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Hippocampal Glucose Transport and Oxidation in Response to Disrupted Blood Flow in an Aging Rat Model of Heart Failure.

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It is well established that cardiovascular pathologies are primary risk factors for the development neurodegenerative diseases, and cardiovascular disease may facilitate neurodegenerative processes by predisposing neurons to impaired substrate metabolism due to chronic hypoperfusion. However, hypoperfusion may stem either from 1) a decrease in perfusion caused by a limitation in cerebral blood flow or 2) from mechanical damage resulting from higher cerebral blood flow and/or pulsatility. However, it remains poorly understood whether these distinct hypoperfusion mechanisms differentially affect substrate metabolism in the brain. **Purpose:** Address whether the transport and oxidation of glucose in the brain is differentially affected by high (right) and low (left) cerebral blood. **Methods:** 4-week-old male and female Sprague-Dawley rats underwent transverse aortic constriction (TAC, n=13) or control (SHAM, n=18) surgeries. Rats were sacrificed at 44 weeks, and right and left hippocampal samples were isolated: ~11mg was homogenized in respiration media and the remainder was homogenized in RIPA buffer. Hippocampal mitochondrial oxygen consumption rate was measured via liquid-phase respiration and a substrate-uncoupler-inhibitor titration (SUIT) protocol. Protein expression of glucose transporters (GLUT1, GLUT3) and markers of mitochondrial quality control (HSP-60, FIS1, DRP1, MFN2, and L-, S-OPA1) were measured via western blot. A two-way ANOVA was used to determine the effects of Condition (TAC v SHAM) and Hemisphere (right v left) on mitochondrial respiration and protein expression of target proteins. **Results:** There was a significant main effect of Hemisphere for complex I-linked respiration (p=0.02), with simple main effects revealing TAC animals have higher respiration in the left (low flow) hippocampus when compared to the right (high flow) (4.1 ± 0.22 v 3.4 ± 0.21 nmol/ml/min, p =0.04). There was a significant interaction effect (p = 0.04) in complex II-linked respiration and simple main effects showed lower (p = 0.015) complex II-linked respiration in the right hippocampus compared to the left (3.4 ± 0.27 v 2.5 ± 0.25 nmol/ml/min, p =0.015) in TAC but not SHAM. Lastly, TAC animals had higher expression of S-OPA1 and HSP-60 when compared to SHAM (1.09 ± 0.07 v 0.89 ± 0.06 AU, p = 0.024, 0.97 ± 0.09 v 0.71 ± 0.05 AU, p = 0.008, respectively). **Conclusion**: Hypoperfusion from high pulsatile blood flow impairs hippocampal respiration more than hypoperfusion from low cerebral blood flow and upregulation of mitochondrial quality control markers in TAC (compared to SHAM) is similar regardless of cause of hypoperfusion**. Novelty:** The mechanisms behind brain hypoperfusion may induce specific brain metabolic changes during cardiovascular disease, and may help better understand the intersection between cardiovascular disease and neurodegeneration.

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