Do corticosteroids treat or exacerbate tendinopathy? A study of substance P regulation by dexamethasone

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BACKGROUND Corticosteroid drugs are frequently used for treating tendinopathy; although their mechanism of action is controversial. Several randomized trials and systematic reviews have demonstrated acute pain-relief in patients with tendinopathy who receive corticosteroid injections, although there are increased risks of rupture or long-term recurrence of tendon pain. Dexamethasone, as a potent member of glucocorticoid class, has a range of effects on cell survival, cell signalling and gene expression [1]. SP has previously been shown to be correlated to pain levels in tendinopathy. SP can be endogenously produced by tendon fibroblasts, particularly when these cells are subjected to repetitive mechanical loading [2]. We hypothesize that glucocorticoids reduce the SP production in tendon fibroblasts. If this hypothesis is confirmed, it would lead us to speculate that reduced SP production by tendon in response to dexamethasone can lead both to short-term pain relief and to a longer term decrease in tensile strength of the tendons.

METHODS Human tendon fibroblasts were isolated from healthy Achilles or hamstrings tendons of male and female recreational athletes aged 22-40 (N=6). Each protocol was approved by the local ethics committee. Cells were cultured in the presence or absence of dexamethasone (1 to 400 nM), an inhibitor of the glucocorticoid receptor (RU486), recombinant TGF-beta (2.5 or 5.0 ng/ml), or an inhibitor of the TGF-beta receptor (A83.01), recombinant human IL-1β and IL-6. Expression levels of the genes encoding for SP (TAC1) and its preferred receptor (NK1R), IL-1α, IL-1β and IL-6 were determined with qPCR, and protein levels of SP were examined by enzyme immunoassay and Western blot.

RESULTS Exposure of human tendon cells to dexamethasone resulted in a time-dependent reduction of mRNA for SP in both hamstrings and Achilles tenocytes, whereas NK1R was unaffected. SP protein was also substantially decreased by dexamethasone. The reduction of SP mRNA was dependent on signalling through the glucocorticoid receptor. Dexamethasone also down-regulated the expression of SP induced by IL-1β and cyclic mechanical loading.

CONCLUSION Dexamethasone is a potent inhibitor of SP expression which blocks the induction SP by tensile loading and inflammatory cytokines in tendon fibroblasts. This effect might have a pivotal role in short term pain relief after dexamethasone therapy of tendinopathy. Our study suggests that targeting SP signaling might be a crucial point for future treatments of tendinopathy.

REFERENCES

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