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Cell-Physiological and Systems-Biological Study on Mitochondrial Na^+ Dynamics

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Summary

To clarify the coupling between mitochondrial and cytoplasmic Na^+ dynamics, we performed time-lapse imaging of cytoplasmic and mitochondrial Na^+ using SBFI and CoroNaRed, respectively, in A20 B lymphocytes, and created a mathematical model of mitochondrial ion dynamics and energy metabolisms using object-oriented programming method. We first confirmed the mRNA expressions of mitochondrial Na^+-HCO_3^- cotransporter (SLC4A7) and mitochondrial Na^+-Ca^{2+}exchanger (NCLX) in A20 B lymphocytes and HL-1 cardiomyocytes. In A20 B lymphocytes, an NCLX inhibitor CGP-37157 did not significantly affect cytoplasmic Na^+ (SBFI fluorescence), while a Na^+-HCO_3^- cotransporter inhibitor S0859 slightly increased cytoplasmic Na^+. It was speculated that mitochondrial Na^+ transporters make little impact on cytoplasmic Na^+. The inhibition of plasma membrane Na^+-K^+ ATPase by ouabain induced increases of both cytoplasmic and mitochondrial Na^+ (CoroNaRed fluorescence). CGP-37157 suppressed the ouabain-induced increase of mitochondrial Na^+, suggesting a contribution of NCLX to Na^+ influx into mitochondria. S0859 markedly increased mitochondrial Na^+, suggesting that mitochondrial Na^+-HCO_3^- cotransporter functions as a Na^+ extruder. We successfully created a mathematical model of mitochondrial ion (H^+, Na^+, Ca^{2+}, K^+) dynamics and energy metabolism under the conditions that mitochondrial CO_2 production and processing are not considered. This model reproduced well experimental data. The above findings suggested that cytoplasmic Na^+ influences mitochondrial Na^+ while mitochondrial Na^+ little affects cytoplasmic Na^+. This is probably due to a small volume ratio of mitochondria to cytoplasm, approximately 8%. Mitochondrial Na^+-HCO_3^- cotransporter was suggested to function as a Na^+ extruder, indicating HCO_3^- extrusion out of mitochondria. The Na^+-HCO_3^- cotransporter may be involved in processing vast amounts of CO_2 produced by mitochondrial metabolism. Mitochondrial Na^+ dynamics should be reexamined in terms of mitochondrial metabolism.