Death by Glucose: Limiting Pyruvate Kinase Activity Reduces Cytotoxic Effects of Spike Protein of SARS-CoV-2

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COVID-19 infection causes disordered sugar metabolism, both in acute infection and long COVID. Diabetic COVID-19 patients with hyperglycemia have higher mortality rates, and infection elevates risks of new-onset diabetes in non-diabetics. Understanding cellular mechanisms underlying these observations would guide the design of metabolic therapy. In human cells, SARS-CoV-2 and its surface protein Spike impair respiration and increase glycolytic flux, which favors viral replication. Since reducing activity of the glycolytic enzyme pyruvate kinase (PK) activates respiration and increases resistance to oxidative stress, it was hypothesized that limiting PK activity may reduce effects of Spike on respiration. This was studied in yeast, since yeast and human cells have similar glucose metabolic pathways. Results showed that Spike induced elevated PK activity, which was associated with increased glycolysis, impaired ATP production and inhibited aerobic growth. These effects were worsened at high glucose levels (10% instead of 2% glucose), and were caused by Spike-induced oxidative stress. Notably, in cells with reduced PK activity from PK mutation or pharmacological PK inhibition, Spike caused significantly less inhibition of ATP and growth, even at high glucose levels. Hence, under high glucose conditions, increased PK activity caused by Spike likely prevents negative feedback inhibition of glycolysis, inducing mitochondrial oxidative stress, which kills cells and drives diabetes. This novel mechanism potentially explains the link between COVID-19, diabetes and poor clinical outcomes in hyperglycemic COVID-19 patients. The rescue of Spike-exposed cells with a PK inhibitor provides proof of concept that this novel therapeutic strategy is potentially relevant to such patients.

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