



Ileal Effect on Blood Glucose, HbA1c, and GLP-1 in Goto-Kakizaki Rats

Henry Buchwald · Hector J. Menchaca ·
Van N. Michalek · Nestor T. Bertin

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Abstract

Background There have been enumerable studies on the effects of glucagon-like peptide-1 (GLP-1) on satiety and pancreatic islet function, stimulating the advocacy of surgical transposition of the ileum (rich in GLP-1-generating L-cells) higher in the gastrointestinal tract for earlier stimulation. In the Goto-Kakizaki rat with naturally occurring type 2 diabetes, we studied the influence of ileal exclusion (IE) and ileal resection (IR) on blood glucose, hemoglobin A1c (HbA1c), and GLP-1. **Methods** In six control (Ctrl), 10 IE, and 10 IR rats, over 12 weeks of follow-up, we determined blood glucose, HbA1c, and GLP-1.

Results Two animals in the IE and IR groups did not survive to week 13. Both operated groups weighed more than the Ctrl group at baseline and at 13 weeks; thus, IE and IR did not retard weight gain ($p < 0.05$). All three groups were equally hyperglycemic at week 13: 255 ± 10.2 Ctrl, 262 ± 11.0 IE, 292 ± 17.8 IR (mg/dl \pm SEM). The three groups had statistically identical markedly elevated HbA1c percentages at week 13: 14.7 ± 28 Ctrl, 11.7 ± 3.4 IE, 13.8 ± 3.5 IR (% \pm SEM). The end-study GLP-1 values (pM \pm SEM) were 5 ± 0.9 Ctrl, 33 ± 8.9 IE, and 25 ± 6.7 IR. *P* values for intergroup differences were IE vs. Ctrl 0.02, IR vs. Ctrl 0.02, and IE vs. IR 0.59.

Conclusions Neither IE nor IR resulted in a decrease in the mean GLP-1 level. On the contrary, the exclusion or resection of the L-cell rich ileum raised GLP-1 levels 5- to 6-fold. This increase in the GLP-1 was not associated with the mitigation of hyperglycemia or elevated HbA1c levels.

Keywords Intestinal exclusion · Intestinal resection · Blood glucose · Hemoglobin A1c · GLP-1

Introduction

There have been enumerable studies published demonstrating the effects of L-cell elaborated glucagon-like peptide-1 (GLP-1) on satiety and pancreatic islet cell function. The hormone works in concert with peptide YY (PYY), the PYY (3–36) form, one augmenting the actions of the other in an interdependent biofeedback loop [1]. GLP-1 and PYY are secreted in increasing amounts as a function of the caloric content of ingested food [2]. Their quantitative response is influenced by the intestinal site of stimulation [3–5], bile acids [6], central neural and vagal mechanisms [7–9], and other hormones (vasoactive intestinal polypeptide [10], gastrin [11]). The hormones centrally stimulate the arcuate nucleus of the hypothalamus, resulting in a reduced sensation of hunger and an increased sensation of satiety [12–14]. GLP-1 is involved in the “ileal brake” phenomena of delayed gastric emptying, delayed mouth to cecum transit time, and a decreased jejunal wave pressure [15–17]. GLP-1 also contributes to the incretin effect, defined as the concentration of the insulin released by oral glucose stimulation that exceeds the insulin concentration elicited by the same amount of intravenous glucose [18]. With respect to circulating glucose control, GLP-1 stimulates glucose-dependent insulin secretion, preinsulin gene expression, β -cell proliferation, and anti-apoptotic pathways and inhibits glucagon release [19, 20].

These effects of GLP-1 have stimulated experimental metabolic/bariatric operations to mitigate type 2 diabetes. Most prominent among them has been ileal transposition higher in the gastrointestinal tract, first advocated by Edward Mason [21] and now practiced, in one form or another, by several surgeons worldwide [22, 23]. Rationale for ileal transposition can be found in several rat experiments [24–26].

We have recently completed a study measuring GLP-1, PYY, and leptin levels after the stimulation of the terminal

H. Buchwald (✉) · H. J. Menchaca · V. N. Michalek · N. T. Bertin
Department of Surgery, University of Minnesota, 420 Delaware St.
SE, MMC 290, Minneapolis, MN 55455, USA
e-mail: buchw001@umn.edu

ileum or cecum by a static infusion of a food hydrolysate in morbidly obese patients undergoing a duodenal switch procedure [27]. We found that direct stimulation of both the human terminal ileum and cecum elicits plasma GLP-1 and PYY elevations and concurrent leptin decreases. The ileal GLP-1 and PYY elevations exceeded those of the cecum; the hydrolysate effect on the PYY plasma concentration was about three-fold than that of the GLP-1. All hormonal changes reached their maximum at 90 to 100 min. It is questionable, therefore, that the translocation of a segment of the ileum by ileal transposition would enhance the immediate postprandial release of GLP-1 and PYY over that obtained by direct stimulation in situ and, thereby, produce earlier satiety. This work, however, does not challenge whatever effect GLP-1 has on type 2 diabetes and how the elaboration of GLP-1 is related to ileal integrity.

We thus undertook a study in an animal model of naturally occurring type 2 diabetes, the Goto-Kakizaki (GK) rat, of the influence on blood glucose levels, hemoglobin A1c (HbA1c), and GLP-1 subsequent to ileal exclusion (IE) and ileal resection (IR).

Methods

Protocol

Phase I—Establishment of surgical and blood drawing techniques and appropriate anesthesia in 10 animals, four Wistar rats and six GK rats.

Phase II—Planned study of 26 GK rats blindly and randomly divided by animal age into three cohorts, namely six control (Ctrl), 10 IE, and 10 IR animals. Each rat was scheduled for 12 weeks of follow-up with no oral intake restrictions. Blood draws at surgery (week 0), at mid-term (week 9), and at the end of the study (week 13), by cecal or tail veins, were obtained for blood glucose levels. Variability in blood draw sites was due to difficulty in obtaining sufficient sample volumes from a single site. Blood draws by cardiac puncture at week 13 at the end of the study were used for blood glucose, HbA1c, and GLP-1 level determinations. In addition, animal weights were recorded throughout the study, and intestinal lengths were measured at autopsy.

Animal Care

The Wistar and GK rats, 9–10 weeks of age, weighing 275–300 g, were obtained from a commercial vendor. The animals were housed in individual cages at a constant temperature (70 °F) with a 12-h day/night light cycle. All animals received standard species-specific chow (Ralston Purina Co., St. Louis, MO or Harlan Teklad, Indianapolis, IN) and water ad libitum. The animals in phase II, after a

1-week acclimatization period, were randomized to three groups as follows: Ctrl, IE, and IR.

For pain relief postoperatively, the rats were given Ketoprofen 5 mg/kg SQ immediately after surgery, followed by Ibuprofen in a 500-ml water bottle at a dose of 15 mg/kg for 3 days. The rats were given sulfa-Trimethoprim elixir in the water bottle at 1 mg/ml for 6 days of the 12-week follow-up. The animals were closely monitored, and any animal in distress was euthanized.

Surgery

Surgery consisted of either distal IE or distal IR. IE was performed by a side-to-side ileocecal anastomosis using running 6/0 Monocryle suture, approximately 15–20 cm from the ileocecal valve, with ligature closure of the distal ileum with 3/0 Ethibond suture isoperistaltic from the anastomosis. The excluded ileum was retained in the abdominal cavity, its blood supply intact, with egress into the cecum via the ileocecal valve. IR was performed in a similar fashion except for the ligature of the terminal ileum with 3/0 Ethibond at the ileocecal valve and resection of the terminal ileum using multiple 6/0 Ethibond sutures for the ligation of the ileal mesentery. Peritoneal/abdominal wall closure was performed with a running 3/0 Vicryl suture and skin closure with a running 4/0 Vicryl suture. Surgery was performed under a mixture of ketamine (75 mg/kg) and xylazine (10 mg/kg) intra-peritoneal anesthesia.

Termination Euthanasia

At week 13 (12-week follow-up), the animals were anesthetized with the same ketamine/xylazine mixture for cardiac blood draws and then sacrificed by intravenous injection of pentobarbital and phenytoin (1 ml/5–10 kg).

Blood Samples and Analyses

The amounts of blood utilized for analyses were glucose 0.2 ml, HbA1c 0.5 ml, and GLP-1 0.5 ml. Analytical chemistry methods employed were glucose by oxidase biosensor, HbA1c by endpoint reflectance spectrophotometry with direct percent A1c calculation, and GLP-1 by enzyme-linked immunosorbent assay.

Statistics

Minimum sample size was determined by the following:

$$N = \frac{(\text{Confidence} \times \text{Std Deviation})^2}{\text{Difference}^2}$$

for a confidence level of 95 % and an expected standard deviation >6.75 % and a difference value >5.5 %. On this basis, a minimum sample size of six animals per group was calculated. Knowing the fragility of the GK animal model, the authors allowed up to 40 % animal loss in the study. Thus, the 20 % actual loss in the IR and IE groups fell within acceptable limits. Group comparisons were performed by Student's *t* test.

Results

Study Protocol

Two animals in the IE group and two in the IR group did not survive to week 13. Tail blood draw glucose values were on the average of 23.4 % lower than mesenteric vein samples.

Weight

At week 0, the mean weights (gm±SEM) for the three groups were Ctrl 350±5.4, IE 371±5.0, and IR 363±5.7. The *p* values

for the differences between groups were IE vs. IR 0.32, IE vs. Ctrl 0.02, and IR vs. Ctrl 0.13. Thus, the six Ctrl animals weighed statistically significantly less than the IE animals at the initiation of the study.

At week 13, the average weights (gm±SEM) for the three groups were Ctrl 379±10.4, IE 424±5.0, and IR 410±7.9. The *p* values for the differences between groups were: IE vs. IR 0.15, IE vs. Ctrl 0.01, and IR vs. Ctrl 0.05. Thus, both operated groups weighed statistically significantly more than the non-operated controls, and there was no statistical significant difference in weight between the IE and IR groups.

The average weight gain in the Ctrl was 29 g, in the IE group 53 mg, and in the IR group 47 g. IE or IR surgery, therefore, did not retard weight gain and exceeded the actual average weight gain in the non-operated Ctrl group (*p*<0.05).

Small Intestinal Lengths

At week 13, the measured average intestinal length from the pylorus to the ileocecal anastomosis was 73±3.9 (SEM) cm in the IE group and 78±4.0 cm in the IR group, with the average length of the anastomosis to the ileocecal valve measured at

Table 1 Total blood glucose values (mg/dl)

	Week 0				Week 9		Week 13			
	Tail		Cecal mesent.		Tail	Tail	Tail	Cecal mesent.		
Ctrl										
1					116	117	178	170	277	271
2					131	131	185	186	264	274
3	99	105	122*	130*			221	206	306	295
4	131	134	162*	165*			181	177	222	221
5	117	121	144*	149*			215	220	265	268
6	110	113	136*	139*			159	158	198	203
IE										
1					107	108	204	194	273	281
2					106	108	180	176	201	198
3					116	116	168	173	226	228
4	252*	248*	329	324			268	263	308	296
5	217*	217*	283	283			171	166	215	220
6	192*	189*	250	247			221	221	247	249
7	186*	188*	243	246			170	172	312	298
8	195*	208*	254	272			238	236	316	325
IR										
1					148	152	223	225	293	293
2					96	99	125	125	164	164
3					110	110	264	267	379	386
4					93	96	172	178	252	246
5	189*	205*	247	268			233	239	382	385
6	152*	166*	199	217			232	238	274	288
7	235*	241*	307	314			220	223	254	253
8	244*	245*	318	320			264	273	318	339

*Denotes calculated value, 23.4 % higher in cecal mesenteric vein samples in comparison to tail vein samples

Table 2 Mean blood glucose values (mg/dl \pm SEM)

	Week 0 Tail vein	Week 9 Tail vein	Week 13 Tail vein
Ctrl	116 \pm 4.3	124 \pm 4.2	188 \pm 6.5
IE	210 \pm 13.1*	110 \pm 1.9	201 \pm 8.8
IR	209 \pm 7.7*	113 \pm 8.4	219 \pm 11.6

* p <0.01 for IE and IR vs. Ctrl

25 \pm 3.3 cm in the IE group. The Ctrl group pylorus to ileocecal valve distance averaged 85 \pm 2.3 cm.

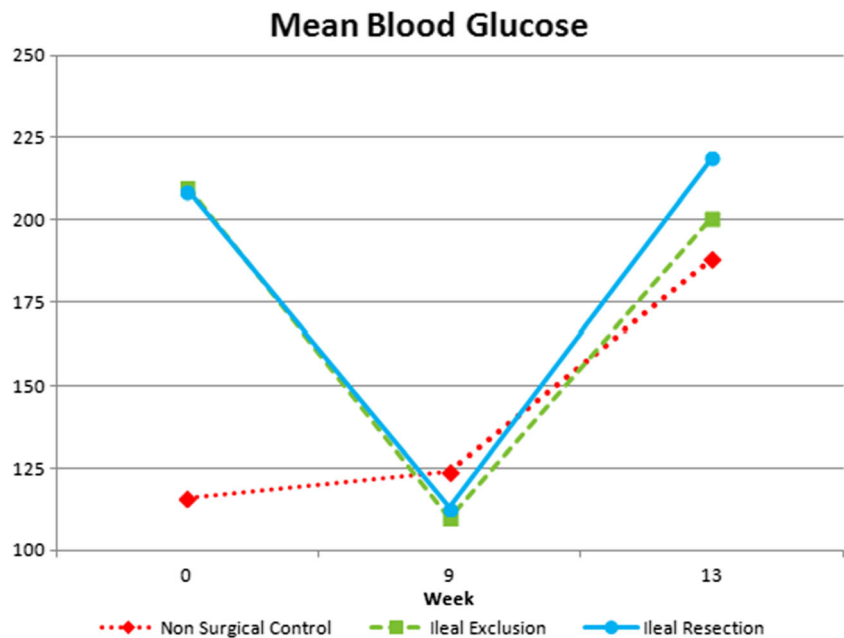
Blood Glucose

Duplicate values for all blood glucose determinations as well as anatomic sites of blood drawing are given in Table 1. At baseline, blood drawings were made from the tail vein in the Ctrl group and from a mesenteric vein in the IE and IR groups. A calculated correction factor of 23.4 % was used to compensate for the difference in peripheral and central glucose determinations. The mean blood glucose values (mg/dl \pm SEM) by tail vein determinations are given in Table 2 and plotted in Fig. 1. The animals in the Ctrl group became progressively more hyperglycemic from week 0 to week 13. The IE and IR animals were hyperglycemic in week 0, markedly dropped their glucose levels in week 9, and regained their preoperative hyperglycemia in week 13. At week 13, the three groups were essentially equally hyperglycemic.

HgA1c

HgA1c levels were determined only at the termination of the study, week 13, by cardiac puncture under anesthesia prior to

Fig. 1 Mean blood glucose values (mg/dl \pm SEM)



euthanasia. The value for each animal plus the group means (% \pm SEM) are shown in Table 3 and plotted in Fig. 2. The p values for intergroup differences were all NS: IE vs. IR 0.61, IE vs. Ctrl 0.52, and IR vs. Ctrl 0.85. Though certain individual animals maintained HgA1c levels <6 %, the majority of the animals had markedly elevated HgA1c values, in keeping with the group means.

GLP-1

GLP-1 levels were determined only at the termination of the study, week 13, by cardiac puncture under anesthesia prior to euthanasia. The values for each animal plus the group values \pm means (pM \pm SEM) are shown in Table 4 and plotted in Fig. 3. The p values for intergroup differences were statistically significant for IE vs. Ctrl (p =0.02) and IR vs. Ctrl (p =0.02), but not for IE vs. IR (p =0.59). The mean GLP-1 value for the IE group (33 pM \pm 8.9 SEM) was over six-fold that of the Ctrl group (5 pM \pm 0.9 SEM). The mean GLP-1 value for the IR group (25 pM \pm 6.7 SEM) was five-fold that of the Ctrl group. Neither IE nor IR resulted in a decrease in the mean circulating GLP-1 level but, instead, a marked increase in the mean GLP-1 level occurred.

Discussion

This study questions both the effect of GLP-1 on type 2 diabetes and the role of the ileum per se in glucose homeostasis. Simply stated, if the ileal segment of the intestinal tract plays a role in glucose regulation, and this effect may be

Table 3 HbA1c values week 13 (%)

	Animal								Group $\bar{X} \pm \text{SEM}$
	1	2	3	4	5	6	7	8	
Ctrl	21.8	3.8	22.0	14.6	14.6	11.2			14.7±2.8
IE	3.6	3.6	3.0	22.1	4.0	23.2	11.4	23.0	11.7±3.4
IR	23.0	2.7	3.6	3.5	9.6	22.2	22.7	23.1	13.8±3.5

p values—IE vs. IR 0.61, IE vs. Ctrl 0.52, IR vs. Ctrl 0.85

enhanced by ileal transposition higher in the intestinal tract, why then do IE and actual IR lead to a marked increase (5–6-fold), and not a decrease, in the circulating GLP-1 level? And if an increase in GLP-1 is beneficial in type 2 diabetes, why did it not affect the hyperglycemia and elevated HbA1c levels in these GK rats?

In this animal study, the operative procedures did not induce weight loss; indeed, weight gain in the IE and IR groups statistically significantly exceeded that in the Ctrl group. This finding may have influenced the study’s results with regard to glucose metabolism and the rat model’s type 2 diabetes.

We purposely studied IR as well as IE since we postulated that the bypassed or excluded ileum might still be stimulated to excrete L-cell-derived GLP-1 by a neurohormonal pathway. When, however, the ileum is excised and there is a five-fold increase in circulating GLP-1, this increased incretin level cannot have been generated from ileal mucosal L-cells. Since the entire gastrointestinal tract is rich in L-cells, with the concentration of L-cells increasing from proximal to distal bowel [2, 28], the increased circulating GLP-1 came from elsewhere in the gut. Possibly, in the absence of the terminal ileum and the ileocecal valve, this site was the now earlier stimulated cecum, which has a marked capacity for GLP-1 elaboration [27]. In any event, the ileum may have a cardinal role in GLP-1 secretion, but this function is not intrinsic to the ileal L-cells and may actually be heightened by the absence of the ileum from the functioning intestinal tract.

Table 4 GLP-1 values week 13 (pM)

	Animal								Group $\bar{X} \pm \text{SEM}$
	1	2	3	4	5	6	7	8	
Ctrl	9	3	5	5	3	6			5±0.9
IE	52	2	9	14	27	27	71	58	33±8.9
IR	32	10	62	23	16	40	13	5	25±6.7

p values—IE vs. IR 0.59, IE vs. Ctrl 0.02, IR vs. Ctrl 0.02

Contrary to the general belief that the ileum is a major site of GLP-1 production, we have created in this experiment, in this rat model, a marked increase in circulating GLP-1 by IE or IR. At the same time, having now generated sustained, greatly elevated GLP-1 levels, there was no amelioration of the elevated blood glucose levels or HbA1c. These animals had no benefit with regard to their type 2 diabetes.

This study, however, does not challenge the relationship of GLP-1 and type 2 diabetes in humans, nor does it question a role for the ileum in human hormonal regulation of glucose homeostasis. It does, however, place into question the mechanism for the GLP-1 effect and its elaboration in this rat model. Further, these data raise a serious doubt of the applicability of findings in the GK rat model to humans or, for that matter, any rat model. Rats are relatively inexpensive and easily managed experimental subjects, but rat findings may have little or no bearing on human physiology, biochemistry, and disease.

The postulate that rats are not good models for humans, in particular when the ileum is involved, can be illustrated by the history of the partial ileal bypass operation for hyperlipidemia. In 1964, the first author demonstrated in rabbits and in pigs, and subsequently in humans, that the exclusion of the distal ileum markedly reduced circulating cholesterol levels [29]. The operative mechanism for partial ileal bypass is increased cholesterol and bile acid excretion, resulting in increased cholesterol synthesis and its conversion to bile acids, with

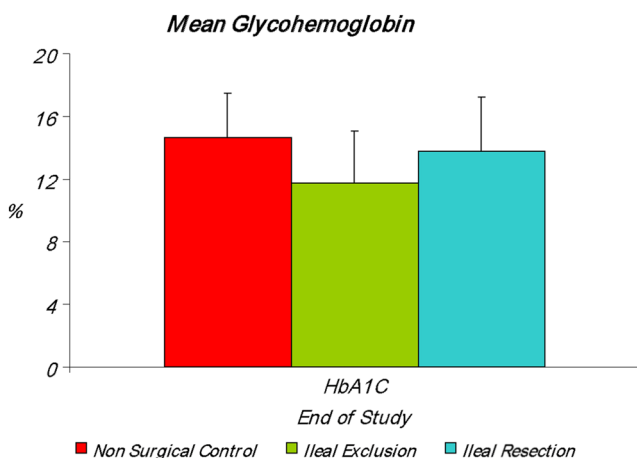


Fig. 2 HbA1c values week 13 (%±SEM)

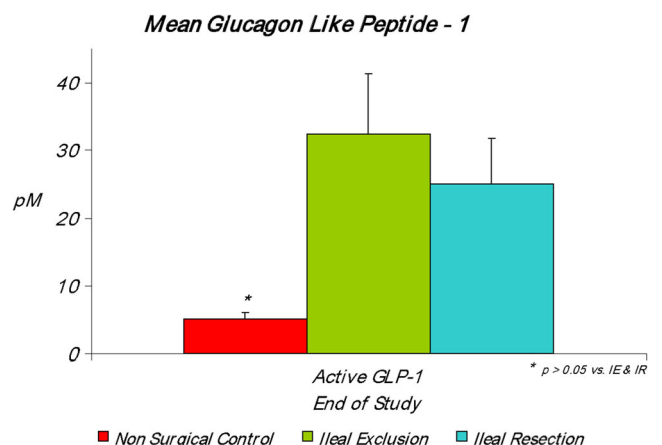


Fig. 3 GLP-1 values week 13 (pM ± SEM)

increased cholesterol turnover, but a resultant decrease in the cholesterol body pools [30]. This experimental work was repeated by several authors in several different species, including the dog [31], the White Carneau pigeon [32], and the Rhesus monkey [33, 34]—all with comparable results. There was, however, a statement made by the group of Brown and Goldstein, who won the Nobel Prize for their elucidation of the LDL-receptor, that questioned the validity of the partial ileal bypass concept since they could not duplicate our findings in a rat preparation. Apparently, the rat can compensate for the intestinal loss of cholesterol and bile acids by an extraordinary increase in cholesterol synthesis.

The advent of the partial ileal bypass procedure led to the Program on the Surgical Control of the Hyperlipidemias (POSCH) trial, a \$65 million dollar NHLBI investigator-initiated, four institutions, secondary intervention, randomized controlled trial, which was the first statistically significant study to show the clinical and radiographic efficacy of lowering the plasma cholesterol, in particular the LDL-cholesterol fraction [35]. POSCH outcomes included the statistically significant reduction of the combined endpoint of death and recurrent myocardial infarction, occurrence of peripheral vascular disease, serial coronary arteriography atherosclerotic progression with actual significant lesion regression, and overall mortality [35–37]. The increase in life expectancy in the partial ileal bypass intervention group over the control group was seen to persist for over 25 years [38]. All this may not have come to pass if the initial animal investigations were carried out in the rat.

In summary, in the type 2 diabetic GK rat, IE and IR raised the circulating GLP-1 concentration 5- to 6-fold. This increase in GLP-1 was not associated with the mitigation of hyperglycemia or elevated HbA1c levels. These outcomes may not have translational relevance to human responses.

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Conflict of Interest Henry Buchwald, Hector J. Menchaca, Van N. Michalek, and Nestor T. Bertin Suguitani have nothing to disclose.

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