The role of pyruvate dehydrogenase kinase in glucose and ketone body metabolism

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Abstract:

The expression of pyruvate dehydrogenase kinase (PDK) 2 and 4 are increased in the fasted state to inactivate the pyruvate dehydrogenase complex (PDC) by phosphorylation to conserve substrates for glucose production. To assess the importance of PDK2 and PDK4 in regulation of the PDC to maintain glucose homeostasis, PDK2 knockout (KO), PDK4 KO, and PDK2/PDK4 double knockout (DKO) mice were generated. PDK2 deficiency caused higher PDC activity and lower blood glucose levels in the fed state while PDK4 deficiency caused similar effects in the fasting state. DKO intensified these

effects in both states. PDK2 deficiency had no effect on glucose tolerance, PDK4 deficiency produced a modest effect, but DKO caused a marked improvement, lowered insulin levels, and increased insulin sensitivity. However, the DKO mice were more sensitive than wild-type mice to long term fasting, succumbing to hypoglycemia, ketoacidosis, and hypothermia. Stable isotope flux analysis indicated that hypoglycemia was due to a reduced rate of gluconeogenesis. We hypothesized that hyperglycemia would be prevented in DKO mice fed a high saturated fat diet for 30 weeks. As expected, DKO mice fed a high fat diet had improved glucose tolerance, decreased adiposity, and were euglycemic due to reduction in the rate of gluconeogenesis. Like chow fed DKO mice, high fat fed DKO mice were unusually sensitive to fasting because of ketoacidosis and hypothermia. PDK deficiency resulted in greater PDC activity which limited the availability of pyruvate for oxaloacetate synthesis. Low oxaloacetate resulted in overproduction of ketone bodies by the liver and inhibition of ketone body and fatty acid oxidation by peripheral tissues, culminating in ketoacidosis and hypothermia. Furthermore, when fed a ketogenic diet consisting of low carbohydrate and high fat, DKO mice also exhibited hypothermia, ketoacidosis, and hypoglycemia. The findings establish that PDK2 is more important in the fed state, PDK4 is more important in the fasted state, survival during long term fasting depends upon regulation of the PDC by both PDK2 and PDK4, and that the PDKs are important for the regulation of glucose and ketone body metabolism.

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