Transcriptomic changes in endothelial cells triggered by Na,K-ATPase inhibition: a search for upstream Na/K-sensitive genes

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Gene expression is regulated by diverse stimuli to achieve tissue-specific functional responses. Recently, we found that 3-hr inhibition of Na,K-ATPase by ouabain or by K^+-free medium sharply affects transcriptomes in vascular smooth muscle cells from rat aorta, the human adenocarcinoma cell line HeLa, and human umbilical vein endothelial cells (HUVEC). Importantly, mRNA levels' changes in these cells were highly correlated between two stimuli thus indicating that transcriptomic changes are triggered by the Na^+_i/K^+_i-mediated signaling pathway. According to the generally accepted paradigm, the Na^+_i/K^+_i-sensitive mechanism of excitation-transcription coupling is driven by changes in $[Ca^{2+}]_i$ and activation of several Ca^{2+}-sensitive pathways. In contrast, we found that Ca^{2+}-depletion using extra-and intracellular Ca^{2+}-chelators elevated rather than decreased the number of Na^+_i/K^+_i-sensitive genes. Thus, we suggest that along with canonical Ca^{2+}_i-mediated signaling, sustained elevation of the Na^+_i/K^+_i-ratio affects gene transcription via unknown Ca^{2+}_i-independent mechanism(s). In this study, we utilized Affymetrix arrays and performed a comparative analysis of time-dependent modulation of the Na^+_i/K^+_i-ratio and transcriptomic changes in HUVEC triggered by incubation with ouabain and K^+-free medium in order to identify intermediates of the upstream signaling pathway. According to our data, microRNAs, transcription factors, and proteins involved in immune response and inflammation might be considered as key components of Na^+_i/K^+_i-mediated excitation-transcription coupling. We speculate that Na^+_i/K^+_i imbalance mediates transcriptomic changes directly, through the change of DNA conformation of G-quadruplexes. Verification of the Na^+_i/K^+_i-sensitive transcription regulation mechanism should be continued in forthcoming studies.
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