has been implicated in the pathogenesis of sepsis. We recently demonstrated that ET-1 plays an important role in the development of ALI in a rat model of sepsis. As an extension of recent study, in this investigation we investigated whether landiolol hydrochloride, an ultra-short-acting β-blocker, can play an important role in ameliorating LPS-induced ALI through the normalization of ET-1. Male Wistar rats at 8 weeks of age were administered with either saline or lipopolysaccharide (LPS) for 3 h and some LPS-administered rats were continuously treated with landiolol for 3 h. The features of acute lung injury were observed at sepsis model. At 3 h after LPS administration, both circulatory and pulmonary TNF-α levels increased and PaO2 significantly decreased LPS administration. LPS induced a time-dependent expression of ET-1 in the lungs compared to control, peaking and increasing by 3 fold at 6 h after induction of endotoxemia, whereas levels of ET (B) receptor, which has vasodilating effects, were remarkably down regulated time-dependently. We conclude that time-dependent increase of ET-1 and ET (A) receptor with the down regulation of ET (B) receptor may play a role in the pathogenesis of acute lung injury in endotoxemia. Finally, treatment of LPS-administered rats with landiolol for 3 h failed to normalize the upregulated pulmonary ET-1 and TNF-α levels. Another study found that landiolol can ameliorate ALI in LPS-induced sepsis model. These data taken together, led us to conclude that landiolol mediated ALI improvement in sepsis does not involve pulmonary ET system. 

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Blockade of TRPC6 is a novel therapeutic approach against pathological cardiac remodeling

Hideyuki Kinoshitaa, Koichiro Kuwaharaa, Motohiro Nishib, Hitoshi Kurosek, Shigeki Kiyonakac, Yasuo Moric, Chinatsu Yamadaa, Kazuhiro Nakaoa, Yoshihiro Kuwabarab, Shinji Yasunob, Yasuaki Nakagawaa, Toshio Nishikimia

aDepartment of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Kyoto, Japan
bDepartment of Pharmacology and Toxicology, Kyusyu University Graduate School of Pharmaceutical Sciences, Japan
cDepartment of Synthetic Chemistry and Biological Chemistry, Kyoto University Graduate School of Engineering, Japan
E-mail address: kinoskuhp.kyoto-u.ac.jp (H. Kinoshita)

Background: Expression of transient receptor potential subfamily C (TRPC) 6, receptor-operated Ca2+ channels, is increased in hypertrophic and failing hearts. TRPC6 has been shown to be a positive regulator of calcineurin-NFAT signaling that drives pathological cardiac remodeling. In this study we examined the effect of TRPC inhibition on the pathological cardiac hypertrophy. Methods and results: In cultured neonatal rat ventricular myocytes, overexpression of TRPC6 increased basal and ET-1-induced NFAT-dependent RACAN1 promoter activity. BTP2, a selective TRPC channel blocker, significantly and dose-dependently inhibited activation of the RACAN1 promoter, and attenuated hypertrophic response of cultured cardiac myocytes. Knocking-down of TRPC6 and 3 using siRNAs significantly inhibited ET-1- or Ang II-induced increases in Ca2+ oscillation, and knocking down either TRPC6 or 3 had a similar effect. In model mice lacking GC-A, which is a common receptor for atrial and brain natriuretic peptides, the expression of TRPC6 and RACAN1 was increased and BTP2 significantly attenuated the cardiac hypertrophy observed in GC-A KO mice without affecting blood pressure. BTP2 also inhibited AngII-induced cardiac hypertrophy in mice. Compatible with the notion that TRPC6 and 3 form heteromultimeric cation channels, Pyrazole-3, a selective TRPC3 blocker, which can inhibit the ion channel activity of TRPC3/6 hetero-complex, also significantly inhibited Ang-II induced cardiac hypertrophy in mice. Conclusions: Blockade of TRPC6 could be a novel therapeutic strategy for preventing pathological cardiac remodeling.

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Effects of landiolol hydrochloride, an ultra-short-acting β-blocker, on cardiac endothelin system in a rat model of endotoxemia: A possible relevance with cardiac functional compensatory events at the early phase of sepsis

Yoshimoto Seki, Subrina Jesmin, Nobutake Shimojo, Majedul Islam, Tanzila Khatun, Hideaki Sakuramoto, Keiichi Hagiya, Satoru Kawano, Taro Mizutani

Department of Emergency and Critical Care Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
E-mail address: yseki@asahi-net.email.ne.jp (Y. Seki)

Landiolol, an ultra-short-acting and highly cardioselective beta-1 blocker, has become useful for various medical problems. Recent studies have demonstrated that co-treatment with landiolol protects against acute lung injury and cardiac dysfunction in a rat model of lipopolysaccharide (LPS)-induced systemic inflammation which was associated with a significant reduction in serum levels of the inflammation mediator HMGB-1 and histological lung damage. Endothelin (ET)-1, a potent vasoconstrictor, has been implicated in the pathogenesis of sepsis and sepsis-induced multiple organ dysfunction syndrome. In the current study, we investigated whether landiolol hydrochloride can play an important role in ameliorating the LPS-induced altered cardiac ET system in a rat model of endotoxemia. Male Wistar rats at 8 weeks of age were administered LPS for 3 h and some LPS-administered rats were continuously treated with landiolol for three hours. At 3 h after LPS administration, circulatory TNF-alpha level was highly increased. Blood lactate concentration and percentage of fractional shortening of heart have also significantly increased after LPS administration. In addition, LPS induced a significant upregulated expression of various components of ET-1 system in the cardiac tissues compared to control. Finally, treatment of LPS-administered rats with landiolol for 3 h potentially normalized the increased blood lactate level, cardiac functional compensatory events without an effect on plasma TNF-alpha and ET-1 levels. Most strikingly, landiolol treatment has greatly normalized the various components of ET-1 system in endotoxicemic heart. These data taken together, led us to conclude that landiolol may be cardio protective in endotoxemia normalizing the vasoactive peptide like endothelin without altering the circulatory level of potential inflammatory cytokine like TNF-alpha.

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Inhibitory effect of eicosapentaenoic acid on cardiomyocyte in endothelin induced hypertrophy via PPAR-α

Nobutake Shimojoa, Subrina Jesmini, Satoshi Sakai, Seiji Maedar, Takeaki Miyachi, Satoru Kawanob, Taro Mizutanic, Kazutaka Aonumac

aCardiovascular Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
bEmergency and Critical Care Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
E-mail address: nokesismojo@yahoo.co.jp (N. Shimojo)

Growing body of evidences state the cardiovascular benefit of fish oil including eicosapentaenoic acid (EPA) in humans and experimental animals, but the effect of EPA on endothelin (ET)-1-induced...