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Long, Xin

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Committee Chair:	Sturek, Michael Stephen
Committee Members:	Considine, Robert V. Gunst, Susan J. Herring, B. Paul Tune, Johnathan D.
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Abstract:

Adenosine is widely thought to elicit coronary vasodilation and attenuate smooth muscle cell (SMC) proliferation, thereby providing cardioprotection. We cloned the porcine adenosine A1 receptor (A1R) subtype and found that it paradoxically stimulated proliferation of cultured coronary SMC by the extracellular signal-regulated protein kinases 1 and 2 (ERK1/2)

signaling pathways, thus suggesting A1R dysregulation could play a role in coronary artery disease (CAD), restenosis, and regulation of coronary blood flow (CBF). We utilized the Ossabaw swine model of metabolic syndrome (MetS) to test the hypothesis that A1R activation contributes to development of CAD, in-stent stenosis, and CBF regulation. Swine were fed standard chow (Lean) or excess calorie atherogenic diet for over 20 weeks, which elicited MetS characteristics and coronary atherosclerosis compared to Lean. We observed increased A1R in native CAD in MetS, which was reversed by exercise training, and upregulation of A1R expression and A1R-ERK1/2 activation in an in vitro organ culture model of CAD. Intracoronary stent deployment followed by different durations of recovery showed A1R upregulation occurred before maximal in-stent stenosis in vi vivo. More importantly, selective A1R antagonism with 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX)-eluting stents decreased coronary ERK1/2 activation and reduced in-stent stenosis comparable to Taxus® (paclitaxel-eluting stents). A1R antagonism potentiated vasodilatory effects of some vasodilators other than adenosine in porcine coronary microcirculation under basal conditions. Short-term exercise training around stenting prevented stent-induced microvascular dysfunction and attenuated native atheroma in the genetically lean Yucatan swine. Conclusions: A1R upregulation and activation contributes to coronary in-stent stenosis in vivo in MetS, plays a role in the development of coronary atherosclerosis in vitro, and might involve in CBF dysregulation in dyslipidemia and stenting. Exercise training decreased A1R expression in atherosclerosis, reduced native atheroma, and prevented stent-induced microvascular dysfunction. Selective pharmacological antagonism of A1R holds promise for treatment of CAD.

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