Choline

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Choline is an essential micronutrient with a pivotal role in several metabolic pathways contributing to liver, neurological, and hematological homeostasis. Although choline is commonly administered to improve physical performance, its effects on muscle are still unclear. Our scoping review elucidates and summarizes the
crucial role of choline in modulating muscle fat metabolism, muscle proteins homeostasis, and the
modulation of inflammation and autophagy.

Keywords: choline ; skeletal muscle ; striated muscle ; review ; muscle fat ; muscle protein ; autophagy ; inflammation ; muscle performance ; vitamin B complex

1. Definition

Choline is a water-soluble quaternary amine of the vitamin B group considered as an essential nutrient by the Food and Nutrition Board of the Institute of Medicine[1].

2. Introduction

Choline endogenous synthesis from amino acid methionine is insufficient to support human choline requirements, so it is essential to maintain an appropriate dietary intake of choline, consuming fish, eggs, and meats[2]. Adequate choline daily intakes ranged from 330 to 468 mg for men, 269 to 444 mg for women, and 356 mg/day as mean estimate intake in pregnant women[3]. This micronutrient plays an important role in phospholipid synthesis and triglycerides metabolism contributing to structure and function of cell membranes, including skeletal muscle cells[4]. Low concentration of choline is associated with several changes in myoblasts up to muscle wasting as demonstrated by increased serum creatine kinase (CK)[5]. Moreover, choline seems to exert an ancillary role in inflammatory muscle diseases with anti-fibrotic effects[6]. From a functional point of view, choline is involved in muscle contraction being a precursor of the main neurotransmitter of α-motor neurons, acetylcholine (ACh)[7]. These effects might have clinical implications as suggested by the observation of poor physical performance in healthy people with low serum choline[8][9][10].

Despite available knowledge about effects of choline on both muscle histomorphology and function, pathways involved in these processes are still poorly investigated.

3. Choline: An Essential Nutrient for Skeletal Muscle

3.1. Choline and Muscle Fat Metabolism

Adequate amount of choline improves mitochondrial energy metabolism and lipid metabolism by decreasing FA synthesis. Choline deficiency impairs the incorporation of FAs in PC, increasing their availability for DAG and TAG synthesis, and consequently favoring accumulation of TAG in muscle cells[11]. Choline influences fat metabolism also modulating expression of genes involved in FA genesis (ACC and FASN) as well as those involved in fat intracellular transportation (LPL and CD36)[12]. Moreover, high levels of choline reduce biosynthesis of long-chain FAs in muscle lowering intramuscular fat content. This effect could be explained also by an insulin-mediated gene modulation. In fact, choline supplementation improves insulin signaling that upregulates AMPK, downregulates mTORC1, a modulating factor of proteostasis in skeletal muscle[13], and decreasing lipogenesis[14].

Choline also downregulates Diacylglycerol O-acyltransferase (Dgat1/2), reducing FA esterification and TAG formation. On the other side, an experimental study reported that additional choline supplementation did not result in significant difference in “carcass fat levels” when compared to control[15]. Accumulation of lipid intermediates in skeletal muscle (intermuscular and/or intramuscular adipose tissue, IMAT) leads to cellular dysfunction and death. An excess of lipids in diet could impair choline metabolism. This effect reduces the consumption of lipids for intracellular synthesis of PC,

increasing DAG and FA accumulation, causing adipocyte hyperplasia and hypertrophy, chronic inflammation, lipotoxicity, and insulin resistance, key mechanisms involved in sarcopenic obesity[16]. However, it should be underlined that polyunsaturated FAs, such as PAM, reduce the expression of plasma membrane choline transporter CTL1/SLC44A1 inducing cell membrane fragility because of poor choline availability for PC synthesis. Moreover, choline deficiency shifts CDP-choline pathway toward TAG formation and lipid droplets accumulation resulting in lipotoxicity. Conversely, monounsaturated FAs, such as OLA, seem to exert a protective activity on muscle by increasing mitochondrial FA oxidation and stimulating PC synthesis. In a clinical scenario, Gao et al. demonstrated that choline supplementation improved body composition by lowering body fat and increasing lean mass, suggesting a pivotal role of this micronutrient in promoting FA β-oxidation and translocation into the mitochondria[17].

3.2. Choline and Muscle Proteins

Choline is an essential nutrient for protein metabolism. As methyl-group donor, this micronutrient influences protein homeostasis, increasing synthesis and reducing breakdown. Robinson et al. reported a reduced whole-body protein synthesis in piglets fed with methyl deficient diet, due to 50% reduction of protein synthesis in skeletal muscle[18]. In the early stages, impaired protein synthesis did not lead to a poor body growth, probably because of a simultaneous slow protein catabolism. However, a chronic choline diet restriction undoubtedly determines a low muscle protein content, resulting in impaired muscle growth and function. Vice versa, choline-rich diet increases serum IGF2 and decreases IGFBP-2 in skeletal muscle fibers. IGF2 enhances proliferation and growth of muscle tissue promoting amino acid and glucose uptake[19][20]. It has been also hypothesized that methyl-donors nutrients, including choline, increases the expression of follistatin (FST), a member of the TGF-β family that causes hypertrophy and hyperplasia of muscle cells through binding ACTIIB receptor, and thus inhibiting myostatin[21][22](Figure 1).

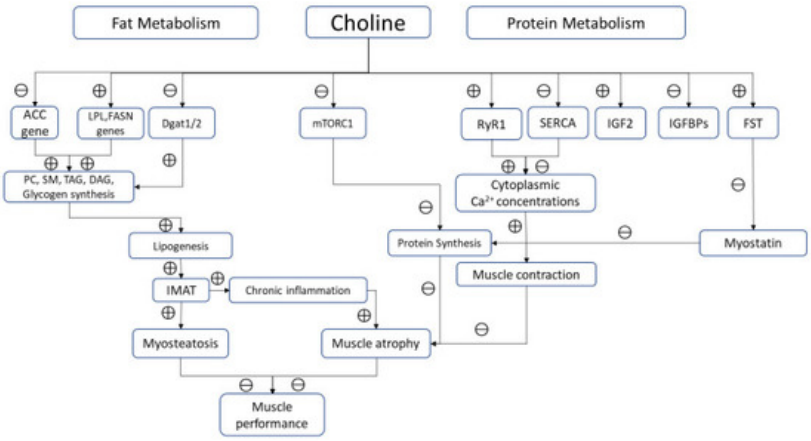

Figure 1. Biological pathways modulated by choline in skeletal muscle. Note: ⊕ and ⊖ indicate positive and negative modulation, respectively.

From a functional point of view, potential actions of choline in modulating key mechanisms of muscle contraction beyond its role as precursor of Ach should be considered. Ions replacement of K^+ with choline+ results in a potent inhibition of SERCA in sarcoplasmic/endoplasmic reticulum of skeletal muscle as demonstrated in animal models[23]. This effect is reached through a dual mechanism: $choline^+$ inhibits both the cytosolic Ca^{2+} uptake into SR and, at the same time, SERCA ATPase activity, probably uncoupling Ca^{2+} transport from ATP hydrolysis.

Choline regulates intracellular calcium and therefore muscle contraction also by modulating the binding of calmodulin and RYR1[24]. This mechanism could increase the cytoplasmic calcium concentrations into myofibrillar spaces improving its bioavailability for muscle contraction. However, this seems not true in muscle affected by pathological conditions. Alves et al. reported that choline supplementation (5 g/kg choline) paradoxically increased SERCA activity reducing calcium cytosolic content in mice models of Duchenne Muscular Dystrophy (mdx)[6].

3.3. Choline and Inflammation

Choline influences inflammation through different mechanisms. In animal exposed to endotoxin choline improves activation of vagal anti-inflammatory system[25][26][27]. In the same animal model, choline counteracts the endotoxin-induced tissue damage reducing serum levels of urea, uric acid, lactate dehydrogenase (LDH), creatine kinase (CK), and creatine kinase myocardial isoform (CK-MB)[19], probably through improved tissue perfusion as well as enhanced cholinergic neurotransmission.

3.4. Choline, Apoptosis, and Autophagy

Choline modulates cell apoptosis and autophagy; thus, contributing to maintain intercellular homeostasis. Da Costa et al. [28] reported that choline deficiency was associated with significant DNA damage resulting in lymphocyte apoptosis. Authors found an increase of activated caspase-3 in lymphocytes in patients fed with choline deficient diet. This could be the main mechanism of apoptosis, probably occurring earlier than the reduced cytoplasmatic availability of choline for PC synthesis. Lower membrane PC concentration seems to contribute to plasma membrane fragility of myocytes[5].

Choline is an important regulator of autophagy. Taylor et al. reported that choline supplementation restores insulin receptor substrate 1 (IRS1) levels, a key factor in the IGF1-Akt-mTOR pathway with significant anabolic effects on skeletal muscle[14]. Choline prevents phosphorylation of mTORC1, defined as “the main gateway to autophagy”[29]. Autophagy is a critical survival mechanism of cells and its alteration conduce to skeletal muscle damage in different disorders. For example, Pompe disease, an inherited deficiency of the lysosomal enzyme acid α-glucosidase, is characterized by significant accumulation of autophagosomes containing LC3 (microtubule-associated protein 1 light chain 3), a pivotal factor for autophagy in type I muscle fibers. Two forms of LC3 have been described: a cytoplasmic protein (LC3-I), and a specifically associated autophagosomes form (LC3-II). Higher levels of LC3-II provoke a dramatic and disruptive autophagic effect on skeletal muscle[30]. Choline reduces lipidation of LC3, lowering LC3-II/LC3-I ratio and its accumulation in autophagy-lysosomal system[31]. This ratio is also influenced by FAs. PAM increases intracellular content of PC precursor providing more lipids for LC3 lipidation and autophagosome formation stimulating autophagy.

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