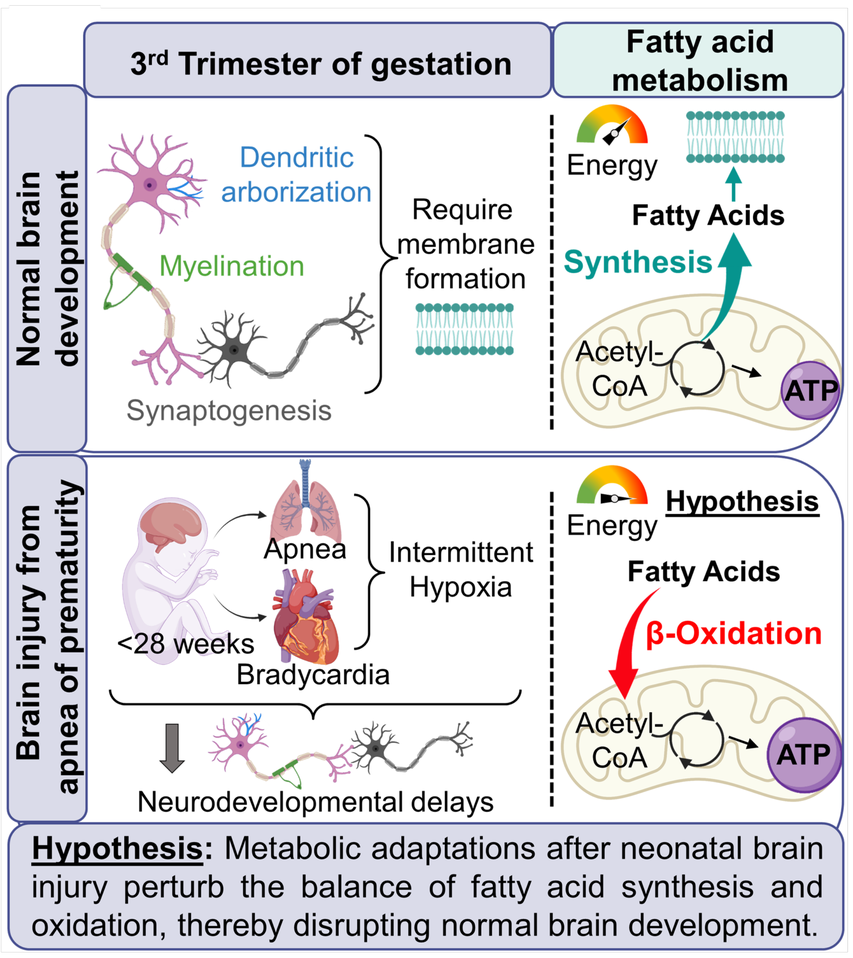
Adaptations of Fatty Acid Metabolism After Neonatal Brain Injury

Regina F. Fernandez[1,2], Ann B. Moser[1], Susanna Scafidi[3], and Joseph Scafidi[1,2]

[1]Hugo W. Moser Research Institute, Kennedy Krieger Institute, Baltimore, MD. [2]Department of Neurology and [3]Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, Baltimore, MD

Graphical Abstract



Hypothesis: Metabolic adaptations after neonatal brain injury perturb the balance of fatty acid synthesis and oxidation, thereby disrupting normal brain development.

Experimental Design

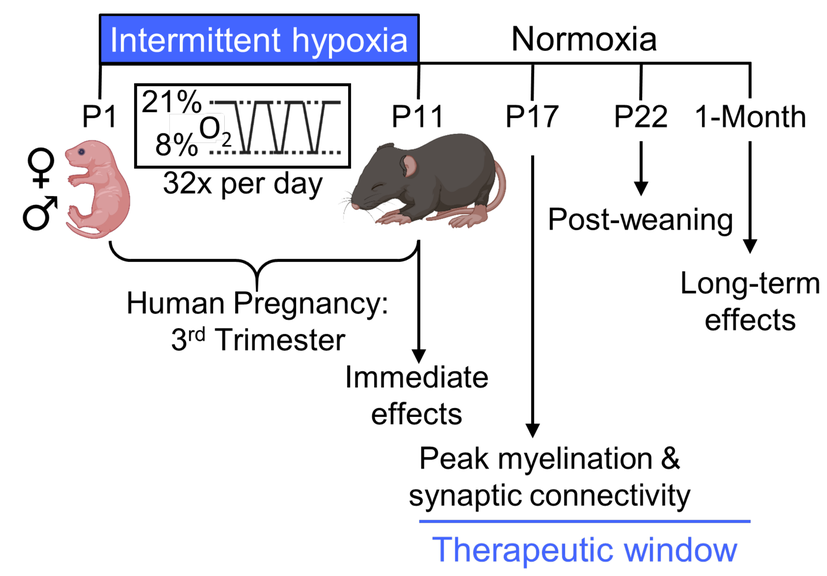


Figure 1. Intermittent hypoxia (IHx) as a model for neonatal brain injury from apnea of prematurity. Postnatal day (P). Data analysis for all experiments: *p<0.05 Unpaired Mann-Whitney 2-tailed test unless otherwise stated.

Behavioral Outcomes

Figure 2. 1-Month IHx mice display sensorimotor and cognitive recognition memory deficits. (A) Number of foot slips on the inclined beam walking task. **(B)** Recognition index on the novel object recognition test after a 12-hour delay. n=5-6; *p<0.05.

Scan here for references, methods, and **more data**

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Proteomics

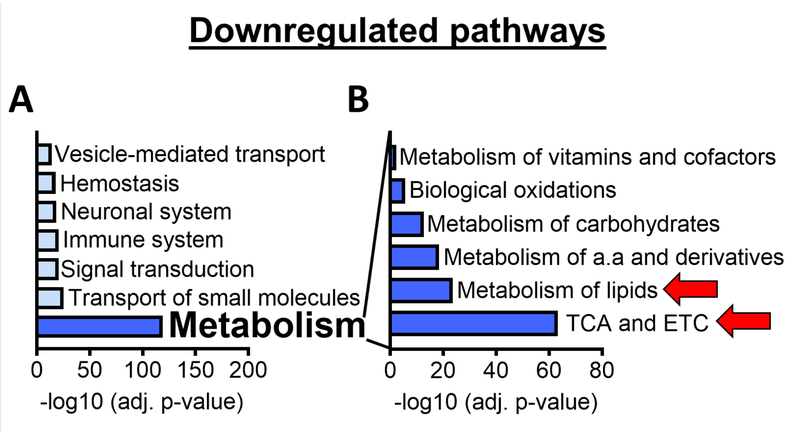

Figure 3. Unbiased proteomics analysis from P11 male hippocampus after IHx. (A) Pathway analysis of downregulated proteins (B) Within the metabolism pathway, TCA cycle, ETC, and lipid metabolism were highly enriched. n=4; *p<0.05.

Fatty Acid Levels

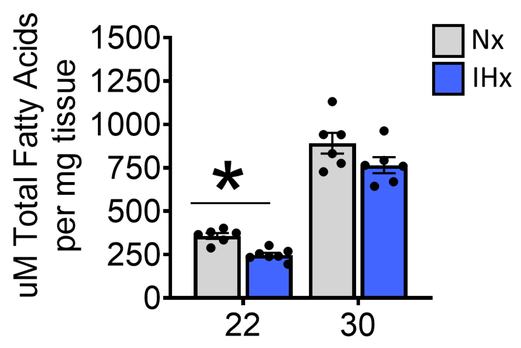

Figure 4. Total fatty acids were decreased at P22 but not at P30 in the IHx-injured mice. Fatty acids were measured by GC-MS; n=6-7; *p<0.05.

De Novo Lipogenesis

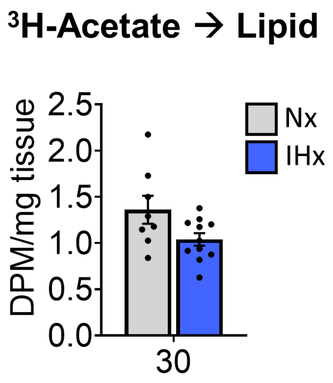

Figure 5. Brain ^{3}H-Acetate incorporation into lipids is not different from Nx at P30. *Ex-vivo* hippocampal acetate incorporation (0.1uCi). n=8-11

Fuel Dependency

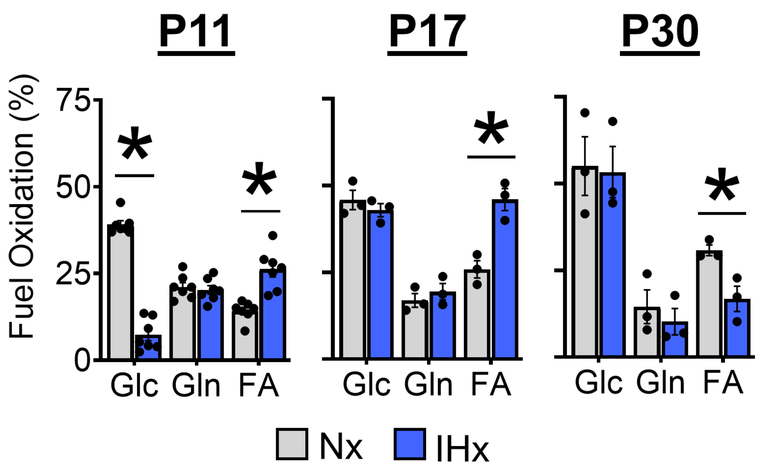

Figure 6. Dependency on fatty acids for energy is increased at P11 and P17. SeahorseXF Mito Fuel Flex test performed in single cell suspensions from hippocampus. Glucose (Glc), glutamine (Gln), and fatty acid (FA) n=3-7 mice; *p<0.05.

Substrate Oxidation

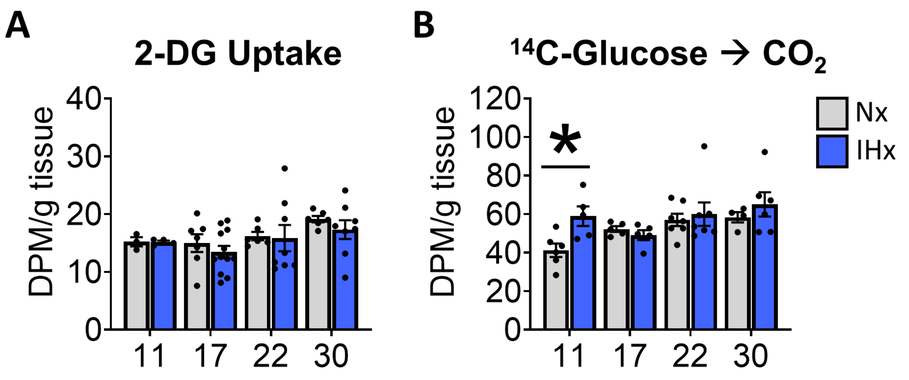

Figure 7. Brain ^{14}C-glucose oxidation is increased only at P11. (A) *In-vivo* 2-Deoxyglucose (2-DG) uptake and (B) *ex-vivo* hippocampal U-^{14}C-glucose oxidation (0.1 uCi) ; n=6-8; *p<0.05.

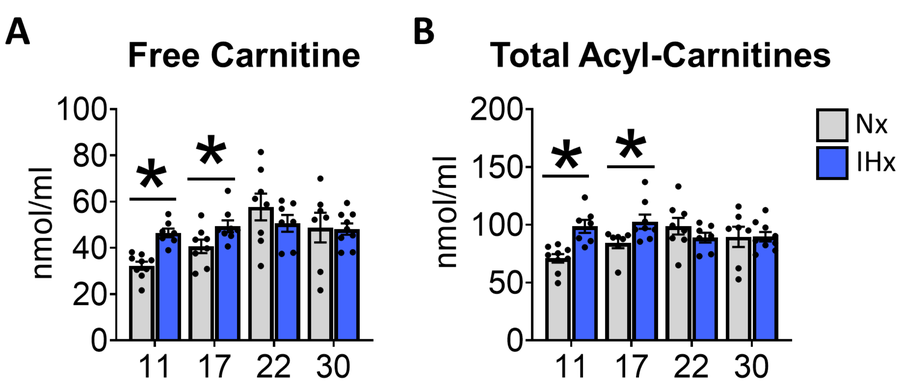

Figure 8. Hippocampal acyl-carnitines provide evidence of increased fatty acid oxidation at P11-17. (A) Free carnitine and **(B)** total acyl-carnitines measured by LC-MS/MS. n=7-8; *p<0.05.

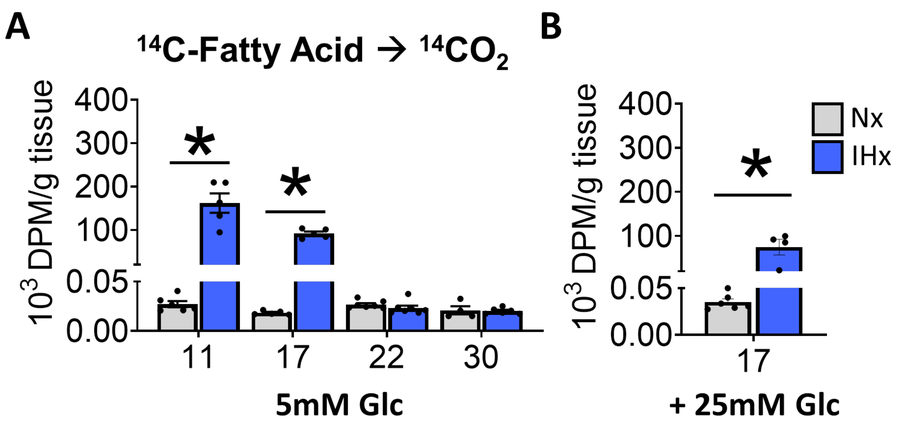

Figure 9. Brain ^{14}C-fatty acid oxidation is increased at P11 and P17 and remained high despite additional glucose supplementation. *Ex-vivo* hippocampal 1-^{14}C-Oleic acid oxidation (0.12 uCi) in media with **(A)** 5 or **(B)** 25mM glucose. n=8; *p<0.05.

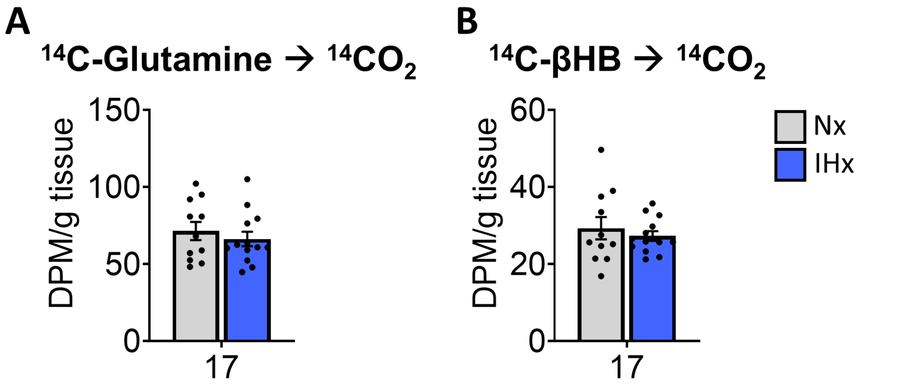

Figure 10. Brain ^{14}C-glutamine and ^{14}C-βHB oxidation is unchanged after IHx at P17. *Ex-vivo* hippocampal substrate oxidation (0.2uC). n=11-13; *p<0.05.

Conclusions: Our data showed that after IHx, the brain increases fatty acid oxidation to meet immediate metabolic demands. These metabolic adaptations contribute to the perturbed brain development evident in children born extremely preterm.

Future directions: Determine the effect of IHx on brain *de novo* fatty acid synthesis and on lipid composition.