



<b>Title</b>	<b>Interaction between IP, TP, and 5-HT2 receptors during contractions to prostacyclin in rat renal arteries</b>
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### Interaction Between IP, TP, and 5-HT<sub>2</sub> Receptors During Contractions to Prostacyclin in Rat Renal Arteries

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**Introduction.** Endothelium-dependent contractions are augmented in isolated arteries of hypertensive animals. Prostacyclin has been identified as a major endothelium-derived contracting factor (EDCF) in preparations of the spontaneously hypertensive rat (SHR) – activating TP receptors on vascular smooth muscle cells, but the role of IP receptors is unknown.

**Aims.** To define the role of IP receptors in renal arteries in EDCF-mediated responses.

**Methods.** Isometric tension was recorded in Halpern-Mulvany myographs in quiescent (L-NAME 300 µmol/L) renal artery rings of SHR and normotensive Wistar Kyoto (WKY) rats (*n*=6).

**Results.** SHR renal artery rings contracted significantly more upon exposure to 60 mmol/L high potassium (high K<sup>+</sup>) depolarizing solution compared to WKY (16.6±0.6 vs 13.8±0.5 mN; *P*<0.001). The augmented EDCF-mediated responses to acetylcholine in SHR (74±5% vs 44±3% of high K<sup>+</sup> in WKY) were abolished by 10 µmol/L indomethacin and 100 nmol/L S18886. They were not affected by the IP receptor antagonist CAY10441 (1 µmol/L) in SHR but significantly increased in WKY (65±3% high K<sup>+</sup>; *P*<0.01) preparations. This compound also facilitated contractions to exogenous prostacyclin (in the presence of indomethacin, *P*<0.001) in arteries from both strains and unmasked contractions to the prostanoid during TP receptor blockade with S18886 (abolishing U46619-induced contractions also in the presence of CAY10441). These fully preserved contractions to prostacyclin during combined IP and TP receptor blockade were prevented by the 5-HT<sub>2</sub> receptor antagonist ketanserin (1 µmol/L).

**Discussion.** These findings suggest that the presence of IP receptors critically affects EDCF-mediated responses, and that contractions of renal arteries partially depend on 5-HT<sub>2</sub> receptor activation besides TP receptor signalling, when IP receptors are inhibited. Amplifying effects of endogenous serotonin may be involved in the regulation of renal artery vasomotor tone by prostanoids.

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### Oxidative Stress in Metabolic Diseases: Role of Antioxidant Nutraceuticals As Adjuvant Therapy

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**Introduction.** Visceral adiposity is considered an important source of oxidative stress (OS), which may play a key role in CVD development (1), carcinogenesis and angiogenesis. In the obese, adipose tissue is highly infiltrated with macrophages and, circulating PBMC are activated (2), contributing to increased OS as a result of high levels of ROS and reduced antioxidant status. Selenium (Se), an essential micronutrient, is incorporated in antioxidant Glutathione Peroxidase (GPx) enzymes which protect cells from OS and cell damage.

**Aims.** To investigate the effect of Se supplementation in modulating OS state representative of obese individuals and regulating angiogenic processes.

**Methods.** U937 monocyte cells were supplemented or not with Se and OS was induced by addition of 1mM paraquat (PQ)/0.7mM SNAP. Cell viability, ROS generation and GPx1-4 gene expression were assessed. A co-culture system of primary human endothelial cells and fibroblasts was used to study angiogenesis and MCAM antibody staining to assess tubule formation.

**Results.** PQ/SNAP treatment significantly reduced U937 cell viability and increased ROS generation compared to untreated control. Supplementation with 100nM Na<sub>2</sub>SeO<sub>3</sub> significantly increased cell viability by 33% and significantly reduced ROS generation by 32% in cells treated with PQ/SNAP. Correspondingly, GPx1-4 genes expression was increased by 146% and 77%, respectively. Se showed 95% inhibitory effect on tubule formation after 7 days incubation compared to untreated co-culture.

**Discussion.** Se supplementation may be effective in counteracting OS by significantly increasing antioxidant genes expression: enhancing, therefore, endogenous antioxidant protection to quench ROS generation more effectively and improve cell viability. Data from this *in vitro* study provides support for using Se as nutraceutical and adjuvant therapy to minimize OS damaging effects in metabolic diseases.

(1) Wadley A, et al. (2013) *AGE* 35, 705. (2) Dandona P *et al.* *J Clin Endocrinol Metab* 2004;89: 5043.