Piezo1-Nitric Oxide Signaling in a Population-based Model of Arterial Myocytes in Acute Hyperglycemia

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Acute hyperglycemia (HG) plays a key role in the development of arterial complications. Mechanistically, Piezo1 appears to mediate shear stress-induced activation of cytosolic endothelial nitric oxide synthase (NO), through incompletely elucidated pathways. Hyperglycemia upregulates Piezo1 expression in endothelial cells. Here, we hypothesize that Piezo1 contributes to the organ-specific detrimental effects of HG on arterial myocytes vasoreactivity and excitability by activating NO signaling. We integrated our *in silico* model of Piezo1 channel into Morotti et al. 2017 implementation of a model of rat arterial myocytes. To simulate Piezo1-NO signaling in HG-induced simulations, we set $[NO] = Piezo1\ Ca^{2+}\ flux \times c$, where c was calculated so that the model yields ~2 fold increase in $[Ca^{2+}]_i$, consistent with *in vitro* data. We explored the influence of individual ionic currents and transporters on global cytosolic $[Ca^{2+}]_i$ (Cai) and membrane potential (Em) in a sensitivity analysis on a virtual population of 1000 model variants, generated by introducing random perturbations to the conductances/maximal transport rates of all ion channels and transporters. Specifically, each parameter in the baseline model was independently varied with a standard deviation of 0.1, allowing for changes between -30% and +50% of the original value. Next, a regression analysis was performed to identify correlations between the parameter variations and their effects on Cai and Em. Our results suggest the intensified contribution of L-type Ca^{2+} channel (LTCC) on Cai in HG. Similarly, the impact of large conductance Ca^{2+}-activated K^+ channel (BKCa) on Em and Cai increased in HG, in accord with reported BKCa channel activity and sensitivity to Ca^{2+} *in vitro*. Remarkably, Piezo1 perturbations instigated opposing effects on Em and Cai in control vs. HG-induced conditions. This would imply a possible role of Piezo1-NO signaling in the heterogeneity of organ-specific vasoactive response to HG in arterial myocytes and thus a promising therapeutic avenue.