Pharmacological Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Skeletal muscle atrophy: Potential therapeutic agents and their mechanisms of action

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ARTICLE INFO

Article history:
Received 6 March 2015
Received in revised form 24 May 2015
Accepted 24 May 2015
Available online xxx

Keywords:
Atrophy
Cachexia
Eicosapentaenoic acid
Resveratrol
Cox2 inhibitor
Histone decetylase inhibitor
Phosphodiesterase inhibitor
β-Adrenoceptor agonists
Megestrol acetate
Anti-cytokines

Chemical compounds studied in this article:
EPA (PubChem CID: 446284)
β-Hydroxy-β-methylbutyrate (PubChem CID: 69362)
Cis-resveratrol (PubChem CID: 1548910)
Trans-resveratrol (PubChem CID: 445154)
Ghrelin (PubChem CID: 44576256)
Celecoxib (PubChem CID: 2662)
Meloxicam (PubChem CID: 54677470)
Trichostatin A (PubChem CID: 444732)
Torbafylline (PubChem CID: 65888)
Pentoxifylline (PubChem CID: 4740)
Formoterol (PubChem CID: 3410)
Clenbuterol (PubChem CID: 2783)
Enobosarm (PubChem CID: 11326715)
Thalidomide (PubChem CID: 5426)
Megestrol acetate (PubChem CID: 11683)

ABSTRACT

Over the last two decades, new insights into the etiology of skeletal muscle wasting/atrophy under diverse clinical settings including denervation, AIDS, cancer, diabetes, and chronic heart failure have been reported in the literature. However, the treatment of skeletal muscle wasting remains an unresolved challenge to this day. About nineteen potential drugs that can regulate loss of muscle mass have been reported in the literature. This paper reviews the mechanisms of action of all these drugs by broadly classifying them into six different categories. Mechanistic data of these drugs illustrate that they regulate skeletal muscle loss either by down-regulating myostatin, cyclooxygenase2, pro-inflammatory cytokines mediated catabolic wasting or by up-regulating cyclic AMP, peroxisome proliferator-activated receptor gamma coactivator-1α, growth hormone/insulin-like growth factor1, phosphatidylinositide 3-kinases/protein kinase B(Akt) mediated anabolic pathways. So far, five major proteolytic systems that regulate loss of muscle mass have been identified, but the majority of these drugs control only two or three proteolytic systems. In addition to their beneficial effect on restoring the muscle loss, many of these drugs show some level of toxicity and unwanted side effects such as dizziness, hypertension, and constipation. Therefore, further research is needed to understand and develop treatment strategies for muscle wasting. For successful management of skeletal muscle wasting either therapeutic agent which regulates all five known proteolytic systems or new molecular targets/proteolytic systems must be identified. Q2

Abbreviations: Cox, cyclooxygenase; CREB, cAMP response element binding protein; CACS, cancer-related anorexia and cachexia syndrome; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; DAG, des-acyl ghrelin; ERK, extracellular signal-regulated kinase; EPA, eicosapentaenoic acid; FoxO, forkhead box O; Epac, exchange protein directly activated by cAMP; eIF4G and eIF4E, eukaryotic translation initiation factor 4G and 4E; HAT, histone acetyltransferase; HDAC, histone deacetylase; HETE, hydroxyeicosatetraenoic acid; HMB, β-hydroxy-β-methylbutyrate; LLC, Lewis lung carcinoma; MAC, murine adeno-carcinoma; NY, neuropeptide Y; NFκB, nuclear factor kappa; PUFA, polyunsaturated fatty acid; PIF, proteolysis-inducing factor; PPARγ, peroxisome proliferator-activated receptor; PGE, prostaglandin; PDE, phosphodiesterase; PKA, protein kinase A; PTX, pentoxifylline; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; SARM, selective androgen receptor modulator; SOD, superoxide dismutase; TNFα, tumor necrosis factor; TWEAK, TNFα like weak inducer of apoptosis; TLR, toll-like receptor; TPA, 12-0-tetradecanoylphorbol-13-acetetate; TGFβ1, transforming growth factor beta 1; TSA, trichostatin A; CKD, chronic kidney disease; Activin type II receptor, ActRIIB, ActRIIA; Activinlike kinase, ALK4, ALK5; MuRF1, muscle-specific RING-finger 1.

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http://dx.doi.org/10.1016/j.phrs.2015.05.010
1043-6618/

Please cite this article in press as: V. Dutt, et al., Skeletal muscle atrophy: Potential therapeutic agents and their mechanisms of action, Pharmacol Res (2015), http://dx.doi.org/10.1016/j.phrs.2015.05.010

Contents

1. Introduction

In the current literature, three factors that can initiate loss of skeletal muscle mass have been identified. They are (1) chronic diseases (cachexia) like diabetes, cancer, chronic obstructive pulmonary disease (COPD), acquired immune deficiency syndrome (AIDS), and renal/cardiac failure, (2) disuse conditions (atrophy) like denervation, immobolization, and microgravity (3) aging (sarcopenia). These factors gradually lead to distinct phenotypic changes in the skeletal muscle by accelerating protein degradation [1–5]. Muscle wasting and weakness generated in each of these conditions (cachexia, atrophy, and sarcopenia) is a complex and highly regulated phenomenon, characterized by substantial decrease in muscle fiber cross-sectional area, myonuclear number, protein content and muscle strength while increasing in fatigability and resistance to insulin [2,6–8]. In addition, it is also associated with an increased risk of death.

Beyond a reduced survival rate, wasting is also linked to poor functional status and quality of life. Up to one-third of all cancer patients die due to direct consequences of cachexia and not from cancer, while in AIDS, more than 5% weight loss over a period of 4-months are associated with an increased risk of death and opportunistic infections. Studies have revealed that different types of molecular triggers/catabolic players such as myostatin, pro-inflammatory cytokines i.e. tumor necrosis factor alpha (TNFα), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), TNF-like weak inducer of apoptosis (TWEAK), interferon gamma (IFNγ) are involved in muscle wasting under above mentioned clinical settings [7,9,10]. These cytokines on binding to their respective receptor results in activation of the NFκB, a common transcription factor in most of the protein catabolic pathways leading to proteolysis in skeletal muscles (Supplementary Fig. 1). This makes nuclear factor kappa B (NFκB) an attractive pharmaceutical target for therapeutic interventions. Other important targets include anabolic pathways (phosphatidylinositide 3-kinases/protein kinase B; PI3K/Akt) and five major proteolytic machineries like Ca^{2+}-dependent calpain, Ca^{2+}-independent cathepsin L, autophagy, ubiquitin (Ub)–proteasome system and the caspase system [3,11,12]. Caspases are critical not only for muscle atrophy but also for the apoptotic process. The majority of the muscles wasting studies have demonstrated that autophagy system uses lysosomal enzymes (like cathepsin L) for the processing of damaged cellular components [12]. There are some studies which have reported enhanced cathepsin L activity without any change in the level of autophagy related markers under atrophic conditions [13–15]. These studies highlight the possibility of cathepsin L dependent and independent autophagy systems. Moreover, several reports in literature indicate that cathepsin L may be present in extracellular compartment independent to lysosomal fraction which further illustrates the probable special role of this protease during atrophy [16,17].

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phrs.2015.05.010

In spite of many promising therapeutic targets for treating muscle wasting, not even a single drug is clinically proven to be safe. In this review, we classify nineteen potential drugs (that are in use at laboratory/preclinical level of investigation using different atrophic models) into six categories and then discuss their mechanism of action (Fig. 1).

2. Classification and mechanisms of actions of drugs

2.1. Natural compounds

The mechanisms of action of four natural compounds are discussed in this section. These compounds are (A) eicosapentanoic acid, (B) β-hydroxy-β-methylbutyrate, (C) resveratrol, and (D) ghrelin and its receptor agonists.

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