TOBACCO SMOKE COOPERATES WITH INTERLEUKIN-1β TO ALTER β-CATENIN TRAFFICKING IN VASCULAR ENDOTHELIUM RESULTING IN INCREASED PERMEABILITY AND INDUCTION OF CYCLOOXYGENASE-2 EXPRESSION *IN VITRO* AND *IN VIVO*

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Cigarette smoking impacts all phases of atherosclerosis from endothelial dysfunction to acute occlusive clinical events. We explored activation by exposure to tobacco smoke of two genes, β-catenin and COX-2, that play key roles in inflammation and vascular remodelling events. Using both *in vivo* and *in vitro* smoke exposure, we determined that tobacco smoke (TS) induced nuclear β-catenin accumulation and COX-2 expression and activity, moreover, interacted with IL-1β to enhance these effects. Exposure of cardiac endothelial cells to tobacco smoke plus IL-1β (TS/IL-1β) enhanced permeability of endothelial monolayers and disrupted membrane VE-cadherin/β-catenin complexes, decreased β-catenin phosphorylation, and increased phosphorylation of GSK-3β, Akt and EGFR. Transfection of endothelial cells with β-catenin-directed siRNA suppressed TS/IL-1β-mediated effects on COX-2 modulation. Inhibitors of EGFR and phosphatidylinositol-3-kinase also abolished both the TS/IL-1β-mediated modulation of the Akt/GSK-3β/β-catenin pathway and enhancement of COX-2 expression. Moreover, increased levels of Akt and GSK-3β phosphorylation, nuclear β-catenin accumulation, COX-2 expression, and IL-1β were observed in cardiovascular tissue of ApoE-/- mice exposed to cigarette smoke daily for two weeks. Our results suggest a novel mechanism by which cigarette smoking can induce proinflammatory and proatherosclerotic effects in vascular tissue.