Intermittent chronic cold exposure causes skeletal muscle atrophy and impairs aerobic physical performance without changing PGC-1a in mice

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Abstract

Introduction: Antarctica is considered the coldest and driest continent, thus, researchers and militaries experience severe thermal stress which may cause skeletal muscle disorders (*e.g.,* pain and atrophy) deteriorating their physical capacity and, consequently, their labor activities. In animal models, cold exposure (CE) for 24h/day induces muscle atrophy, through a reduction in Akt and FoxO phosphorylation, leading

to an increase in proteolysis by the ubiquitin-proteasome system (UPS). However, this model of continuous chronic CE may cause sleep deprivation and, as a result, muscle loss. To avoid the sleep disturbance, our group developed a murine model of intermittent chronic CE (ICCE), to mimic the conditions faced by the researchers, *i.e.*, CE exclusively during the awaked phase **Objective:** To evaluate the effects of ICCE on aerobic physical performance and adaptation on muscle mitochondria, fiber type and their intracellular signaling in mice. **Methods:** Adult male CD-1 mice were exposed to cold environment (~4 °C; COLD, n=11) for 28 nights during awake phase (*i.e.*, 7 pm to 7 am), but returned to thermoneutral environment (~29 °C) from 7 am to 7 pm. Control (CON, n=11) group was kept in a thermoneutral environment. Aerobic performance [(*i.e.*, maximal speed (V_{peak}, time to exhaustion (TTE) and running distance (RD)] was assessed by incremental treadmill before and after 28 nights of ICCE. Animals were euthanized 48h after last CE session to collect samples of skeletal muscle to analyze the protein content of PGC-1α, OxPhos, myosin heavy chains (MHC) types and Atrogin-1, by western blot. All experiments and protocols were approved by Universidade Federal de Minas Gerais (UFMG) - The Ethics Committee on Animal Use (CEUA 84/2020). **Results:** At day 28, ICCE caused a marked reduction of aerobic performance by decreasing TTE (27%), V_{peak} (19%) and RD (32%). However, protein content of PGC-1α, OxPhos subunits and the ratio between fast and slow MHC remains unchanged. These deleterious effects of ICCE on aerobic performance was associated with reduced muscles mass of tibialis anterior (6%) and triceps surae (6%). Unexpectedly, the protein levels of Atrogin-1, a E3-ligase related to UPS, was reduced by 19% by ICCE, which might suggest a physiologic attempt to mitigate muscle wasting. Conclusion: Our model of ICCE induced a decrease in muscle mass that may be responsible for a decrement of aerobic performance in the animals. Finally, we intend to investigate the effects of exercise training, in both humans and mice, to improve physical performance and mitigate the deleterious effects of ICCE.

Keywords: Aerobic physical performance; Mitochondria; Muscle atrophy; Fiber type, Thermal stress.

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