Ecology, physiology and behaviour

Fuel source shift or cost reduction: context-dependent adaptation strategies in closely related *Neodon fuscus* and *Lasiopodomys brandtii* against hypoxia

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Oxygen is essential for most life forms. Insufficient oxygen supply can disrupt homeostasis and compromise survival, and hypoxia-induced cardiovascular failure is fatal in many animals, including humans. However, certain species have adapted and evolved to cope with hypoxic environments and are therefore good models for studying the regulatory mechanisms underlying responses to hypoxia. Here, we explored the physiological and molecular responses of the cardiovascular system in two closely related hypoxia-adapted species with different life histories, namely, Qinghai voles (*Neodon fuscus*) and Brandt's voles (*Lasiopodomys brandtii*), under hypoxic (10% O_2 for 48 h) and normoxic (20.9% O_2 for 48 h) exposure. Kunming mice (*Mus musculus*) were used for comparison. Qinghai voles live in plateau areas under hypoxic conditions, whereas Brandt's voles only experience periodic hypoxia.

Histological and hematological analyses indicated a strong tolerance to hypoxia in both species, but significant cardiac tissue damage and increased blood circulation resistance in mice exposed to hypoxia. Comparative transcriptome analysis revealed enhanced oxygen transport efficiency as a coping mechanism against hypoxia in both *N. fuscus* and *L. brandtii*, but with some differences. Specifically, *N. fuscus* showed up-regulated expression of genes related to accelerated cardiac contraction and angiogenesis, whereas *L. brandtii* showed significant up-regulation of erythropoiesis-related genes. Synchronized up-regulation of hemoglobin synthesis-related genes was observed in both species. In addition, differences in cardiometabolic strategies against hypoxia were observed in the rodents. Notably, *M. musculus* relied on adenosine triphosphate (ATP) generation via fatty acid oxidation, whereas *N. fuscus* shifted energy production to glucose oxidation under hypoxic conditions and *L. brandtii* employed a conservative strategy involving down-regulation of fatty acid and glucose oxidation and a bradycardia phenotype. In conclusion, the cardiovascular systems of *N. fuscus* and *L. brandtii* have evolved different adaptation strategies to enhance oxygen transport capacity and conserve energy under hypoxia. Our findings suggest that the coping mechanisms underlying hypoxia tolerance in these closely related species are context dependent.