# Effect of Dietary Carbohydrates on Insulin and Glucagon Receptors in a New Model of Noninsulin-Dependent Diabetes-SHR/N-Corpulent Rat (42957)

SAM J. BHATHENA[1], BRUCE W. KENNEDY, JACQUELYN JONES, PATRICIA M. SMITH, OTHO E. MICHAELIS IV, NANCY CARSWELL, CARL T. HANSEN, NANCY R. VOYLES, AND LILLIAN RECANT

*USDA, ARS, BHNRC, Carbohydrate Nutrition Laboratory, Beltsville, Maryland 20705; Small Animal Section, Veterinary Resources Branch, DRS, NIH, Bethesda, Maryland 20892; Diabetes Research Laboratory, VA Medical Center, Washington, DC 20422*

*Abstract.* **A new congenic strain of rat, the SHR/N-corpulent, provides a good model for noninsulin-dependent diabetes and was used in the present study. Corpulent rats as compared to their lean littermates are obese, hyperlipidemic, and severely hyperinsulinemic, and show an age-dependent loss of glucose tolerance. Mild fasting hyperglycemia is seen only in corpulent rats fed sucrose. Since dietary sucrose is more lipogenic than starch and since insulin and glucagon are involved in lipid and carbohydrate metabolism, we studied the effect of the type of dietary carbohydrate on insulin and glucagon levels and their receptors in lean and corpulent SHR/N rats. A significant phenotypic effect was observed (corpulent > lean) on plasma levels of triglyceride, cholesterol, and insulin. Dietary sucrose increased these parameters in corpulent rats but not in lean rats. Insulin and glucagon binding to liver plasma membranes was lower in corpulent rats than in lean; decreases were due to fewer receptors without a significant change in affinity. Thus, in corpulent rats, in addition to hyperinsulinemia, fewer glucagon receptors and their failure to be regulated by plasma glucagon levels appear to contribute to the hyperlipidemia. Furthermore, the hyperglycemia observed in sucrose-fed corpulent rats may be due to extreme resistance to insulin despite lower plasma glucagon and fewer glucagon receptors.** [P.S.E.B.M. 1989, Vol 192]

A new rodent model for noninsulin-dependent diabetes has recently been developed by Hansen (1) at the National Institutes of Health by mating the spontaneously hypertensive rat with the Koletsky rat which contains the corpulent (*cp*) gene. The resulting homozygous corpulent (*cp/cp*) rat is obese and mildly hypertensive, while the homozygous lean (*+/+*) and heterozygous lean (*cp/+*) littermates are lean and markedly hypertensive. Both lean and corpulent rats acquire the characteristic traits of noninsulin-dependent diabetes (2, 3). However, corpulent rats become diabetic much earlier, as early as 9 weeks, versus 12 months for lean rats, exhibiting hyperinsulinemia, hyperglycemia, glycosuria, and proteinuria (4). Corpulent rats also show a tendency toward obesity, as early as 5 weeks of age, and develop hypertriglyceridemia and hypercholesterolemia (2). Recently, Voyles *et al.* (4) reported impaired insulin secretion in response to elevated glucose levels as well as a paradoxical higher secretion of insulin at low plasma glucose levels in corpulent rats but observed normal responses in lean littermates. Similar results have been reported by Leahy and Weir (6) in diabetic rats produced by neonatal streptozotocin treatment. The SHR/N-corpulent rat differs from other obese rat models, such as the LA/N-corpulent and fatty Zucker rats, in that the latter do not develop the metabolic and pathologic changes observed in diabetes, although Zucker fatty rats may show abnormal responses to oral glucose loads (7).

Different dietary carbohydrates have been reported to differ quantitatively in their effect on lipid and

[1] To whom requests for reprints should be addressed at ARS, USDA, BHNRC, Carbohydrate Nutrition Laboratory, Room 315, Building 307, BARC-East, Beltsville, MD 20705.

Received February 21, 1989. [P.S.E.B.M. 1989, Vol 192]
Accepted May 5, 1989.

0037-9727/89/1921-0066$2.00/0
Copyright © 1989 by the Society for Experimental Biology and Medicine

carbohydrate metabolism. Feeding sucrose as compared to starch results in a greater lipogenic response and higher plasma glucose levels in normal as well as obese humans (8–10) and animals (11–13), including both lean and obese SHR/N-corpulent rats (2, 3). Various carbohydrates also produce quantitatively different effects on plasma insulin and glucagon levels (12, 14) and on glucagon and insulin receptors studied in humans and animals (13–16).

Glucagon has been shown to be catabolic and hypolipidemic in normal humans (17, 18) and animals (19, 20), and a decrease in net glucagon activity has been proposed as a mechanism in the development and maintenance of hyperlipidemia in humans (21). Mild hyperglucagonemia is also observed in human diabetic subjects (22, 23) and in experimental diabetes in animals (24, 25). We have examined the hypothesis that dietary carbohydrates affect glucagon and insulin receptors in this new model of diabetes in a manner similar to that observed in other models of diabetes.

## Materials and Methods

Five-week-old male obese homozygous SHR/N-*cp/cp* (corpulent) rats were used in the present study. the lean controls consisted of both homozygotes (*+/+*) and heterozygotes (*cp/+*) and were not further characterized. The rats were housed individually in stainless steel cages with open mesh bottoms. The room was environmentally controlled for temperature (22–25°C) and humidity with a reverse 12-hr dark-light cycle. Animals were cared for in accordance with National Institutes of Health principles. The rats were fed *ad libitum* for 15 weeks a diet containing either 54% sucrose or 54% starch with 10% casein, 10% lactalbumin, 4% corn oil, 4% coconut oil, 4% lard, 4% beef tallow, 5.9% cellulose, 3.1% AIN-76 Salt mix (26) (prepared without sucrose), and 1% vitamin mix (26) (#40060 Teklad test diet, Madison, WI). At the end of the feeding period, the rats were decapitated after an overnight fast. Blood was collected in tubes containing 1000 units of Trasylol (Aprotinin) (FBA Pharmaceutical, New York, NY) and 10.5 mg of ethylenediaminetetraacetic acid. Plasma was separated and analyzed enzymatically for glucose (27), triglyceride (28), and cholesterol (29) using the Centrifichem automated system (Baker Instrument Corp., Pleasantville, NY). Immunoreactive glucagon was measured by the method previously described (24). Antibody 04A was purchased from Dr. R. Unger (The University of Texas Health Science Center, Dallas, TX). Immunoreactive insulin was determined by using a kit from Immunonuclear Corp., Stillwater, MN (catalogue no. 0600). Rat insulin (gift from Eli Lilly and Co., Indianapolis, IN) was used as standard. Plasma membranes were prepared from liver according to the method of Neville (30) and stored at −70°C. Plasma membrane protein was assayed according to the method of Lowry *et al.* (31).

To measure glucagon binding, membranes (80–120 μg of protein) were incubated for 30 min at 30°C in 0.5 ml of Tris buffer, pH 7.6, with 50 pg of [$^{125}$I]glucagon in the presence of 0–10 μg/ml native porcine pancreatic glucagon. Insulin binding was measured by incubating membranes for 60 min at 30°C in 0.5 ml of Tris buffer, pH 7.6, with 50 pg of [$^{125}$I]insulin in the presence of 0–10 μg/ml native porcine pancreatic insulin. The composition of the buffer used and the method of separating bound from free hormone have been described previously (24, 32, 33). Native pancreatic porcine insulin and glucagon were gifts from Eli Lilly and Co. Monoiodinated [$^{125}$I]insulin and [$^{125}$I]glucagon were purchased from New England Nuclear Corp., Boston, MA. The hormone binding data were analyzed by Scatchard plots (34) and competition-inhibition plots (33). The numbers of insulin and glucagon receptors were assessed from the intercept on the abscissa of Scatchard plots. Affinity was determined from competition-inhibition plots as the amount of native hormone required to displace 50% of bound tracer. Statistical analysis was carried out by analysis of variance to evaluate the effect of phenotype (lean vs obese), diet (starch vs sucrose), and phenotype × diet interactions (35). Differences between means were determined by Duncan's multiple range test (35). Differences with $P$ values less than 0.05 were considered statistically significant.

As shown in Table I, corpulent rats had significantly greater weight gain, liver weight, and epididymal adipose tissue weight than lean littermates. Dietary carbohydrate source had no significant effect on either the weight gain or the adipose tissue weight of either lean or corpulent rats. However, in corpulent rats, but not in lean rats, liver weight of rats fed sucrose was significantly greater than that of rats fed starch, due to the accumulation of fat.

Table II summarizes the data on plasma levels of glucose, triglyceride, and cholesterol. Fasting plasma glucose was significantly higher in corpulent rats fed sucrose but not in those fed starch. However, both sucrose- and starch-fed corpulent rats showed abnormally high glucose levels after an oral glucose load as well as significant glycosuria (4). A significant phenotypic effect (corpulent > lean) was observed for plasma triglyceride and cholesterol. Corpulent rats fed sucrose had significantly higher plasma triglyceride and cholesterol than rats fed starch. Although dietary sucrose tended to increase plasma triglyceride and cholesterol in lean rats, the effect was not significant. However, the overall diet effect was significant as seen from the analysis of variance (ANOVA). There was also an interaction between phenotype and diet for these parameters.

The effect of dietary starch and sucrose on plasma

**Table I.** Effect of Dietary Carbohydrates on Weight Gain, Liver Weight, and Adipose Weight in Lean and Corpulent SHR/N Rats

| Phenotype | Diet | Weight gain[a] (g) | Liver weight (g) | Epididymal adipose weight (g) |
|---|---|---|---|---|
| Lean | Starch | 228.5 ± 2.5[b,*] | 9.8 ± 1.6* | 5.1 ± 0.6* |
| | Sucrose | 257.3 ± 18.2* | 12.3 ± 0.4*,† | 6.9 ± 0.4* |
| Corpulent | Starch | 363.7 ± 15.7† | 19.3 ± 0.2†,§ | 10.0 ± 0.5† |
| | Sucrose | 369.0 ± 22.2† | 31.4 ± 2.2# | 11.0 ± 0.4† |
| ANOVA[c] | | | | |
| Phenotype | | 0.001 | 0.0001 | 0.001 |
| Diet | | NS[d] | 0.001 | NS |
| Phenotype × diet | | NS | 0.01 | NS |

[a] Final weight minus initial weight during 15-week feeding period.
[b] Mean ± SE of six rats. Means within a column not sharing a common symbol are statistically different according to Duncan's multiple range test at $P < 0.05$.
[c] The data were analyzed by analysis of variance (ANOVA) using 2 × 2 factorial design.
[d] NS, not significant.

**Table II.** Effect of Dietary Carbohydrates on Plasma Glucose, Triglyceride, and Cholesterol in Lean and Corpulent SHR/N Rats

| Phenotype | Diet | Plasma glucose[a] (mmol/liter) | Plasma triglyceride (mmol/liter) | Plasma cholesterol (mmol/liter) |
|---|---|---|---|---|
| Lean | Starch | 5.2 ± 0.3[b,*] | 0.59 ± 0.04* | 1.22 ± 0.06* |
| | Sucrose | 5.1 ± 0.1* | 0.86 ± 0.10* | 1.65 ± 0.10* |
| Corpulent | Starch | 5.1 ± 0.2* | 4.55 ± 0.24† | 2.45 ± 0.34† |
| | Sucrose | 7.5 ± 1.2† | 13.07 ± 2.22§ | 4.28 ± 0.37§ |
| ANOVA[c] | | | | |
| Phenotype | | NS[d] | 0.005 | 0.0005 |
| Diet | | NS | 0.05 | 0.01 |
| Phenotype × diet | | NS | 0.05 | 0.05 |

[a] Plasma glucose in response to oral glucose load and urine glucose levels in these rats are given elsewhere (4).
[b] Mean ± SE of six rats. Means within a column not sharing a common symbol are statistically different according to Duncan's multiple range test at $P < 0.05$.
[c] The data were analyzed by analysis of variance using a 2 × 2 factorial design.
[d] NS, not significant.

hormones and their receptors in liver plasma membranes is shown in Table III. There was a significant phenotypic effect on plasma insulin and on insulin and glucagon binding to liver plasma membranes. Plasma glucagon levels in corpulent rats tended to be lower than in lean rats, but due to the large standard error of the mean the decrease was not significant. Analysis of variance indicated a significant diet effect ($P < 0.05$) for plasma insulin level in that sucrose-fed lean as well as corpulent rats had higher levels than those fed starch. However, the range test did not distinguish between diets within phenotype. No significant interaction between phenotype and diet was observed for any of the parameters.

The elevation in plasma triglyceride and cholesterol in corpulent rats correlated negatively, though weakly, with glucagon binding in that lower glucagon binding was associated with higher plasma lipids.

To determine whether the lower values in insulin and glucagon binding in corpulent rats than in lean rats was due to a decrease in either the number of receptors or the receptor affinity, the binding data were analyzed by Scatchard and competition-inhibition plots. Quantitative data showing the number and affinity of insulin and glucagon receptors are reported in Table IV. Corpulent rats had significantly fewer insulin receptors ($P < 0.01$) than lean littermates. When the insulin binding data were analyzed by competition-inhibition plots, no statistically significant differences were observed in the affinity of the insulin receptors between lean and corpulent rats. Diet had no significant effect on either the number or the affinity of the insulin receptors in either lean or corpulent rats. Scatchard analysis of glucagon binding likewise revealed significantly fewer receptors in corpulent rats than in lean littermates ($P < 0.05$). Competition-inhibition plots revealed no significant

**Table III.** Effect of Dietary Carbohydrates on Plasma Insulin and Glucagon and on Insulin and Glucagon Binding to Liver Plasma Membranes of SHR/N Rats

| Phenotype | Diet | Plasma insulin (nmol/liter) | Plasma glucagon (ng/liter) | Insulin binding[a] (%/50 μg of protein) | Glucagon binding[a] (%/25 μg of protein) |
|---|---|---|---|---|---|
| Lean | Starch | 1.58 ± 0.08[b],* | 220 ± 32* | 5.18 ± 1.38* | 37.9 ± 5.6* |
| | Sucrose | 1.98 ± 0.34* | 246 ± 57* | 5.01 ± 0.62* | 32.4 ± 3.9* |
| Corpulent | Starch | 24.55 ± 3.44† | 133 ± 20* | 0.87 ± 0.23† | 14.7 ± 1.2† |
| | Sucrose | 29.09 ± 3.92† | 145 ± 13* | 0.90 ± 0.14† | 13.2 ± 2.2† |
| ANOVA[c] | | | | | |
| Phenotype | | 0.0001 | NS[d] | 0.0001 | 0.005 |
| Diet | | 0.05 | NS | NS | NS |
| Phenotype × diet | | NS | NS | NS | NS |

[a] Percentage of specific binding. Nonspecific binding (binding in the presence of 10 μg/ml hormone) was subtracted from total binding to obtain specific binding.
[b] Mean ± SE of six rats. Means within a column not sharing a common symbol are statistically different according to Duncan's multiple range test at $P < 0.05$.
[c] The data were analyzed by analysis of variance using a 2 × 2 factorial design.

**Table IV.** Effect of Dietary Carbohydrates on the Number and Affinity of Insulin and Glucagon Receptors on Liver Plasma Membranes of Lean and Corpulent SHR/N Rats

| Phenotype | Diet | Insulin receptors | | Glucagon receptors | |
|---|---|---|---|---|---|
| | | Number[a] | Affinity[b] | Number[a] | Affinity[b] |
| Lean | Starch | 2.64 ± 0.22[c],* | 14.5 ± 2.9* | 0.72 ± 0.08* | 4.5 ± 0.51* |
| | Sucrose | 3.23 ± 0.41* | 11.7 ± 1.9* | 0.59 ± 0.04*,† | 5.3 ± 0.40* |
| Corpulent | Starch | 0.98 ± 0.10† | 8.2 ± 1.1† | 0.35 ± 0.03† | 3.5 ± 0.40* |
| | Sucrose | 1.25 ± 0.11† | 8.7 ± 1.6* | 0.31 ± 0.03† | 4.2 ± 0.32* |
| ANOVA[d] | | | | | |
| Phenotype | | 0.01 | NS[e] | 0.05 | NS |
| Diet | | NS | NS | NS | |
| Phenotype × diet | | NS | NS | NS | NS |

[a] Number of receptors is measured from the intercept on the abscissa of the Scatchard plots.
[b] Affinity of the receptors is measured from the competition-inhibition plots as the amount of native hormone required to displace 50% of the bound tracer. Number and affinity for each animal were derived from individual plots. A higher number indicates a rightward shift in the competition-inhibition plot, thereby indicating a decrease in the affinity of the receptors.
[c] Mean ± SE of the six rats. Means within a column not sharing a common superscript symbol are statistically different according to Duncan's multiple range test at $P < 0.05$.
[d] The data were analyzed by analysis of variance using a 2 × 2 factorial design.
[e] NS, not significant.

differences in the affinity of glucagon receptors between lean and corpulent rats. Dietary carbohydrates had no significant effects on either the number or the affinity of glucagon receptors according to analysis of variance.

## Discussion

In the present study we have utilized a new animal model of Type II noninsulin-dependent diabetes resembling human Type II diabetes in that the corpulent rat is obese and hyperlipidemic, and shows postprandial hyperglycemia, fasting as well as postprandial hyperinsulinemia, glycosuria, proteinuria, islet hyperplasia, and renal lesions resembling human glomerulosclerosis (2–5). The corpulent rats, however, show fasting hyperglycemia only when fed sucrose. Significant hyperglycemia is observed in the fed state (5) as well as after an oral glucose load regardless of the type of carbohydrate fed (3, 4), similar to that seen in human diabetic subjects. The alteration in renal function in this rat model also resembles that observed in human diabetes (3, 36). This model differs from that of humans, though, in that the corpulent rat tended to have lower glucagon levels, although not statistically significant, than lean littermates, whereas noninsulin-dependent human diabetic subjects usually have higher plasma glucagon levels than non-diabetic subjects (22). Lower plasma glucagon levels are also observed in other models of genetically obese rats, namely, the fatty Zucker rat (14) and the LA/N-corpulent rat (12).

In SHR/N-corpulent rats, dietary sucrose produced a more severe alteration in carbohydrate and lipid metabolism than did dietary starch (2). Sucrose feeding significantly increased liver weight and plasma glucose, triglyceride, and cholesterol in corpulent rats but not

in lean littermates. Since lean SHR/N rats show a diabetic tendency much later in life (after approximately 12 months of age), it is possible that sucrose feeding significantly alters these parameters in lean rats only after prolonged feeding. Also, the hypertriglyceridemia seen in the corpulent rat fed sucrose is extremely severe. Other models of obesity which do not have the associated complication of diabetes, such as the fatty Zucker rat or LA/N-corpulent rat, do not show such high levels of plasma triglycerides (11, 13, 14).

In the present study, we have shown significant decreases in glucagon receptors in corpulent diabetic rats in spite of a tendency for lower than normal plasma glucagon levels. Decreases in glucagon receptor numbers along with low plasma glucagon levels have been observed in other models of genetic obesity (13, 14). Decreased glucagon binding to liver plasma membranes in diabetic animals and to lymphocytes in diabetic human subjects has also been observed (24, 25, 37). However, in these cases, decreased glucagon binding was associated with hyperglucagonemia, suggesting regulation of glucagon receptors by circulating plasma glucagon levels. Similar control of glucagon receptors by plasma glucagon levels occurs in fasting (38, 39) and in experimental hyperglucagonemia produced by glucagon injection or infusion (24, 39). Thus, corpulent rats failed to show the anticipated regulation of glucagon receptors by plasma glucagon level. It appears that down- or up-regulation of glucagon receptors by plasma glucagon levels is not as universal as that of insulin receptors. The decrease in glucagon binding in the diabetic SHR/N-corpulent rats was due to a decrease in the number of receptors. This decreased binding, in association with decreased plasma glucagon levels, indicates a state of decreased glucagon activity. Decreased glucagon activity has been postulated to account for the hyperlipidemia of genetic and diet-induced obesity (40, 41) and may be responsible for the hyperlipidemia observed in this model of diabetes. However, others have observed no glucagon resistance in hyperlipidemic human subjects (42, 43) or in obese hyperlipidemic animals (44). In the present study, we observed a weak negative correlation between plasma triglyceride and cholesterol and glucagon binding to liver membranes indicating that decreased glucagon activity may be at least partly responsible for hyperlipidemia. The negative correlation between plasma glucagon level and plasma lipid, although present, was even weaker. Increased plasma insulin in corpulent rats may be more responsible for hyperlipidemia than a decrease in plasma glucagon.

In the present study we also observed lower insulin binding to liver plasma membranes in obese diabetic rats than in their lean littermates, which was due to a decrease in the number of receptors. Decreased insulin binding in obesity and diabetes has been shown previously from many laboratories and is not surprising. Thus, like other models of diabetes and obesity such as *ob/ob* mice, obese Zucker rats, *db/db* mice, obesity produced by gold thioglucose, spontaneous obesity, and hypothalamic obesity in monkeys (16), where hyperinsulinemia is present, this model also shows fewer insulin receptors.

We have previously shown decreased numbers of glucagon receptors on liver plasma membranes in two other rat models of hyperlipidemia associated with obesity (13, 14). In the present study we report decreased glucagon receptors in this model, the SHR/N-corpulent, in which hyperlipidemia is associated with diabetes as well as obesity. All three models have either the same or lower plasma glucagon levels than their lean normolipidemic littermates. In addition to the hyperinsulinemia seen in these models, decreased glucagon activity, as evidenced by fewer glucagon receptors and their failure to be regulated by plasma glucagon levels, appears to be a component of the mechanisms underlying hyperlipidemia. Furthermore, the hyperglycemia observed in sucrose-fed corpulent rats may be due to an extreme resistance to insulin in spite of lower plasma glucagon and fewer glucagon receptors.

Based on this and other past studies, the SHR/N-corpulent rat shows many of the characteristic features of noninsulin-dependent diabetes seen in humans, differing only in regard to plasma glucagon levels. This genetic syndrome is a useful model for the laboratory study of noninsulin-dependent diabetes.


1. Hansen CT. Two congenic rat strains for nutrition and obesity research. Fed Proc **42**:537, 1983.
2. Michaelis OE IV, Ellwood KC, Judge JM, Schoene NW, Hansen CT. Effect of dietary sucrose on the SHR/N-corpulent rat: A new model for insulin-independent diabetes. Am J Clin Nutr **39**:612–618, 1984.
3. Michaelis OE IV, Patrick DH, Hansen CT, Canary JJ, Werner RM, Carswell N. Animal model of human disease. Insulin independent diabetes mellitus (type II). Spontaneous hypertensive/NIH-corpulent rat. Am J Pathol **123**:398–400, 1986.
4. Michaelis OE IV, Ellwood KC, Emberland JJ, Hansen CT, Canary JJ. Effect of dietary carbohydrate on expression of diabetes in the SHR/N-corpulent rat: A new model for obesity-induced diabetes. J Obes Weight Regul **4**:168–178, 1985.
5. Voyles NR, Powell AM, Timmers KI, Wilkins SD, Bhathena SJ, Hansen CT, Michaelis OE IV. Reversible impairment of glucose-induced insulin secretion in SHR/N-corpulent rats: A genetic model of type II diabetes. Diabetes **37**:398–404, 1988.
6. Leahy JL, Weir GC. Unresponsiveness to glucose in astreptozotocin model of diabetes. Inappropriate insulin and glucagon responsiveness to a reduction of glucose concentration. Diabetes **34**:653–659, 1985.
7. Sheehan PM, Reynolds LK, Thye FW, Ritchey SJ. Blood glucose and plasma lipids of Zucker rats fed diets containing cornstarch or sucrose. Nutr Rep Int **29**:1337–1344, 1984.
8. Nestal PJ, Carroll KF, Havenstein N. Plasma triglyceride response to carbohydrates, fats and caloric intake. Metabolism **19**:1–18, 1970.
9. Ahrens RA. Sucrose hypertension and heart disease: An historical

perspective. Am J Clin Nutr **27**:403–422, 1974.
10. Reiser S, Hallfrisch J, Michaelis OE IV, Martin RE, Prather ES. Isocaloric exchange of dietary starch and sucrose in human. Effects of levels of fasting blood lipids. Am J Clin Nutr **32**:1659–1669, 1979.
11. Michaelis OE IV, Ellwood KC, Hallfrisch J, Hansen, CT. Effect of dietary sucrose and genotype on metabolic parameters of a new strain of genetically obese rat: LA/N-corpulent. Nutr Res 3:217–228, 1983.
12. Ellwood KC, Michaelis OE IV, Emberland JJ, Bhathena SJ. Hormonal and lipogenic and gluconeogenic enzymatic responses in LA/N-corpulent rats. Proc Soc Exp Biol Med **179**:163–167, 1985.
13. Bhathena SJ, Revett K, Michaelis OE IV, Ellwood KC, Voyles NR, Recant L. Genetic obesity and dietary sucrose decrease hepatic glucagon and insulin receptors in LA/N-corpulent rats. Proc Soc Exp Biol Med **181**:71–77, 1986.
14. Bhathena SJ, Aparicio P, Revett K, Voyles N, Recant L. Effect of dietary carbohydrates on glucagon and insulin receptors in genetically obese female Zucker rats. J Nutr **117**:1291–1297, 1987.
15. Beck-Nielsen H, Pedersen O, Sorensen NS. The diabetogenic effect of sucrose in man: Sucrose as a regulator of insulin receptors and insulin sensitivity. In: Reiser S, Ed. Metabolic Effects of Utilizable Dietary Carbohydrates. New York: Marcel Dekker, pp261–284, 1982.
16. Bhathena SJ. Insulin receptor. In: Kalimi MY, Hubbard JR, Eds. peptide Hormone Receptors. Berlin: Walter de Gruyter, pp179–285, 1987.
17. Amatuzio DS, Grande R, Wade S. Effect of glucose on serum lipids in essential hyperlipemia and in hypercholesterolemia. Metabolism **11**:1240–1249, 1962.
18. Schade DS, Eaton RP. Modulation of fatty acid metabolism by glucagon in man. Diabetes **24**:502–509, 1975.
19. Vaughn M, Steinberg D, Pitman R. On the interpretation of studies measuring uptake and esterificationof 1-c palmitic acid by rat adipose tissue in vitro. Biochim Biophys Acta **84**:154–166, 1964.
20. Eaton RP. The hypolipemic action of glucagon in experimental endogenous lipemia in the rat. J. Lipid Res **14**:312–318, 1973.
21. Eaton RP, Conway M, Schade DS. Endogenous glucagon regulation in genetically hyperlipemic obese rats. Am J Physiol **230**:1336–1341, 1976.
22. Unger RH. Diabetes and the alpha cell. Diabetes **25**:136–151, 1976.
23. Gerich JE, Tsalikian E, Lorenzi M., Schneider V, Bohannon NV, Gustafson G, Karam JH. Normalization of fasting hyperglucagonemia and excessive glucagon responses to intravenous arginine in human diabetes mellitus by prolonged infusion of insulin. J Clin Endocrinol Metab **41**:1178–1180, 1975.
24. Bhathena SJ, Voyles NR, Smith S, Recant L. Decreased glucagon receptors in diabetic rat hepatocytes. Evidence for regulation of glucagon receptors by hyperglucagonemia. J Clin Invest **61**:1488–1497, 1978.
25. Lockwood DH, Hamilton CL, Livingston JN. The influence of obesity and diabetes in the monkey on insulin and glucagon binding to liver membranes. Endocrinology **104**:76–81, 1976.
26. American Institute of Nutrition. Report of the American Institute of Nutrition Ad Hoc Committee on Standards for Nutritional Studies. J Nutr **107**:1340–1348, 1977.
27. Bondar RJL, Mead DC. Evaluation of glucose-6-phosphate dehydrogenase from leuconostoc mesenteroids in the hexokinase method for determining glucose in serum. Clin Chem **20**:586–590, 1974.
28. Megraw RE, Dunn DE, Beggs, HG. Manual and continuous-flow colorimetry of triacylglycerols by a fully enzymatic method. Clin Chem **25**:273–278, 1979.
29. Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem **20**:470–475, 1974.
30. Neville DM Jr. Isolation of an organ-specific antigen from cell-surface membrane of rat liver. Biochim Biophys Acta **154**:540–552, 1968.
31. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem **193**:265–275, 1951.
32. Abernathy CO, Bhathena SJ, Recant L, Zimmerman HM, Utili R. Effects of acute and chronic endotoxin treatment on glucagon and insulin receptors on rat liver plasma membranes. Horm Metab Res **14**:468–471, 1982.
33. Bhathena SJ, Gazdar, AF, Schechter GP, Russell EK, Soehnlen FE, Gritsman A. Expression of glucagon receptors on T- and B-lymphoblasts: Comparison with insulin receptors. Endocrinology **111**:684–692, 1982.
34. Scatchard G. The attraction of proteins for small molecules and ions. Ann NY Acad Sci **51**:660–672, 1949.
35. SAS Institute Inc. SAS User's Statistics, Version 5 Edition, Cary, NC: SAS Institute, 1982.
36. Velasquez MT, Kimmel PL, Michaelis OE IV, Carswell N, Abraham A, Bosch JP. The type of dietary carbohydrate affects the progression of diabetic nephropathy in the SHR/N-corpulent (corp) rat. Proceedings of the Xth International Congress of Nephrology (abstr), 1987.
37. Goldstein S, Blecher M, Binder R, Perrino PV, Recant L. Hormone receptors. 5. Binding of glucagon and insulin to human circulating mononuclear cells in diabetes mellitus. Endocrinol Res Commun **2**:367–376, 1975.
38. Fouchereau-Peron M, Rancon F, Freychet P, Rosselin G. Effect of feeding and fasting on the early steps of glucagon action in isolated rat liver cells. Endocrinology **98**:755–760, 1976.
39. Srikant, CB, Freeman D, McCorkle K, Unger RH. Binding and biologic activity of glucagon in liver cell membranes of chronically hyperglucagonemic rats. J Biol Chem **252**:7434–7436, 1977.
40. Eaton RP, Schade DS, Conway M. Hypothesis: Decreased glucagon activity: A mechanism for both genetic and acquired endogenous hyperlipemia. Lancet **2**:1545–1547, 1974.
41. Martin RJ, Gahagan J. Serum hormone levels and tissue metabolism in pair-fed lean and obese Zucker rats. Horm Metab Res **9**:181–186, 1977.
42. Elkeles RS, Hambley J. Glucagon resistance as a cause of hypertriglyceridemia. Lancet **2**:18–20, 1976.
43. Nosadini R, Solda G, De Biasi F, Tiengo A. Metabolic effects of glucagon in endogenous hypertriglyceridemia. Acta Diabetol Lat **15**:251–258, 1978.
44. Nosadini R, Meneghel, A, Del Prato S, Fedele D, Tiengo A. Hypolipemic glucagon activity in isolated liver of genetic or acquired hypertriglyceridemic rats. Diabet Metab **6**:129–133, 1980.