Hyperuricemia-induced Stabilization of Kv1.5 protein

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Background

Hyperuricemia has been known to induce oxidative stress, causing intracellular damage. We have reported that hyperuricemia increased atrial Kv1.5 protein and activity through activation of uric acid transporters to increase oxidative stress-dependent phosphorylation of ERK. However, the mechanism is unknown.

Purpose

To reveal how uric acid-dependent phosphorylation of ERK increase Kv1.5 proteins in atrial myocytes.

Methods and Results: HL-1 cells were used for all experiments. Although uric acid (7mg/dl) did not change the mRNA of Kv1.5 using qRT-PCR, chase experiment showed that uric acid significantly delayed the degradation of Kv1.5 protein to increase its level. It was accompanied by phosphorylation of ERK1/2 and heat shock factor (HSF)-1 to increase HSP70 and HSP90 proteins, which was confirmed by inhibition of ERK1/2, HSP70 and HSP90. Knock-down of HSP70 and HSP90 by their respective siRNAs did not reverse the increase on p-ERK level, while inhibition of ERK1/2 abolished the change on HSP70 level, suggesting the ERK1/2 as upstream to the HSPs to affect the Kv1.5 protein.

Conclusion

Hyperuricemia causes oxidative stress to the atrial-derived cardiomyocytes through the production of ROS. This stress condition induces the phosphorylation of both ERK1/2 and HSF-1 to upregulate the stress-response proteins HSP70 and HSP90, which stabilized Kv1.5 protein.

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