N-acetylcysteine infusion enhances skeletal muscle Na^+,K^+-ATPase activity and plasma K^+ regulation, and delays fatigue, during prolonged submaximal exercise in well-trained individuals

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The production of reactive oxygen species (ROS) in skeletal muscle has been linked with muscle fatigue (for review see Reid, 2001). Recently, we showed that intravenous infusion of the antioxidant *N*-acetylcysteine (NAC) increased each of muscle NAC (total and reduced), cysteine and glutathione (reduced) and improved prolonged submaximal exercise performance in well-trained individuals (Medved *et al.*, 2004). We have found depressed Na^+,K^+-ATPase activity in skeletal muscle during exercise, which may contribute to disturbed muscle ionic homeostasis and fatigue (Leppik *et al.*, 2004). This study investigated whether ROS may be involved in this process, by examining the effect of NAC infusion on skeletal muscle Na^+,K^+-ATPase activity and potassium (K^+) regulation during prolonged submaximal endurance exercise, in well trained individuals.

Eight well-trained subjects participated in a double blind, randomised, crossover design study, receiving either an NAC or saline (CON) infusion into a superficial forearm vein (Medved *et al.*, 2003). NAC was intravenously infused at 125 $mg.kg^{-1}.hr^{-1}$ for 15 min, then 25 $mg.kg^{-1}.hr^{-1}$ for 20 min prior to and throughout exercise, which was continued until fatigue. Subjects completed cycling exercise comprising 45 min at 70% VO_{2peak}, then to fatigue at 90% VO_{2peak}. Muscle biopsies were taken from the vastus lateralis before exercise, at 45 min and at fatigue and analysed for maximal *in vitro* Na^+,K^+-ATPase activity (maximal K^+-stimulated 3-*O*-methyfluorescein phosphatase, 3-*O*-MFPase). Blood was sampled at pre-infusion, immediately prior to exercise, during exercise at 15, 30, 45 min and at fatigue. Blood was analysed for plasma [K^+] as well as blood haemoglobin concentration ([Hb]) and hematocrit (Hct).

Time to fatigue at 90% VO_{2peak} was reproducible in preliminary trials (CV 5.6±0.6%) and with NAC was enhanced by 20.8±9.1% (NAC 6.4±0.6 vs CON 5.3±0.7 min, $P<0.05$) (Medved *et al.*, 2004). Maximal 3-*O*-MFPase activity decreased by 21.6±2.8% at 45 min and by 23.9±2.3% at fatigue when compared to rest ($P<0.05$). NAC attenuated the percentage change in maximal 3-*O*-MFPase activity at 45 min ($P<0.05$) compared to control but not at fatigue. However, the change in 3-*O*-MFPase activity to work ratio was attenuated by NAC both at 45 min and at fatigue ($P<0.005$). The rise in plasma [K^+] and plasma Δ[K^+]-to-work ratio during exercise were both attenuated by NAC ($P<0.05$). There was no significant correlation between time to fatigue and each of maximal 3-*O*-MFPase, rise in plasma [K^+] and plasma Δ[K^+]-to-work ratio.

In conclusion, our data show that NAC infusion in well-trained individuals attenuated the depression in muscle Na^+,K^+-ATPase and enhanced K^+ regulation, which may be important in delaying fatigue during prolonged submaximal exercise. This suggests that ROS play a role in skeletal muscle fatigue and specifically in Na^+,K^+-ATPase regulation and K^+ regulation during submaximal exercise.

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