BMC Pharmacology

Meeting abstract

Inhibition of growth factor mediated Akt phosphorylation in vascular smooth muscle cells by resveratrol: the contribution of SH2 domain containing phosphatase 2 and reactive oxygen species

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from 14th Scientific Symposium of the Austrian Pharmacological Society (APHAR)
Innsbruck, Austria. 21–22 November 2008

Published: 5 November 2008

BMC Pharmacology 2008, **8**(Suppl 1):A12 doi:10.1186/1471-2210-8-S1-A12

This abstract is available from: http://www.biomedcentral.com/1471-2210/8/S1/A12

The polyphenol resveratrol (RV) was previously shown by us to inhibit the angiotensin (Ang) II and epidermal growth factor (EGF)-mediated phosphorylation of Akt in vascular smooth muscle cells (VSMC) and fibroblasts. In fibroblasts, RV was shown to activate the SH2 domain containing phosphatase 2 (Shp2) leading to subsequent dephosphorylation of Gab1 and an impaired recruitment of the phosphoinositide 3-kinase (PI_3K) to this adapter protein at the EGF receptor. The present study aims (i) to verify a role for Shp2 regarding the Akt inhibitory effect of RV in VSMC, and (ii) to examine whether the RV effect on Akt phosphorylation depends on a redox sensitive mechanism. An siRNA knock-down of Shp2 protein levels to 50% in VSMC still allowed RV to significantly inhibit EGF- as well as Ang II-mediated Akt phosphorylation, though less pronounced compared to control cells, neither verifying nor denying Shp2 as a potential target of RV in VSMC. EGF and Ang II are reported to require reactive oxygen species (ROS) to transduce their signal probably by inactivating redox-sensitive phosphatases. Indeed, intracellular ROS (measured by H_2DCFDA) was significantly induced by Ang II and EGF stimulation, and RV pre-treatment kept intracellular ROS even below basal control levels. Pre-treatment of VSMC with the antioxidant N-acetyl cystein (NAC) and flavoprotein inhibitor diphenylene iodonium (DPI) followed by stimulation with Ang II and EGF, respectively, showed that NAC and DPI were able to inhibit Ang II-mediated Akt phosphorylation. However, they failed to inhibit phosphorylation of Akt upon stimulation with EGF. This confirms that Ang II signalling requires ROS to transactivate the EGF receptor, whereas the signalling downstream of the EGF receptor towards Akt seems to occur largely independently from ROS. Since RV was shown to interfere downstream of the EGF receptor with the PI_3K/Akt pathway, we conclude that Akt inhibition by RV most likely occurs redox-independently. Thus, if Shp2 is a target for RV, it seems not to be redox-regulated by RV.