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The mechanism of acute and chronic vascular effects of ivabradine in control and diabetic rats

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Topic(s):
Basic Science - Vascular Diseases: Drugs, Drug Targets

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S51

Introduction/Background: Ivabradine (IVA) is a selective inhibitor of If (f, funny) channel in the sinoatrial node and reduces both resting and exercise-induced heart rate without affecting contractility. IVA is indicated in heart failure and angina pectoris primarily for this effect. IVA’s target for inhibitory action, HCN channels, have different isoforms and they exist in the sinoatrial node, cardiac ventricles, brain, neuronal network and the endothelium of human aorta. Their expression pattern depends on the species and tissue and differs in certain pathologies such as hypertension and hypertrophy. Many experimental and clinical studies suggest that IVA has other beneficial effects on cardiovascular system. The exact mechanism of these effects unrelated to heart rate is currently not known. However, accumulating evidence indicate that it may be related to prevention of endothelial injury primarily by antioxidant effects of IVA. Purpose: Diabetes mellitus (diabetes) causes endothelial injury. Due to its potential effect on endothelium, diabetic endothelial dysfunction model was selected to investigate IVA’s pleiotropic effects. In our previous studies, we showed that IVA dose-dependently induced a relaxation in aortic rings with intact endothelium in control and 8-week diabetic rats and that these effects were significantly inhibited by pretreatment with L-NAME, but not affected by propranolol. Methods: In this study, IVA’s preventive/reversing effect on endothelial dysfunction was investigated in streptozotocin (STZ)-induced diabetic rats chronically treated with the drug. Diabetes was induced in Sprague Dawley rats with a single dose of (40mg/kg/ip) STZ. After 8 weeks of diabetes, animals were divided into 4 groups (control, diabetic, control+IVA, diabetic+IVA) and treated with IVA (10mg/kg/day, PO) or vehicle for 4 weeks. Results: STZ-diabetes caused an endothelial injury as shown by a slight reduction in endothelium-dependent relaxations induced by acetylcholine (10-9M-3x10-5M) and treatment with IVA tended improve endothelial dysfunction. Confirming our previous results in 8-week diabetic rats, a dose-dependent relaxation with IVA was observed in control and diabetic rat aorta treated with vehicle and these relaxations were significantly inhibited by L-NAME treatment and unaffected by propranolol. To further investigate the mechanism of vascular relaxations induced by IVA, control and diabetic rat aorta were pre-incubated with tetrathylammonium chloride (TEA), a non-selective K+ channel blocker. Pretreatment with TEA significantly inhibited IVA-induced relaxations in both control and diabetic rat aorta treated with vehicle. Conclusion/Future Direction: These results show that IVA has pleiotropic vascular effects that are mediated by endothelium and potassium channels. We’ll next examine the expressions vascular HCN channel proteins and whether these will be affected by diabetes and/or IVA treatment.