the β-D-glucose anomer is eliminated when water suppression is used.[76] The coupling pattern[14] of the α-anomer at 270 MHz 1H NMR is ABC-MNO-X, where A, B, C, M, N, O, and X correspond to ^{5}CH, ^{6}CH, $^{6'}$CH, ^{2}CH, ^{3}CH, ^{4}CH, and ^{1}CH, whereas for the β-anomer, it is AB-MNOP-X, where A, B, M, N, O, P, and X correspond to ^{6}CH, $^{6'}$CH, ^{5}CH, ^{4}CH, ^{3}CH, ^{2}CH, and ^{1}CH. The chemical shifts and coupling constants of the two anomers have been published.[14,77,78] The values presented in Table 1 are from Perkins *et al.*[14] For both the α- and β-anomers, most resonance groups occur in the range 3.2–3.88 ppm. However, differences occur for the doublet of the ^{1}CH hydrogen that appears at 5.22 ppm for the α-anomer and at 4.63 ppm for the β-anomer. Its ^{1}H-MRS spectrum consists of a complex multiplet pattern, although this collapses at low-field strengths into two multiplets centered at 3.43 and at 3.8 ppm; the latter overlaps strongly with other in-vivo metabolite signals. Direct observation of these resonances has been demonstrated in animals at higher B_o using 1-D[76] and 2-D[79] NMR methods, and the ^{1}CH resonance of α-D-glucose at 5.23 ppm has been observed in human brain at 4.0 T.[80]

Glutamate (Glu)

Glu is the most abundant amino acid in human brain and is nonessential. It is the main excitatory neurotransmitter in the CNS[81] and believed to have other functions too.[2,82] Glu has two CH_2 groups and a CH group that are strongly coupled, forming an AMNPQ spin system.[83] These groups give rise to a complex spectrum, resulting in low intensities of individual peaks despite its relative high abundance. We previously reported the spin system parameters for Glu and glutamine (Gln).[84] The signal from the single hydrogen of ^{2}CH is spread over a doublet-of-doublets centered at 3.74 ppm, while the resonances from the four hydrogens of the two methylene groups are closely grouped in the range 2.04–2.35 ppm. Overlap with resonances of GABA, NAA, and Glu complicates the unambiguous identification of their individual signal contributions in vivo, unless some type of editing or homonuclear decoupling scheme is used.[55,85,86] Cerebral Glu concentration is reported as being altered in hepatic encephalopathy[87] and in neurodegenerative[88] and neuropsychiatric[89,90] disorders.

Glutamine (Gln)

Gln is a nonessential amino acid and a precursor and storage form of Glu in astrocytes. Gln is structurally similar to Glu with two CH_2 groups and a CH group, and accordingly, its coupling pattern is similar to that of Glu. A triplet from the CH hydrogen resonates at 3.75 ppm. The multiplets from the four methylene hydrogens are closely grouped from 2.12 to 2.46 ppm. The two amide hydrogens appear at 6.82 and 7.53 ppm because they are chemically nonequivalent. In addition, the 6.82 ppm resonance has a much higher signal intensity than the 7.53 ppm resonance because these amide hydrogens exchange with water-hydrogens at different rates.[91] Separation of Glu and Gln resonances is difficult at $B_0 \leq 3$ T, and their contributions are commonly combined when analyzing in-vivo spectra and referred to as a *Glx* contribution. It has been reported that these metabolites can be separately identified in vivo at $B_0 > 4$ T.[92–94]

Glutathione (GSH)

GSH is an antioxidant and a storage form of cysteine.[95,96] It is a tripeptide of glycine (Gly), cysteine, and Glu. GSH is present in two forms in living systems: reduced (GSH) and oxidized (GSSH). It is present in the living brain almost entirely as GSH, which is primarily located in astrocytes.[96] The methylene hydrogens of the Gly moiety resonate as a singlet at 3.77 ppm. The $^{7'}CH_2$ and ^{7}CH hydrogens of the cysteine moiety form an ABX spin system with three doublet-of-doublets at 2.93, 2.98, and 4.56 ppm. The CH hydrogen of the Glu moiety gives a doublet-of-doublets at 3.77 ppm, and the CH_2 hydrogens give two separate multiplets at approximately 2.15 and 2.55 ppm. We have only optimized the coupling constants of the cysteine moiety (Table 1). Choi *et al.*[97] have refined the chemical shifts and coupling constants of hydrogens in the Glu moiety. The resonances of GSH overlap with those of Glu, Gln, GABA, Cr,

Asp, and NAA at ≤3 T. This, together with its low concentration makes GSH difficult to unambiguously detect and quantify in human brain in vivo, but recent studies have reported quantification of GSH using optimized pulse sequences.[94,97,98]

Glycerol (Gro)

Gro is the structural backbone of phospholipids. Although free Gro is embedded within membrane phospholipids, ^{1}H NMR resonances from it are not observed in normal brain. Gro is also an end product of degradation of membrane phospholipids and its increased concentration has been reported in traumatic brain injury[99] and in homogenate of bovine brain samples.[100] The spectrum of Gro consists of two doublet-of-doublets arising from two CH_2 groups and a multiplet for the CH hydrogen. The two doublet-of-doublets are centered at 3.55 and 3.64 ppm, and the multiplet is centered at 3.77 ppm. As there is considerable overlap with resonances of m-Ins in the 3.50–3.65 ppm range, care should be taken in interpreting this region for tissue homogenate studies.

Glycine (Gly)

Gly is a nonessential amino acid that functions as an inhibitory neurotransmitter and is distributed throughout the CNS. Gly has two methylene hydrogens that coresonate at 3.55 ppm. For in-vivo NMR measurements in healthy subjects, the glycine resonance overlaps with those of m-Ins, making unambiguous observation of Gly impossible at low magnetic field strengths. However, its concentration can be quantified with high confidence at 7 T.[101] The concentration of Gly is reported as being elevated in patients with hyperglycinemia[102] and brain tumors.[103,104]

Histamine

Histamine acts as a neurotransmitter and is synthesized in the brain from histidine. It is nonuniformly distributed in the brain, with highest concentrations in the hypothalamus and lowest in the cerebellum.[105] Histamine has a total of six hydrogens, two in the imidazole ring, and four in its aliphatic side chain. The resonances of the imidazole ring hydrogens depend on the solution pH: at pH = 7.0 the resonances are at 7.09 and 7.85 ppm. The aliphatic α-CH_2 hydrogens give a multiplet at 2.98 ppm, and the β-CH_2 hydrogens appear at 3.29 ppm as a triplet.

Histidine (His)

Histidine (His) is an essential amino acid (meaning that the body cannot synthesize it and therefore must acquire it from food sources) that is essential for the production of histamine. His has five hydrogens, out of which two are in a five-membered imidazole ring and the remaining three are in its aliphatic side chain. In addition, it has four water-exchangeable amine hydrogens that are normally not observed at physiological temperature. The pH-dependence of its resonances at 7.8 and 7.1 ppm,[106] enable pH measurements in vivo using ^{1}H NMR.[107] Increased brain His and histamine, especially in the hypothalamus, have been shown to occur with hepatic encepalopathy[108,109] and in histidinemia,[110] a defect of amino acid metabolism.

Homocarnosine (HCar)

Homocarnosine (HCar), a dipeptide of His and GABA, is synthesized from GABA in neurons.[111] It is believed to act as an inhibitory neuromodulator[111]. The ^{2,5}CH hydrogens in the histidine–imidazole of HCar resonate at 8.08 and 7.08 ppm. These hydrogens are also sensitive to the local chemical environment, providing another possible metabolite for measuring intracellular pH.[112] The α-hydrogen of the His moiety is the source of a six-line multiplet at 4.47 ppm and its two β-hydrogens give two doublet-of-doublets at 3.19 and 3.00 ppm. The hydrogens of the three methylene groups of the GABA moiety of HCar are very similar to those of GABA, with three multiplet groups at 2.96, 2.37, and 1.89 ppm. The spin–spin couplings of the groups contributing to the region upfield from water are complex and presently undetermined. Elevated levels of HCar in the CSF and brain tissues are characteristic of homocarnosinosis, a metabolic disorder associated with spastic paraplegia, progressive mental retardation, and retinal pigmentation[113–115]; and elevations are also reported in patients treated with an antiepileptic drug.[111]

2-Hydroxyglutarate (2-HG)

The physiological concentration of 2-HG is very low in healthy brain and is essentially not measurable using in vivo MRS. However, 2-HG may be overproduced in certain types of brain tumors (i.e., gliomas) that bear mutations in isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2)[116,117] and in two neurometabolic disorders due to genetic errors.[118–120] The 2-HG concentration can increase more than 100-fold in IDH mutant tumors in humans,[117,121] and thus, it may serve as an MRS biomarker for the IDH mutation. 2-HG has five nonexchangeable scalar-coupled hydrogens in three groups, ^{2}CH, $^{3}CH_2$, and $^{4}CH_2$ that provide multiplets at approximately 4.02, 2.25, and 1.9 ppm, respectively, at 3 T [122,123] and higher magnetic fields.[17,124] However, observation of these multiplets is challenging with conventional MRS methods,[125] owing to their overlap with resonances from NAA, Glu, Gln, and GABA. Hence, optimized acquisition parameters of a standard 1-D sequence, spectral editing, and 2-D-NMR methods have all been utilized to improve quantification of 2-HG in vivo.[123,126,127]

Myo-inositol (m-Ins)

m-Ins is a cyclic sugar alcohol and is the most predominant stereoisomeric form of inositol found in the brains of mammals.[128] The functions of m-Ins are not well understood, although it is suggested that it is an osmolyte and storage form of glucose that is essential for cell growth.[2] It has been proposed also to be a glial marker,[129] and altered levels of m-Ins have been associated with neurodegenerative,[130] neuro-inflammatory,[131] and psychiatric[132] diseases and brain injury.[133] m-Ins has six hydrogens yielding four groups of resonances. A doublet-of-doublets centered at 3.52 ppm and a triplet at 3.61 ppm are the two prominent multiplets, each corresponding to two hydrogens. A triplet at 3.27 ppm is typically hidden under Cho, and another at 4.05 ppm is typically not observed because of water suppression.

Scyllo-inositol (*s*-Ins)

s-Ins is the second most abundant stereoisomeric form of inositol that is found in the brains of mammals.[134] It has six hydrogens and gives a singlet resonance at 3.34 ppm. In humans, its concentration is reported to be closely coupled with that of m-Ins, with a 12 : 1 ratio,[134] although an elevated s-Ins concentration has been suggested to indicate cerebral pathology.[135] Its potential use for treating Alzheimer's disease is currently being explored.[136,137]

Lactate (Lac)

Lac is an end product of anaerobic glycolysis, normally present in healthy brain tissue at low concentrations[138] and therefore generally not observed by in-vivo MRS studies. The CH_3 and CH groups of Lac form an A_3X spin system and provide a doublet at 1.31 ppm for the CH_3 hydrogens and a quartet at 4.09 ppm for the CH hydrogen. The quartet is typically not completely observed in vivo owing to its close proximity to the water resonance, so Lac detection is commonly carried out via the doublet at 1.31 ppm. The presence of lipid resonances in this spectral region at short echo times (TE) complicates the observation of this doublet, so observation is commonly performed at longer TE where the relative lipid contribution is diminished. Lac concentration increases rapidly following hypoxia and its observation is therefore of great interest in pathological conditions such as stroke, trauma, or tumors.[139] Transient increases of lactate have also been observed in human brain following functional activation and hyperventilation.[140,141]

Phenylalanine (Phe)

Phe is an essential aromatic amino acid and a precursor for catecholamine synthesis. It has eight hydrogen atoms, five in the phenyl ring, and three in the aliphatic side chain. Its high-resolution NMR spectrum contains a multiplet, spread between 7.30 and 7.45 ppm from three groups of chemically and magnetically nonequivalent hydrogens in the phenyl ring. The α-hydrogen gives a doublet-of-doublets at 3.98 ppm, and the β-hydrogens give rise to two doublet-of-doublets centered at 3.11 and 3.28 ppm. Phenylalanine is reported to be elevated in phenylketonuria, an inborn error of phenylalanine metabolism; ^{1}H-MRS has been utilized to quantify Phe in patients with phenylketonuria.[142–144]

Pyruvate (Pyr)

Pyr is a keto-acid and an end product of glycolysis. It has a methyl group (CH_3) that gives a singlet resonance at 2.36 ppm. As its resonance is very close to the resonance from succinate (Suc) at 2.39 ppm, caution must be exercised before unequivocally assigning it to Pyr. Its concentration is low in healthy brain tissue and therefore generally not observed by in-vivo MRS studies. Its concentration is reported to increase in cystic lesions.[20,145,146]

Serine (Ser)

Ser is a nonessential amino acid that has ^{2}CH and $^3CH_2$ groups, forming an ABX spin system that gives three closely spaced doublet-of-doublets at 3.83, 3.94, and 3.98 ppm, respectively. However, it is challenging to detect these resonances in human brain in vivo because of its relatively low concentration and the overlap of these resonances with the $^2CH_2$ resonance of Cr. Choi *et al.*[147] have reported serine concentration in the frontal cortex utilizing a spectral editing method at 7 T.

Succinate (Suc)

Suc is an intermediate in the citric acid cycle that has lately been recognized as being associated with the inflammatory response.[148] It has two methylene groups ($^2CH_2$, $^3CH_2$) and all the four hydrogens contribute to a singlet resonance at 2.39 ppm. Its resonance overlaps with resonances originating from Glu, Gln, GABA, and Pyr under in vivo conditions. Increased Suc has been reported in brain abcesses[149] and leukoencephalopathy.[150,151]

Taurine (Tau)

Tau is an amino sulfonic acid that is reported to have a number of biological functions, including anticonvulsant, thermoregulation, modulation of neuronal excitability, and anti-tremor actions,[152] and it has been proposed as a marker of apoptosis in tumors.[153] It has four hydrogens in two adjacent methylene ($^1CH_2$, $^2CH_2$) groups, forming an AA′XX′ spin system or A_2X_2 spin system because the chemical shift separation between the nonequivalent hydrogens in each group is very small. The methylene groups provide two triplet resonances at 3.25 and 3.42 ppm in ^{1}H-MRS spectra. At lower field strengths, these resonances overlap with resonances from Cho, m-Ins, and Glc. Special MRS acquisition techniques have been demonstrated to improve observation of Tau.[55,154]

Threonine (Thr)

Thr is an essential amino acid that has a CH_3 and two CH groups, forming an A_3MX spin system. The ^{2}CH hydrogen gives a doublet at 3.58 ppm, and the ^{3}CH hydrogen resonates at 4.25 ppm to give an eight-line multiplet because of its coupling with the ^{2}CH and CH_3 hydrogens. The $^4CH_3$ hydrogens give a doublet at 1.32 ppm because of their coupling with the ^{3}CH hydrogen.

Tryptophan (Trp)

Trp is an essential amino acid and is a precursor to niacin, serotonin, and melatonin.[155,156] Trp has eight hydrogens. The ^{2}CH hydrogen gives a singlet at 7.31 ppm, and the four phenyl ring hydrogens give two multiplets centered at 7.20 and 7.28 ppm. The three aliphatic side chain hydrogens give three doublet-of-doublets between 3.29 and 4.05 ppm. Both lower and higher levels of brain Trp are associated with neuropsychiatric and other disorders.[156–159]

Tyrosine (Tyr)

Tyr is a nonessential neutral amino acid that can be synthesized in the body from Phe. It is a precursor to neurotransmitters (dopamine, epinephrine, and norepinephrine) and hormones (triiodothyronine and thyroxine). Tyr has seven water nonexchangeable hydrogens, four from the phenyl ring, and three from its aliphatic side chain. The four phenyl ring hydrogens give a multiplet spread between 6.89 and 7.19 ppm. The CH and CH_2 aliphatic hydrogens form an ABX spin system and give three doublet-of-doublets between 3.04 and 3.93 ppm.

Valine (Val)

Val, an essential amino acid, has eight hydrogens present in two CH_3 and two CH groups. The hydrogens of the CH_3 groups provide two doublets, which overlap with resonances of leucine and isoleucine in the 0.95–1.05 ppm region. For in-vivo studies, this pseudo triplet appears as a single broad line that is difficult to distinguish from macromolecular resonances in this spectral region.[160] A complex multiplet appears at 2.26 ppm from the ^{3}CH hydrogen that overlaps with resonances of GABA and Glu. The ^{2}CH hydrogen gives a doublet at 3.60 ppm that overlaps with resonances of m-Ins. Hypervalinemia[161] and brain abscess[149,162] are some of the diseases or conditions in which Val level is reported to be elevated.

Conclusions

In this article, a detailed compilation of published ^{1}H NMR spectral parameters (i.e., δ, J) of 38 low-molecular-weight metabolites found in mammalian brain at physiologically normal or pathological conditions has been presented. The values for most of the metabolites have been obtained under physiologically normal conditions (see section titled 'Experimental Conditions'). As noted at the outset, the spectral parameters reported here should find use for identifying metabolites from spectra acquired in vivo, for simulating composite spectra to facilitate spectral fitting, and for the optimization of sequence parameters, e.g., for improving the quality of acquired spectra, or for spectral editing. However, it is important to recognize that the spectral parameters of metabolites may vary in vivo owing to differences in the local cellular environment, as compared to the phantom solutions from which the current data were derived. Differences in pH, temperature, ionic strength, binding of metabolite groups with membranes, solvent–isotope interactions (e.g., dipolar coupling in studies involving D_2O), magnetic field strength, effects of magnetization transfer on signal amplitudes, the relative populations of different configurational isomers (i.e., L- and D-isomers) and rotomers, and the variations of line-widths due to differences in relaxation rates between molecular groups are all known factors that can confound peak detection and assignment.

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Biographical Sketch

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