Protective effects of statins on brain vascular plasticity altered by 3-methylcholanthrene through an AhR/RhoA-mediated decreases in fibronectin/integrin induction and adherin junction stability

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We previously demonstrated that FAK/RhoA alteration by 3-methylcholanthrene (3MC) is involved in anti-migratory effects of 3MC in human umbilical vascular endothelial cells (HUVEC). Herein, we extend our previous finding to elucidate their interwoven relationship in the alteration of cerebral endothelial cell (CEC) plasticity and therapeutic intervention by simvastatin and pravastatin. PTEN phosphorylation by 3MC-mediated RhoA activation increased the proteosome degradation of β-catenin through PKCδ/pGSK3β-mediated β-catenin phosphorylation that further led to decreased expression of fibronectin and α5β1 integrin. Additionally, the decreased β-catenin was in a concomitant decrease in protein interaction among FAK/VE-cadherin/Vinculin/β-actin that could cause the adherin junction destability. The additional simvastatin or pravastain treatment reversed the 3MC-mediated alterations in CEC cells by RhoA inactivation. Novel functional TCF/LEF binding sites in the promoter regions of fibronectin and α5/β1 integrin were identified by EMSA and CHIP assay, of which their binding activities are decreased in CEC treated with 3MC. The effect of the in vitro findings was further verified in Balb/c mice using assay of blood–brain barrier (BBB) integrity. Collectively, the increased β-catenin degradation by 3MC decreased expression of fibronectin and α5β1 integrin, and adherin junction stability that was rescued by simvastatin and pravastatin. Herein, we demonstrate for the first time that simvastatin or pravastatin is a potential therapeutic intervention to protect CEC cells from 3MC-mediated alteration in brain vascular plasticity.