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REVIEW ARTICLE

Oral Insulin: The Rationale for This Approach and Current Developments

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Abstract

Insulin remains the most effective and durable hypoglycemic agent for the treatment of diabetes. The addition of an effective oral insulin dosage form to the antidiabetes armamentarium may have significant benefits in terms of fostering compliance and adherence among patients, as well as physiologic advantages due to the fact that such a dosage form replicates the natural route of insulin secretion and absorption through the portal vein and targets the liver directly. Several companies have developed technological platforms that protect polypeptides and proteins from enzymatic hydrolysis, enable their transport across the epithelial lining, and promote their absorption from the gastrointestinal tract. A review of the potential physiological rationale and advantages, as well as of current pertinent technologies used specifically with insulin, is herewith provided.

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Introduction

The introduction of insulin therapy was hailed as one of the therapeutic miracles of modern times, saving lives and preserving the health of millions of people worldwide. In the years since insulin was introduced, research on many fronts has resulted in significant developments in production, purification, and pharmaceutical formulation and in refinements in devices for parenteral insulin administration. Despite these advances, realizing the dream of administering insulin orally, and hence replicating physiological patterns of insulin secretion with the accompanying advantages, remains an elusive goal. Recent advances in science and technology have brought about methods to (1) overcome the barriers to absorption presented in the gastrointestinal tract and (2) protect the insulin while in transit in the harsh adverse environment of the gastrointestinal tract. This review addresses the physiological advantages that may be derived from oral insulin administration and examines the various technologies at the forefront of oral insulin delivery.

Potential Physiological Advantages of Insulin Delivery into the Portal Hepatic System

Normally, insulin is secreted from pancreatic β cells into the portal vein, which in turn ferries it directly into the liver. Up to 80% of secreted insulin is extracted on its first path through the liver and binds to insulin receptors.[1–3] This large extraction gives rise to the "portal signal" and to the portal-peripheral gradient, a significantly (2.5- to 3-fold) higher insulin concentration in the portal

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Abbreviations: (GRAS) Generally Recognized as Safe, (HDV) hepatic-directed vesicle, (HGP) hepatic glucose production

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vain as compared to that seen in systemic circulation. Oral insulin mimics this precise physiologic route as it is absorbed from the gastrointestinal tract into the portal vein (to be differentiated from parenteral insulin, which is absorbed into the systemic circulation) and consequently may have salutary metabolic consequences due to direct engagement of the liver and resumption of its role in glucose metabolism.[4] Furthermore, oral insulin is likely to convey additional advantages with plausible beneficial clinical ramifications, including the reduction of hyperinsulinemia, the forestalling of weight gain associated with systemic insulin therapy, and reducing the risk of hypoglycemia.

The liver, the portal signal, and glucose-stimulated insulin release are intertwined processes governing glucose metabolism.[4,5] In healthy individuals, the liver assumes a pivotal role in maintaining euglycemia within a relatively narrow range. Following food ingestion, glycemia is regulated by three mechanisms, which include the suppression of hepatic glucose production (HGP), stimulation of hepatic glucose uptake, and induction of glucose uptake by peripheral tissue. In the postprandial state, the difference in the glucose excursion between a nondiabetic and a diabetic individual is accounted for by failure to adequately suppress hepatic glucose release in the latter[6] (**Figure 1**). This is mainly because

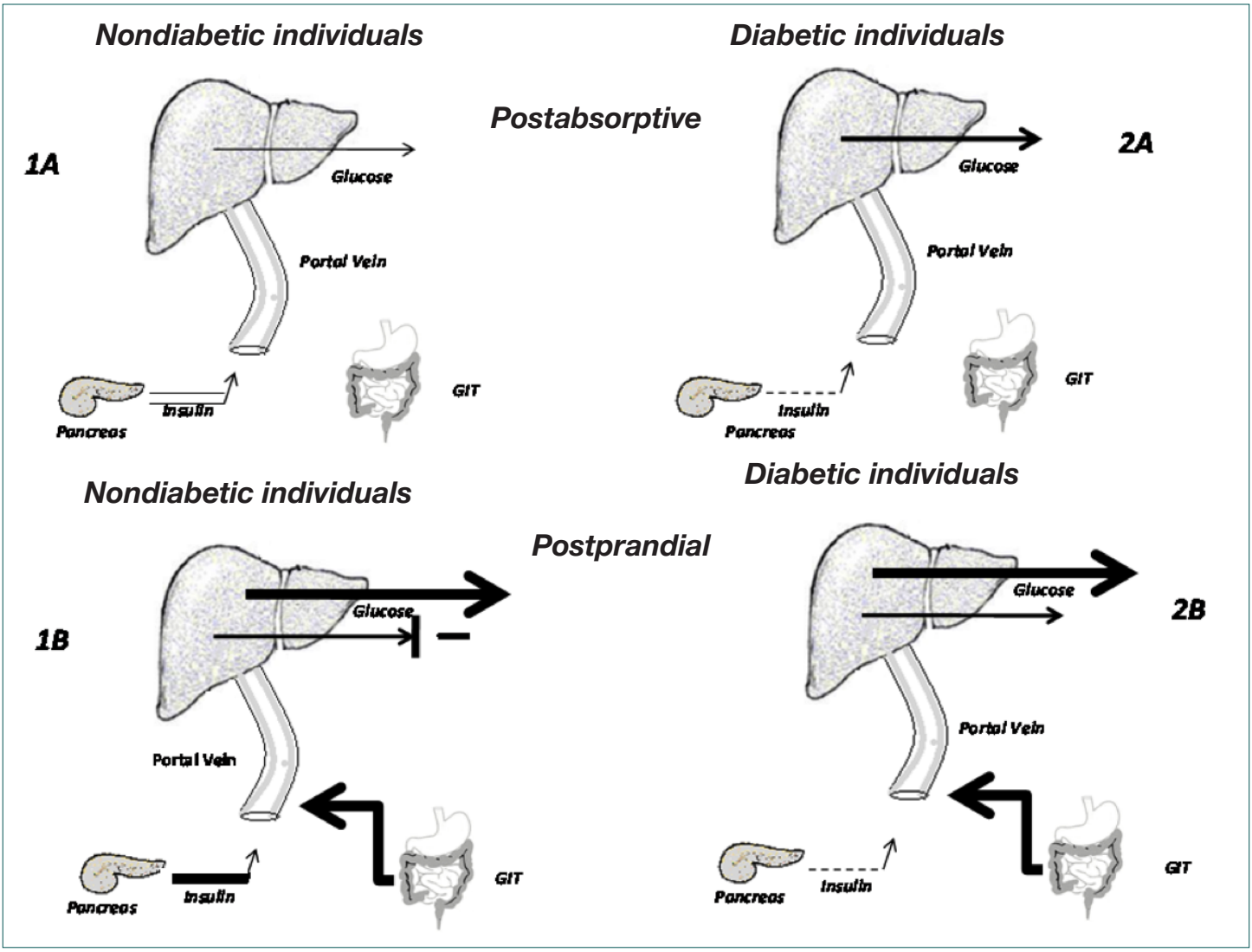

Figure 1. Hepatic glucose output (HGO): role of (portal) insulin. **Left**: (1) nondiabetic individuals in postabsorptive (**1A**) and fed (**1B**) states. **Right**: (2) diabetic individuals (type 2 diabetes mellitus, T2DM) in postabsorptive (**2A**) and fed (**2B**) states. (**1A**) For nondiabetic individuals in the fasting state, plasma glucose is derived from glycogenolysis and is secreted tonically under the control of basal insulin. (**1B**) For nondiabetic individuals in the fed state, plasma glucose is derived from the ingestion of nutrients, HGO is governed by gluconeogenesis, and glycogenolysis is restrained under the control of insulin with the net effect of a physiologic postprandial glucose excursion. (**2A**) For individuals with diabetes (T2DM) in the fasting state, because of insulin deficiency in the portal circulation, HGO governed by glycogenolysis and gluconeogenesis in the liver is unrestrained and manifests as elevated fasting blood glucose. (**2B**) For individuals with diabetes in the fed state, again because of insulin deficiency in the portal circulation, suppression of HGO is ineffective, resulting in elevated hepatic glucose production, which now adds up to plasma glucose derived from the ingestion of nutrients with the net effect of postprandial hyperglycemia. GIT, gastrointestinal tract.

of insufficient or lack of insulin secretion in response to meal ingestion and failure to suppress glucagon release as occurs in diabetic patients.[7] Hepatic extraction of glucose and glucose disposal in peripheral tissue in the diabetic individual remain intact and not different than in the nondiabetic individual.[8]

Similar to the postprandial state, in the fasting state, hyperglycemia is attributed to inadequate suppression of hepatic glucose output[9,10] (**Figure 1**). Unrestrained hepatic glucose release is likely the consequence of insulin resistance and can be overcome with a relatively small increase in baseline hepatic sinusoidal insulin levels.[9,11,12] This sinusoidal insulin increment can be achieved either by raising the portal insulin concentration, for example, by way of oral insulin, or by a conventional subcutaneous injection (systemic insulin). The latter is, however, an inefficient approach to suppress HGP as it requires over three times as much circulating insulin because of the difference in the anatomical contribution of the portal vein and hepatic artery to the total hepatic blood flow. Thus, exploiting the parenteral route to establish a relevant rise in portal insulin concentration needed to suppress HGP requires large amounts of insulin. It can be achieved, but only at the expense of creating peripheral hyperinsulinemia with the implication of increasing the risk of hypoglycemia, promoting lipogenesis, and possibly intensifying insulin resistance.[13–15]

The role of the liver in buffering the entry of glucose from the portal vein into the systemic circulation to minimize large glucose fluctuations is well known, while its role in controlling the rate of insulin release into the circulation is less appreciated. The liver contains an adaptable mechanism that allows it to regulate systemic insulin levels by varying the amount it extracts from the portal vein. The fraction of intraportally infused insulin reaching the systemic circulation decreases with higher doses of insulin, and a reduction in hepatic insulin clearance results from the ingestion of oral glucose or a meal, thereby increasing the systemic availability of insulin.[1,2,16,17] This mechanism enables the fine-tuning of insulin release into the systemic circulation, avoiding peaks and troughs in insulin concentrations and in glycemic excursions.

The suggestion that portal insulin delivery may be associated with a reduced risk of hypoglycemia and less erratic glucose swings has been gleaned from numerous studies. It has been observed in studies comparing insulin infusion into the peritoneal cavity versus infusion into the subcutaneous space (~50% of intraperitoneal substances are absorbed via the portal circulation) and from observational studies of diabetic patients on peritoneal dialysis when insulin was administered together with the peritoneal dialysate.[15,18–23] Similar observations were made in patients receiving islet cells and pancreatic transplants. Indeed, the prime indication for performing these procedures was intractable hypoglycemia; in most cases, results were dramatic with resolution of hypoglycemic episodes.[24–27]

One other area where portal (oral) insulin may act differently than parenteral insulin is in weight control. A number of mechanisms have been invoked as the cause of weight gain on initiating insulin therapy, including decreased glycosuria due to improved glycemic control, the anabolic effects of insulin itself, a decreased metabolic rate, and defensive overeating to prevent hypoglycemia. The anabolic effect mediated by high circulating levels of insulin most likely plays a role in weight gain, but its magnitude is not precisely determined. The deposition of fat is insulin dependent, and weight gain cannot occur when insulin deficiency is present, even if food is consumed in large amounts. In diabetic patients, weight gain is proportional to the intensity of treatment and is accounted for by an increase in nonlean muscle mass, i.e., fat. Furthermore, hyperinsulinemia has been implicated in shifting the anabolic balance toward lactate, the predominant gluconeogenic precursor, and glucose, when in excess, further fuels lipogenesis.[28]

Potential Problems with Oral Insulin

While oral insulin may have physiological advantages, it may raise problems inherent to oral medication in general. For instance, the rate and extent of absorption of an oral drug are often affected by food and may differ if the drug is administered shortly before a meal or after a meal (fed conditions) as compared to administration under fasting conditions. The optimal timing for oral insulin ingestion depends at least in part on the technology used for drug delivery and will need to be determined for each oral insulin in development. The food effect is likely to determine how the oral insulin will be used and for what indication.

One other issue is that all the polypeptide and protein delivery platforms developed thus far have relatively low bioavailability. Low bioavailability is a harbinger of significant inter- and intrasubject variability. A way to reduce variability is to increase the amount of insulin in the dosage form. Until recently such a proposition was impractical for insulin because of commercial

considerations. At the present time, however, the supply of insulin and its price can support such a strategy. Low bioavailability also implies that most of the insulin ingested is not absorbed and remains in the gastrointestinal tract. It is most likely that insulin retained in the gastrointestinal tract will be degraded by peptidases and proteases. Nevertheless, a concern that will need to be addressed in long-term safety studies is whether insulin, a known mitogen implicated in an increased risk of several cancers, including colon cancer, will increase the incidence of cancer when given orally.[29–31] Finally, while insulin per se may not be toxic, the chemical compounds employed in the various delivery systems as excipients or absorption promoters need to be deemed safe and effective in long-term toxicological and clinical studies.

Current Developments

Numerous attempts at creating an oral dosage of insulin have been made since the discovery of the hormone, but these were never consummated, largely because systems that protect insulin from enzymatic degradation and technologies that enable the transport of large molecules across the gastrointestinal epithelial lining and increase their absorption were nonexistent. Major advances in these areas, bolstered by the availability and lower cost of insulin, have prompted renewed interest in developing an oral insulin.

Several companies across the globe are developing oral insulin based on different technology platforms. Generic to all these efforts is a system that provides protection of the insulin while in transit in the gastrointestinal tract and which can take the form of physical encapsulation or the creation of a modified insulin resistant to degradation. In addition, some companies use an added component designed to enhance the transepithelial transport of the drug. Merrion Pharmaceuticals, a company based in Ireland, uses its GIPET® platform to deliver macromolecules and polypeptides, including insulin. The GIPET system is based on promoting drug absorption through the use of matrices consisting of medium-chain fatty acids and formulated as solid dosage forms. The matrices enjoy food additive status (Generally Recognized as Safe, GRAS) and are normal dietary components with long records of safe use. Insulin and the other ingredients are prepared as a physical mix and are formulated into a tablet designed to be released in the duodenum. Biocon Limited, a biotechnology company located in India, is continuing the work of Nobex Corporation, developing an oral insulin based on a modified form of insulin that possesses specific physicochemical characteristics that allow it to withstand enzymatic degradation in the stomach and facilitate its absorption. The conjugated insulin product (IN-105) is recombinant human insulin conjugated covalently with a monodisperse, short-chain methoxy polyethylene glycol derivative that is crystallized and lyophilized into the dry active pharmaceutical ingredient after purification.[32] An ascending dose study in type 2 diabetes has been presented.[33] Diasome, a U.S.-based company, is employing a hepatic-directed vesicle (HDV) for insulin delivery. A HDV consists of liposomes (≤150 nm diameter) encapsulating the insulin, which also contain a hepatocyte-targeting molecule in their lipid bilayer. The targeting molecule directs the delivery of the encapsulated insulin to the liver cells and therefore relatively minute amounts of insulin are required for effect. Diabetology Limited, a U.K.-based company, is using its Axcess™ delivery technology system, which is based on a capsule containing a simple mixture of the drug, an absorption enhancer, and a solubilizer that allows absorption of the drug in the small intestine. The excipients used in the formulation are inert (GRAS) and are normal dietary components with long records of safe use. The company recently presented the results of a phase II, 10-day repeat-dose study of oral insulin in 16 patients with type 2 diabetes.[34] Emisphere Technologies, a U.S.-based company, uses a system of carriers—designed low molecular weight chemical entities—that interact weakly and noncovalently with a protein drug. By altering the protein conformation and increasing its lipophilicity the carriers are able to enhance the transport of the protein across the gastrointestinal epithelium and into the bloodstream.[35] Oramed platform technology is based on components aimed at providing protection of the protein during passage through the gastrointestinal tract in combination with an absorption enhancer. Oramed's protectants and absorption enhancers consist of known pharmacopeia adjuvants with a long safety track record. Oramed has completed phase I trials in healthy volunteers; results have shown that oral insulin delivered with their system is safe, well tolerated, and consistently leads to a desired reduction in glucose and C-peptide (**Figure 2**).[36]

Of note, two other routes of insulin delivery systems—buccal and inhaled—are being advanced. Generex Biotechnology developed an oral–buccal insulin formulation whereby insulin is delivered directly into the mouth via a metered dose spray (RapidMist device). The insulin is not absorbed through the portal system but rather is a systemic insulin. Generex's insulin has been approved and is available for clinical use in a

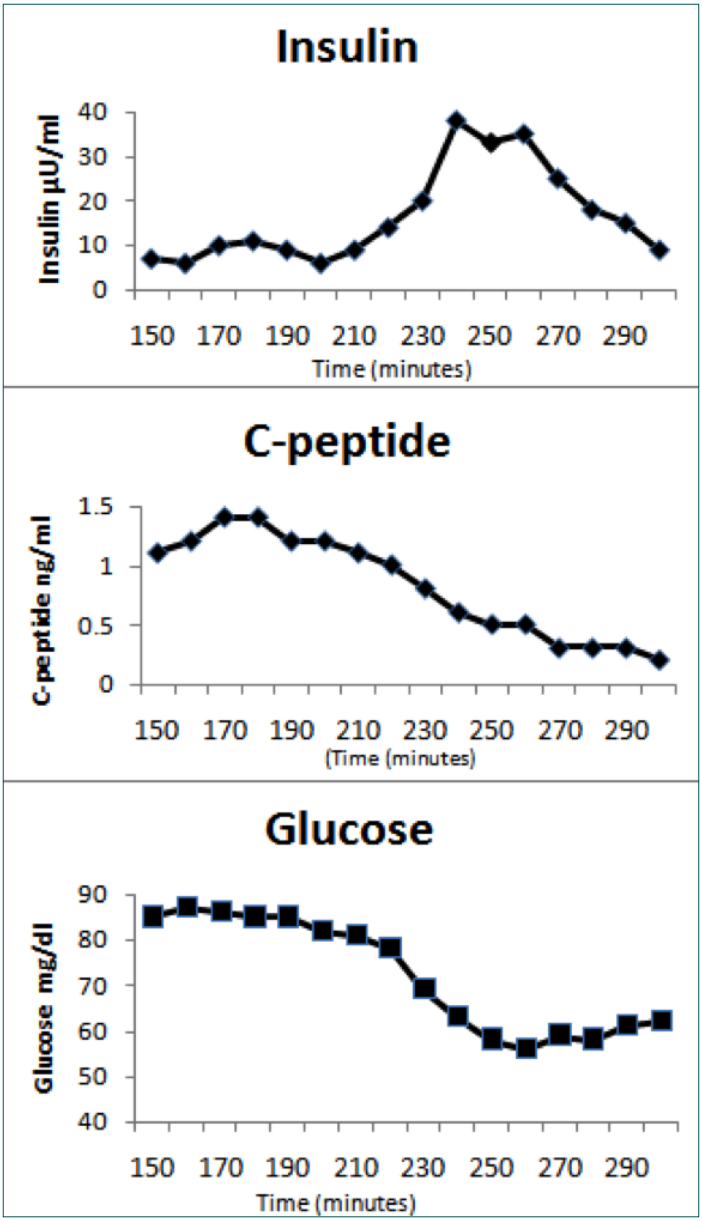

Figure 2. Glucose, C-peptide, and insulin plasma concentrations vs time (150–300 minutes). An illustrative case from a pharmacokinetic and pharmacodynamic study in healthy subjects: The capsule of oral insulin (8 mg insulin/capsule) given at time 0. After a lag of ~200 minutes, insulin appears in plasma with a corollary decrease in C-peptide and glucose.

few countries. MannKind is in phase III clinical trials with an inhaled insulin formulation based on designed microparticles optimized for inhalation deep into the lung.

Conclusion

Alternative routes to insulin injections are on the horizon. By replicating the physiological route of insulin secretion and absorption, oral insulin may have definite advantages not attained by systemic insulin administration, yet it may raise new concerns inherent to oral drug products that will need to be addressed. There is much anticipation among patients and clinicians for insulin provided by an alternative route that replaces injections. Such insulin would be a practical means to start insulin at a much earlier stage than currently practiced and will likely foster better long-term adherence and compliance, resulting in improved glycemic control in the population.

Disclosure:

Dr. Miriam Kidron is chief scientific officer at Oramed Pharmaceuticals Inc. and is a partner and stock holder. Ehud Arbit, M.D., is director of medical research at Oramed Pharmaceuticals Inc.

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