Bacterial toxin, streptolysin O caused vascular endothelial dysfunction: Relationship between dysbiosis and hypertension

Masashi Mukohda[1], Sho Nakamura[2], Kosuke Takeya[3], Akira Matsuda[4], Takanori Yano[5], Risuke Mizuno[1], Hiroshi Ozaki[1]

[1]Lab. of Vet. Pharm., Faculty of Vet. Med., Okayama Univ. of Science, [2]Lab. of Animal Health, Faculty of Vet. Med., Okayama Univ. of Science, [3]Lab. of Biochem., Faculty of Vet. Med., Okayama Univ. of Science, [4]Lab. of Internal Med., Faculty of Vet. Med., Okayama Univ. of Science, [5]Dept. Applied Microbio., Faculty of Science, Okayama Univ. of Science

Emerging evidences provide a microbial imbalance (dysbiosis) is linked to several diseases including cardiovascular diseases. It has been reported that Gram-positive *Streptococcus* genus is increased in feces of spontaneous hypertensive rat (SHR) with increased intestinal permeability. However, the mechanism by which the dysbiosis induces increased blood pressure remains unknown. We hypothesized that bacterial toxin derived from gut *Streptococcus* genus in hypertension may cause dysregulation of blood pressure. In this study, we examined the effect of streptolysin O, a streptococcal pyrogenic exotoxin, on vascular function using Wistar rat. Treatment with streptolysin O (10-1000 ng/ml, 30 min) did not change contractile responses to phenylephrine or serotonin in aorta (n=4). In contrast, streptolysin O significantly impaired acetylcholine-induced endothelial dependent relaxation in a dose-dependent manner (n=6, $p<0.05$), while sodium nitroprusside-induced endothelial independent relaxation was unchanged (n=4). Streptolysin O increased the level of eNOS phosphorylation at Thr495 (n=6). Endothelial dysfunction caused by streptolysin O was attenuated by pan protein kinase C (PKC) inhibitor (Ro 31-8222, n=6, $p<0.05$), PKCβ inhibitor (LY 333531, n=5, $p<0.05$) or selective PKCβ2 inhibitor (GCP53353, n=3, $p<0.05$). We conclude that streptolysin O may cause increment of blood pressure through vascular endothelial dysfunction, which is mediated by PKCβ2-induced phosphorylation of eNOS inhibitory site.