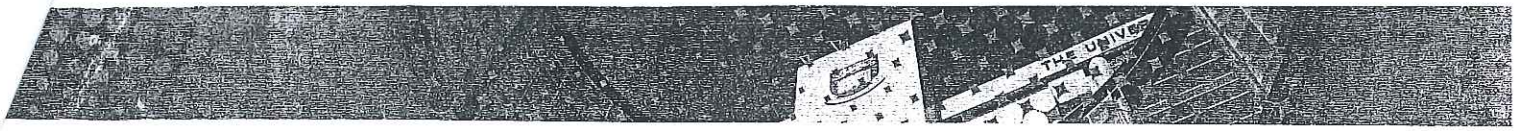

2.15

Up-regulation of Heme Oxygenase-1 Impairs Endothelium-dependent Contractions

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Endothelium-dependent contraction is a hallmark of endothelial dysfunction in cardiovascular diseases. It is characterized by the release of endothelium-derived cyclooxygenase (COX)-dependent vasoconstrictor prostanoids, which consequently diffuse to the underlying smooth muscle and activate thromboxane – prostanoids (TP) receptors. Reactive oxygen species (ROS) are team players with prostanoids in endothelium-dependent contractions. Heme oxygenase (HO) attenuates the production of ROS through its ability to degrade heme, to produce carbon monoxide (CO) and biliverdin/ bilirubin, and to release free iron. The present experiments were designed to investigate whether or not up-regulation of HO-1 by using the pharmacological agent hemin impairs endothelium-dependent contractions. Spontaneous hypertensive rats (SHR; 36 weeks old) were divided into a hemin treatment and a control group. Aortae of the rats were isolated for testing. Hemin treatment (50mg/kg, 24 hours) significantly attenuated both acetylcholine- and A23187-induced endothelium-dependent contractions. A lower intracellular ROS production and a lower release of prostaglandin $F_{1\alpha}$ (the major stable metabolite of prostacyclin) were observed in the hemin treatment group as compared to the controls, explaining the impaired contractions. However, the expression level of COX-1 and COX-2 were comparable in the two groups, indicating that hemin treatment only decreased the activity of the enzymes. Therefore, the present study demonstrates that up-regulation of HO-1 improves endothelial function by attenuating endothelium dependent contractions.

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2.16

Role of Epac1 in Pathogenesis of Diabetic Retinopathy

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Diabetic retinopathy is a leading cause of blindness in the world. It is characterized by blood retinal barrier (BRB) breakdown with endothelial cell dysfunction and pericyte loss, which may contribute to hypoxia and ischemic condition in the retina causing glial cell reactivation and neuronal cell death. Previously, it has been shown that exchange protein directly activated by cAMP 1, Epac1, which is a PKA-independent cAMP mediator, plays an important role in the HUVEC endothelial-endothelial junctional barrier function. However, it is not clear whether Epac1 also plays a role in endothelial junction of retinal microvessels. Firstly, we confirmed that only Epac1 is expressed in the human retinal microvascular endothelial cell line (HRMECs). To determine whether these endothelial cells respond to exogenous glucose level, we have treated these cells with normal (5.5 mM) and high (25 mM and 35 mM) glucose levels and determined the differential expressions of Epac1 and Epac2 in such conditions. Interestingly, the level of Epac1 expression was significantly downregulated under 35 mM glucose level compared to that of normal (5.5 mM) glucose level. Here, we hypothesize that the downregulation of Epac1 under hyperglycemic condition may contribute to the retinal endothelial barrier dysfunctionand may contribute to blood retinal barrier breakdown and the pathogenesis of diabetic retinopthy. We are currently investigating the significance of Epac1 downregulation under hyperglycemic condition using Epac1-deficient mice.