Flow-metabolism Uncoupling and Extended Longevity as Observed with a Transgenic Mice Model

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Introduction: Mitochondria are the predominate source (> 98%) of energy production in mammals, yielding ATP through oxidative phosphorylation of glucose. Since brain has the highest energy demands among all organs, the cerebral metabolic rates of glucose (CMRglc) and oxygen (CMRO2) are quite high at baseline (1). Because glucose and oxygen are mainly delivered by the circulation, CMRglc, CMRO2 and cerebral blood flow (CBF) are constantly observed tightly coupled with one another at resting state in normal conditions (1). On the other hand, numerous studies have shown that CMRglc, CMRO2 and CBF decline with age and do so in an accelerated, uncoupled manner in neurodegenerative disorders (2, 3). As a result, mitochondrial integrity is generally viewed as being highly associated with lifespan and healthspan, with preserved mitochondrial function (i.e. preserved CMRO2 level) being indicative of healthy aging.

Recent studies, however, indicate that longevity can be increased by reduced mitochondrial function (thus reduced oxygen consumption). Specifically, increased lifespan is observed in mice with a mitochondrial mutation in an assembly protein (Surf1 knockout; Surf1−/−) for electron-transport chain complex IV, which results in a reduction in the level of cytochrome c oxidase (COX) (4). In these mice, oxygen consumption in fibroblasts has been observed to decrease approximately 40% (preliminary data from our lab). Nonetheless, whether flow and metabolism remain coupled or whether the metabolic pathway is shifted to glycolytic metabolism is unknown. The purpose of the study, therefore, is to use the multi-meter neuroimaging methods (e.g. MRI and PET) to determine the basal CBF and CMRglc and the flow-metabolism coupling relationship in the Surf1−/− mice.

Material and Methods: Wild type (WT) and Surf1−/− mice (N = 2, respectively) were used for the study. CBF MRI was acquired using the Arterial spin labeling (ASL) technique at a horizontal 11.7T Biospec system (Bruker BioSpin, Ettlingen, Germany). A small circular surface coil (ID = 1.1 cm) was placed on top of the mouse head. A circular labeling coil (ID = 0.8 cm), built into the cradle, was placed at the heart position for continuous ASL. The two coils will be positioned parallel to each other, separated by 2 cm from center to center, and will be actively decoupled. Paired images were acquired in an interleaved fashion with FOV = 12.8 × 12.8 mm², matrix = 64 × 64, slice thickness = 1 mm, 9 slices, labeling duration = 2100 ms, TR = 3000 ms per segment, and TE = 15 ms. CMRglc was determined with the 18F-FDG concentration in the mouse brain using PET. The mouse was placed on the bed of the microPET scanner (Siemens Medical Systems). 18F-FDG at a dose of 0.39 MBq/g of body weight dissolved in 1 cc of physiologic saline was injected through the tail vein, and emission data was then acquired for 20 min after 40 min of injection. Data Analysis: ASL image analysis employed codes written in Matlab and STIMULATE software (University of Minnesota). Blood-flow signals (SCBF) in the brain with intensity in unit of mL/g/min was calculated using SCBF = α/T1 ([SNL-SL]/[SL+(2α-1)SNL]), where SNL and SL are signal intensities of the non-labeled and labeled images, respectively. α is the labeling efficiency, T1 is the water tissue-blood partition coefficient, and T1 is the longitudinal relaxation rate of the blood. FDG images were analyzed with the Mango image analysis software (http://ric.uthscsa.edu/mango). CMRglc was obtained using the mean standardized uptake value (SUVmean) equation: [PETuptake (mCi)/brain’s weight (g)] / [injected dose (mCi) / mouse’s weight (g)]; where PETuptake is the tissue radioactivity concentration obtained from the PET FDG images. Student t test was used to determine the statistical significance of the CBF and CMRglc between the WT and the Surf1−/− mice.

Results: The CBF and CMRglc values and their relative changes between the WT and the Surf1−/− mice are listed in Table 1. The basal CBF of the Surf1−/− mice was observed 20% lower than that of the WT (P < 0.05). In contrast, the cerebral glucose uptake of the Surf1−/− mice increased 85% compared to the WT (P < 0.001). Maps of the CBF and glucose uptake of a WT and a Surf1−/− mice are shown in Figure 1 and Figure 2, respectively.

Discussion: Our results demonstrated that the basal flow and metabolism were uncoupled in the Surf1−/− mice. The data further demonstrated that the metabolic pathway of the Surf1−/− mice has shifted from oxidative to glycolytic metabolism (with decreased oxygen consumption, but with increased glucose uptake). It is thus speculated that the lifespan of the Surf1−/− mice is extended due to the metabolic pathway shifting. However, whether brain function can be preserved with age and whether neuroprotection can be facilitated due to this metabolic pathway-shifting remain unclear. Future studies are needed to determine the relationship between the flow-metabolism uncoupling, cognitive integrity and healthspan in these transgenic mice. In conclusion, extended longevity-associated flow-metabolism uncoupling was observed with neuroimaging in the study. With the novel mice model and the concurrent MRI-PET measurements, it our goal to further study the impact of mitochondrial function in longevity and in neurodegenerative disorders.

Table 1. The CBF and CMRglc values and their relative changes between the WT and the Surf1−/− mice

![Figure 1](image1.png)  
![Figure 2](image2.png)  

References: (1) Raichle et al., PNAS 2001; 98:676-682.  
(3) Powers et al., PNAS 2007; 104:2945-2949.  