**Polymer-based micelle-type antioxidant enhances exercise performance**

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Exercise is good for health. However, excessive or unfamiliar exercise may worsen exercise performance and health. While moderate levels of reactive oxygen species (ROS), which are produced by respiration, produce energy and improve exercise performance, excess levels of ROS cause degeneration and tissue damage, resulting in reducing exercise performance. High-intensity or prolonged exercise causes the destruction of red blood cells (RBCs) and gastrointestinal (GI) syndrome owing to excessive amounts of ROS. Although conventional antioxidants are used to suppress the damage caused by overproduced ROS, they are ineffective at improving health and exercise performance and rather may cause damage as their rapid clearance and dysfunction of intracellular redox balance. To increase bioavailability and decrease intracellular dysfunction, we developed polymer-based micelle-type antioxidants (RNPs) (Figure 1). Biocompatible poly(ethylene glycol) (PEG) shell prolongs the long circulation of RNPs in vivo. Several tens of nanometer sizes in RNPs reduce cellular uptake and prevent mitochondrial dysfunction. 2,2,6,6-Tetramethylpiperidine-1-oxyl free radical (TEMPO), used as antioxidants for RNPs, is catalytically and highly scavenging ROS. Running model mice and rats were used to evaluate RNPs on exercise performance. We confirmed that high-intensity running caused serious damage to the RBCs and GI tract, resulting in decreasing their exercise performance. LMW antioxidant did not function at all. Interestingly, subcutaneous injected RNPN (pH-sensitive, long blood circulation micelle), significantly improved exercise performance in a dose-dependent manner by effectively removing ROS in the blood and maintaining RBC numbers. It is further interesting that orally administered RNPO (pH-insensitive, specific retention in the GI tract) scavenged intestinal ROS and protected the damage of the GI tract, thus preventing endotoxin leakage which prevented the systemic damage (e.g. RBCs, skeletal muscle). As a result, RNPO enhanced exercise performance in a dose-dependent manner. Based on these results, we concluded that polymer micelle-type antioxidants are effective for improving exercise performance owing to preventing side effects in mitochondria and exerting tissue-specific antioxidant effects.



Figure 1. Schematic illustration of self-assembling antioxidant nanoparticle (NanoAO)

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