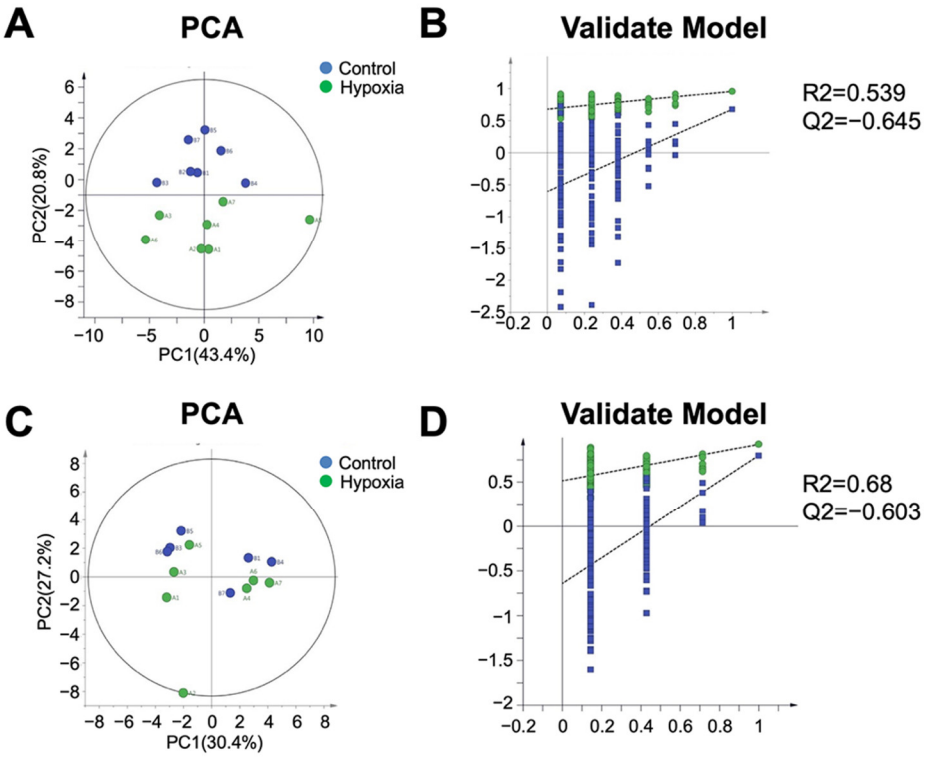
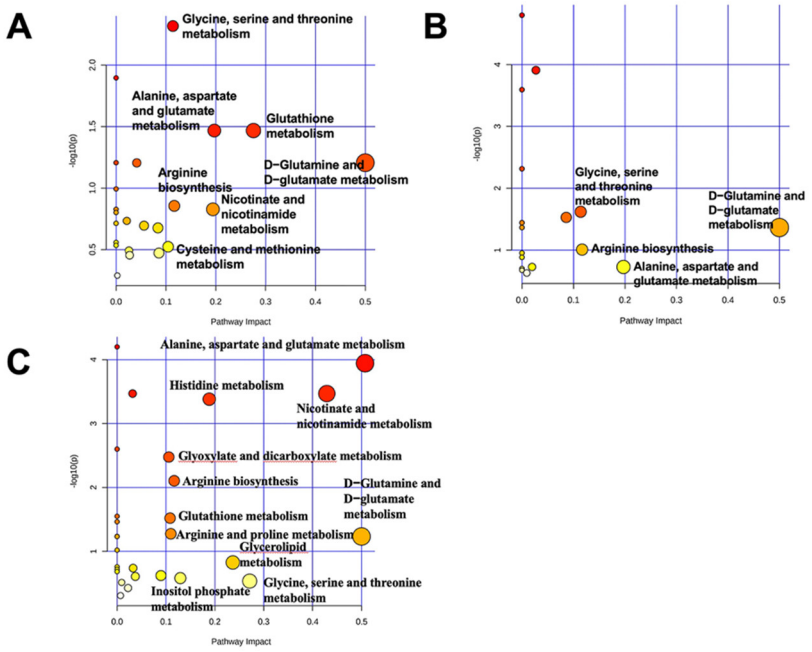
# Supplementary Material




**Supplementary Figure S1. PLS-DA score plots and validation plots of 1D $^{1}$H NMR data for aqueous extracts derived from the kidney and brain of mice.** (A, B) Hypoxia kidney *vs.* normoxic kidney; (C, D) Hypoxia brain *vs.* normoxic brain. The PLS-DA models were cross-validated to evaluate the robustness by a random permutation test (200 cycles). n=6-7 mice/group.




**Supplementary Figure S2. Significantly altered metabolic pathways associated with the hypoxia mice relative to normoxic mice.** (A) Hypoxia liver *vs.* normoxic liver; (B) Hypoxia kidney *vs.* normoxic kidney; (C) Hypoxia brain *vs.* normoxic brain. Based on the significant metabolites, significantly altered metabolic pathways were identified with $p$ values < 0.005, using the Pathway Analysis module provided by MetaboAnalyst 4.0.

**Supplementary Table S1. Comparison of metabolite levels between two groups of mice based on relative integrals calculated from the 1D $^{1}$H NMR spectra of liver.**

| Metabolites | Mean ± standard deviation | | Hypoxia |
|---|---|---|---|
| | Normoxic liver | Hypoxic liver | *vs.* Normoxia |
| 3-Hydroxyisobutyrate | 0.201±0.034 | 0.295±0.072 | * |
| Acetate | 0.512±0.118 | 0.519±0.1266 | NS |
| Alanine | 3.134±0.408 | 3.612±0.314 | * |
| Asparagine | 0.225±0.029 | 0.220±0.026 | NS |
| Aspartate | 0.089±0.016 | 0.090±0.015 | NS |
| Betaine | 1.372±0.217 | 2.219±0.617 | * |
| Choline | 2.183±0.214 | 1.443±0.405 | ** |
| Creatine phosphate | 0.354±0.059 | 0.363±0.041 | NS |
| Dimethylamine | 0.078±0.010 | 0.068±0.005 | * |
| Ethanol | 0.512±0.132 | 0.594±0.410 | NS |
| Fumarate | 0.119±0.029 | 0.135±0.034 | NS |
| Glucose | 4.493±1.335 | 5.442±0.967 | NS |
| Glutamate | 1.149±0.213 | 1.481±0.206 | * |
| Glutamine | 1.761±0.234 | 1.932±0.312 | NS |
| Glutathione | 0.587±0.158 | 0.404±0.073 | * |
| Histamine | 0.131±0.020 | 0.131±0.015 | NS |
| Inosine | 0.280±0.032 | 0.230±0.030 | * |
| Isoleucine | 0.345±0.064 | 0.339±0.048 | NS |
| Lactate | 10.956±0.820 | 9.267±1.091 | * |
| Leucine | 1.501±0.267 | 1.591±0.254 | NS |
| Malate | 0.287±0.038 | 0.326±0.071 | NS |
| Methionine | 0.278±0.035 | 0.658±0.244 | ** |
| Methylguanidine | 0.031±0.005 | 0.025±0.007 | NS |
| Niacinamide | 0.173±0.020 | 0.147±0.017 | * |
| N-Methylhydantoin | 0.179±0.025 | 0.160±0.013 | NS |
| Phenylalanine | 0.174±0.029 | 0.173±0.027 | NS |
| Lysine | 0.826±0.123 | 0.866±0.113 | NS |
| sarcosine | 0.114±0.023 | 0.110±0.018 | NS |
| Succinate | 0.741±0.151 | 0.621±0.223 | NS |
| Trimethylamine | 0.102±0.023 | 0.085±0.009 | NS |
| Tyrosine | 0.180±0.034 | 0.163±0.023 | NS |
| Valine | 0.558±0.101 | 0.599±0.095 | NS |
| β -Alanine | 0.431±0.051 | 0.471±0.054 | NS |
| Acetone | 0.047±0.007 | 0.061±0.013 | * |
| N,N-Dimethylglycine | 0.029±0.006 | 0.023±0.003 | * |
| Ornithine | 0.483±0.066 | 0.484±0.041 | NS |
| Glycine | 1.379±0.167 | 1.231±0.120 | NS |
| Ascorbate | 0.213±0.029 | 0.147±0.030 | ** |
| Mannose | 0.188±0.060 | 0.175±0.049 | NS |

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|---|---|---|---|
| Glycerophosphocholine | 2.469±1.082 | 1.550±0.484 | NS |
| uridine | 0.300±0.065 | 0.175±0.028 | ** |
| uracil | 0.053±0.013 | 0.057±0.008 | NS |
| Adenosine 5'-monophosphate | 0.099±0.036 | 0.065±0.038 | NS |
| Dihydrouracil | 0.483±0.053 | 1.022±0.331 | ** |

Note: NS, $p > 0.05$; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$ for hypoxia liver *vs.* normoxic liver as determined the Student's t test. Red and blue colors denote that the difference is positive (i.e. A was increased compared to B) and negative, respectively.

**Supplementary Table S2. Comparison of metabolite levels between two groups of mice based on relative integrals calculated from the 1D $^{1}$H NMR spectra of kidney.**

| Metabolites | Mean ± standard deviation | | Hypoxia |
|---|---|---|---|
| | Normoxic kidney | Hypoxic kidney | *vs.* Normoxia |
| Threonine | 0.458±0.502 | 0.431±0.095 | NS |
| O-Phosphocholine | 1.364±0.181 | 0.978±0.249 | ** |
| Pantothenate | 0.080±0.006 | 0.119±0.042 | NS |
| Isoleucine | 0.249±0.039 | 0.317±0.061 | * |
| Leucine | 1.108±0.193 | 1.398±0.282 | * |
| Valine | 0.433±0.072 | 0.576±0.119 | * |
| 3-Hydroxyisobutyrate | 0.028±0.004 | 0.042±0.008 | ** |
| Ethanol | 0.176±0.044 | 0.164±0.030 | NS |
| 3-Hydroxybutyrate | 0.112±0.016 | 0.147±0.023 | ** |
| Lactate | 6.205±0.948 | 6.822±1.751 | NS |
| 2-Phenylpropionate | 0.154±0.019 | 0.172±0.028 | NS |
| Alanine | 1.211±0.166 | 1.482±0.301 | NS |
| Acetate | 0.390±0.108 | 0.367±0.082 | NS |
| Glutamate | 2.938±0.561 | 2.297±0.496 | * |
| Methionine | 0.310±0.032 | 0.371±0.073 | NS |
| Succinate | 0.570±0.112 | 0.543±0.157 | NS |
| 5,6-Dihydrouracil | 0.378±0.037 | 0.452±0.080 | NS |
| Aspartate | 0.217±0.022 | 0.214±0.041 | NS |
| Asparagine | 0.196±0.030 | 0.216±0.044 | NS |
| Trimethylamine | 0.068±0.020 | 0.054±0.012 | NS |
| Dimethylamine | 0.049±0.006 | 0.049±0.001 | NS |
| N,N-Dimethylglycine | 0.031±0.005 | 0.045±0.010 | ** |
| N-Methylhydantoin | 0.020±0.003 | 0.022±0.003 | NS |
| Creatine phosphate | 0.759±0.155 | 1.028±0.218 | * |
| Creatinine | 0.164±0.020 | 0.196±0.035 | NS |
| N,N-Dimethylformamide | 0.111±0.012 | 0.124±0.021 | NS |
| Malonate | 0.199±0.027 | 0.221±0.061 | NS |
| Ethanolamine | 0.663±0.083 | 0.681±0.163 | NS |
| Choline | 7.272±0.706 | 5.958±1.616 | NS |
| Cystine | 0.406±0.063 | 0.338±0.073 | NS |
| Betaine | 3.096±0.547 | 3.995±0.789 | * |
| sn-Glycero-3-phosphocholine | 2.553±0.473 | 2.189±0.468 | NS |
| myo-Inositol | 2.594±0.355 | 2.481±0.488 | NS |
| Taurine | 4.160±0.561 | 3.872±0.951 | NS |
| Methanol | 1.642±0.844 | 0.903±0.488 | NS |
| Glycine | 2.569±0.422 | 2.176±0.460 | NS |
| Glycerol | 1.263±0.165 | 1.255±0.353 | NS |
| Glucose | 0.361±0.116 | 0.422±0.172 | NS |
| Inosine | 0.535±0.046 | 0.537±0.108 | NS |

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|---|---|---|---|---|
| Mannose | | 0.063±0.018 | 0.066±0.017 | NS |
| Glucuronate | | 0.029±0.005 | 0.039±0.021 | NS |
| Allantoin | | 0.043±0.006 | 0.061±0.015 | * |
| Uracil | | 0.089±0.012 | 0.095±0.021 | NS |
| Uridine | | 0.237±0.022 | 0.251±0.058 | NS |
| Nicotinamide dinucleotide | adenine | 0.011±0.001 | 0.012±0.002 | NS |
| Fumarate | | 0.031±0.005 | 0.030±0.005 | NS |
| Tyrosine | | 0.174±0.029 | 0.214±0.043 | NS |
| Histamine | | 0.064±0.010 | 0.075±0.018 | NS |
| Anserine | | 0.011±0.004 | 0.008±0.002 | NS |
| Phenylalanine | | 0.392±0.070 | 0.482±0.112 | NS |
| Imidazole | | 0.032±0.003 | 0.036±0.009 | NS |
| Niacinamide | | 0.137±0.015 | 0.143±0.030 | NS |
| Tryptophan | | 0.019±0.004 | 0.024±0.006 | NS |
| Xanthine | | 0.109±0.013 | 0.111±0.030 | NS |
| 4-Pyridoxate | | 0.072±0.012 | 0.078±0.042 | NS |
| 3-Methylxanthine | | 0.015±0.004 | 0.018±0.003 | NS |
| Adenine | | 0.662±0.123 | 0.696±0.133 | NS |
| Formate | | 0.008±0.002 | 0.008±0.001 | NS |
| Inosinic acid | | 0.011±0.002 | 0.011±0.003 | NS |

Note: NS, $p > 0.05$; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$ for hypoxic kidney *vs.* normoxic kidney as determined by the Student's t test. Red and blue colors denote that the difference is positive (i.e. A was increased compared to B) and negative, respectively.

**Table S3. Comparison of metabolite levels between two groups of mice based on relative integrals calculated from the 1D $^{1}$H NMR spectra of brain.**

| Metabolites | Mean ± standard deviation | | Hypoxia |
|---|---|---|---|
| | Normoxic brain | Hypoxic brain | *vs*. Normoxia |
| Isoleucine | 0.071±0.005 | 0.082±0.009 | * |
| Leucine | 0.255±0.019 | 0.298±0.028 | ** |
| Valine | 0.127±0.005 | 0.134±0.016 | NS |
| 3-Hydroxyisobutyrate | 0.039±0.005 | 0.039±0.006 | NS |
| Ethanol | 0.541±0.228 | 0.456±0.216 | NS |
| 3-Hydroxybutyrate | 0.119±0.029 | 0.148±0.032 | NS |
| Lactate | 9.252±1.322 | 7.779±1.010 | NS |
| Alanine | 0.650±0.086 | 0.655±0.074 | NS |
| 4-Aminobutyrate | 2.324±0.213 | 2.678±0.297 | * |
| Acetate | 0.667±0.101 | 0.769±0.116 | NS |
| N-Acetylaspartate | 2.571±0.177 | 2.584±0.190 | NS |
| Glutamate | 2.790±0.131 | 3.173±0.199 | ** |
| Glutamine | 1.686±0.165 | 1.545±0.125 | NS |
| Succinate | 0.171±0.042 | 0.232±0.047 | * |
| Aspartate | 0.648±0.259 | 0.739±0.047 | ** |
| Creatine phosphate | 4.693±0.184 | 4.765±0.441 | NS |
| Taurine | 3.292±0.350 | 3.122±0.325 | NS |
| O-Phosphocholine | 0.585±0.081 | 1.111±0.140 | *** |
| sn-Glycero-3-phosphocholine | 1.123±0.076 | 1.215±0.127 | NS |
| Myo-Inositol | 2.072±0.072 | 2.240±0.132 | * |
| Caffeine | 0.182±0.262 | 0.160±0.037 | NS |
| Glycine | 0.798±0.060 | 0.683±0.071 | * |
| Glycerol | 0.824±0.059 | 0.746±0.064 | * |
| Ascorbate | 0.277±0.019 | 0.277±0.029 | NS |
| Glucose | 0.008±0.006 | 0.005±0.003 | NS |
| Uracil | 0.021±0.003 | 0.024±0.003 | NS |
| Uridine | 0.052±0.001 | 0.050±0.003 | NS |
| Guanosine triphosphate | 0.020±0.002 | 0.023±0.002 | * |
| Inosine | 0.304±0.016 | 0.312±0.017 | NS |
| Fumarate | 0.059±0.009 | 0.061±0.004 | NS |
| Tyrosine | 0.063±0.005 | 0.064±0.007 | NS |
| Histamine | 0.015±0.002 | 0.019±0.002 | * |
| Adenosine | 0.015±0.002 | 0.018±0.005 | NS |
| Inosinic acid | 0.023±0.005 | 0.028±0.008 | NS |
| Formate | 0.004±0.001 | 0.006±0.001 | *** |
| Adenine | 0.120±0.013 | 0.1189±0.026 | NS |

| | | | |
|---|---|---|---|
| Adenosine monophosphate | 0.023±0.005 | 0.028±0.008 | NS |
| Niacinamide | 0.056±0.002 | 0.062±0.004 | ** |
| Nicotinamide adenine dinucleotide | 0.003±0.002 | 0.006±0.001 | ** |

Note: NS, $p > 0.05$; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$ for hypoxic brain *vs*. normoxic brain as determined by the Student's t test. Red and blue colors denote that the difference is positive (i.e. A was increased compared to B) and negative, respectively.