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A novel designer natriuretic peptide CD-NP suppresses TGF-beta 1 induced collagen Type I production in human cardiac fibroblasts

Tomoko Ichiki*, Brenda K Huntley, S Jeson Sangaralingham, Horng H Chen and John C Burnett Jr

Address: Cardiorenal Research Laboratory, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, 55905, USA

Email: Tomoko Ichiki* - ichiki.tomoko@mayo.edu

* Corresponding author

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Background

TGF-beta 1 (TGF), is one of the potent profibrotic factors which plays a fundamental role in myocardial remodeling. Cardiac fibrosis results from excessive deposition of extracellular matrix including collagen type I (Col I) which is mainly produced by cardiac fibroblasts. CD-NP is a novel engineered designer natriuretic peptide (NP) which consists of the ring structure of human C-type NP (CNP) and the C-terminal tail of Dendroaspis NP (DNP). This unique chimeric represents the first dual particulate gaunylyl cyclase receptor activator known to co-activate both natriuretic peptide receptor (NPR)-A and NPR-B. Previously we reported that CD-NP stimulates the production of the NPR-A/B and the second messenger cyclic guanosine monophosphate (cGMP) in human cardiac fibroblasts (CFs). Here we hypothesized that CD-NP would suppress Col I expression stimulated by TGF in CFs.

Methods

CFs were cultured in fibroblast media on non-coated plates and passages 2 though 5 were used for experiments. Protein expression of NP receptors in CFs was determined by immunocytochemistry using custom made NP receptor antibodies. Col I protein expression was determined by commercially available Enzyme-linked immunosorbent assay kits. After 30 minutes preincubation with or without CD-NP (10^{-8} to 10^{-6} mol/l), cells were treated with or without TGF (5 or 10 ng/ml) for 48 hours.

Results

Immunocytochemistry confirmed expression of all three NPRs; NPR-A, NPR-B, and NPR-C in human CFs. Col I protein expression was significantly increased by treatment with 10 ng/ml TGF for 48 hours ($p < 0.0001$). TGF stimulated Col I protein expression demonstrated 20% inhibition by 10^{-6} mol/L CD-NP ($p < 0.0001$).

Conclusion

Human cardiac fibroblasts express all NPs receptors. CD-NP suppresses TGF-beta 1 enhanced Col I production in CFs. These results suggest that CD-NP may play therapeutic role as an anti-fibrotic peptide in cardiac remodeling warranting further studies in models of cardiac fibrosis. Circulating corin increases with age and is higher in males than females, which may have physiologic and pathophysiologic implications on NP processing.