Actions of the antioxidant *N*-acetylcysteine on cell signaling response to exercise in human skeletal muscle

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Production of reactive oxygen species (ROS) in skeletal muscle is markedly increased during exercise and may be essential for exercise adaptation. We therefore investigated the effects of infusion with the antioxidant *N*-acetylcysteine (NAC) on exercise-induced activation of signaling pathways and genes involved in exercise adaptation in human skeletal muscle. Subjects completed two exercise tests, 7 days apart, with saline (control, CON) or NAC infusion before and during exercise. Exercise tests comprised of cycling at 71% VO_{2peak} for 45 min, then 92% VO_{2peak} to fatigue with *vastus lateralis* biopsies at pre-infusion, after 45 min cycling and at fatigue. Analysis was conducted on the mitogen-activated protein kinase (MAPK) signaling pathways, which are involved in growth, metabolism, differentiation, transcription, translation, and remodeling and also nuclear factor-κB (NFκB) signaling, which is a major stimulator of genes involved in inflammation and muscle protein turnover. We found that exercise increased phosphorylation of the MAP kinases c-Jun N-terminal kinase (JNK), p38 MAPK, and extracellular signal regulated kinases 1 and 2 (ERK 1/2), and that NAC had no effect on these kinases. NF-κB p65 phosphorylation was unaffected by exercise; however it was reduced in NAC at fatigue by 14% ($p<0.05$) compared to pre-infusion. Additionally, we analysed expression of exercise and/or ROS sensitive genes involved in stress-response (heat shock protein 70, HSP70), inflammation (interleukin-6, IL-6; monocyte chemotactic protein-1), anti-oxidant defense (manganese superoxide dismutase, MnSOD) and mitochondrial biogenesis (peroxisome proliferator-activated receptor coactivator-1α, PGC-1α). Exercised induced mRNA expression was ROS dependent for MnSOD (Figure), but not PGC-1α, interleukin-6, MCP-1, or heat-shock protein 70. These results suggest that inhibition of ROS attenuates some skeletal muscle cell signaling pathways and gene expression involved in adaptations to exercise.