The evaluations of how affected Alpha1-Adrenergic Receptor-dependent vasocontractile Responses by Serotonin, Isoprenaline and *ex-vivo* Modifications in STZ-diabetic rat.

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Background

Cardiovascular diseases (CVDs) have very high mortality and morbidity rates in the world. Diabetes and its complications are an independent risk factor for CVDs, and they cause further increased cardiovascular risks. As a resistance artery, the mesenteric arteries have an important regulatory role for total peripheral resistance and maintaining blood pressure. The vascular tonus and blood pressure are regulated by different systemic and local mechanisms, and these can be altered by high glucose and diabetic state. The imbalance in diabetes between vascular contraction and relaxation mechanisms leads to the development of hypertension and the other CVDs. In experimental diabetic models, including streptozotocin (STZ), have shown that increased vascular sensitivity to sympathetic nervous system and local hormones. Furthermore, endothelial- and smooth muscle-dependent vasorelaxant responses have been decreased in diabetes. In addition to these diabetes-induced changes, the lack of well-blood glucose control, and inappropriate therapeutic preferences for cardiovascular disease cannot provide effective treatment but worsens disease complications in diabetics. Thus, in this study, we plan to investigate how alpha1-adrenergic receptor-induced contractile responsiveness was changed by various agonist and antagonist and explore how tissue bath *ex vivo* modifications that are designed to mimic ineffective treatments in diabetes affect contractile response in STZ-diabetic rat.

Material & Methods

8-10-week old male Sprague-Dawley rats were injected with STZ (30mg/kg). Following STZ-injections, the blood glucose levels were checked and the rats whose blood glucose levels between 300-350 mg/dl were selected for the experiments. After 8 weeks of STZ-injection, the mesenteric arteries were obtained from anesthetized rats (40mg/20mg.kg-1ketamine/xylazine). The superior mesenteric arteries (SMA) were isolated and cleared under a cold-light supported microscope in Krebs-Buffer (KB). The third branch of SMA were dissected and mounted in a micro-vessel system and the vessel's pressure was adjusted to 100 mmHg tension. Selective α1-adrenergic receptor agonist Phenylephrine (PE)-induced vasocontraction were examined in the presence and absence of non-selective Beta-receptor antagonist Timolol (Tim, 0.1μM), non-selective Beta-receptor agonist Isoproterenol (Iso, 1μM) and Serotonin (5-HT, 0.1μM) in control (C) and STZ-diabetic (D) groups. These protocols were repeated once more in the presence of high-glucose (HG, 25mM) in KB. The maximal contractile responses and EC_{50} value obtained from PE-induced concentration-response curves were analyzed, and the statistical differences were determined using One-way ANOVA, Tukey's multiple comparison test.

Results

PE-induced maximal contractile responses (MCR) in D groups were 50% higher than in C groups in normal KB and HG-KB. Tim decreased PE-induced MCR by 40% in the C group, however, PE-

induced MCR was attenuated by 24% in HG-KB. Although the same concentration of Tim was used in C and D groups, it did not change PE-induced MCR in D groups in normal KB and HG-KB. Furthermore, Iso-incubation decreased PE-induced MCR by 10 to 15 % and this profile was maintained by HG-KB in both C and D groups. 5-HT-incubation caused a small increase (200-300mg) of PE-induced MCR levels and this elevation was increased two-fold in HG-KB both C and D groups. There were no statistical differences in EC_{50} values in all groups.

Conclusion

The increased α1-adrenergic receptor-depedent vasocontractile responses are further increased by 5-HT and HG in STZ-diabetics. Beta2 adrenergic receptor-dependent response of isoprenalin that depressed maximal contraction did not change in STZ-diabetics. Thus, treatment with a non-selective beta-receptor antagonist such as Timolol is an inappropriate therapeutics preference for diabetics.