Title	Genistein acutely potentiates acetylcholine-induced relaxation through a G-protein coupled pathway in spontaneously hypertensive rats
Author(s)	Lin, AHY; Leung, GPH; Leung, SWS; Man, RYK
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ABSTRACTS

Abstracts for Oral Communications:

OC5.

GENISTEIN ACUTELY POTENTIATES ACETYLCHOLINE-INDUCED RELAXATION THROUGH A G-PROTEIN COUPLED PATHWAY IN SPONTANEOUSLY HYPERTENSIVE RATS

AHY Lin, GPH Leung, SWS Leung, RYK Man
Department of Pharmacology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

Objectives: Genistein, a phytoestrogen rich in soy beans and soy products, was reported to be a vasorelaxant. This study examined the receptor and related signaling pathways in the rapid vascular actions of genistein.
Methods: Isometric tension was measured in isolated aortic rings from 32-weeks-old male spontaneously hypertensive rats (SHR).
Results: Acute exposure to genistein at 10 μM, a concentration with no direct relaxation effect, potentiated acetylcholine (ACh)-induced relaxation and reduced ACh-induced contraction in the presence of L-NAME (100 μM). Both actions were insensitive to 10 μM actinomycin D (transcription inhibitor) and 10 μM cycloheximide (translation inhibitor). The potentiation of ACh-induced relaxation by genistein in the absence or presence of indomethacin was inhibited by 10 μM NF023 and 10 μM GP antagonist-2A, the selective G_i and G_q α-subunit antagonists, respectively, but not by 10 μM NF449, a selective G_s α-subunit antagonist. Interestingly, NF023, NF449 and GP antagonist-2A did not alter the inhibitory effect of genistein on ACh-induced contraction. To further elucidate the mechanism of the vascular response given by genistein, the involvement of G-proteins was inspected in A23187-induced relaxation and contraction. NF023 and GP antagonist-2A, but not NF449 inhibited the potentiating effect of genistein on A23187-induced relaxation in the presence of indomethacin. Reduction of A23187-induced contraction by genistein was unaffected by all three G-protein inhibitors.
Conclusion: These results demonstrate that rapid vascular actions of genistein in modulating ACh-induced relaxation and contraction responses in SHR are mediated by non-genomic pathways. $G\alpha_i$ and $G\alpha_q$, but not $G\alpha_s$, were involved in the potentiating effect of genistein in ACh and A23187-induced relaxations, but none were involved in the inhibitory effect of genistein in ACh and A23187-induced contractions. Involvement of G-proteins in the enhancement of ACh-induced relaxation by genistein suggests that genistein exerts its effect through a putative G-protein coupled phytoestrogen receptor.

OC6.

ESTROGEN SUPPRESSES THE CA^{2+}/CALMODULIN-DEPENDENT PROTEIN KINASE II THUS CONFERRING CARDIOPROTECTION

Y Ma, WT Cheng, S Wu, TM Wong
Department of Physiology, The University of Hong Kong, Hong Kong SAR, China

Estrogen confers cardioprotection by down-regulating β_1-adrenoceptor and suppressing the expression and activity of protein kinase A. We hypothesized that estrogen may also protect the heart by suppressing the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), another signaling messenger activated by β_1-adrenoceptor via the Gs protein that enhances apoptosis. We first determined the expression of CaMKII in the heart of sham operated rats and ovariectomized rats with and without estrogen replacement. Both CaMKIIδ and phosphorylated CaMKII were up-regulated in the heart from ovariectomized rats, which was restored to normal by estrogen replacement. We then determined the injury and contractile responses to ischemic insult with or without β-adrenoceptor stimulation with isoprenaline (10^{-7}M) in isolated perfused hearts and isolated ventricular myocytes. The infarct size and lactate dehydrogenase release from the heart in response to ischemic insult were significantly greater after ovariectomy. Similarly the cardiac contractility, the amplitude of the electrically induced intracellular Ca^{2+} transient, which is directly correlated to the shortening of the myocyte, and TUNEL-positive cells, were also greater in the ovariectomized rats upon ischemia/reperfusion in the presence or absence of isoprenaline. Most importantly, the responses to ischemic insult in ovariectomized rats were reversed not only by estrogen replacement, but also by blockade of CaMKII with a selective inhibitor, KN93 (2.5 μM). The observations indicated that estrogen confers cardioprotection by suppressing the CaMKII. The CaMKII isoform involved may be CaMKIIδ. The effect of estrogen on CaMKII is independent of β-adrenoceptor in addition to its effect of down-regulating the receptor.