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Substance P Inhibitor Prevents Dexamethasone-Induced Tendon Degradation in a Collagenase-Induced Tendinopathy Rat Model

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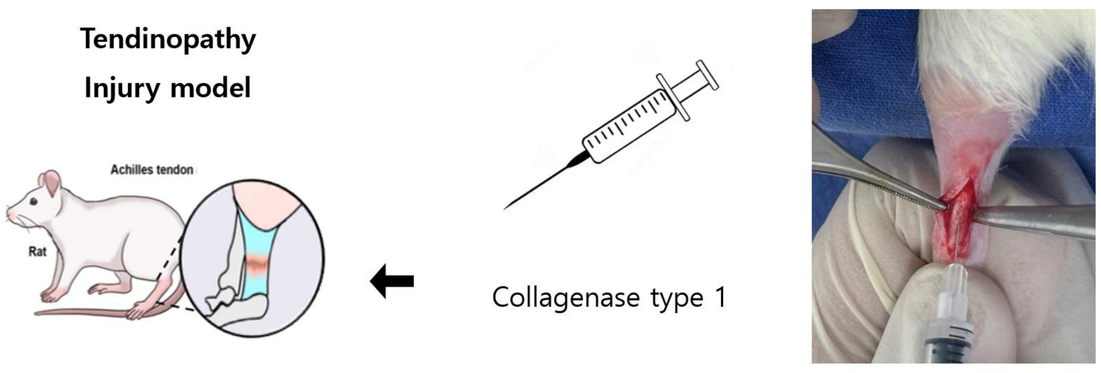
Background

- Corticosteroids are widely used to treat tendinopathy but can induce tendon degeneration, including reduced tenocyte activity and ECM disruption.
- Substance P (SP) is involved in inflammation and tendon remodeling, suggesting that its inhibition may counteract corticosteroid-induced damage.
- This study aimed to evaluate whether a Substance P inhibitor (SPI) can attenuate Dexamethasone-induced tendon degradation in a collagenase-induced tendinopathy rat model.

Material and methods

1. Animal model (collagenase induced tendinopathy model)

- Chronic Achilles tendinopathy (CIT) was induced in 8-week-old Sprague–Dawley rats by intratendinous injection of collagenase type I (3 mg/mL) into the mid-portion of the Achilles tendon.



2. Drug administration

- Animals were randomly assigned to four groups as follows

1) **CIT** control group: Received PBS administered using the same dosing schedule and injection volume as the SPI group.
2) **Dex** group: Dexamethasone(Dex) (2.5 mg/kg) was administered subcutaneously once daily for 4 consecutive days, starting 7 days post-induction.
3) **SPI** group: Substance P (SPI, 5 mg/kg) was administered intraperitoneally three times per week for 2 weeks, starting 3 days after CIT induction.
4) **SPI+Dex** group: Received both SPI and Dex according to the same dosing schedule as described above.

3. Real-time PCR analysis

- Total RNA was extracted from tendon tissues.
- Quantitative real-time PCR was performed using specific primers and SYBR Green Master Mix on a QuantStudio™ 6 Pro Real-Time PCR System (Thermo Fisher Scientific).
- Expression levels of tenogenic markers (Tnmd, SCX) and Extra cellular matrix (ECM)-related genes (TNC-C, Col I, Col III) were analyzed.

4. Statistical analysis

- Data were analyzed using one-way ANOVA, with statistical significance set at $p < 0.05$.

Results

1. Dex treatment led to a profound downregulation of tenogenic marker Tnmd (Figure 1).

- This finding suggests corticosteroid-induced tenocyte impairment and tissue atrophy
- Co-administration of SPI and Dex rescued this downregulation.

2. Co-administration of SPI and Dex increased tenogenic marker SCX (Figure 2A) and ECM-related gens (TNC-C, COL I) expression (Figure 2B and 2C).

3. Co-administration of SPI and Dex optimized the ECM-related genes Collagen I/III ratio toward tendon maturation (Figure 3).

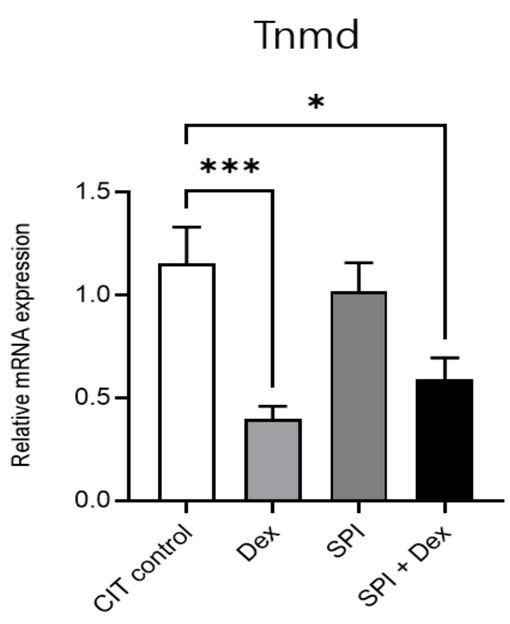


Figure 1. Co-administration of SPI and Dex rescued dexamethasone-induced downregulation of tenogenic marker Tnmd.
Relative mRNA expression levels of Tnmd in tendon tissues from each experimental group (CIT control, Dex, SPI, and SPI+Dex). Dex treatment significantly downregulated Tnmd expression ($p < 0.001$), whereas co-administration with SPI effectively restored its expression.

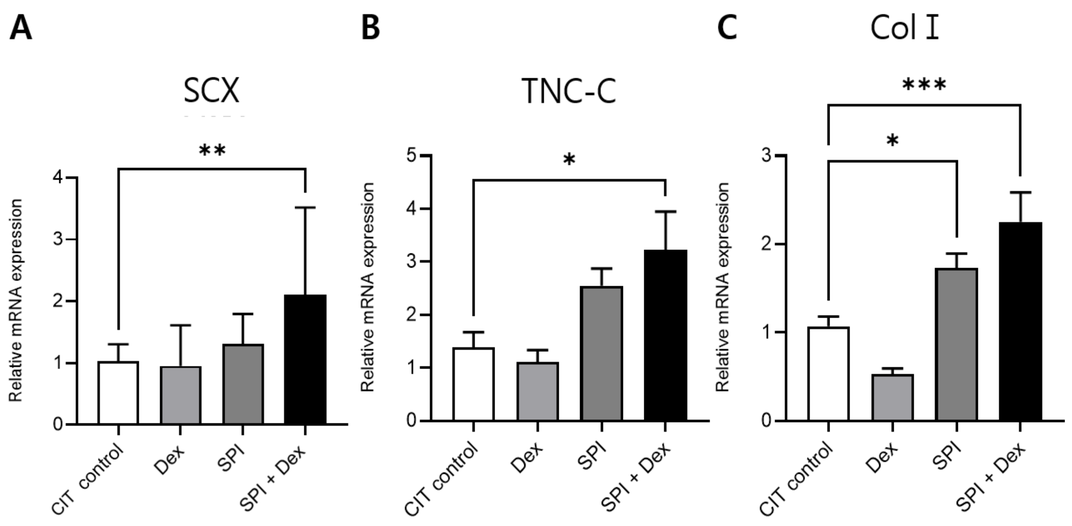


Figure 2. Co-administration of SPI and Dex increased tenogenic marker SCX expression (Figure 2A) and ECM-related genes (TNC-C, Col I) expression (Figure 2B and 2C).
Relative mRNA expression levels of SCX, TNC-C and Col I in tendon tissues from each experimental group (CIT control, Dex, SPI and SPI+Dex). Co-administration of SPI and Dex increased SCX ($p < 0.01$), TNC-C ($p < 0.05$) and Col I ($p < 0.001$) expression, compared to the CIT control group.

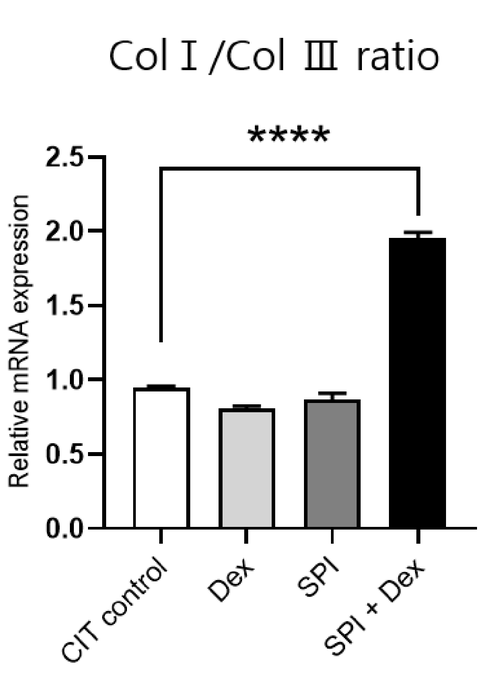


Figure 3. Co-administration of SPI and Dex optimized the ECM-related genes Collagen I/III ratio toward tendon maturation.
Relative mRNA expression ratio of Col I to Coll III ($p < 0.0001$) in tendon tissues from each experimental group (CIT control, Dex, SPI and SPI+Dex). The SPI+Dex group showed a markedly higher Col I/III ratio compared to the CIT control group, indicating improved extracellular matrix remodeling.

➢ Data are presented as mean ± SD.
*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

Conclusion

➢ Co-administration of a Substance P inhibitor can provide a protective effect against Dexamethasone-induced tendon degradation by preserving tenogenic markers and promoting high-quality ECM remodeling.

Acknowledgements

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