There has never been an outcome measure for human health more important than VO2peak, yet we know nothing about the molecular triggers for its decline with aging. Peak aerobic capacity (VO2peak) is a strong predictor of morbidity and mortality. Lifetime-apex VO2peak is the highest value for VO2peak during the life course and declines beginning the 3rd decade of human life. I examined the ability of chronic voluntary wheel running, or 5-weeks of AICAR administration, to delay the chronological age at which the decline of lifetime-apex VO2peak begins and potential underlying molecular mechanisms. Experiment one consisted of female rats with (RUN) and without (NO RUN) running wheels that underwent frequent VO2peak tests beginning at 10-weeks of age and continuing until 27-weeks of age. Lifetime apex-VO2peak occurred at 19 weeks of age in both groups, decreasing thereafter. On average, VO2peak measured across experiment one was ~25% higher in RUN. Experiment two used the AMPK-agonist AICAR, beginning at 17-weeks of age to test if the chronological age for lifetime-apex VO2peak decline could be shifted to an older age. Two groups of female rats, AICAR (0.5 mg/kg daily) and vehicle (VEH, saline) were used for 5-weeks and all animals were sacrificed at 22-weeks of age. Compared to VEH group, AICAR rats showed significantly higher body weights, muscle weights, heart weights and lower % body fat. Additionally, AICAR was able to delay the initial decline by one-week, from 19- to 20-weeks of age, but was lowered to VEH levels at 22-weeks of age. Transcriptomic analysis of the lateral head of the tricep muscle from experiment one animals revealed mRNA differences in RUN vs. NO RUN, suggesting differing skeletal muscle gene regulation immediately prior to lifetime-apex VO2peak decline. Two phases of life were examined, pre-apex VO2peak (17- to 19-weeks of age) and post-apex (19- to 27-weeks of age). These data indicate that rat wheel running increases VO2peak 25% and is not sufficient to delay the chronological age of lifetime-apex VO2peak decline, whereas AICAR delayed it one week. Transcriptomic analysis of experiment one offers target molecules that play a role in: 1) the causation of the decline occurring at 19-weeks of age, and 2) potential genes and mechanisms contributing to the initiation of decline in lifetime-apex VO2peak.