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Exogenous CGRP upregulates profibrogenic growth factors through PKC and JNK signaling pathway in kidney proximal tubular cells

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Objectives : Kidney denervation prevents the development of tubulointerstitial fibrosis, but local infusion of calcitonin gene-related peptide (CGRP) into the denervated kidneys upregulates profibrogenic growth factors and restores the fibrotic feature. However, it is not clear how CGRP contributes to the upregulation of profibrogenic factors.

Methods : Both human HK-2 and pig LLC-PK1 kidney proximal tubular cells undergoing a 6 hours exposure to CGRP were treated with CGRP receptor antagonist (CGRP8-37), a specific protein kinase C (PKC) inhibitor chelerythrine, or a potent JNK inhibitor SP600125. Levels of transforming growth factor-β1 (TGF-β1) production and PKC activity were measured by enzyme-linked immunosorbent assay. Western blot analysis performed to determine the protein levels of connective tissue growth factor (CTGF) expression and c-Jun N-terminal protein kinase (JNK) phosphorylation.

Results : Administration of 1 nM CGRP significantly increased the levels of TGF-β1 production and CTGF expression at 6 and 24 hours after the onset. The exogenous CGRP also increased their protein levels in the incubation media, indicating release of their proteins from the cells. Treatment with 100 nM CGRP8-37 immediately after the onset significantly inhibited the increase in intracellular and released protein levels of TGF-β1 and CTGF during CGRP exposure. Furthermore, treatment with 1 thru 10 μM chelerythrine markedly reduced the upregulation and release of TGF-β1 and CTGF after 6 hours exposure to CGRP. Finally, inhibition of JNK phosphorylation using 1 μM SP600125 prevented the increase in TGF-β1 and CTGF upregulation and release after 6 hours exposure to CGRP.

Conclusions : Exogenous CGRP induces the upregulation and secretion of profibrogenic TGF-β1 and CTGF proteins through CGRP receptor/PKC/JNK signaling pathway in proximal tubular cells, and this pathway might be a cause of triggering inflammation cascade and tubulointerstitial fibrosis. (NRF-2016R1C1B2012080)

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