Abstract: P491

Therapeutic effect of carvedilol on cardiac function in streptozotocin-diabetic rats

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

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S119

Background: Carvedilol is a 3rd generation β-blocker that blocks α1, β1 and β2 adrenergic receptors. It is indicated for the treatment of heart failure, hypertension and to prevent ventricular dysfunction that can develop after myocardial infarction. It is not only superior in effectiveness to other drugs that are used to prevent myocardial infarction and cardiovascular mortality, but is also preferable since it does not cause metabolic disorders such as insulin resistance or diabetes which can occur with other β-blockers in chronic use. β-arrestin proteins have been shown to stimulate certain intracellular events in addition to mediating β-adrenergic receptor desensitization. Interestingly, carvedilol was the first 3rd generation β-blocker with this so-called "biased agonist" activity. Carvedilol antagonises the adrenergic receptors while behaving like "agonist" through activating β-arrestin proteins. β-arrestins initiate common intracellular signaling (i.e. ERK 1/2) as a result of their interaction with some receptors (i.e. β2 adrenergic receptors) and contribute to a diverse spectrum of effects such as insulin release and sensitivity. Purpose: Beneficial effects of carvedilol in insulin sensitivity and diabetes in addition to its superiority amongst other cardiovascular drugs might be attributed to its biased agonist efficacy on β-arrestin proteins. A type I diabetes model was utilized in this study to induce metabolic and cardiac disorders.

Methods: Diabetes was induced in Sprague Dawley rats with a single dose of (40mg/kg/ip) streptozotocin. After 8 weeks of diabetes, animals were divided into 4 groups [control (CV), diabetic (DV), control+carvedilol (CC), diabetic+carvedilol (DC)] and treated with vehicle or carvedilol (10mg/kg/day, PO) for 4 weeks. Cardiac function, as LVDP, LVEDP and ±dP/dt, was determined by electrically stimulated Langendorff heart preparations by the end of treatments. Results: As expected, basal cardiac function was deteriorated in diabetic rats compared to control rats treated with vehicle. Carvedilol treatment significantly improved LVDP and -dP/dt in diabetic rats but had no effect on cardiac function in control animals. Heart function was evaluated in the same hearts with isoproterenol, a non-selective β-adrenergic receptor agonist. Isoproterenol dose-dependently increased LVDP and ±dP/dt in diabetic hearts. Carvedilol treatment inhibited these changes as observed by similar cardiac parameters between control and carvedilol-treated diabetic hearts. Conclusion/Future Direction: A preventive effect associated with antioxidant properties of carvedilol has previously been reported in 5-week diabetic animals. Our results showed that chronic treatment reversed cardiac deterioration. We’ll next examine the expressions cardiac β-arrestin proteins and phosphorylated ERK 1/2 as the intracellular indicator of β-arrestin activation and whether these will be affected by diabetes and/or carvedilol treatment.