Effect of Resveratrol on Distinct Skeletal Muscle Components

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Resveratrol is a natural polyphenol utilized in Chinese traditional medicine and thought to be one of the determinants of the “French Paradox”. Some groups evidenced its properties as a calorie-restriction mimetic, suggesting that its action passes through the modulation of skeletal muscle metabolism. Accordingly, the number of studies reporting the beneficial effects of resveratrol on skeletal muscle form and function, in both experimental models and humans, is steadily increasing.

resveratrol skeletal muscle clinical trials

1. Introduction

Skeletal muscle contraction is initiated by the nervous system with the generation of a signal that travels through motor neurons to the NMJ, inducing the release of acetylcholine, which binds to receptors on the sarcolemma of the muscle fiber. This action starts a process, the excitation–contraction coupling, that leads to the filaments sliding and muscle contracting. Skeletal muscles are attached to bones and other structures via tendons, allowing movement and respiration. Although the main component of the skeletal muscle is represented by myofibers, an optimal physical performance depends on the integration of several histological and anatomical structures with different roles in skeletal muscle contraction. Attesting to the need for efficient coordination between myofibers and associated tissues to achieve optimal skeletal muscle function, studies on aging and muscle unloading demonstrate that the loss of muscle strength is considerably greater compared to the associated alteration to the muscle mass [1][2][3]. This divergence could be ascribable to modifications to the NMJ, connective sheets, tendons and blood vessels, which work together to guarantee optimal contraction performance [4]. Consequently, the efficient improvement of skeletal muscle function in different physio-pathological conditions requires a strategy capable of targeting multiple muscle structures [4]. In this context, RES, initially reported to modulate the form and function of the skeletal muscle cell [5], has been demonstrated to be a pleiotropic molecule able to interact with different muscle structures, as summarized below.

2. Resveratrol and Skeletal Muscle Fiber

RES has been reported to act on myofibers by modulating metabolism, catabolism and oxidative stress. As largely reported, RES interacts with the AMPK-SIRT-1 pathway to trigger several signaling pathways, which induces a general myofiber remodeling similar to that seen by exercise training and calorie restriction.

RES induces the expression of genes involved in mitochondrial biogenesis and oxidative phosphorylation through the peroxisome proliferator-activated receptor gamma coactivator-alpha (PGC-1-alpha) [6]. As a result, muscle fibers from treated animals have better oxidative profiles and/or present more oxidative type I fibers, which are resistant to fatigue [6][7]. In turn, mitochondrial activity and PGC-1-alpha modulation have been demonstrated to be strictly associated with better fatty acid oxidation and lipid metabolism [6].

RES has been shown to modulate glucose metabolism by improving glucose uptake in several experimental models. As a result, mice on a high-fat diet supplemented with RES have lower circulating levels of insulin and improved glucose tolerance compared to the control group [6][8], diabetic rats display a better glucose tolerance upon RES treatment [9][10] and, more interestingly, preliminary studies confer to RES potential as an antidiabetic molecule in humans [11].

Despite the presence in the literature of conflicting data, it is suggested that RES may prevent muscle wasting in different conditions. Actually, RES has been shown to inhibit protein degradation in several in vitro models [5] by interfering with nuclear factor kappa beta (NF-kB) activation and nuclear translocation, inhibiting the signaling pathway that contributes to muscle mass loss [12]. Accordingly, RES supplementation has been shown to attenuate age-dependent fiber area decrease [13]. Interestingly, the administration of RES in rats undergoing hindlimb suspension did not prevent fiber atrophy during the period of disuse, but it increased the cross-sectional area of type II fibers in response to reloading, most probably by reducing pro-apoptotic signals [14].

3. Resveratrol and the NMJ

The NMJ is the point of communication between the motor neuron and the skeletal muscle cell, and it is the site for the transmission of action potential to activate contraction. The integrity of the NMJ is perturbed in neuromuscular disorders and in skeletal muscle aging and disuse [3][15][16][17], with a consequent loss of its organization, fragmentation and degeneration, contributing to reduced muscle performance. Already in 2006, Lagouge and collaborators [6], based on the evidence that RES improved the motor coordination and traction force in mice fed on a high-fat diet, suggested that RES could modulate neuromuscular communication. Later, analogously to the reported evidence that calorie restriction and exercise can attenuate age-dependent NMJ modifications [18], RES was reported to slow aging of the NMJ by reducing its fragmentation and denervation [19].

Although the molecular pathways regulating the NMJ-specific domain targeted by RES remain quite unexplored (the research in PubMed with the words “resveratrol neuromuscular junction” issued only five results), several research articles exploring RES effects on nervous tissue reveal significant neuroprotective action. Actually, in various experimental models, RES administration has been shown to reduce nerve cell senescence [20] and to ameliorate oxidative stress [21], endoplasmic reticulum stress [22] and inflammation [23], thereby improving locomotor function. This evidence suggests that RES has the potential to target the presynaptic component of the NMJ. Further work is needed to understand if and how RES can target the postsynaptic domain of the skeletal muscle cell.

4. Resveratrol, Connective Sheaths and Tendons

Connective sheaths and tendons are formed by an insoluble scaffold of the extracellular matrix (ECM), rich in collagen and elastic fibers, proteoglycans, glycoproteins and laminins, which is synthesized by fibroblasts. Connective sheaths serve as structural support for muscle fibers; participate in lateral and longitudinal force transmission; host immune system cells, satellite cells, nerves and capillaries; and form a strict connection with bones to displace the different parts of the skeleton [24].

In general, ECM homeostasis is maintained by the fine regulation of the production of its components and the activation of degrading enzymes [1]. In the context of a muscle, the presence of continuous excitation–contraction cycles requires an appropriate remodeling of the ECM, which can be highly impacted by exercise, age and pathological conditions [24]. For example, in aging individuals, the ECM undergoes fibrotic changes that lead to an increase in skeletal muscle stiffness, strength loss and injury predisposition [2][25]. Moreover, attesting to the crucial role of connective sheaths, muscle contraction can be impaired in ECM-specific disorders but also in apparently unrelated pathologies that result in connective tissue impairment [26]. For instance, patients affected by Ehlers–Danlos syndrome often display neuromuscular involvement [27]. Although these subjects experience skeletal muscle symptoms such as pain, fatigue and cramps, they have normal skeletal muscles, suggesting that muscle symptoms depend on the associated connective tissue [28]. Interestingly, patients affected by chronic kidney disease present reduced muscle performance accompanied by fibrosis, capillary rarefaction and weakness, which can be partially reverted by dialysis [26][29].

The effects of RES on the ECM are quite conflicting, which may be due to the different biochemical properties of the ECM in different tissues and the experimental models tested. It has been suggested that RES may modulate both the deposition and the degradation of the ECM components. RES has been shown to increase collagen deposition, improving wound healing and neovascularization after laparotomy in rats [30] but also to reduce cardiac fibrosis in several experimental models via the diminution of ECM component deposition and the regulation of metalloproteinase (MMP) activity [31]. In the context of skeletal muscle, there are few observations. Gliemann and collaborators reported that RES inhibits the training-induced expression of the metallopeptidase inhibitor-1 (TIMP-1) and reduces the levels of thrombospondin-1 (TSP-1), and they interpreted these data as an inhibition of the proangiogenic response and capillarization [32]. Considering the metalloproteinase-inhibiting function of TIMP-1 and the role of TSP-1 in promoting fibrosis [33], it could be hypothesized that RES plays an antifibrotic role also in the skeletal muscle.

Interestingly, because RES is a pleiotropic molecule and ECM is a highly elaborate and plastic tissue structure, modifications to connective sheaths could also depend on indirect RES actions, such as the scavenging of ROS, inhibition of the production of advanced glycation end products (AGEs), improvement of the inflammatory response and regulation of hormones [34].

5. Resveratrol and Skeletal Muscle Vascularization

In the skeletal muscle, microcirculation is responsible for the delivery of oxygen, nutrition and hormone molecules to and from muscle fibers and for the removal of heat and waste products [35]. To these aims, within the skeletal muscle, fiber type, fiber size, oxidative capacity and capillarization are strictly regulated to adapt to physiological needs [35][36][37]. Attesting to its crucial role, reduced capillarization impacts oxygen supply to muscles, contributing to exercise intolerance. Accordingly, poor capillarization levels are observed in hypertensive conditions, concurrent with metabolic dysregulation [38] and associated with lower muscle performance in older adults [39].

Based on the idea of the capillary bed as a target to improve skeletal muscle health, there is a growing interest in RES's potential to modulate capillarization, because studies in humans and animal models have provided promising results regarding both the skeletal muscle [40][41] and the cardiovascular system [42].

As suggested by Diaz and collaborators [43], the impact of RES on blood vessels is ascribable to a multilevel action, which starts from molecular regulation, passes through a biochemical response and converges to bring better blood supply to the tissue. RES has been shown to positively regulate vasculature through several mechanisms. It has been suggested that RES promotes angiogenesis via thioredoxin-1, heme oxygenase-1 and vascular endothelial growth factor (VEGF) [44] and regulates vasodilation by scavenging ROS and modulating nitric oxide synthesis. RES inhibits NFkB activation, leading to the reduction of inflammation markers and cytokines [40][45][46]. Ultimately, the improvement of capillarization in the skeletal muscle can also be credited with secondary effects, such as a decrease in fibrosis of the associated connective tissue [26][29] or an improvement in the cardiac hemodynamic properties, as shown in RES-treated diabetic rats [47].

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