

Conference abstract PO-46

Growth Factor-Induced Vascular Smooth Muscle Cell Proliferation is Inhibited by Tylophorine

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Sci Pharm. 2009; 77: 245

doi:10.3797/sciopharm.oephg.21.PO-46

Tylophorine, a phenanthroindolizidine alkaloid, is the main active component of *Tylophora indica* (*Asclepiadaceae*) which is used in ayurvedic medicine to treat various allergic and inflammatory disorders, including bronchial asthma, rhinitis, whooping cough and catarrh. Various analogues of this compound showed inhibitory action against tumor cell proliferation. Thus, the activity profile of *Tylophorine* might be promising to treat vasculo-proliferative disorders, such as restenosis or atherosclerosis. The aim of the study was to examine the effect of *Tylophorine* on platelet-derived growth factor (PDGF)-induced rat aortic vascular smooth muscle cell (VSMC) proliferation and to identify the signaling pathways that are affected. At concentrations as low as 100 nM to 1 µM *Tylophorine* inhibits dose-dependently proliferation of PDGF-activated VSMCs as demonstrated by reduced BrdU-incorporation. Flow cytometric cell cycle analysis indicated an arrest of cells in the G₀/G₁-phase of the cell cycle, which was confirmed by hypophosphorylated retinoblastoma protein (Rb) and the look of c-Myc and Cyclin D expression. Moreover, *Tylophorine* was not able to block cell cycle progression in cells that had been arrested in early S-phase by the DNA-polymerase inhibitor *Aphidicolin* and subsequently released by washout of *Aphidicolin*. To identify upstream signaling pathways that are affected by *tylophorine* we performed western blot analyses, which demonstrated that neither the protein kinase Akt or the Jak/STAT3 signaling pathways nor the mitogen-activated protein kinases (MAPK) ERK1/2 and p38 are inhibited by *Tylophorine*. Although the signaling pathway affected by *Tylophorine* in PDGF-activated VSMC is not yet identified we consider *Tylophorine* due to its strong antiproliferative activity an interesting lead that warrants further investigation.