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Resveratrol-Mediated Inhibition of Ang II-Induced Akt Phosphorylation in VSMC – Is it an Antioxidant Activity?

**C. E. SCHREINER¹, M. KUMERZ¹, J. GESSLBAUER¹,
A. G. ATANASOV¹, E. H. HEISS¹, T. ERKER², V. M. DIRSCH¹**

¹ University of Vienna, Department of Pharmacognosy, Althanstr. 14, 1090 Vienna, Austria

² University of Vienna, Department of Pharmaceutical Chemistry, Althanstr. 14, 1090 Vienna, Austria

E-mail: cornelia.schreiner@univie.ac.at (C. E. Schreiner)

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It was previously shown by us that resveratrol (RV) is able to inhibit the angiotensin (Ang) II-induced phosphorylation of the protein kinase Akt in vascular smooth muscle cells (VSMC).¹ In addition, in Ang II-activated VSMC the transactivation of the epidermal growth factor (EGF)-receptor and subsequent downstream signalling events such as Akt phosphorylation are known to depend on reactive oxygen species (ROS). We therefore aimed to examine whether RV acts as antioxidant to inhibit Akt in Ang II-activated VSMC. Consistent with published data, we measured significantly increased intracellular ROS level in Ang II-activated VSMC using H₂DCFDA. In addition antioxidants like N-acetyl cystein (NAC) and the flavoprotein inhibitor diphenylene iodonium (DPI) were able to inhibit Ang II-induced Akt activation. The same concentration of RV (50 µM) that was shown to inhibit Akt kept ROS even below basal control levels in Ang II-activated VSMC. Whereas NAC and DPI act via an impaired transactivation of the EGF receptor, our previous data showed that the EGF-receptor is still phosphorylated after Ang II stimulation in the presence of RV [1]. However, an involvement of ROS and a possibly spatially restricted antioxidant effect of RV in other downstream signalling steps of Ang II are unclear. To elucidate whether the observed antioxidant property of RV is responsible for the inhibition of Ang II-mediated Akt phosphorylation, we employed a redox-inactive derivative of RV. The phenolic groups are the most important active groups of RV and are well known to mediate its antioxidant effect. A putative redox inactive derivative of RV, namely 3,4',5'-trimethoxyresveratrol (TM-RV) was synthesized. Cells were stimulated with Ang II and pre-incubated with either RV or TM-RV and Akt phosphorylation was detected. In contrast to the inhibitory effect of RV on Akt phosphorylation, TM-RV was not able to influence this signalling step in VSMC. According to these results it seems that RV inhibits the Ang II-mediated phosphorylation of Akt at least partly by inhibiting ROS.

- [1] Haider UG, Roos TU, Kontaridis MI, Neel BG, Sorescu D, Griendling KK, Vollmar AM, Dirsch VM. Mol Pharmacol. 2005; 68: 41–48. doi:10.1124/mol.104.005421