

Highlights from the International Symposium of the Brazilian Diabetes Society, Campinas, SP, Brazil, November 18, 2006

Incretins: Clinical Physiology and Bariatric Surgery – Correlating the Entero-endocrine System and a Potentially Anti-dysmetabolic Procedure

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The digestive tract is well known for its endocrine functions. Recently, many studies have been reinforcing its role as a therapeutic target for both diabetes and obesity. Losing weight is clinically very difficult for most obese patients and the reason for this could be the effect of the physiological adipostatic system that triggers central nervous stimuli to compensate for variations in food intake and in physical activity. Gut hormones seem to have a key role in this complex, regulating body weight and satiety and contributing to glucose homeostasis. The enteroinsular axis appears to be impaired in both obese and diabetic patients. Recent data on bariatric surgery shows its striking effects on glucose control soon after the procedure, before a significant weight loss is achieved. The procedure appears to work beyond anti-obesity having a key metabolic impact possibly sharing a common mechanism with the new class of agents to treat type 2 diabetes mellitus: the incretin mimetics. This symposium discussed new data on the upcoming perspectives on both the pharmacological and the surgical approach to diabetes and obesity.

Key words: Incretins, diabetes, bariatric surgery, GLP-1, ghrelin, enteroinsular axis, exenatide, DPP-IV inhibitors

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Introduction

The “incretin effect” is the phenomenon described in physiological studies which shows that orally administered glucose evokes a greater insulin response than a corresponding intravenous glucose load. This term derives from the gastrointestinal hormones – incretins, which stimulate insulin secretion.

More than 400 physicians attended this Symposium that took place in Campinas, SP, Brazil, Nov 18, 2006. The event provided a forum for the exchange of experiences between Researchers, Clinicians and Surgeons on this paramount topic in endocrinology and diabetes.

The metabolic, neural and hormonal effects of the small intestine on the pancreatic islets are referred as the *enteroinsular axis*. One of the most important incretins known is the first described gastric inhibitory polypeptide, also called glucose-dependent insulinotropic peptide (GIP), which is secreted by the entero-endocrine K-cells in the jejunum and accounts for more than 50% of the total incretin effect. The other key hormone is the glucagon-like peptide 1 (GLP-1), a product of proglucagon gene and formed mainly in the intestinal L-cells; GLP-1

plasma levels increase >6 times after a carbohydrate meal. Several studies have demonstrated that the effect of incretins is reduced in type 2 diabetes mellitus (T2DM) patients.^{1,2} When GLP-1 is administered, it effectively stimulates insulin secretion both in normal subjects and in T2DM patients.³ In contrast, GIP insulinotropic effect is highly reduced in diabetic patients.⁴ Thus, the therapeutic potential of GLP-1 has been extensively studied, emphasizing not just its hypoglycemic effect through stimulation of insulin secretion but also other likely beneficial properties, such as retardation of gastric emptying and induction of satiety.⁵

Thus, there is an increasing interest in this area, with one new agent of the incretin mimetic class already available for clinical use, the exenatide (exendin-4), and others recently approved and coming soon. The role of incretins and the enteroinsular axis in glucose homeostasis has been even more emphasized after results from obese diabetic patients submitted to bypass bariatric surgery, revealing rapid glycemic resolution in most cases, with this axis being implicated as a potential mechanism for such an effect.⁶ The Symposium congregated many specialists in the field and fomented exhaustive discussion over all the presented themes.

Physiological Aspects of the Entero-endocrine System

Dr. David E. Cummings (University of Washington, Seattle, USA) pointed out recently published data concerning gastrointestinal endocrinology and regulation of body weight, focusing especially on the role of ghrelin and other peptides on individual meals and glucose homeostasis. According to the facts, weight loss is difficult to be achieved by obese patients, probably because of the compensatory effect of an adipostatic system, which physiologically works to maintain stable body weight, despite variations in physical activity and caloric intake. Satiety signals arise from multiple sites in the GI system, including stomach, small intestine, colon and pancreas. There are two main mechanisms through which ingested food promotes satiety: gastric distention and release of peptides from entero-endocrine cells. The entero-endocrine pep-

tides involved in the regulation of the adipostatic control of body weight act both locally and centrally and could be divided into two broad groups: 1) those involved mainly in the long-term control of adiposity such as leptin, insulin, ghrelin and PYY which inform the brain about the body fat deposits, and 2) the other group which is constituted by molecules associated with short-term meal-related regulation such as ghrelin and CCK and other gut-derived factors. The hindbrain is the principal central site receiving input from short-acting satiety signals.⁷ Among the several gut peptides that regulate food intake and are secreted along the gastrointestinal system, there are the CCK in duodenum, Apolipoprotein A-IV in the jejunum, GLP-1, PYY and Oxyntomodulin in the ileum and colon, and Amylin, Enterostatin, Glucagon, Insulin and PP in the pancreas. The stimulation for secretion of all these peptides comes mainly from ingested food, but the mechanisms by which it occurs are quite diverse. Different properties of food stimulate these gut cells to secrete peptides that activate vagal and enteric afferent nerves and enter the circulation reaching the central nervous system. For example, GLP-1 release by L-intestinal cells involves a mechanism related to cellular uptake and intracellular metabolism of glucose. However, it has been described that entero-endocrine cell activation can occur without nutrient uptake by a mechanism that is quite similar to the oral tasting sensation.

Ghrelin is produced primarily by stomach and proximal intestine, being highly conserved across species. Contrary to the other incretins like GLP-1, ghrelin increases food intake and GI motility and decreases insulin secretion from the pancreatic islets, acting endogenously as a growth hormone (GH) secretagogue. Ghrelin acutely and transiently stimulates appetite, and its surge predicts voluntary meal intake. Ghrelin levels rise and fall shortly before and after meals along the day, and this secretion seems to be stimulated by the neural branch of the sympathetic nervous system.^{8,9} Conversely, ingested food inhibits ghrelin secretion, and this effect depends on both the amount of ingested food as well as on its composition because lipids seem to be less efficient. This mechanism involves insulin and enteric nervous signaling but not the vagus nerve.

Regarding long-term body weight regulation, there are several evidences in the literature that show that ghrelin levels increase after diet-induced weight loss and conversely that this hormone is down-regulated after weight gain. Ghrelin affects body-weight control centers in the brain, and increases in ghrelin levels are related to weight gain, while blockage of the hormone or its physiological effects induces weight loss. Ghrelin increases food intake and preference for fat, but interestingly it is not a common cause for obesity, because its overproduction has not been demonstrated in obese populations, being observed only in specific conditions like Prader-Willi syndrome.¹⁰

A brief report about the effects of incretins on beta cells was presented by Dr. Freddy G. Eliaschewitz (University of São Paulo, SP, Brazil). Beta-cell mass is critical in the development of diabetes, not only for T1DM, in which massive pancreatic islet destruction occurs before the clinical diagnosis, but also for T2DM in which beta-cell mass decreases progressively with evolution of the disease. Therefore, strategies to preserve or increase the number of available beta cells are crucial for the future perspectives in diabetes treatment. The source for replenishing beta cells in the adult is not clear and could supposedly arise from either ductal cells or acinar cells transdifferentiating into beta cells and also from adult pancreatic stem cells. Several substances have been shown to induce proliferation of beta cells both in vitro as well as in animal models, such as GLP-1, GIP, gastrin, IGF-1 and others.¹¹ An in vivo evidence for an incretin effect in inducing islet proliferation is the report of hyperinsulinemic hypoglycemia in patients after gastric bypass surgery with high levels of circulating incretins.¹² Other attempts to test this effect in vivo are evidenced in studies of the administration of GLP-1 to patients who received islet transplantation and fail to maintain good glucose control without exogenous insulin, and some interesting results were reported.¹³ Subsequently, some pre-clinical and experimental data suggest that incretins can possibly restore beta-cell mass; nevertheless, the clinical relevance of this data is still under investigation.

Incretins and the central control of food intake and energy expenditure was the subject highlighted by Dr. Licio A Velloso (State University of Campinas, Campinas, SP, Brazil), focusing especially on GLP-1 and GIP action in the central nerv-

ous system (CNS) and their role in thermogenesis and weight control. Glucagon-Like Peptide 1 (GLP-1) is a 30 aminoacids peptide, produced by L-cells in the colon and ileum, secreted after nervous and nutrient stimuli and degraded by the enzyme dipeptidyl-peptidase IV (DPP-IV). Gastric inhibitory polypeptide (GIP), formed by a 42 aminoacids chain, is synthesized and postprandially released from the duodenum and proximal jejunum, being cleaved by the same enzyme.^{14,15} Both of these incretins have receptors in the CNS, although GLP-1 but not GIP has receptors identified in the hypothalamus. Indeed, GLP-1 has been demonstrated to interact with these receptors, including those in the hypothalamus altering the glucose influx to neurons in these regions, suggesting a functional modulation. Intra-ventricular infusion of GLP-1 induces c-fos activation in paraventricular neurons in the hypothalamus. These incretin receptors are G-protein coupled receptors, which increase intracellular cyclic AMP. However, this pathway has not been described so far as an important one for adipostatic control in the CNS. Receptors involved with the PI3K/AKT pathway, which is activated by insulin and those involved with JAK/STAT controlled by leptin stimulus are the ones known to be important to the adipostatic command in the CNS.^{16,17}

After injection of GLP-1 directly into the CNS, there is rapid inhibitory effect on food intake, which is not sustained later.¹⁸ Studies from knockout models for GLP-1R KO, GIPR KO and for both receptors (DIRKO) do not show any significant alteration in terms of weight gain and food intake. The double knockout has a trend to gain less weight later in life.¹⁹

An exciting review of recently published findings about cardiovascular effects of GLP-1 was summarized by Dr. Wilson Nadruz Jr (State University of Campinas, Campinas, SP, Brazil). GLP-1 has receptors on cardiovascular cells, especially on the endothelium, and interest in this area increased after it was suggested that administration of GLP-1 to rats induced a dose-dependent increase in the blood pressure. However, studies in humans suggested improvement in endothelial dysfunction after GLP-1 injection in T2DM patients with stable coronary artery disease and no effect in healthy volunteers.^{20,21} GLP-1R KO mice develop left ventricular hypertrophy later in life. Studies in dogs of dilated cardiomyopathy, showed that the infusion of GLP-1

for 48 h induced an increase in the systolic pressure on the left ventricle (LV) and a decrease in the end-diastolic pressure on LV, improving contractility and decreasing heart rate.²² In one study in patients with LV dysfunction after acute myocardial infarction who were submitted to primary angioplasty, the group who received GLP-1 during angioplasty showed better ejection fraction than controls. A study in rats submitted to a high salt diet showed that those treated with GLP-1 had lower blood pressure and excreted more sodium.²⁴ Therefore, GLP-1 probably has beneficial CV effects and can be an important therapeutic tool, but future studies are necessary to clarify its role on arterial hypertension as well as on endothelial dysfunction.

Clinical Implications of Incretin Physiology

Diabetes and obesity-related pathophysiological aspects such as insulin and leptin resistance and its connection with impaired incretin function were discussed by Dr. Bruno Geloneze (State University of Campinas, Campinas, SP, Brazil). According to the data presented, women with previous gestational diabetes and other diabetes-prone individuals show insulin resistance but normal GLP-1 and GIP secretion, similar to what had been previously described in healthy offspring of T2DM patients.^{25,26} Young adult men with low birth weight history, another example of a high-risk population, have also normal incretin secretion and action.²⁷ Leptin stimulates GLP-1 secretion and leptin receptors have been described in intestinal L-cells from both mice and humans, suggesting a link between leptin resistance seen in obesity with impaired incretin secretion implicated in diabetes pathophysiology.^{28,29} Furthermore, obese patients show decreased GLP-1 levels and this could be at least partially explained by increased DPP-IV activity which also rises in parallel with HbA1c levels, in T2DM patients.^{30,31} Progressive doses of metformin, conversely, decrease DPP-IV activity, enhancing GLP-1 antidiabetic effects.³² It thus seems reasonable to implicate and understand the impaired incretin function and secretion in the diabetic disease process, indicating a potential therapeutic role of this new drug class on diabetes treatment.

The clinical use of incretin-mimetics was reviewed by Dr. Jorge L. Gross (Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil), including information from clinical trials with exenatide (exendin-4), a 39-amino acid incretin mimetic that exhibits glucoregulatory activities similar to GLP-1 and other mimetics. Data from three clinical trials lasting 30 weeks and including a total of 1,446 T2DM patients using oral agents such as metformin and sulfonylurea indicate that administration of exenatide 10 µg bid significantly reduced HbA1c in 0.8 md/dL approximately.³³⁻³⁵ Another study, involving 551 T2DM patients over 26 weeks compared the effect of exenatide 10 µg bid treatment with insulin glargine once daily. Results showed similar glucose control between groups, with an average HbA1c reduction in both treatments of 1.11%. Patients treated with exenatide had a weight loss of 2.3 kg compared to a gain of 1.8 kg in those using insulin glargine. Other studies also showed a tendency of exenatide to promote weight loss.³⁶ Nausea and diarrhea are the most frequent adverse events reported with exenatide treatment. A long-acting formulation of exenatide for once weekly administration is currently under development.

Liraglutide, another long-acting GLP-1 analog suitable for once-daily administration, is still under phase III clinical development. According to a study involving 193 patients for 12 weeks, liraglutide 0.75mg daily, the highest dose used in the study, promoted a significant reduction in HbA1c of 0.75%, compared to placebo. DPP-IV inhibitors are another type of incretin-mimetic that prolong the half-life of endogenous incretins, antagonizing the enzyme responsible for their metabolism. Clinical data published shows that Vildagliptin has a glucose lowering effect ranging from 0.7 to 1.7% depending on the baseline values. Sitagliptin, another DPP-IV inhibitor, showed similar efficacy.³⁸

Dr. Marcos Tambascia (State University of Campinas, Campinas, SP, Brazil) presented further results from clinical trials regarding incretin-based treatment. Liraglutide, the long-acting, acylated GLP-1 analog, acts as a full agonist toward the GLP-1 receptor. Initial clinical studies showed a dose-dependent improvement in HbA1c, and in one open labeled study with 190 patients, higher doses of liraglutide (0.6 and 0.75 mg) showed a similar effect on HbA1c than glicemipiride after 12 weeks.³¹

Exenatide (synthetic exendin-4), a GLP-1R agonist, has 50% amino acid homology compared to human GLP-1 but displays high affinity for its receptor. Exenatide administration to T2DM patients can improve not just postprandial glucose levels, blocking glucagon secretion and restoring first phase insulin secretion, but it can also reduce fasting glycemia, which suggests a possible sensitizing effect on the overnight hepatic response to insulin.⁴⁰⁻⁴² The improvement in insulin secretion clinically observed in T2DM patients treated with exenatide is corroborated with animal studies showing increase in pancreatic islet size.⁴³

Another possibility for improving incretin action in diabetic patients is the administration of DPP-IV inhibitors. Sitagliptin is associated with inhibition of 80% of DPP-IV activity and augmentation of active GLP-1 and GIP levels after an OGTT. In one study involving 1,172 patients with a median baseline HbA1c of 7.5%, sitagliptin compared to glipizide provided similar HbA1c lowering effect over 52 weeks in patients on ongoing metformin therapy. Similarly, in patients with baseline HbA1c of 8.1% receiving pioglitazone, addition of sitagliptin 100 mg once daily improved HbA1c 0.7% compared to placebo ($P < 0.001$). Proinsulin levels were significantly reduced with sitagliptin compared to placebo. The drug was well-tolerated, exhibiting a similar incidence of hypoglycemia as placebo.⁴⁶ Vildagliptin, another DPP-IV inhibitor, showed similar effectiveness. In a randomized study with drug-naïve T2DM patients, after 24 weeks, vildagliptin 50 mg twice daily was equally effective as rosiglitazone (8 mg/day), but without weight gain. Vildagliptin also improves postprandial glycemia, restores GLP-1 levels and reduces glucagon secretion after meals. The hypoglycemic effect appears to be related to an improvement in beta-cell function.⁴⁷⁻⁴⁹

Enteroinsular Axis Implications on Bariatric Surgery

Possible hormonal mechanisms for weight loss and diabetes resolution of bariatric surgery was the topic of another talk presented by Dr. David Cummings (University of Washington, Seattle, USA). He introduced the subject stating that bariatric surgery

seems to overcome the adipostatic system of body weight regulation that makes non-surgical methods of weight loss traditionally unsuccessful.

Data from the Swedish Obese Subjects Study, reporting follow-up data of more than 1,000 patients for up to 10 years, showed that Roux-en-Y gastric bypass (RYGBP) promoted the greatest weight loss of about 38% of total body weight, maintaining in the region of 30% after 10 years. Gastric banding (GB) and gastroplasty (GP) are less effective but still induce far more weight loss than non-surgical treatment, which was ineffective in the long-term.⁵⁰

The mechanisms for such an impressive loss of weight are not totally clear. Gastric restriction is probably not the major factor, because the final stomach volume is comparable between RYGBP, GB and GP. Malabsorption seems not to be clinically significant in the long-term follow-up after the surgery, and magnitude of dumping symptoms does not correlate with the weight loss observed. On the other hand, some gut hormones seem to be related to this mechanism. Ghrelin is known to be one of the long-term adipostatic hormones that work for the maintenance of body weight. Ghrelin levels classically increase after weight loss, and this physiologic response is absent or impaired after RYGBP. The mechanism underlying this could be vagotomy (intentional or unintentional) after the RYGBP operation. The diverse bariatric surgical operations could partially explain the observed differences in ghrelin dysregulation after bariatric surgery among different surgical obesity centers.⁵¹⁻⁵⁴ Furthermore, other gut hormones like peptide YY (PYY) and GLP-1 are mediators of the ileal brake phenomenon which triggers satiation after meals, and their levels are increased after RYGBP.^{55,56} Different reports have shown improvement in glucose homeostasis and even diabetes resolution after RYGBP, and this is probably related to increased GLP-1 levels after the procedure.^{57,58}

The role of hindgut stimulation on promoting the increase in these hormone levels is reinforced by animal studies with ileal transposition, where there is no volume restriction and no malabsorption but still marked increase in GLP-1 and PYY levels and reduction in food intake and body weight.⁵⁹ However, if enhanced delivery of nutrients to the distal intestine and increased secretion of hindgut signals improve glucose levels, altered transit excluded from the foregut also appears to play a role

independent of effects on food intake, body weight and malabsorption.⁶⁰

Published data from the experience at the Hackensack University Medical Center supports that all forms of weight loss surgery lead to caloric restriction, weight loss, decrease in fat mass and improvement in T2DM. This suggests that these beneficial effects in glucose metabolism and insulin resistance following bariatric surgery result in the short-term from decreased stimulation of the enteroinsular axis, by decreased caloric intake and in the long-term by decreased fat mass and resulting changes in release of adipocytokines.⁶¹ This information was given by Dr. Garth Ballantyne (Hackensack University Medical Center, Hackensack, NJ, USA), who summarized this data. According to the published data, both laparoscopic Roux-en-Y gastric bypass (LRYGBP) and laparoscopic adjustable gastric banding (LAGB) significantly elevate basal and meal-simulated PYY levels, which may mediate suppression of appetite, improving weight loss.⁶² A study aimed to evaluate the short-term changes in insulin resistance, comparing LAGB and LRYGBP, using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR). Preoperative values were compared to levels 90 days after surgery, and baseline HbA1c was 5.7% in both groups. After 90 days, insulin resistance dropped in both groups, but significantly more in the LRYGBP group. In both groups postoperative HOMA-IR correlated with preoperative values but not with weight loss. The authors argued that these findings suggest that caloric restriction plays a significant role in improving insulin resistance after both LAGB and LRYGBP.⁶³ Looking at the data from the vast experience of his center, he concluded that bariatric operations decrease insulin resistance through three separate, but overlapping mechanisms: 1) severe caloric restriction, 2) alterations in the enteroinsular axis, and 3) fat loss (adipo-insular axis).

Given the reported results on body weight, and its metabolic consequences on glucose homeostasis after bariatric surgery, the question that arises is if there is any other abdominal surgical procedure that could be beneficial in improving blood glucose levels. This was the central feature of the presentation by Dr. Jose Carlos Pareja (State University of Campinas, Campinas, SP, Brazil). One study evaluated visceral fat removal in an animal model of diet-induced obe-

sity (DIO) and diabetes mellitus. Before surgery, DIO mice were diabetic and insulin-resistant compared to controls. After surgery, all parameters were reversed and even peripheral insulin signal transduction through its receptor, insulin receptor substrates IRS-1, IRS-2 and Akt, was improved in muscle.⁶⁴

A pilot study performed in a single center in Sweden compared the effects of omentectomy performed with bariatric surgery (adjustable gastric banding). Fifty patients who underwent bariatric surgery were randomized for omentectomy or no omentectomy, with the surgical procedure. After 2 years of follow-up, omentectomized patients had a significant improvement in oral glucose tolerance test and fasting plasma glucose and insulin, independent of weight loss. Subjects who underwent omentectomy tended to lose more weight than controls, although the weight loss was not significant.⁶⁵

Ileal transposition is another possibility for metabolic surgery that could determine metabolic benefits through increasing the incretin circulating levels. A pilot study in 19 obese patients (mean BMI=40.2) in which this procedure was performed with concomitant partial gastrectomy found 46% weight loss after 16 months. Among 5 patients with diabetes diagnosed at baseline, the glucose levels were normalized 3 weeks after the surgery.⁶⁶ Another possibility is duodenal exclusion as a mediator mechanism for improvement in glucose homeostasis through altered signals from the excluded foregut, as has been shown in a study with a T2DM rat model, in which the bypass ameliorated diabetes.⁶⁰

This International Symposium on Incretins and its importance in the clinical and surgical approach to the diabetic and obese population brought to light several possibilities and trends in this area, that need to be further explored in the near future, opening more possibilities in this new and exciting field.

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(Received March 20, 2007; accepted March 30, 2007)