Increased susceptibility of hERG channels to d-sotalol hydrochloride due to an addition, which may partly explains the mechanism of Myr lowering heart rate.

Methods: Renovascular hypertension was induced by two-kidney one-clip (2KC). Dyrk1A and ASF protein expression were measured by western blotting, and real-time PCR was used to determine the alternative splicing of CaMK IIβ.

Results: After two-kidney one-clip (2KC), rats were treated with valsartan (30 mg/kg per day) for 8 weeks; hypertrophic parameter analysis showed that valsartan attenuated cardiac hypertrophy in renovascular hypertensive rats. Western blot analysis showed that valsartan significantly attenuated 2KC-induced increase in the transcriptional expression of Dyrk1A, while significantly reversed 2KC-induced nuclear speckle transportion of ASF in renovascular hypertensive rats. RT-PCR demonstrated that valsartan adjusted 2KC-induced imbalance in alternative splicing of CaMK IIβ by up-regulating the mRNA expression of CaMK IIβ and down-regulating the mRNA expression of CaMK IIαA and CaMK IIβ.

Conclusions: The results suggested that valsartan inhibition of cardiac hypertrophy in renovascular hypertensive rats might be at least partly mediated by Dyrk1A/ASF regulated alternative splicing of CaMK IIβ.

GW25-e2405
Myricetin Inhibits Kv1.5 Channel Expressed in HEK 293 Cells
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Objectives: Myricetin (Myr) is a flavonoid. The previous studies reported that Myr had antiarrhythmic effect. The potential ionic mechanisms are, however, not understood. The present study was designed to investigate the effect of Myr on Kv1.5 channel expressed in HEK 293 cells using a whole-cell patch-clamp voltage-clamp technique and western blotting.

Methods: We recorded the current of Kv1.5 expressed in HEK 293 cells with a whole-cell patch voltage-clamp technique and western blotting.

Results: Myr reduced I_{K1.5} from 211.0407 ± 48.37848 (pA/pF) to 897.20239 ± 17.75726 (pA/pF) (n=9, P=0.013<0.05, V5 Control) in a dose-dependent manner. Current suppression ratio (0.3101 ± 0.1234) increased to (0.5497±0.1000) under the effect of Myr from 5 min to 20 min. I_{K1.5} was 897.20239 ± 17.75726 (pA/pF) at 0.5, 1, 3, 4 Hz, respectively. Moreover, Myr inhibited hKv1.5 protein in a dose-dependent manner.

Conclusions: We have demonstrated that Myr inhibit I_{K1.5} and its protein in hK1.5, 1.5 expressed of HEK 293 cell, which was dose-, use- and frequency-dependent. In addition, which may partly explains the mechanism of Myr lowering heart rate.

GW25-e2438
Increased susceptibility of hERG channels to d-sotalol hydrochloride due to a compound mutation L539fs/C4774
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Objectives: The purpose of this study was to explore molecular mechanisms underlying the d-sotalol hydrochloride-induced QT prolongation associated with a compound mutation L539fs/C4774.

Methods: The L539fs/C4774 hERG plasmids were transfected into the HEK293 cells stably expressing WT-hERG channels to simulate heterozygous mutation (Wt+L539fs/C4774-hERG). Whole cell patch-clamp technique were used to measure hERG currents in the control condition and exposed to d-sotalol hydrochloride. Additionally, laser confocal scanning microscopy was used to evaluate the membrane distribution of hERG channel protein using a green fluorescent protein tagged to the N-terminus of hERG.

Results: D-sotalol hydrochloride caused inhibition of WT-hERG and heterozygous L539fs/C4774-hERG currents in HEK293 cells. However, the effect was more significant in the cells expressing heterozygous L539fs/C4774-hERG channels. The maximal density of tail currents in cells expressing WT-hERG channels and heterozygous L539fs/C4774-hERG channels exposed to d-sotalol hydrochloride were 34.71±2.9 pA/pF and 8.89±1.1 pA/pF, respectively, compared with the control condition. Conversely, d-sotalol hydrochloride showed 46.35% inhibition effect on heterozygous L539fs/C4774-hERG and 26.10% inhibition effect on WT-hERG. Additionally, d-sotalol hydrochloride also altered the outward currents of d-sotalol hydrochloride on the kinetics of activation, inactivation, recovery from inactivation and deactivation. In the molecular biological experiments, we found that d-sotalol hydrochloride also caused a reduction of hERG channel protein expression on the cell membrane and resulted in retention in the endoplasmic reticulum. However, the retention and retention was much more serious in the cells expressing heterozygous L539fs/C4774-hERG compared to the cells expressing WT-hERG.

Conclusions: The compound mutation L539fs/C4774-hERG obviously enhanced the susceptibility of hERG channels to d-sotalol hydrochloride. This may explain the drug-induced LQT3 and TdP related symptoms during the administration of sotalol.

GW25-e2511
The activation of the G protein-coupled estrogen receptor subsequently triggers the PKA/CREB phosphorylation pathway causes decline in collagen deposition and a parallel stimulation of elastogenesis in cultures of human cardiac fibroblasts
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Objectives: It has been previously reported that the activation of G-protein coupled estrogen receptor (GPER) can alleviate the maladaptive ventricular hypertrophy and the process that develops in mice after experimental cardiac infarction.

Methods: Our present studies, performed on cultures of human cardiac fibroblasts investigated whether such beneficial effects of this receptor would be exercised through the mechanisms interfering with deposition of major components of extracellular matrix; elastin and collagen.

Results: We found that treatment with 10-7 to 10-5 mol/L G1 (agonist of the GPER) not only resulted with a significant inhibition of collagen deposition, but also enhanced production of new elastic fibers. Knockdown of GPER using short hairpin RNAs (shRNAs) significantly reduced this effects of G1. Interestingly, we further demonstrated that the pro-elastogenic effect occurs after the selective activation of GPER subsequent initiates the downstream PKA/CREB phosphorylation pathway.

Conclusions: In our summary, our data validate a novel mechanisms in which both anti-collagenogenic and pro-elastogenic effects occurs after the selective activation of GPER further initiated the PAK/CREB pathway, induces a crucial balance between collagenous and elastic fibers that would allow for the best possible resiliency of the post-infarct scars and the optimal cardiac function.

GW25-e2521
ApoE knockout mice of different weeks of atherosclerosis of blood lipid and pathological histology observation
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Objectives: The ApoE knockout mice progress of atherosclerosis in different time points, to explore different diet of ApoE knockout mice to progression of atherosclerosis.

Methods: 8 weeks of age ApoE gene defects in mice, only 20 is given only to a high-fat diet, respectively gives ordinary diet, respectively from 8, 12, 16, 20, 24-week-old anesthesia executed 5 points each time 4 lipid and the pathological examination, determination of serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL-c), low density lipoprotein (LDL-c) content, frozen section method line sis icly drug, red oil O staining observation atherosclerotic aorta plaque formation.

Results: 16 weeks of ApoE knockout mice on a high-fat diet group in serum triglyceride levels: 2.20±0.47 mmol/L (P<0.05), total cholesterol: 17.9±1.08 mmol/L (P<0.01) and low density lipoprotein level: 4.32±0.89 mmol/L (P<0.01), blood lipid level three group was obviously higher than that of normal mice, high-density lipoprotein cholesterol (HDL-c) levels in high-fat diet group was obviously lower than normal mice group, the tendency for 0.17±3.65 mmol/L (P<0.01), ApoE knockout mice of atherosclerotic plaque area (29.20±10.38) % was significantly higher than the normal mice (3.61±1.04) % (P<0.01), with the age growth and associated with significant difference. With the time increases given different diet, ApoE knockout mice gradually aggravate the extent of atherosclerosis, a high-fat diet group than normal diet group of ApoE knockout mice serious pathological changes of atherosclerosis. The aortic root in 16 weeks of ApoE knockout mice visible lipid plaques.

Conclusions: ApoE knockout mice fed on high-fat diet, the formation of fatty streaks and fiber growths of time faster than normal mice group. So the ApoE knockout mice is the most advantageous tool in atherosclerosis research field.

GW25-e3156
Lack of non-synonymous mutation in Orai1 gene of patients with atrial fibrillation
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