Nitric Oxide and skeletal muscle: from myogenesis to therapeutic perspectives for the Duchenne muscular dystrophy

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Muscular dystrophies are clinically and molecularly heterogeneous diseases characterized by a primary wasting of skeletal muscle that compromises patient mobility. In the most severe forms, such as Duchenne muscular dystrophy, regeneration is exhausted and skeletal muscle is progressively replaced by fat and fibrous tissue. This condition leads the patient to progressive weakness and eventually death by respiratory and/or cardiac failure. Although the underlying molecular defects are now known, no satisfactory therapy is still available. Several pharmacological strategies have been attempted, including protease inhibitors, drugs that regulate calcium homeostasis or enhance muscle anabolic activity. None of them, however, yielded favourable outcomes in clinical trials and entered the clinical practice. Thus, the current pharmacological approach to muscular dystrophies is to control chronic inflammation, mainly with steroids administered in various protocols. These treatments result in modest beneficial effects and are accompanied by severe side-effects.

In the last few years experimental approaches alternative to classical pharmacological treatments have been developed. These include replacement of the defective gene via gene therapy with adenoviral or adeno-associated viral vectors, or injections of plasmid DNA, or DNA-RNA chimeric oligonucleotides. These treatments, although showing promising results in clinical trials, only target subsets of patients and are extremely expensive and not affordable for the public health systems.

Several lines of evidence indicate in the short-lived messenger nitric oxide (NO) an ideal candidate to delay muscle damage. The role of NO generated by skeletal muscle itself in regulating skeletal muscle function has been thoroughly investigated. It regulates excitation-contraction coupling, in such a way that it prevents the muscle from being damaged during its contractile activity. In addition, it regulates resting potential and activity-dependent synaptic suppression at developing neuromuscular synapses. NO appears also relevant in regulating energy supply to muscle. In particular, it contributes to vasodilation, and thus supply of oxygen during exercise and increases glucose uptake. In addition, it is a potent trigger for mitochondrial biogenesis and regulates enzymes relevant to cell energy metabolism, such as glyceraldehyde 3-phosphate dehydrogenase, aconitase and creatine kinase. In the course of several years we also found that NO contributes to myogenesis by enhancing the renewal of the myogenic precursor cells, and by favouring their activation and fusion. In this presentation I will review the role of NO in myogenesis and how NO-based therapies were developed in preclinical models of muscular dystrophy and then tested in clinical trials in which both safety and efficacy were assessed. These pharmacological therapies potentially target all patients affected by Duchenne muscular dystrophy and at affordable costs for the public health systems.