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Stimulation of insulin release by glyceraldehyde may not be similar to glucose

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Abstract

Glyceraldehyde (GA) has been used to study insulin secretion for decades and it is widely assumed that β-cell metabolism of GA after its phosphorylation by triokinase is similar to metabolism of glucose; that is metabolism through distal glycolysis and oxidation in mitochondria. New data supported by existing information indicate that this is true for only a small amount of GA's metabolism and also suggest why GA is toxic. GA is metabolized at 10–20% the rate of glucose in pancreatic islets, even though GA is a more potent insulin secretagogue. GA also inhibits glucose metabolism to CO_2 out of proportion to its ability to replace glucose as a fuel. This study is the first to measure methylglyoxal (MG) in β-cells and shows that GA causes large increases in MG in INS-1 cells and D-lactate in islets but MG does not mediate GA-induced insulin release. GA severely lowers NAD(P) and increases NAD(P)H in islets. High NADH combined with GA's metabolism to CO_2 may initially hyperstimulate insulin release, but a low cytosolic NAD/NADH ratio will block glycolysis at glyceraldehyde phosphate (GAP) dehydrogenase and divert GAP toward MG and D-lactate formation. Accumulation of D-lactate and 1-phosphoglycerate may explain why GA makes the β-cell acidic. Reduction of both GA and MG by abundant β-cell aldehyde reductases will lower the cytosolic NADPH/NADP ratio, which is normally high.

Keywords: Glyceraldehyde; Methylglyoxal; NAD(P)/NAD(P)H ratio; Glyceraldehyde metabolism; Aldehyde reductase; Glyoxalase; D-Lactate; Pancreatic islet β-cell

Over 200 publications of D-glyceraldehyde (GA)'s[1] use in studies of insulin secretion have appeared since it was first discovered to mimic the electrophysiologic effect of glucose on the β-cell [1] and to be a potent insulin secretagogue [2,3]. Glucose, the most potent physiologic insulin secretagogue, stimulates insulin secretion by aerobic glycolysis and GA has been assumed by many researchers including ourselves [4] to stimulate insulin release very similarly to glucose; that is solely by entering the glycolytic pathway via the triokinase reaction to form triose phosphates and from this step onward undergoing glycolytic and mitochondrial metabolism identical to that of glucose (Fig. 1). The current work presents evidence to suggest that this pathway accounts for only a small portion of GA's metabolism and uses our new data and data previously reported by us and others to support the idea that GA metabolism by the β-cell differs significantly from glucose metabolism. GA is generally observed to be a more potent insulin secretagogue than glucose at equimolar or lower concentrations [3,5–18] even though, as shown herein, the rate of oxidation of GA to CO_2 by pancreatic islets is much lower than that of glucose. It has been suggested previously that stimulation of insulin release by GA is only partially similar to that of glucose [19,20] or does not require its metabolism [18]. It has also been proposed that GA's insulinotropism is related to its

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[1] *Abbreviations used:* GA, glyceraldehyde; GAPDH, glyceraldehyde phosphate dehydrogenase; MG, methylglyoxal.

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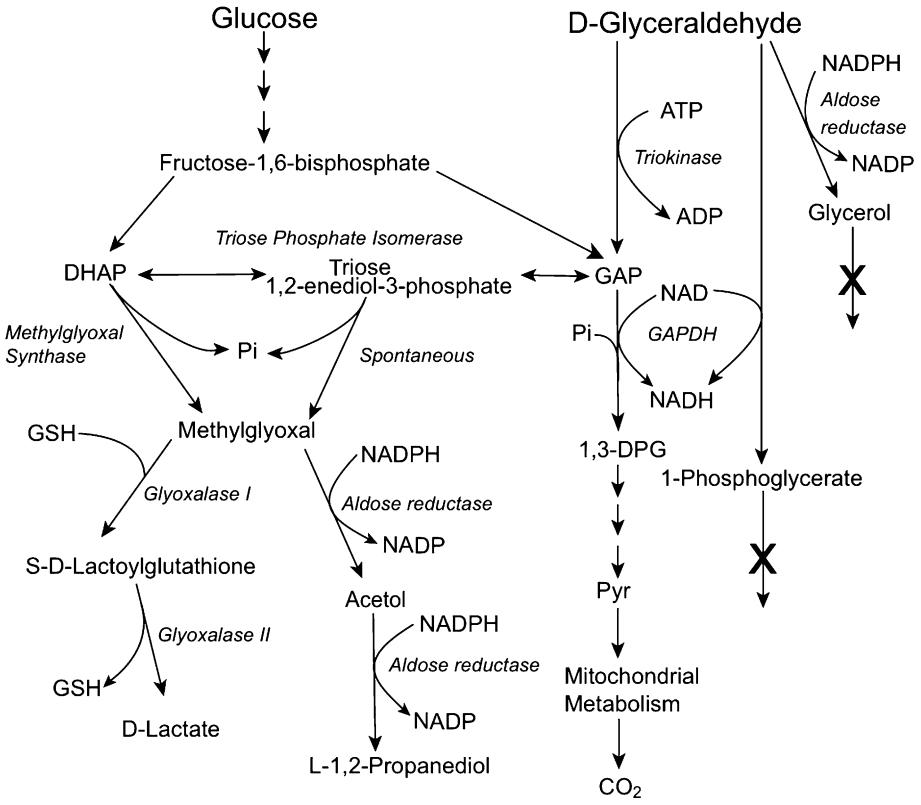

Fig. 1. Pathways of glucose and glyceraldehyde metabolism in the insulin cell.

metabolism to methylglyoxal and/or is caused by methylglyoxal contaminating glyceraldehyde preparations [21–23]. The current work is the first to report measurements of methylglyoxal in the β-cell and shows that although GA forms a massive amount of methylglyoxal, methylglyoxal formation does not account for GA's insulinotropism. The current study also shows that the β-cell contains a high level of glyoxalase I the first enzyme of the glyoxalase pathway [24] and that methylglyoxal formed from GA in the β-cell (Fig. 1) [24] is converted to high levels of D-lactate via this pathway.

A major difference between GA and other secretagogues is that GA is toxic to the β-cell. Pancreatic islets that have been exposed to GA do not release insulin in response to metabolizable secretagogues and monolayers of insulin cell lines maintained in the presence of GA for several hours cells die and may even become detached and floating in the medium. Best et al. [17,18] have shown that GA acidifies the β-cell, while other secretagogues, such as glucose and α-ketoisocaproate, cause a slight alkalinization of the β-cell. We propose this is because GA metabolism forms high concentrations of acidic products 1-phosphoglycerate and D-lactate in the β-cell. GA can be a substrate in the reaction catalyzed by glyceraldehyde phosphate dehydrogenase, an enzyme that is extremely abundant in β-cells. In contrast, the activity of triokinase, the enzyme that allows GA to enter the glycolysis pathway by converting it to glyceraldehyde phosphate (Fig. 1), is very low in the β-cell [19]. By comparing the relative activities of the two enzymes in β-cell cytosol with GA as a substrate it can be calculated that, at insulinotropic concentrations of GA, the rate of product formation from GA in the glyceraldehyde phosphate dehydrogenase reaction is 20-fold higher than in the triokinase reaction. When GA is a substrate in the glyceraldehyde phosphate dehydrogenase reaction, the theoretical product is 1-phosphoglycerate which is not a physiologic intermediate and cannot be further metabolized [19].

The current work shows that GA increases NAD(P)H and lowers NAD(P) levels and increases the L-lactate/pyruvate ratio in the islet without significantly increasing L-lactate. This is consistent with GA lowering the cytosolic NAD/NADH ratio by acting as a substrate in the glyceraldehyde phosphate dehydrogenase reaction. When GA is applied to an islet, the immediate effect of increased NADH plus early metabolism of a small amount of GA completely to CO_2 might explain GA's ability to hyperstimulate insulin release, but the long term effect of a very reduced NAD/NADH ratio will be to block glycolysis at the step catalyzed by glyceraldehyde phosphate dehydrogenase. As shown in the current study, GA's ability to interfere with glucose oxidation out of proportion to its ability to replace glucose as a fuel, plus the increased levels of glyceraldehyde phosphate and dihydroxyacetone phosphate previously observed in GA-exposed pancreatic islets [27], are also consistent with a block of glycolysis at glyceraldehyde phosphate dehydrogenase. Increased glyceraldehyde phosphate will be diverted to methylglyoxal formation (Fig. 1). The extreme decrease in flux through glycolysis will limit