Thyroid hormones and tendon: current views and future perspectives. Concise review

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Summary

Thyroid hormones (THs) T3 and T4, play an essential role in the development and metabolism of many tissues and organs, and have profound metabolic effects in adult life. THs action is mediated mainly by the thyroid hormone receptor (TRs) which seem to be ubiquitous. To-date thyroid-associated disease are not thought to be related in tendinopathies and tendons tears. Recent study demonstrated the presence of TRs in tendons and their possible role in the proliferation and apoptosis of human tenocyte isolated from tendon. We review new discovery that revisit our current thinking on the tendon biology focusing on thyroid hormones (THs) T3 and T4, and their possible role on human tenocyte.

KEY WORDS: thyroid hormones, T3, T4, tenocytes, rotator cuff tendons, tendon tears.

Introduction

Thyroid hormones (THs), T3 and T4, play an essential role in the development and metabolism of many tissues and organs, and exert profound metabolic effects in adult life, including changes in oxygen consumption, protein, carbohydrate, lipid, and vitamin metabolism[1]. The effects of THs are mediated mainly through T3, which regulates gene expression by binding to the TH receptors (TR)-α and -β. TRs belong to a large superfamily of nuclear hormone receptors which includes steroid hormones, retinoic acid, Vitamin D and peroxisomal proliferator receptors (PPARs)[2]. These receptors also bind to enhancer elements in the promoters of target genes, and can regulate both positive and negative transcription. Recent evidence has characterized some of the molecular mechanisms by which THs regulate transcription, as co-repressors and co-activators have been identified, and their effects on histone acetylation examined[3]. THs also manifest rapid effects that do not require transcription. These can occur via TRs or other cellular proteins, and typically occur outside the nucleus[4].
Tendinopathies and tendons tears are not thought to be related to thyroid diseases, but to our knowledge no studies have evaluated in a systematic fashion this association. In any case, thyroid hormone receptors (TRs) seem to be ubiquitous[5].
The relationship between thyroid disorders and shoulder pain has been suspected since the late 1920s[6], but it has not been systematically investigated[7-11]. More recently, however, such association has been more formally hypothesized[12], and some orthopedic surgeons theorize that thyroid diseases should be linked to idiopathic tendinopathies[13,14].
Thyroxine is important for both collagen synthesis and matrix metabolism[2]. Hypothyroidism causes accumulation of glycosaminoglycans (GAGs) in the extracellular matrix, which may, in turn, predispose to tendon calcification[15]. GAGs are involved in the pathogenesis of carpal tunnel syndrome during hypothyroidism[15]. Elevation of (GAGs), IL6 and TNF has also been reported in exophtalmos in hyperthyroidism[16-18].
Tendinopathy can be the presenting complaint in hypothyroidism, and symptomatic relief can be obtained by appropriate management of the primary thyroid deficiency[19], while calcific tendinopathy has been associated with thyroid dysfunctions[20].

Thyroid hormones receptors and tenocyte

To date, the presence and effects of THs *in vivo* and *in vitro* on tenocytes have not been previously investigated. A recent study (Oliva et al. 2013) demonstrat-

ed by Western Blot analysis that thyroid hormone α/β nuclear receptor isoforms are express at high levels in healthy and pathological rotator cuff tendons, with no apparent difference in THs expression between tendon from normal subjects and patients with thyroid disease. Furthermore, the expression levels in the tendon from the patients with thyroid disease appear not to be influenced by treatment of the pathological condition[21]. Ayala et al. identified in 1991 by immunocytochemical techniques the expression of T3 within the cell nucleus and between the heteroeuchromatin transition zone in chicks[22]. The authors were able to show that all the chicks that underwent tenotomy showed a decrease in the number of T3 receptors of collagen-forming fibroblasts as the tendons healed, and their capacity to synthetize collagen diminished. Furthermore, the relationship between thyroid disorders and collagen has been long described[23]. In particular, hyperthyroidism is accompanied by increased rates of catabolism of both soluble and insoluble collagen, and hypothyroidism is accompanied by decreased rates of catabolism of collagen.

Tenocytes are specialized fibroblasts which ensure to the homeostasis of the ECM (extracellular matrix) components of tendons, through a wide variety of complex mechanisms. Fibroblasts from different tissue sources, subjected to mechanical stress, show phenotypic and gene expression differences[24]. Skin fibroblasts and tenocytes derive from the mesoderm and have similar characteristics in terms of cell morphology and extracellular matrix components. Indeed, recently attempts to manage tendons disorders have used engineered skin fibroblasts for porcine flexor digital superficial tendon defects[25], human patellar tendinopathy and epycondilitis[26,27].

Several line of evidence indicate that THs regulate several cellular functions. One such function is proliferation. Oliva et al. examined the action of T3 and T4, in an *in vitro* assay, on cell proliferation by time-course and in a dose dependent manner in primary tenocytes from the tendon biopsy of 5 normal patients who underwent surgical reconstruction of rotator cuff tears. The data from this study show that both T3 and T4 act on cell growth in dose dependent manner. At 72 h of hormone treatment at concentration of 10^{-7}M, we obtained the highest increase (19%) for T3 and T4 (10%) compared with primary tenocytes grown without thyroid hormones. The action of thyroid hormones on cell growth has been demonstrated both *in vitro* and *in vivo*[28]. THs regulate cellular metabolic activity, including cell proliferation, apoptosis, and differentiation. Their pleiotropic nature has become more evident by studying amphibian metamorphosis: at cellular level, this entire process is caused by a combination of apoptosis and cell proliferation strictly controlled by THs. Further studies by performing annexin V experiments to investigate the possible action of T3 and T4 on apoptosis on primary tenocytes from healthy rotator cuff tendons show that THs counteracted apoptosis in this primary cells after 48 serum deprivation. Tissue hypoxia and apoptosis have been demonstrated in tears of the rotator cuff[29-30]. Apoptosis should be considered one of the final mechanisms within the picture of the failed healing response typical of tendinopathy. THs seem to have a protective actions against apoptosis induced by serum deprivation[31].

That study has nevertheless several limitations: they did not perform immunohistochemistry to demonstrate the presence of T3 and T4 receptors isoforms *in vivo*; we need to understand whether, with other methods to induce tenocytes apoptosis, THs still exert a favourable action; to our knowledge, furthermore, this is the first report where it is clearly demonstrate that the receptors isoforms for T3 and T4 are present on rotator cuff tendons.

Future perspectives

The relationship between thyroid hormones and tendons diseases appears clinically relevant. The presence of high levels of TR isoforms, their protective action during tenocyte apoptosis, and the capability to enhance tenocyte proliferation *in vitro* in healthy tendons reinforces the idea of a physiological action of THs in the homeostasis of tendons, but does not allow to clarify the role of THs in the pathogenesis of the rotator cuff tears. There is increasing recognition of the prevalence of autoimmune thyroid diseases in patients with connective tissue disorder, highlighting a common mechanism for this disease pathogenesis[23,32,33]. Much research remains to be performed to clarify the exact role of THs in tendon tissues and their implications in tendons ruptures, tendinopathies and tendon healing. If this association is confirmed, assessment and management of patients with tendon conditions may have to be revisited.

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