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Increased Adenosine Monophosphate Degradation Impairs Mitochondrial Function

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Atrophied skeletal muscle has enhanced fatigability due at least in part to a reduction of mitochondria content. Since mitochondrial biogenesis is regulated by the transcriptional coactivator PGC-1α, which in turn is activated by AMP-activated protein kinase, lower levels of AMP might be expected to lower mitochondrial content. Supporting this idea, AMP degrading enzyme AMP deaminase 3 (AMPD3: AMP → IMP $+NH_3$) is highly induced during muscle atrophy. **PURPOSE:** Determine whether increased degradation of cellular AMP will decrease maximal mitochondrial oxidative capacity. **METHODS:** Cellular AMP levels were decreased through overexpressing adenoviruses encoding for AMPD3, AMPD1, and 5'nucleotidase (5'NT: AMP → adenosine + P_i). Adenoviruses were administered to C2C12 myotubes for either a 1- or 5-day period. An adenovirus encoding for GFP was used as the negative control. Oxygen consumption rate (OCR) was assessed using an extracellular flux analyzer. Oligomycin, FCCP, and a mix of antimycin A and rotenone were injected to measure respiration. All values were normalized to the basal GFP. IMP content was also measured via UPLC to assess AMP deaminase activity. **RESULTS:** Repeated measures ANOVA was used to compare the AMP degrading adenoviruses to the control. For the five-day adenovirus, 5'NT significantly decreased maximal respiration from 2.997 to 2.523 ($p = 0.045$) and ATP linked respiration from 0.8534 to 0.7231 ($p = 0.026$). AMPD3, under the five-day adenovirus transduction, decreased maximal respiration from 2.997 to 2.571 ($p = 0.147$), ATP linked respiration from 0.8534 to 0.7314 ($p = 0.092$), and H^+ leak from 0.1509 to 0.1093 ($p = 0.094$). 5'NT also tended to decrease spare respiratory capacity for both the one-day ($p = 0.0587$) and five-day ($p = 0.0918$) adenovirus transduction (from 2.091 to 1.677 and 1.997 to 1.682, respectively). No changes were seen in the one-day adenovirus transduction. AMP deaminase activity was significantly increased with the addition of both the AMPD3 and AMPD1 adenovirus, although, AMPD3 activity was 96 times greater than AMPD1. **CONCLUSION:** AMPD3 and 5'NT were effective long-term regulator of maximal mitochondrial respiration. However, AMPD1 was not able to decrease respiration, suggesting a need for a substantial amount of AMPD to elicit a decrease in respiration.

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