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Steroid Myopathy: Pathogenesis and Effect of Activation of Stem Cells.

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Abstract

Corticosteroids are common drugs to induce myopathy which is presented by muscle pain, fatigue and obvious muscle atrophy. After injury to skeletal muscle, neutrophils, monocytes, and macrophages infiltrate the damaged area. Concomitantly, satellite cells differentiate into transient-amplifying myoblasts, which rapidly proliferate, fuse, and regenerate skeletal myotubes. Dexamethasone causes degeneration of muscle fibre. Also, The cross-sectional area of muscle fibres decreases indicating muscle atrophy. Treatments that include activation or mobilization of stem cells, can provide improvement of muscle degenerative changes caused by dexamethasone.

Keywords: Corticosteroid, myopathy, and stem cells

Introduction

Corticosteroid-induced myopathy is a highly prevalent toxic noninflammatory myopathy that occurs as an adverse effect of prolonged oral or intravenous glucocorticoid use. It was first described in 1932 by Harvey Cushing as part of a

constellation of symptoms seen in Cushing syndrome. With the broader use of corticosteroids as therapeutic tools in the 1950s, corticosteroid-induced myopathy became a more well-known entity(Pereira & de Carvalho, 2011). This toxic noninflammatory myopathy typically has an indolent presentation and predominantly affects pelvic girdle muscles, and is associated with muscle weakness and atrophy without associated pain(Braith et al., 1998).

1 _Pathogenesis of corticosteroid-induced myopathy

The precise molecular mechanisms underlying GCs-induced muscle atrophy have yet to be fully elucidated (Schakman et al., 2009); however, reductions in protein synthesis and elevations in protein degradation through various molecular pathways are believed to contribute to its pathogenesis. Notably, the inhibitory effect of GCs on p70 ribosomal S6 protein kinase (p70S6K) is thought to disrupt protein synthesis machinery and promote atrophy (Schakman et al., 2008) . Simultaneously, activation of the ubiquitin-proteasome system and lysosomal system are postulated to enhance muscle proteolysis and breakdown, with identified genes such as Atrogin-1, MuRF-1, Cathepsin-L, PDK4, p21, Gadd45, and 4E-BP1 functioning in mediating these processes (Bodine et al., 2001).

Moreover, insufficiencies involving insulin-like growth factor 1 (IGF-1) are believed to foster GCs-induced muscle atrophy (Schakman et al., 2013). IGF-1 activates the phosphatidylinositol-3-kinase/Akt pathway, which blocks GCs action and prevents muscular atrophy (Schakman et al., 2009). Conversely, reductions in IGF-1 expression compromise this protective mechanism. Furthermore, overexpression of myostatin (MSTN), a growth factor originating in skeletal muscles that inhibits muscle mass growth and leads to muscle cell atrophy by repressing satellite cells and protein synthesis, exacerbates this form of muscle atrophy (Amirouche et al., 2009). Both augmented IGF-1 expression and deletion of the myostatin gene have been used successfully in animal models to prevent GCs-induced muscle atrophy, suggesting potential therapeutic approaches for preventing or treating this disorder (Van Balkom et al., 1994).

Summarily, molecular mechanisms involving decreased protein synthesis, increased protein degradation, decreased IGF-1, increased MSTN, and regulation of related gene expression are implicated in GCs-induced muscle atrophy. Targeting these mechanisms, stimulating IGF-1, and inhibiting MSTN could become promising therapeutic approaches. A more comprehensive understanding of molecular mechanisms surrounding this disorder may offer insights into its pathogenesis and guide the development of effective therapeutic strategies.

2_ Role of G-CSF in treatment of corticosteroid induced myopathy

Adult skeletal muscle has resident stem cells, called satellite cells, which are responsible for generating new muscle under both physiological and pathophysiologic conditions. Although these muscles have the capacity to regenerate, this capacity has some limitations(Le Grand & Rudnicki, 2007) . There are several skeletal muscle diseases such as skeletal muscle dystrophy, myopathy, severe injury, and disuse syndrome for which there are no effective treatments(Shi & Garry, 2006) . Although several studies have identified various growth factors and cytokines that regulate skeletal muscle development and regeneration, effective control of regeneration hasn't been achieved using these factors in the clinical setting(Buckingham & Montarras, 2008) . Therefore, it is worth elucidating the mechanisms of skeletal muscle regeneration and developing novel regeneration therapies.

After injury to skeletal muscle, neutrophils, monocytes, and macrophages infiltrate the damaged area. Concomitantly, satellite cells differentiate into transient-amplifying myoblasts, which rapidly proliferate, fuse with one another, and regenerate skeletal myotubes. During these processes, inflammation and regeneration are tightly linked. Therefore, it is reasonable to assume that some factors expressed during the inflammatory process influence skeletal muscle regeneration. However, the precise mechanisms remain unknown (Hara et al., 2011).

Previously, when we looked for potent differentiation-promoting factors during embryonic stem cell differentiation(Yuasa et al., 2005) , we noted a marked elevation in the expression of G-CSF receptor (G-CSFR; encoded by *csf3r*) in developing cardiomyocytes(Shimoji et al., 2010) . Interestingly, we also found a marked increase in G-CSFR expression in developing somites. G-CSF was initially identified as a hematopoietic cytokine and has been used in both basic research studies and in the clinic for the mobilization of hematopoietic stem cells (Metcalf, 2008). However, recently, studies suggest that G-CSF also plays roles in cell differentiation, proliferation, and survival(Zaruba et al., 2009) .

These findings encouraged us to investigate the involvement of G-CSF and G-CSFR in skeletal myocyte development and regeneration and to examine the link between inflammation and regeneration.

3_ Role of panax ginseng in treatment of corticosteroid myopathy

Ginseng has two types, Asian (Panax ginseng) and American (Panax quinquefolius), and they are members of the Araliaceae family (genus Panax). The roots of these plants are the most commonly used plant part in natural remedies because they

contain steroidal saponins known as ginsenosides (Vaughn, 2012).

So far, more than 100 ginsenosides have been discovered in ginseng, with several pharmacological validations included. A variety of studies have been performed primarily on the pharmacological and therapeutic aspects of ginsenosides (Siti, Kamisah, & Kamsiah, 2015).

Furthermore, the FDA has classified ginseng as generally recognized as safe (GRAS) (Vaughn, 2012)

According to reports, ginseng's active ingredients have an impact on the central nervous system (Braz et al., 2013), have antioxidant (Kim et al., 2013) and anti-inflammatory properties (Barton et al., 2013) , preserve homeostasis in the body, strengthen liver and immunological function, improve brain function, regulate blood pressure, boost libido, and have anti-aging, anti-tumor, anti-diabetic, anti-fatigue, and anti-stress properties (CHOI, 2008; Kiefer & Pantuso, 2003) , and anti-type 2 diabetes (T2D) mellitus effects(Kim et al., 2011) . Additionally, ginseng is utilized to treat neurological illnesses like Alzheimer's disease (Wang et al., 2016), Parkinson's disease, Huntington's disease, and brain ischemia (Kim et al., 2018) .

MRF4, Myf5, MyoD, and myogenin are among the myogenic basic helix-loop-helix transcriptional factors that control the well-organized, multistage process of myoblast development (Sartorelli & Caretti, 2005).

Effective cell differentiation is ensured by the strict regulation of these myogenic regulatory elements. A key promyogenic kinase, Akt contributes to the heterodimerization of MyoD/E-proteins and changes in chromatin remodeling at loci specific to muscles through Akt signaling (Bae et al., 2010; Lluís et al., 2005; Simone et al., 2004).

Skeletal muscle growth linked to increased protein synthesis is mostly regulated by Akt/mammalian target of rapamycin (mTOR) signaling (Glass, 2003; Rommel et al., 2001) . Additionally, by blocking atrophy-related ubiquitin ligases and FoxO transcriptional factors, phosphatidylinositol 3-kinase/Akt pathways stop muscle atrophy (Stitt et al., 2004) .

Additionally, differentiated myoblasts treated with mountain ginseng had higher amounts of myosin heavy chain (MyHC) (Seok et al., 2021), whereas dexamethasone decrease MyHC (Clarke et al., 2007).

Higher myostatin expression is inhibited by mountain ginseng therapy (Ahmad et al., 2024). Mountain ginseng lowers atrogin1 and MuRF1 (muscle ring-finger protein-

1) expressions (Seok et al., 2021), which both show transcriptional upregulation in atrophic environments (Bodine & Baehr, 2014). It has been demonstrated that during synthetic glucocorticoid therapy, MuRF1 directly contributes to the ubiquitination and destruction of myosin heavy chains (Clarke et al., 2007).

By boosting mitochondrial biogenesis, preventing muscle breakdown, and promoting myoblast proliferation and myotube differentiation, ginsenosides Rb1, Rb2, Rd, Rg1, Rg3, and Rh2 have been shown to have a positive impact on muscular strengthening (Dong et al., 2022)

Dexamethasone cause decrease in mean cross sectional area of muscle fibre. Also, The cross sectional area of muscle fibers was improved and significantly increased in gensing treated rats, it was observed that muscle fibers were regenerated and there were improved muscle degenerative changes caused by dexamethasone. This confirms that ginseng enhances muscle regeneration and can be used for therapeutic intervention of atrophy and muscle weakness (Ahmed et al., 2024).

Muscle stem cells (MuSCs), often referred to as satellite cells, has the capacity for both differentiation and proliferation. Normally quiescent MuSCs are activated and undergo additional differentiation following skeletal muscle injury in order to support muscular tissue regeneration and preserve skeletal muscle homeostasis. Since oxidative stress causes inflammation and damage, skeletal muscle's ability to regenerate itself depends mostly on its ability to self-renew via activating and differentiating MuSCs (Yanay, Rabie, & Nevo, 2020). Many of researches have revealed that MuSC dysfunction has been linked to a number of myopathies, including disused muscular atrophy and Duchenne muscular dystrophy (Liu et al., 2021; Yamakawa et al., 2020).

The MuSC population or function was compromised, which increased its susceptibility to free-radical stress and slowed its rate of damage recovery. Senescent MuSCs mechanically experienced greater oxidative stress and were more readily eliminated through apoptosis or went into an irreversible quiescent state (Picca et al., 2018). A bioactive ingredient taken from ginseng called ginsenoside Rb1 has anti-aging, anti-inflammatory, and antioxidant properties (Zhou et al., 2019). Ginsenoside Rb1 may improve MuSC function and prevent apoptosis by lowering oxidative stress levels, thereby mitigating oxidative damage to MuSCs or revitalizing MuSCs in senescent skeletal muscle (Dong et al., 2022).

Conclusion

Activation of endogenous stem cells by panax ginseng and G-CSF can play important

role in degenerative changes causeg by corticosteroid myopathy.

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