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Title: The effects of angiotensin II and related peptides on intracellular Ca\textsuperscript{2+} release in human lung fibroblasts

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Body: Introduction. Fibroblasts are a key cell type responsible for the deposition of extracellular matrix (ECM) in idiopathic pulmonary fibrosis (IPF). Angiotensin II (AngII) increases fibroblast proliferation and ECM deposition, but little is known about other angiotensin peptides, such as Ang(1-7), or their effects on fibroblasts. Aim. To determine the effects of angiotensin peptides on intracellular Ca\textsuperscript{2+} release in human lung fibroblasts (HLFs). Method. Eight angiotensin peptides were tested for their ability to mobilise calcium in HLFs using a FLIPR assay, and the EC\textsubscript{50} calculated. Peptides that failed to mobilise Ca\textsuperscript{2+} were retested as antagonists. Results. AngI, AngII, AngIII and Ang(3-8) mobilised Ca\textsuperscript{2+} with EC\textsubscript{50} values ranging from 22nM for AngII to >10\textmu M for Ang(3-8). Telmisartan (10nM) completely abolished the Ca\textsuperscript{2+} response in all cases, indicating that all four peptides were acting via angiotensin receptor 1 (ATR1). Neither PD-123319 (ATR2 antagonist) nor A-779 (Ang(1-7) antagonist) had any effect on Ca\textsuperscript{2+} mobilisation. Pretreatment of the fibroblasts with 10\textmu M Ang(1-7) or Ang(1-9) caused 43\% and 60\% inhibition of the maximal Ca\textsuperscript{2+} response to AngII respectively, with an IC\textsubscript{50} of 2.9\textmu M estimated for Ang(1-9) in this assay. Conclusion. Four angiotensin peptides generate a Ca\textsuperscript{2+} response in HLFs via ATR1; this Ca\textsuperscript{2+} release may influence functional responses such as proliferation and ECM deposition. Ang(1-7) and Ang(1-9) inhibit this calcium mobilisation in a manner that is not consistent with simple competitive antagonism; this mechanism of inhibition requires further investigation.