Effect of D-Ribose on Insulin and Blood Glucose: A Chronological Examination

Summary

The effect of D-ribose (ribose) on insulin secretion and plasma glucose has been investigated since 1957, when the effect of insulin on the transport of various sugars, including ribose, across cell membranes was first studied. Over the decades, research has consistently shown that oral or intravenous ribose administration produces a transient, asymptomatic, and dose dependant decrease in plasma blood glucose to a nadir that is reached 30- to 75-minutes post-administration, before returning to baseline levels in approximately 60- to 120-minutes once administration is discontinued.

The mechanism of this blood glucose lowering effect has not been fully elucidated, but several have been studied and more than one appear to contribute to the effect. Suggested mechanisms include direct stimulation of insulin secretion by the pancreas, indirect stimulation of insulin secretion by the liver and other tissues, a saturation of carbohydrate receptors in the liver and various tissues affecting insulin release, increased glucose utilization or decreased glucose production resulting from rising levels of blood ribose, and the competition in the liver for the enzyme phosphoglucomutase responsible for glycogen recruitment. Increased glucose utilization does not appear to materially contribute to the mechanism. Instead, the blood glucose lowering effect of ribose appears to result from a combination of factors including indirect stimulation of pancreatic insulin secretion, stimulation of humoral effectors causing secretion of minor, but important, amounts of insulin from tissues in the hepatic-portal pathway, and delayed glucose recruitment in the liver, likely due to competition for phosphoglucomutase activity.

In the earliest investigation of the relationship between ribose and insulin, Park, et al.[1] infused either glucose, mannose, fructose, xylose, arabinose or ribose into eviscerated rats, with or without simultaneous insulin injection, for one or two hours. The accumulation of sugar in the diaphragm, heart, gastrocnemius and brain were measured and compared to baseline values. Except in the case of ribose, insulin significantly accelerated transport of sugars into muscle. No effect of insulin on ribose transport was observed, and this result was also found in later studies.[3] No insulin effect on any sugar was seen in brain tissue suggesting carbohydrate transport into the brain is not facilitated by insulin. Increased levels of mannitol, ribose and fructose did not appear in the brain following infusion, leading investigators to conclude these sugars did not pass the blood brain barrier to an appreciable extent, and explaining why fructose does not relieve the symptoms of hypoglycemia.

In the same year, Segal, et al.[2] infused 10 or 20 grams of ribose over a period of 10 to 25 minutes into five fasted normal males, three diabetics, and one subject with liver disease, collecting blood for analysis every five- to 10-minutes for 90-minutes, beginning at the onset of infusion. Blood glucose levels fell in all subjects by an amount equal to 16% to 65% of pre-infusion level (i.e., decline in plasma glucose of 11 to 41 mg%). The hypoglycemic response continued for 20- to 50-minutes post-infusion, reaching its nadir at 46- to 89-minutes before returning to baseline level in an average of 115-minutes. The effect was similar in diabetics and normals.

Constant infusion in three subjects of 136 mg/minute to a dose of 12-grams of ribose led to a decrease in blood glucose that was 48% of fasting value following 60- to 65-minutes of infusion. The blood level of ribose after infusion rose to 60 to 80 mg%, but levels of 10 to 19 mg% were evident at the time the nadir was reached in blood glucose levels. The decrease in blood glucose was not accompanied by significant elevation of plasma pyruvate or decline in blood inorganic

phosphate, suggesting that increased peripheral glucose utilization or renal glucosuria is likely not the mechanism of ribose induced hypoglycemia.

Since the level of plasma glucose is dependant on the relative rates of entry and loss of glucose from the blood, Segal and Foley[3] studied the possibility that ribose either inhibits the hepatic mechanisms determining the rate of glucose recruitment or increases peripheral utilization of glucose via an insulin-like effect. The earlier observation that ribose causes a decline in serum glucose level without consistent or significant changes in pyruvate or inorganic phosphate levels suggested an effect other than increased glucose utilization, and led to an analysis of the effect of ribose on the action of hepatic phosphoglucomutase, the enzyme responsible for glycogen recruitment in the liver through the conversion of glucose-1-phosphate to glucose-6-phosphate.

The results of a series of *in vitro* studies using purified hepatic phosphoglucomutase showed that ribose inhibited the mutase reaction in a dose dependant fashion, ostensibly by introducing organic phosphate to compete with that of glucose-1-phosphate, thereby slowing the mutase conversion to glucose-6-phosphate. This mechanism is consistent with the reaction found with galactose-1-phosphate explaining the hypoglycemic effect of galactose seen in galactosemic patients.

Earlier results showing an effect of ribose on blood glucose led investigators to consider the possible role of ribose in treating diabetes. The first such study was conducted in 1959 by Bierman, et al.[4] using four mildly- and four severely diabetic patients. Researchers infused 40- to 50-grams of ribose into subjects over one hour following an overnight fast and from whom insulin had been withheld for a period of 24-hours prior to ribose administration. The study found that blood glucose fell in seven of the eight subjects (average 21 ± 11%), with minimum glucose levels reached in one to three hours from initiation of the infusion.

In a later study, Steinberg, et al.[5] further investigated the effect of oral ribose administration in dabetes. In this study, 34 subjects (13 normal, six probable-, five mild-, and five insulin dependant diabetics) were given 15-grams of ribose in water. Researchers found that as glucose intolerance increased in severity, subjects were less responsive to the blood glucose lowering effect of ribose. In normals and mild diabetics, the hypoglycemic effect was similar, but became insignificant in more severely diabetic subjects. Looking at insulin response, investigators found that while the plasma insulin concentration increased 2.6-fold in mild diabetics, it was unchanged in healthy normals. Researchers concluded that the insulinogenic response to ribose as determined in peripheral venous blood does not account for the hypoglycemic effect of ribose.

To begin what turned into a series of studies on the insulinogenic response to ribose, Steinberg, et al.[6] used nine normal subjects receiving infused ribose at a rate of 750 mg/min for 20-minutes and three subjects receiving the same dose over a five-minute infusion. This infusion rate produced total doses of 15- and 3.75-grams, respectively. In this study, the average increase in serum insulin found in the 20-minute infusion was 17 µU/ml, peaking at between four- and seven-minutes before returning to baseline value within 10-minutes. Modest hypoglycemia was consistently seen, ranging from 7% to 23% below baseline value and reaching its nadir at 40- to 75-minutes after the insulin peak. The five-minute infusion showed a similar insulin response, with a mean peak of 12.7 µU/ml, but, while a slight decease in blood glucose was seen, it was not significant as compared to baseline and was significantly different than the effect seen in the 20-minute infusion. Researchers concluded the hypoglycemic effect elicited by ribose was a function of ribose dose and not of the increase in insulin concentration provoked by either the longer or shorter duration infusions.

In acute experiments, Goetz, et al.[7] used mongrel dogs infused either glucose, galactose, fructose, deoxyglucose, or ribose to determine that glucose, galactose, and ribose all caused increases in insulin secretion rate without the causal influence of a rise in plasma blood glucose concentrations. These results supported the existence of a carbohydrate-sensitive regulator of insulin secretion outside the pancreas, and researchers suggested the liver as a possible site of

such a receptor. Further to this finding was added research by Halter et al.[8] who administered ribose (0.3- or 3.0-grams) orally, intraportally, intrafemorally, or via the external juglar vein to nine mongrel dogs fasted for 18-hours. In this study, lasting a total of 155-minutes, ribose infusions were given as a 5% or 25% solution infused at 0.76 ml/minute for 15-minutes and oral solutions of 12.0 ml ribose as 5% or 25% solutions were administered via a gastric tube.

Results showed that small amounts of ribose given either orally or intravenously gave significant increases in plasma insulin levels despite the drop in serum glucose. Researchers determined that increased plasma insulin levels were not the direct result of β-cell stimulation and that dissociation exists between blood ribose levels and insulin response. Since the animals were not stressed, researchers discounted catecholamine as an ameliorator of epinephrine block of β-cells and suggested the mechanism for insulin release may be associated with the liver. Investigators suggest other sites cannot be discounted, but given the similarity of effect between orally- and intravenously administered ribose, the mechanism is likely not related to gastrointestinal hormone production or release.

Two studies investigating the effect of ribose in glucose turnover in dogs were conducted by Hetenyi and Ishiwata[9] and Ishiwata et al.[10] Studies in normal, nonanaesthetized dogs[9] showed that ribose infusion caused a marked decrease in blood glucose concentration with no, or only a small transient increase in insulin as measured in mixed venous blood. The rate of endogenous glucose production during the first 45-minutes of ribose infusion decreased in test animals, but returned to pre-infusion level within 45- to 100-minutes following infusion. Glucose utilization rates were also found to increase between the 10^{th} and 45^{th} minute of infusion with increased glucose clearance. A second study in pancreatecomized dogs[10] showed that ribose infusion (3.0 mg/kg/min for 300-minutes) did not decrease either the plasma concentration or rate of production of glucose in dogs in which glucose homeostasis was maintained at a normal level by a basal infusion of insulin into the portal vein.

Results of these studies led researchers to conclude that insulin secretion alone is insufficient to explain the drop in blood glucose, since no parallel decrease in plasma inorganic phosphate or increase in pyruvate was observed in the studies, but the lack of ribose-induced hypoglycemia found in pancreatectomized animals to which insulin was administered was suggestive of a significant role in pancreatic insulin secretion. The inhibitory effect of ribose on phosphoglucomutase was offered as an alternative or supportive mechanism. This view is supported by the lack of any hypoglycemic effect of fructose, although fructose stimulates insulin secretion in both test animals and humans. Further validating this conclusion is the observation that the hypoglycemia from ribose outlasts hyperinsulinemia. Researchers suggest it is conceivable that ribose causes a brief spike in pancreatic insulin and then prevents the return of normoglycemia through an effect on hepatic phosphoglucomutase, or by other factors involved related to saturation of carbohydrate receptors affecting insulin secretion or glucose production in tissues outside the pancreas, possibly in the liver.

Using unanaesthetized albino rabbits infused with ribose (25 mg/ml for 200-minutes), Sloviter and Petkovic[11] showed a consistent increase in plasma insulin occurring soon after beginning of infusion with plasma glucose levels reaching nadir 15- to 45-minutes after the peak in insulin concentration, but found that the ratio of decrease in glucose to increase in insulin varied from 0.26 to 2.2. Researchers concluded that, because of the consistent time relationship between insulin secretion and hypoglycemia, the stimulation of insulin secretion is the best explanation for the hypoglycemic effect. They could offer no suggestion as to the lack of consistent relationship between the increase of insulin and level of decrease in plasma glucose, however.

To determine whether ribose or penitols exhibited a direct insulin stimulating property on the pancreas, Malaisse and Malaisse-Lagae[12] exposed rat pancreatic tissue to varying levels of glucose with ribose, ribitol, or xylitol (each at 17 mM) for 90-minutes at 36^{o}C. Their research showed that at low glucose concentrations (0.0 to 3.0 mM) there was no stimulant effect of ribose or penitols to insulin secretion. At glucose levels of 5.0 – 17.0 mM, however, ribose and xylitol

caused significant increases in insulin output, with the optimal effect observed at 8.0 mM glucose. At maximal glucose level (28.0 mM), ribose and penitols did not increase the effect above that observed with glucose alone. These findings led investigators to conclude that ribose and xylitol mimic the effect of glucose on insulin secretion, with the stimulation being most pronounced at glucose levels where small increments in glucose concentration would cause marked changes in insulin output. Xylitol was the most effective of the compounds tested in stimulating insulin release, but its efficiency was calculated to be less than 20% that of glucose in generating the insulinogenic response.

Ginsberg, et al.[13] studied the effect of ribose on plasma insulin, cortisol, and human growth hormone (HGH) in 10 healthy volunteers. Oral (1-gm/kg) or intravenous (15-gm in 7.5% solution over four-minutes) ribose was given. Upon oral administration, plasma glucose levels fell an average of 14 mg% from an average baseline of 80 mg% in test subjects. Plasma glucose levels fell over the first 60-minutes, rose slightly, and then fell again to an average of 50 mg% at three hours post-administration. In these subjects, plasma insulin levels increased within 30-minutes of initiating administration from an average of 13.6 µU per ml (fasting level) to 18.7 µU per ml at one hour and 21.7 µU per ml between two and three hours. Both the one-hour and two or three hour increases were significant. There was no consistent change in HGH.

During intravenous administration blood glucose fell from a fasting mean of 65 mg% to 50 mg% in one hour and returned to baseline within two hours following the injection. Plasma insulin levels more than doubled within three minutes post-infusion, then fell progressively over one-half hour and returned to baseline. There was no change in HGH or cortisol in response to the ribose infusion.

The bi-phasic fall in glucose was accompanied each time by an increase in insulin and the onset of recovery from hypoglycemia following infusion was accompanied by a return of insulin to baseline. Researchers concluded that insulin response to ribose explains, at least in part, the blood glucose lowering effect. They went on to agree with previous suggestions that other mechanisms may also be in play, however, since the blood glucose lowering stimulation of HGH was not observed, but point out that this relationship is not always consistent.

To further the investigation of the insulinogenic effect of ribose in humans, Goodman and Goetz[14] studied 10 healthy human subjects given either orally or intravenously administered ribose in the same dose (0.5 gm/kg b.w.) following an overnight fast. Researchers determined the route of administration of test substance made no difference in the insulin response, which was prompt but brief and was unrelated to the level of ribose in the blood. Epinephrine infusion suppressed the response in both oral and intravenous experiments, but propranolol infusion did not alter the magnitude or promptness of response, suggesting the insulinogenic effect of ribose is not mediated by β-cell receptors.

This study showed the change in insulin levels after ribose administration is modest, contrasting with the large and persisting increases observed when pancreatic insulin output is measured in dogs and the hypoglycemic response is less profound. These factors suggest the possibility that insulin deposition in the liver, or other mechanism affecting liver control of glycemic response, may be evident. Further, the similarity of response to ribose administered either orally or intravenously suggests there are no gastrointestinal factors involved. This strikingly contrasts with glucose, where oral administration produces a more profound increase in insulin secretion than intravenous administration.

These findings led the same group of researchers to further investigate the potential indirect mechanisms of insulin release with ribose administration. Using a canine model, Goetz, et al.[15] found that ribose caused an increase in insulin secretion, but evidence for direct pancreatic β-cell release was contradictory, suggesting an indirect mechanism. Results of this study suggest that ribose-induced insulin release depends on an indirect humoral mechanism, rather than a direct neural effect. Researchers propose that the metabolism of ribose in various tissues, including the

red blood cells, may produce compounds with indirect insulin-releasing properties. Pyridine nucleotides are suggested as the metabolites exhibiting such properties.

This study concluded that ribose has no power to directly stimulate insulin release from the β-cell under physiologic conditions, requiring a secondary, ribose-dependent factor capable of triggering insulin release. This factor could originate in any or all of the tissues and organs lying along the vascular pathway between the portal vein and pancreas and is not a gut hormone. As an alternative to direct neural stimulation, the β-cell trigger could be a small molecule directly resulting from the metabolism of ribose in extrapancreatic tissue. Investigators suggest this could come from red blood cells producing NADPH via the pentose phosphate pathway, with the reduced nucleotide possibly stimulating secretion. The hepato-portal signaling concept is expanded to include other tissues, including the liver.

Ishiwata and co-workers used a similar dog model to further elucidate the influence of ribose on plasma insulin and glucose response.[16] In this study, ribose infusion (3 mg/kg/min for 380-minutes) produced sustained hypoglycemia, with average blood glucose concentrations decreasing by 30 mg% below fasting level after 45-minutes and remaining at the same level until ribose infusion was discontinued. Following the infusion, plasma glucose levels returned to normal in approximately one-hour. Plasma insulin levels in pancreatic effluent blood increased rapidly, peaking at five- to ten-minutes, before declining gradually. Insulin levels remained above baseline during the sustained period of hypoglycemia, but dropped to below baseline after the infusion was discontinued. This pattern was found similarly in pancreatic effluent and mixed blood. There was no change in blood glucagons or canine growth hormone (CGH) with ribose infusion.

The pattern of insulin release during ribose infusion suggests a suppression of insulin release by the fall of blood glucose below the fasting level, leading to a sustained state of hypoglycemia at a constant level. Researchers conclude that previous studies concluding that the effect of insulin release was insufficient to account for hypoglycemia were made from observations of changes in insulin levels in peripheral blood that may not be sensitive enough to sense the small amount of insulin released from the pancreas. Investigators also suggest that previous studies underestimate the efficacy of insulin released into the pancreatic vein to act on the liver to diminish glucose recruitment and release. This study concludes the discrepancy in timing between the insulin release and hypoglycemia can be explained by these reasons and also by the suppression of insulin release in response to hypoglycemia.

In the only long-term study on the topic, Gross and Zollner[17] administered ribose orally and/or intravenously to nine healthy subjects in doses of 83.3- to 222.2 mg/kg/hr for at least four hours. In these subjects, serum ribose increased in a dose-dependant manner to a maximum of 75- to 85 mg% and serum glucose levels decreased after beginning continuous ribose administration and remained reduced as long as ribose was administered. Both oral and intravenous administration of 166.7 mg/kg/hr resulted in an average 25% decrease in serum glucose, but higher doses did not elicit a greater glucose-lowering response, suggesting a saturation of the glucose-lowering mechanism at serum ribose concentrations higher than approximately 30- to 40 mg%.

Oral administration of 166.7 mg/kg/hr caused serum insulin to increase from a mean of 8.4 μU per ml to 10.4 μU per ml, a significant increase. Intravenous administration at this dose did not significantly change serum insulin levels, although it caused an insulin spike of two- to three-fold that returned to baseline within 10 minutes. During the four-hour period of administration the glucose levels remained low in both oral and intravenous studies, and injecting insulin to subjects did not lower glucose levels further. Decreases in serum glucose levels were asymptomatic in all cases. Serum C-peptide concentration remained unchanged regardless of treatment, suggesting there was no deposition of insulin in the liver by increased metabolism of carbohydrate, and there was no difference in response between oral and intravenous administration, making involvement of gastrointestinal hormones unlikely.

Researchers suggested that variations in plasma insulin concentrations in this study do not appear to account for the observed hypoglycemic effect following ribose administration. This observation led them to conclude:

> "Since the data on the investigated hormones cannot completely explain the effect of ribose on the serum glucose level, and increased glucose utilization is unlikely, further mechanisms must be identified. It is known that phosphoglucomutase, the rate-limiting enzyme in the formation of glucose from glycogen in the liver, is inhibited by ribose. This and other, still unknown effects on enzyme activities might cause or contribute to the glucose-lowering effect of ribose."

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