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B-CATENIN SIGNALING CONTRIBUTES TO PDGF-ELICITED BLADDER SMOOTH MUSCLE CELL CONTRACTION THROUGH UPREGULATION OF CX43 EXPRESSION

Hypothesis / aims of study

Increased gap junctions (GJs) contribute to bladder overactivity. However, the factors and mechanisms involved in the regulation of GJs in the bladder have not been well established. Here we examined whether and how platelet derived growth factor (PDGF) regulates connexin43 (Cx43) in bladder smooth muscle cells (BSMCs).

Study design, materials and methods

Cultured rat BSMCs were treated with growth factors with or without agents that interfere with phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK) and β-catenin signaling pathways. Cx43 expression was examined by Western blot, Northern blot and immunochemistry. Functional GJs were evaluated by scrape-loading dye transfer assay. BSMC contraction was measured by collagen gel contraction.

Results

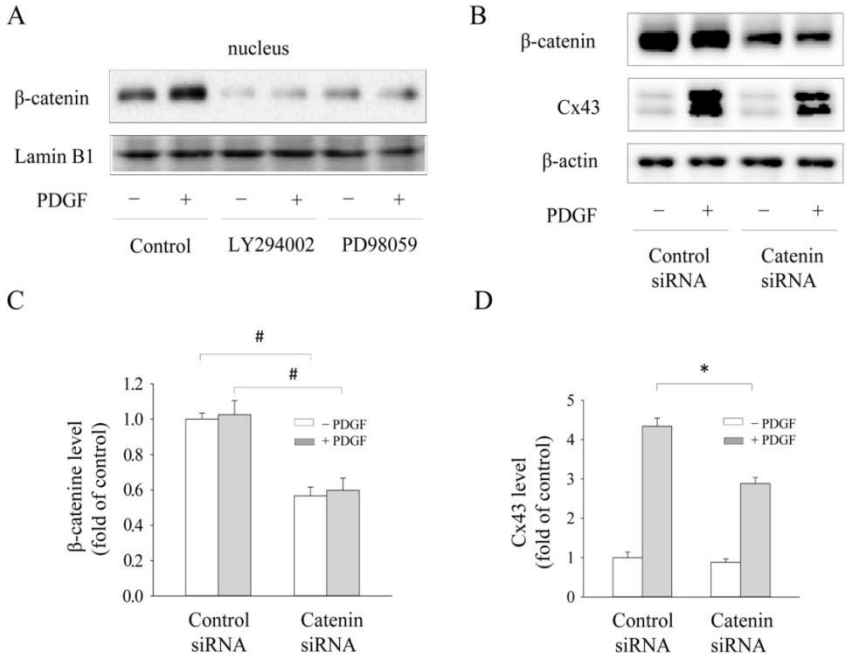
1) PDGF induced a PI3K- and MAPK-dependent accumulation of nuclear β-catenin. This was followed by an elevated Cx43 expression. 2) Downregulation of β-catenin with specific siRNA abolished, whereas stimulation of β-catenin through inhibition of glycogen synthase kinase mimicked the Cx43-elevating effect of PDGF. 3) Basic fibroblast growth factor and epidermal growth factor also induced Cx43 expression. Their effects were potentiated by PDGF. 4) Inhibition of GJs attenuated PDGF-induced BSMC contraction. Consistently, fibroblasts from Cx43 knockout (Cx43-/-) mouse displayed a much weaker contractile response to PDGF than cells from Cx43-wild (Cx43+/+) littermates.

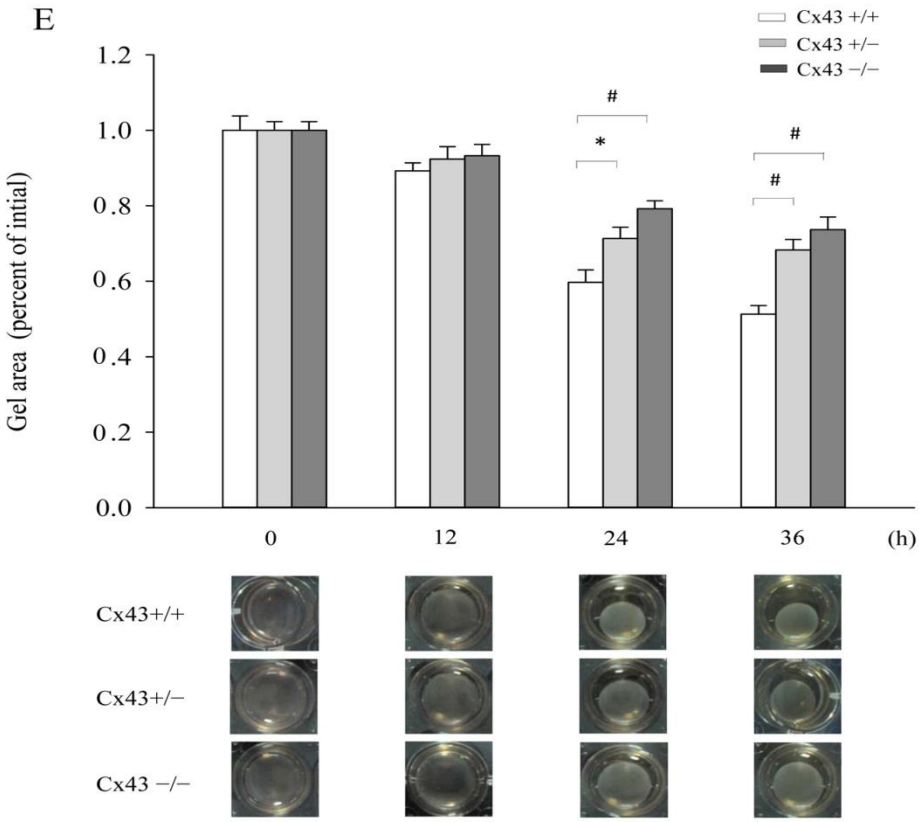
Interpretation of results

PDGF activates β-catenin through PI3K and MAPK pathways. Translocation of β-catenin into nucleus leads to increased Cx43 expression and function. The synergy between PDGF and other growth factors, as well as cAMP-elevating agents in induction of Cx43 may be explained by their cooperation in activation of β-catenin signaling.

Concluding message

PDGF induces Cx43 expression and BSMC contraction through activation of β-catenin signaling. As a convergence point for many signal pathways, β-catenin may be targeted for the treatment of bladder overactivity.





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Disclosures

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