Antifibrotic actions of N-methylethanolamine (MEA) in human dermal fibroblasts

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Tissue fibrosis develops when dysregulation of extracellular matrix (ECM) turnover favors deposition of ECM proteins over degradation. Fibrosis may then lead to organ dysfunction as observed in systemic sclerosis (SSc). In the present study, we investigated the antifibrotic properties of N-methylethanolamine (MEA). MEA suppresses the expression of COLa2(1) mRNA and its protein levels in a dose- and time-dependent manner in human dermal fibroblasts. In the same conditions, MEA enhances the expression of matrix metalloproteinase-1 (MMP-1) mRNA and its protein levels. Together, these observations suggest that MEA may inhibit ECM deposition.

TGF-β, a master cytokine leading to fibrosis, up-regulates the production of type I collagen, but down-regulates the synthesis of MMP-1. In contrast, the proinflammatory cytokine TNF-α exerts antifibrotic activities by reducing the type I collagen expression and inducing the MMP-1 expression. TGF-β signaling is propagated through SMAD pathways. TNF-α signaling involves principally NF-κB and the MAP kinase cascade. Therefore, we investigated which pathway is involved in the action of MEA. Although MEA did not influence SMAD phosphorylation, MEA induced ERK1/2, JNK phosphorylation and inhibited p38 MAPK phosphorylation. Assays using specific inhibitors of MAP kinase, PD98059, JNK inhibitor and SB203580, strongly indicated that MAP kinase pathways is involved in MEA-induced regulation of MMP1 and COLa2(1) production.

In conclusion, our study demonstrates that MEA has an antifibrotic action by reducing type I collagen production and inducing MMP-1 production. Therefore, MEA can be a promising candidate for the treatment of diseases characterized by excessive ECM deposition such as SSc.