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Glucagon Physiology

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Glucagon Physiology

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BACKGROUND

Glucagon is a 29 amino acid polypeptide (molecular weight of 3485 daltons) (Figure 1) which was discovered as a "contaminant" hyperglycemic factor in pancreatic extracts by Kimball and Murlin (1) in 1923 and finally sequenced by Bromer and Behrens (2) in the late 1950s. Studies of its mechanism in the 1960s by Sutherland et al (3) led to the discovery of the second messenger cyclic adenosine monophosphate (cAMP) for which the Nobel Prize was awarded. Full appreciation of importance of glucagon for normal fuel homeostasis in humans and abnormalities in patients with diabetes mellitus did not come until the 1970s when a specific radioimmunoassay was developed and when the availability of somatostatin, an inhibitor of glucagon secretion, permitted investigation of its lack under various experimental conditions (4).

H	His	Ser	Gln	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Tyr	Leu	Asp
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Ser	Arg	Arg	Ala	Gln	Asp	Phe	Val	Gln	Trp	Leu	Met	Asn	Thr	OH	
16	17	18	19	20	21	22	23	24	25	26	27	28	29		

Figure 1. Amino acid sequence of glucagon

BIOSYNTHESIS

Glucagon is synthesized in and secreted from A cells of pancreatic islets. Normally, these cells constitute approximately 15% to 20% of the total islet cell mass. In most species, A cells are located at the periphery of islets juxtaposed to both B cells, which secrete insulin, and D cells, which secrete somatostatin which can inhibit both insulin and glucagon secretion (5). In humans, however, A cells are scattered throughout the islet. Granules in A cells containing glucagon differ in ultrastructure from those in B and D cells containing respectively insulin and somatostatin in having an electron-dense core and no halo (Figure 2).

Glucagon is synthesized initially as a 160 amino acid prohormone (proglucagon) of approximately 12,000 d whose gene is encoded on chromosome 2. Proglucagon ultimately undergoes cleavage into four peptides (Figure 3) (6,7). The whole process takes about 90 minutes. All of these peptides are immunoreactive, but only the 3485-d molecule

is biologically active. L-cells of the small intestine synthesize an identical proglucagon molecule but different processing results in the formation of different polypeptides, of which glucagon-like peptide 1 and 2 are probably of most physiologic importance.

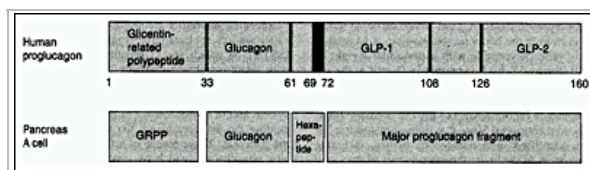


Figure 3. Human proglucagon with differential processing in pancreatic alpha cells and intestinal L cells. In the alpha cells, the major products released into plasma are glicentin related polypeptide, glucagon, a minor and a major proglucagon fragment whereas in the intestinal L cells, the major products released are glicentin, GLI-1 (glucagon-like peptide-1) and GLP-2 (glucagon-like peptide-2). (Copyright 2001 by McGraw-Hill Companies. Reproduced with permission of McGraw-Hill Companies from Masharani U and Karam JH: Pancreatic hormones and diabetes mellitus. In: Basic & Clinical Endocrinology. Greenspan FS and Gardner DG eds. New York: McGraw-Hill, 2001, pp. 623-698.)

PLASMA GLUCAGON

Plasma immunoreactive glucagon concentration varies considerably from individual to individual. The main factors responsible for this variation are the specificity of the antiserum used in the immunoassay and the relative proportion of the total immunoreactivity accounted for by the 3485-d molecule (4,8,9).

Normally, in humans and most other mammalian species, arterial and peripheral venous plasma immunoreactive glucagon concentrations range between 25 and 150 pg·ml⁻¹ (1.0-5.0 x 10⁻⁸M) after a 12- to 16-hour fast. Portal venous levels can average 1.5 to 3.0 times those present in arterial blood because of extraction of glucagon by the liver (10-17). As with other peptide hormones, circulating glucagon immunoreactivity is heterogeneous (9). By using chromatography, four immunoreactive species with apparent molecular weights of >40,000, 9000, 3500, and 2000 have been found (Figure 4) (Table 1). There is considerable individual and species variation in the proportions of each component found in plasma (12,13). In early studies, the 3500-d species usually constituted only about 25% of total plasma glucagon immunoreactivity due to nonspecificity of assay. With subsequent improvements and extraction procedures now available, it probably accounts for 90-95%. The 9000-d molecule, which in some assays has similar immunoreactivity but substantially less bioactivity than the 3500-d molecule, can be converted by trypsin to a smaller immunoreactive peptide of approximately 3500 d (18); it is thought to represent the biosynthetic precursor of glucagon found in the pancreas, which is also convertible to glucagon by trypsin (19). Increased amounts of the 9000-d molecule are found in the plasma of patients with the glucagonoma syndrome (20), with renal failure (14), and hepatocellular damage or carcinoma of the pancreas (8). The 2000-d molecule probably represents an inactive degradation product of glucagon.

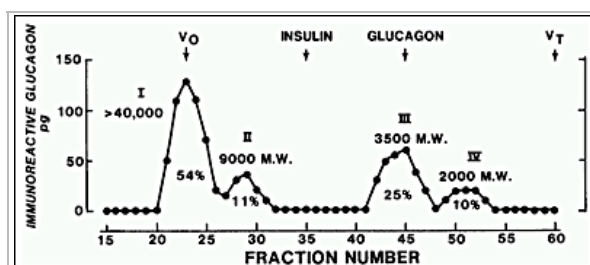


Figure 4. Immunoheterogeneity of human plasma glucagon. (Copyright 1998 by Springer-Verlag. Reproduced with permission of Springer-Verlag from Gerich J and Cryer P. Counterregulatory hormones: molecular, biochemical, and physiologic aspects. In: Principles of Perinatal-Neonatal Metabolism. 2nd edition. Cowett R, ed. New York: Springer-Verlag, 1998, pp. 155-180.)

The heterogeneity of plasma glucagon has complicated the interpretation of in vivo studies of glucagon secretion and metabolism. Changes in plasma glucagon immunoreactivity during stimulation or suppression of A cell secretion are due almost exclusively to changes in the 3500-d fraction (18,21,22). Although the overall distribution of plasma glucagon is not altered in diabetes and most other pathologic conditions in which the study of A cell function might be of interest (9), the relative contribution of the fractions can vary considerably among individuals. Thus comparisons, based on absolute levels of total plasma glucagon immunoreactivity using early assays, may have been misleading.

The pancreatic content of glucagon varies considerably among species; the human pancreas contains approximately 700 to 1000 μg of glucagon, roughly $1\text{-}2 \times 10^{17}$ molecules. For reference, the normal human pancreas contains about ~ 150 U of insulin (23,24) or ~ 5000 μg ; this translates to $\sim 6\text{-}8 \times 10^{17}$ molecules. Thus the normal human pancreas has about 1/3 to 1/10 the number of glucagon molecules as insulin molecules.

Glucagon, stored within A cells in distinctive granules, is secreted by a process called emiocytosis (25), which involves migration of secretory granules to the periphery of cells, fusion of granules with the plasma membrane, and extrusion of granule contents into the extracellular space. Like insulin, secretion of glucagon involves A cell substrate metabolism and consequent signals which affect cellular potassium and calcium channels and cAMP levels as well as protein kinase A and C (Figures 5 and 6) (26,27).

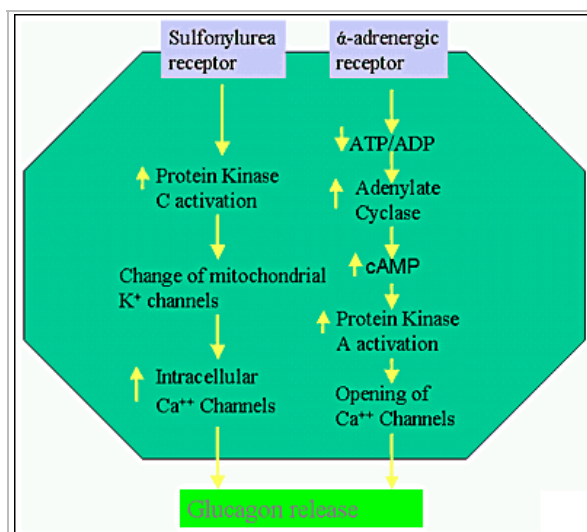


Figure 5. Schematic for stimulators of glucagon release

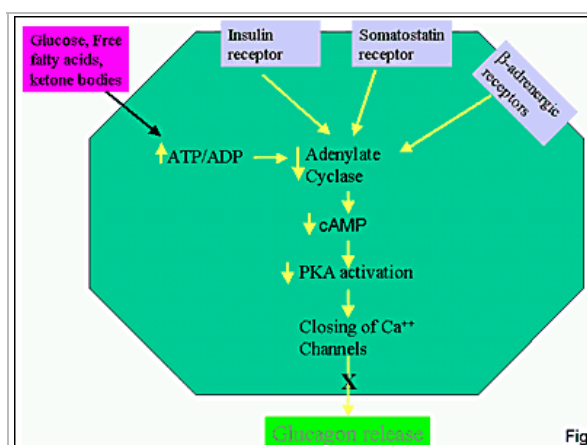


Figure 6. Schematic for inhibition of glucagon secretion

Most substrates (glucose, free fatty acids and ketone bodies) except certain amino acids suppress glucagon secretion (26). Inhibition of the metabolism of these substrates prevents the inhibition (26) suggesting in contrast to insulin secretion by beta cells that generation of ATP inhibits secretion. While this is consistent with the reciprocal roles of insulin and glucagon in glucose homeostasis, a definitive explanation for this difference remains to be elucidated.

Alpha cells contain ATP-sensitive potassium channels as well as sulfonylurea, adrenergic, insulin and somatostatin receptors (28). Sulfonylurea receptors and ATP-sensitive potassium channels are associated with both plasma membranes and secretory granule membranes (29). Sulfonylureas stimulate glucagon release under appropriate conditions (30). This effect is dependent on protein kinase C, mimicked by inhibitors of mitochondrial ATP-sensitive potassium channels and inhibited by K⁺ channel openers (diazoxide) (31).

It has been proposed (31) that the effect of sulfonylureas on alpha cell granules involves alterations in granule pH which renders them more competent for emiocytosis. Since metabolism of substrates would be expected to generate ATP and thus inhibit ATP-sensitive potassium channels like sulfonylureas, it is difficult to reconcile these observations into a consistent molecular mechanism for acute regulation of glucagon secretion. However, it has been proposed that a decrease in the intra-alpha cell ATP/ADP ratio activates adenylate cyclase and the resultant increase in cyclic AMP stimulates protein kinase A which causes opening of calcium channels and an increase in intra-alpha cell calcium which triggers glucagon release (Figure 6).

In vivo secretion of glucagon is the net result of the influence of substrate, neural, ionic, hormonal, and local factors on islet A cell function. The plasma concentration of glucagon depends on the balance between rates of secretion and degradation and also on the sampling site (e.g. peripheral venous versus portal venous). Basal (nonstimulated) secretion rates of glucagon can be estimated from data on portal venous-arterial differences and portal venous plasma flow rates. Secretion rates of glucagon may also be estimated on the basis of the clearance of glucagon under steady-state conditions; such estimation yields a value of approximately 1400 pg·kg⁻¹·min⁻¹ in humans (32). It should be pointed out, however, that these values underestimate secretion of glucagon and merely represent posthepatic delivery of glucagon. From what is known of the pancreatic content of glucagon and secretory rates of glucagon, it can be estimated that at least 25%, and probably more, of the pancreatic content of glucagon is secreted each day.

GLUCAGON CATABOLISM

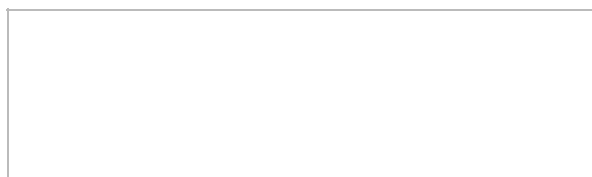
In normal humans, the metabolic clearance rate of glucagon is independent of the prevailing plasma glucagon level. Estimates range between 7 and 14 ml·kg⁻¹·min⁻¹ (32,33). Normal rates occur in patients with diabetes (33) or liver disease (34), whereas decreases have been found in renal failure (35) and starvation (32). Thus the liver and kidney seem to be the major sites of glucagon catabolism, but the relative contribution of each remains unclear (34,35).

Early reports suggested that the liver was not a major site of glucagon degradation (10,14,16). These observations may, however, be explained if the heterogeneity of circulating glucagon immunoreactivity is taken into account. When portal venous and peripheral venous plasma is subjected to gel filtration, it seems that the liver does not appreciably extract the biologically inactive 9000- and >40,000-d plasma glucagon immunoreactivity (14). Thus, the portal-peripheral gradient of glucagon immunoreactivity is almost totally accounted for by extraction of the biologically active 3500-d molecule; this averages approximately 60% and results in a portal-peripheral gradient of 2.5 to 3 for the biologically active molecule.

It has long been known that the kidney is capable of degrading glucagon. Arteriovenous gradients across the kidney in normal animals infused with glucagon indicate extraction of 23% to 39% of the presented glucagon (12,36,37). Because less than 2% of the extracted hormone appears in urine and because nonfiltering kidneys continue to extract appreciable amounts of glucagon (37), it seems that both tubular reabsorption and postglomerular capillary tubular uptake precede renal parenchymal degradation of glucagon. The hyperglucagonemia found in patients with chronic renal failure is due primarily to decreased clearance of the 9000-d molecule and cannot be accounted for by increased secretion of glucagon (3500-d molecule) or its decreased catabolism (38). Bilateral nephrectomy decreases the glucagon metabolic clearance rate of 3500-d glucagon approximately 30% (12). Consequently, liver and kidney can account for 80% to 90% of the metabolic clearance of the biologically active glucagon fraction of plasma glucagon immunoreactivity.

REGULATION OF GLUCAGON SECRETION

Glucose is the most important physiologic regular of glucagon secretion. Hyperglycemia decreases and hypoglycemia increases glucagon secretion (26). In vitro studies, such as those using the isolated perfused pancreas in which most variables operative in vivo can be controlled, indicate that the A cell is as exquisitely sensitive to changes in the ambient extracellular glucose concentration as is the B cell (39) (Figure 7); thus, glucose suppresses basal and stimulated glucagon release at concentrations as low as 5 mM glucose (90 mg·dl⁻¹) (Figure 8). To some extent the inhibition of glucagon secretion is dependent on concomitant stimulation of insulin release. In vivo, a decrease in plasma glucose of 1 to 2 mM increases plasma glucagon (40).



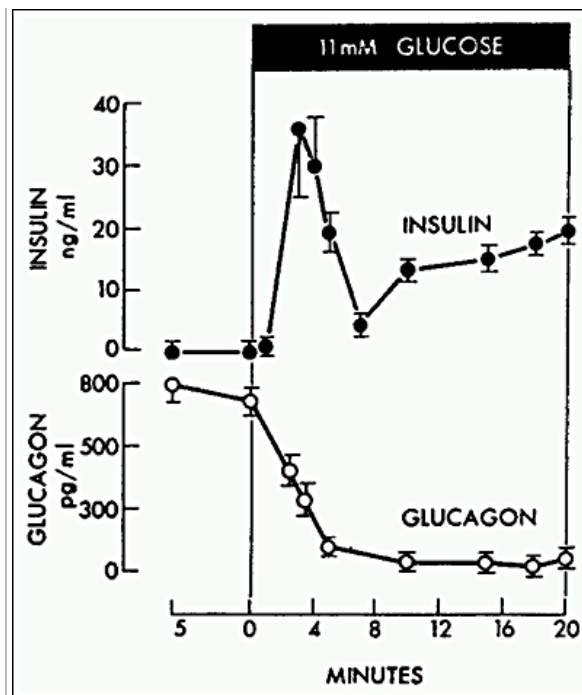


Figure 7. Effect of glucose on glucagon and insulin release from the in vitro perfused rat pancreas. (Copyright 1974 by J Clin Invest. Republished with permission of J Clin Invest from Gerich et al: Characterization of the effects of arginine and glucose on glucagon and insulin release from the perfused rat pancreas. *J Clin Invest* 54:833-841, 1974.)

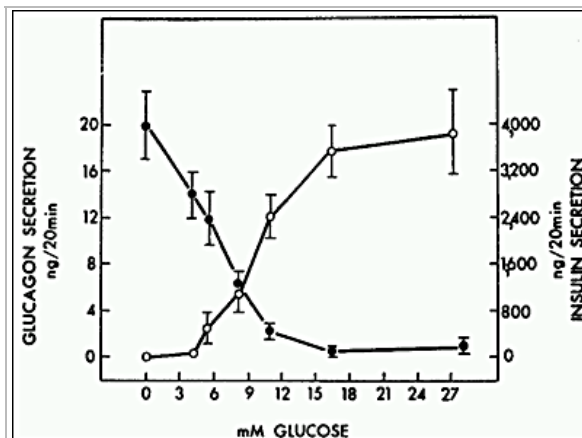


Figure 8. Dose-response relationships for effect of glucose to suppress glucagon and stimulate insulin release from the perfused rat pancreas. (Copyright 1974 by J Clin Invest. Republished with permission of J Clin Invest from Gerich et al: Characterization of the effects of arginine and glucose on glucagon and insulin release from the perfused rat pancreas. *J Clin Invest* 54:833-841, 1974.)

Other substrates also influence glucagon secretion. Various amino acids stimulate A cell release of glucagon (41), while free fatty acids (42) and ketone bodies (43) suppress glucagon secretion (Figure 9). Amino acid stimulation of glucagon release may be important in preventing hypoglycemia, which might otherwise occur because of insulin release accompanying ingestion of a noncarbohydrate meal. Suppression of glucagon secretion by free fatty acids and ketone bodies may be part of a negative feedback system regulating ketogenesis.

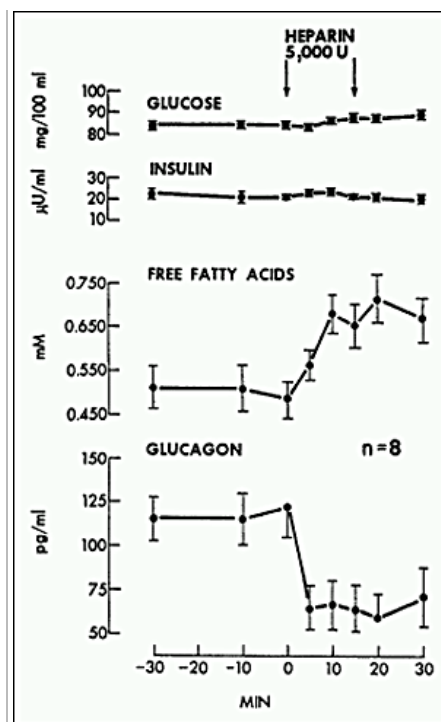
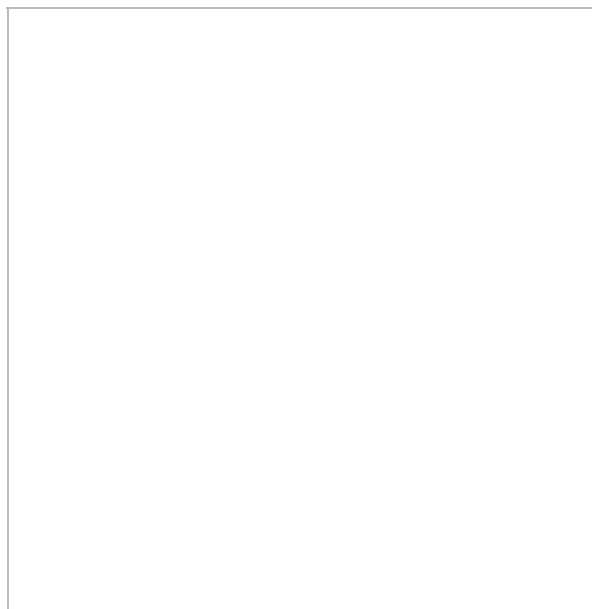


Figure 9. Effect of elevation of plasma free fatty acids on plasma glucagon levels in normal human volunteers. (Copyright 1974 by J Clin Invest. Republished with permission of J Clin Invest from Gerich et al: Effects of alterations of plasma free fatty acid levels on pancreatic glucagon secretion in man. J Clin Invest 53:1284-1289, 1974.)

The islets of Langerhans are richly innervated. Like insulin release, glucagon secretion is influenced by both sympathetic and parasympathetic nervous systems; epinephrine, norepinephrine, and acetylcholine (44,45), and electrical stimulation of mixed pancreatic, splanchnic, and vagus nerves augment glucagon release (46,47). Both A and B cell secretion are influenced in the same direction by parasympathetic (i.e. increase), β -adrenergic (i.e. increase), and α -adrenergic (i.e. decrease) mechanisms. The observation (Figure 10) that glucagon secretion is increased by epinephrine while insulin release is simultaneously decreased can best be explained by postulating that the A cell contains a preponderance of β -adrenergic receptors, while the B cell contains a preponderance of α -adrenergic receptors. Neural input to the A cell is probably important in modulating the increases in plasma glucagon observed during stress and perhaps also after mixed meals.



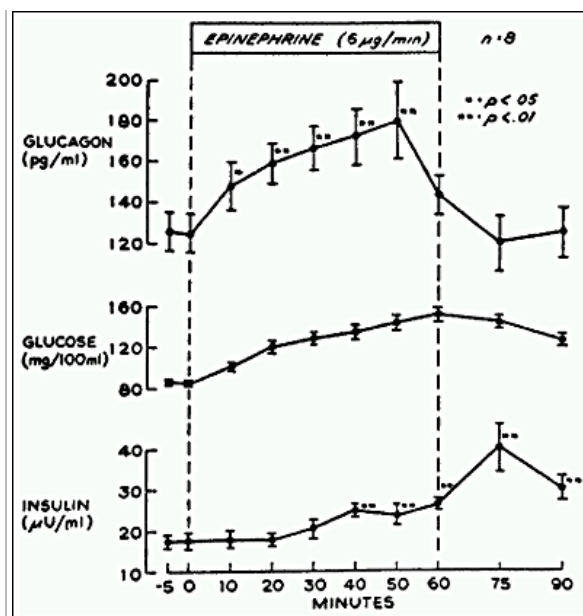


Figure 10. Effect of infusion of epinephrine on plasma glucagon and insulin levels in normal volunteers. (Copyright 1973 by The Endocrine Society. Reproduced with permission of The Endocrine Society from Gerich JE, Karam JH, Forsham PH: Stimulation of glucagon secretion by epinephrine in man. *J Clin Endocrinol Metab* 37:479-481, 1973.)

A variety of hormones have been reported to alter A cell function; epinephrine, gastrin, pancreozymin, vasoactive intestinal peptide, and gastric inhibitory polypeptide increase glucagon release (48,49), while secretin apparently suppresses glucagon secretion (50). Whether these represent true physiologic interactions or merely pharmacologic effects is unclear. Hyperglucagonemia, relative or absolute, has been found in states of growth hormone (51), cortisol (52), and thyroid hormone excess (53). Conceivably, this might play a role in the associated abnormalities of carbohydrate and lipid metabolism.

Alterations in nutrition also influence A cell function. Acute ingestion of pure or high carbohydrate meals suppresses glucagon release, whereas pure or high protein-containing meals stimulate glucagon release. Concomitant changes in plasma glucose and amino acid levels are probably responsible for these changes. Prolonged (i.e. weeks or days) alterations in diet also alter A cell function. During total starvation, there is an acute increase in plasma glucagon lasting 1 to 2 days, probably as a result of increased secretion (54). Prolonged ingestion of high-carbohydrate or isocaloric high-fat diet decreases basal and meal-stimulated plasma glucagon levels (55). Conversely, low-carbohydrate diets or high-protein diets increase basal and stimulated glucagon secretion (55). In obesity, increased plasma glucagon responses have been reported (56).

Hypoglycemia stimulates glucagon secretion through both intraislet and central nervous system mediated autonomic signals (57). Within the islets low glucose concentrations increase A-cell glucagon secretion directly and, by reducing B-cell secretion, decrease tonic A-cell inhibition by insulin. Autonomic adrenergic (i.e. norepinephrine), cholinergic, and peptidergic neural and adrenomedullary hormonal (epinephrine) signals, triggered by hypoglycemia, may also contribute.

ROLE OF GLUCAGON IN FUEL HOMEOSTASIS

Although adipocytes have glucagon receptors and there is evidence that alterations in plasma glucagon can affect lipolysis (58), the main target organ of glucagon is the liver.

Carbohydrate Homeostasis

At concentrations that approximate those found in the portal vein in vivo, glucagon is a potent stimulator of hepatic glycogenolysis, gluconeogenesis, and ketogenesis in vitro (59). These actions of glucagon and the increases in plasma glucagon observed during hypoglycemia (60), exercise (61), trauma (62), infection (63), and other stress (64) provide considerable evidence that glucagon is important in the maintenance of euglycemia in the postabsorptive state and at times when there are increased demands for fuels and when the organism must rely on mobilization of endogenous substrate. Under these conditions, when β -cell function is normal, the major action of glucagon would be to counteract the actions of insulin on storage of glucose and other fuels. Conversely, when β -cell function is deficient, glucagon could accentuate the metabolic consequences of insulin deficiency and be an important

determinant of the magnitude of hyperglycemia and hyperketonemia found in diabetes.

Substantial evidence for the role of glucagon in glucose homeostasis has been provided from studies employing somatostatin; a potent inhibitor of glucagon and insulin secretion which does not itself directly affect substrate metabolism at doses used in vivo. Infusion of somatostatin in normal man results in an acute decrease in the glucose production rate, which is accompanied by a decrease in plasma glucose; this occurs despite a concomitant decrease in plasma insulin and can be prevented by replacement infusion of glucagon. These observations suggest that in the postabsorptive state, glucagon action on the liver balances insulin action on the liver to maintain an appropriate output of glucose to match glucose utilization and, therefore, maintain stable euglycemia. With prolongation of the glucagon deficiency during infusion of somatostatin, glucose production does not exceed normal rates. These changes reflect the effects of the concomitant insulin deficiency and the unopposed actions of other counterregulatory factors. When insulin deficiency is avoided by infusion of replacement amounts of insulin along with somatostatin, which results in an isolated deficiency of glucagon, plasma glucose decreases more than that observed during infusion of somatostatin alone, and both it and the glucose production rate remain suppressed below normal.

In addition to a role for glucagon in the maintenance of euglycemia by antagonizing the effects of postabsorptive (i.e. low) plasma insulin concentrations, there is considerable evidence that glucagon acts in the defense against hypoglycemia by antagonizing the effects of excess plasma insulin (65,66). When hypoglycemia is produced in humans by injection of insulin, release of glucagon is stimulated along with that of other counterregulatory hormones when the plasma glucose decreases below 3.8 mM (~68 mg/dl) (Figure 11). Restoration of euglycemia is due to a compensatory increase in hepatic glucose production. Although secretion of catecholamines, growth hormone, and cortisol are stimulated along with that of glucagon, only the increases in plasma glucagon and catecholamines coincide with or precede the compensatory increase in the glucose production rate (66,67). That glucagon is the major acute glucose counterregulatory hormone is suggested by the fact that inhibition of the plasma glucagon responses by somatostatin markedly attenuates the compensatory increase in the glucose production rate and impairs restoration of euglycemia following insulin administration (Figure 12). Prevention of cortisol secretion (68), adrenergic blockade (66), adrenalectomy (65), or acute growth hormone deficiency (66) does not appreciably affect immediate glucose counterregulation. The effects of glucagon during restoration of euglycemia involves both glycogenolysis and gluconeogenesis, predominantly the former (69).

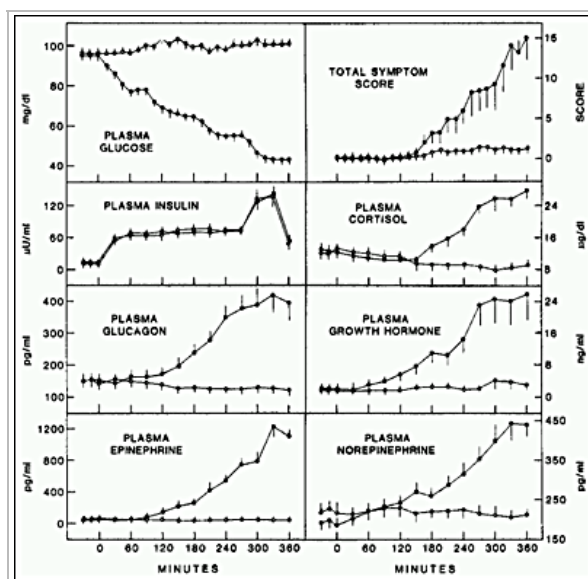


Figure 11. Plasma glucose, insulin, glucagon, epinephrine, norepinephrine, cortisol, and growth hormone concentrations and overall symptom score. o, euglycemia; *, hypoglycemia. (Copyright 1991 by the American Physiological Society. Republished with permission of the American Physiological Society from Mitrakou et al. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol* 260:E67-E74, 1991.)



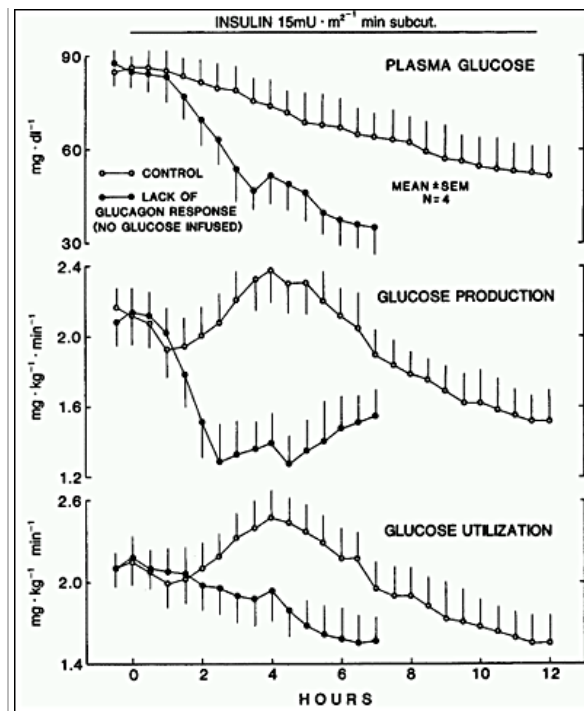


Figure 12. Effect of isolated glucagon deficiency on hypoglycemic action of insulin in normal human volunteers. (Copyright 1998 by Springer-Verlag. Reproduced with permission of Springer-Verlag from Gerich J and Cryer P. Counterregulatory hormones: molecular, biochemical, and physiologic aspects. In: Principles of Perinatal-Neonatal Metabolism. 2nd edition. Cowett R, ed. New York: Springer-Verlag, 1998, pp. 155-180.)

There is also evidence for the role of glucagon in disposal of ingested carbohydrate (70-76). The liver is the main organ responsible for clearance of glucose appearing in the portal vein after ingestion of carbohydrate and presumably also that derived from a meal (77,78). The increases in the portal venous insulin and glucose concentrations act to promote formation of glycogen from the ingested glucose. Suppression of glucagon secretion is probably also important in the decrease of endogenous glucose output and in the formation of glycogen from the ingested glucose. In insulin-dependent diabetics incapable of insulin secretion, suppression of increases in plasma glucagon following ingestion of a mixed meal or glucose load improves postprandial glucose tolerance (79). Moreover, the effectiveness of exogenous insulin in preventing postprandial hyperglycemia and improving diabetic control is markedly augmented when glucagon secretion is suppressed by somatostatin (79).

Ketone Body Homeostasis

Circulating levels of ketone bodies (e.g. acetone, acetoacetic acid, and β -hydroxybutyrate) are determined by the net balance between rates of ketone body production and removal. The plasma ketone body concentration and insulin seem to be the major factors affecting removal of ketone bodies by tissues (80). While there is no evidence to suggest that glucagon influences this process, there are considerable data, mainly from animal studies, that indicate that glucagon may play a key role in the formation of ketone bodies.

Ketone body formation results from β -oxidation of free fatty acids derived from intra- and extrahepatic sources. Two key factors are necessary for ketone body formation: sufficient substrate in the form of free fatty acids and a shift in the hepatic handling of free fatty acids from triglyceride synthesis (i.e. esterification) to oxidation. Glucagon directly acts on the liver *in vitro* to augment ketogenesis (81). This is thought to involve the promotion of transport of free fatty acids across the mitochondrial membrane by acylcarnitine transferase, an important rate-limiting step for free fatty acid oxidation. Glucagon apparently does not directly affect this enzyme but indirectly causes its activation by lowering intrahepatic levels of malonylcoenzyme A (CoA), an inhibitor of acylcarnitine transferase (82). It has been postulated that glucagon is essential for switching the liver to a ketogenic mode (i.e. from an organ primarily esterifying free fatty acids to one oxidizing them) to permit maximal rates of ketogenesis to occur (82). Pharmacologic doses of glucagon given as a bolus have been reported to increase both plasma free fatty acid and ketone body concentrations in normal subjects despite concomitant increases in plasma insulin (83). Following acute withdrawal from insulin in insulin-dependent diabetics, the expected hyperketonemia can be markedly attenuated by suppression of glucagon secretion with somatostatin (3). Under such conditions (e.g. insulin withdrawal and somatostatin administration), infusion of physiologic amounts of glucagon, producing circulating glucagon concentrations less than those reported in ketoacidosis, results in a marked degree of hyperketonemia. There are

thus two prerequisites for glucagon to stimulate ketogenesis: adequate substrate (e.g. free fatty acids) and insulin deficiency or the inability to increase plasma insulin concentrations.

MECHANISM OF ACTION

It is well established that the actions of glucagon on glycogenolysis, gluconeogenesis, and ketogenesis are mediated mainly by cAMP (84) (Figure 13). Binding of glucagon with its receptor activates the catalytic subunit of the membrane bound enzyme adenylate cyclase, which catalyzes the conversion of adenosine triphosphate (ATP) to cAMP which in turn leads to activation of intracellular kinase. For glycogenolysis, this results in phosphorylation of phosphorylase, which activates the enzyme and desphosphorylation of glycogen synthase which inactivates the enzyme. Thus, glycogen formation is inhibited and glycogen breakdown stimulated.

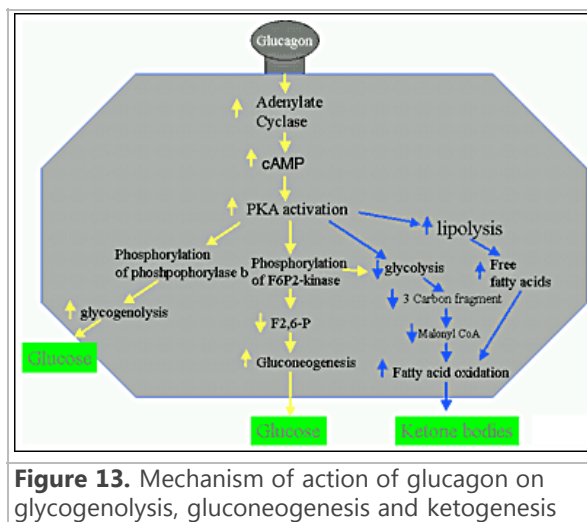


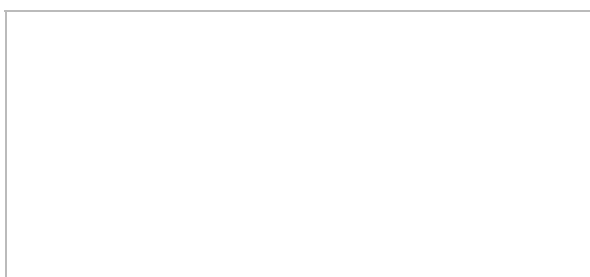
Figure 13. Mechanism of action of glucagon on glycogenolysis, gluconeogenesis and ketogenesis

The actions of glucagon on gluconeogenesis is more complex and involves several steps (85). Glucagon increases hepatic uptake of amino acids, but its main effect is intrahepatic. Glucagon stimulates gluconeogenesis mainly by increasing the rate of phosphoenolpyruvate production and decreasing the rate of its disposal by pyruvate kinase.

Stimulation of ketogenesis by glucagon is linked to some of the biochemical steps involved in its stimulation of gluconeogenesis (86), namely, an inhibition of glycolysis. The rate-limiting step of ketogenesis is the transport of fatty acid CoA esters across the mitochondrial membrane where they undergo β -oxidation. The enzyme catalyzing this transfer is fatty acid carnitine acyl transferase II. This enzyme is inhibited by malonyl-CoA. The inhibition of glycolysis by glucagon lowers intracellular levels of malonyl-CoA and results in activation of the fatty acid CoA acyl transferase.

GLUCAGON SECRETION IN DIABETES MELLITUS

In human diabetes, plasma glucagon concentrations are either increased in an absolute sense or are "normal" but inappropriate for the prevailing plasma glucose concentration (87); they are markedly increased in diabetic ketoacidosis (88). In contrast to the normal situation, carbohydrate ingestion does not appropriately suppress plasma glucagon in people with impaired glucose tolerance and diabetes (89) (Figure 14). This failure to suppress glucagon secretion leads to excessive appearance in plasma of glucose released from the liver which has been correlated with plasma insulin: glucagon molar ratios (Figure 15). Excessive increases in plasma glucagon are observed with protein meals (90), mixed meals (91), and infusion of amino acids (92). Some of these abnormalities, such as the fasting hyperglucagonemia and excessive responses to infusion of arginine, protein, or mixed-meal ingestion, can be improved or corrected by administration of physiologic quantities of insulin, suggesting that they were, in part, the result of insulin deficiency.



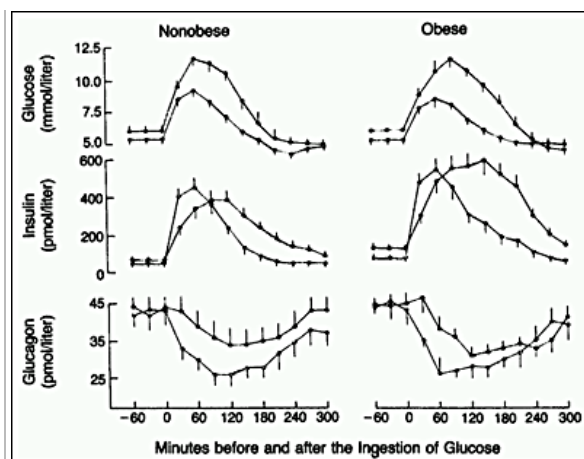


Figure 14. Mean (\pm SE) arterial plasma glucose, insulin, and glucagon concentrations before and after glucose ingestion in 16 normal subjects (o) and 15 subjects with impaired glucose tolerance (*). (Copyright 1992 by the Massachusetts Medical Society. Republished with permission of Massachusetts Medical Society from Mitrakou et al. Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. *N Engl J Med* 326:22-29, 1992.)

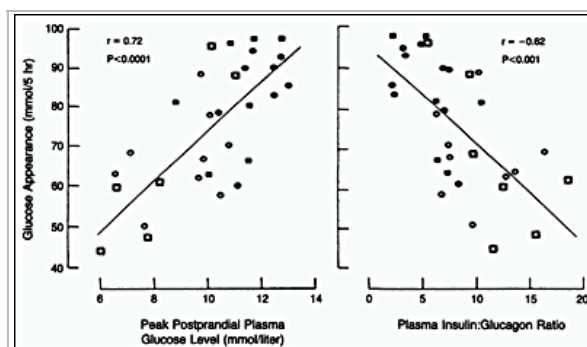


Figure 15. Correlations of systemic glucose appearance with peak plasma glucose concentration and molar ratio of plasma insulin to glucagon in the study subjects. Solid symbols represent subjects with impaired glucose tolerance, and open symbols normal subjects. Squares represent obese subjects, and circles nonobese subjects. (Copyright 1992 by the Massachusetts Medical Society. Republished with permission of Massachusetts Medical Society from Mitrakou et al. Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. *N Engl J Med* 326:22-29, 1992.)

In contrast to the above, acute administration of physiologic or even pharmacologic amounts of insulin have not been able to correct abnormal A-cell responses to glucose in human diabetes (91). These observations suggest that abnormal A-cell responses to glucose may not be solely due to insulin deficiency. Evidence for a selective defect in A-cell glucose recognition independent of insulin deficiency is provided by the findings that plasma glucagon can be suppressed normally in human diabetes by elevation of circulating free fatty acid levels but not by hyperglycemia (93), and that the diabetic A cell fails to respond appropriately to hypoglycemia or to hyperglycemia (94).

METABOLIC CONSEQUENCES OF A-CELL DYSFUNCTION IN DIABETES MELLITUS PATIENTS

At the present time, the preponderance of evidence suggests that the full-blown manifestations of diabetes cannot be explained solely on the basis of insulin deficiency, and that abnormal A-cell function is an important determinant of the magnitude of hyperglycemia and hyperketonemia found in diabetes. The evidence for this can be

summarized as follows. Fasting hyperglycemia and insulin requirements are lower in pancreatectomized patients lacking glucagon (95). Moreover, in such individuals (95) and in insulin-dependent diabetics whose glucagon secretion is suppressed with somatostatin (96), hyperglycemia and hyperketonemia following acute withdrawal of insulin are markedly diminished. The failure to suppress glucagon secretion appropriately after meal ingestion increases postprandial hyperglycemia in people with impaired glucose tolerance and diabetes. In insulin-dependent diabetics, acute suppression of glucagon secretion decreases plasma glucose to concentrations only slightly above normal, and chronic suppression markedly improves diabetic control (97).

Finally, the failure of hypoglycemia to stimulate glucagon secretion in people with type 1 diabetes and in those with type 2 diabetes and marked beta cell dysfunction increases the risk for severe hypoglycemia in these individuals (98). Thus abnormalities in alpha cell function play an important role not only in the pathophysiology of metabolic abnormalities in diabetes mellitus but also in its management.

1. Kimball C, Murlin J 1923 Aqueous extracts of pancreas III. Some precipitation reactions of insulin. *J Biochem* 58:337-348
2. Bromer W, Winn L, Behrens O 1957 The amino acid sequence of glucagon V. Location of amide groups, acid degradation studies and summary of sequential evidence. *J Am Chem Soc* 79:2807-2810
3. Sutherland E, Robison G, Butcher R 1968 Some aspects of the biological role of adenosine 3',5'-monophosphate (cyclic AMP). *Circulation* 37:279-306
4. Gerich J 1981 Physiology of glucagon. *Int Rev Physiol* 24:244-275
5. Gerich J, Lovinger R, Grodsky G 1975 Inhibition by somatostatin of glucagon and insulin release from the perfused rat pancreas in response to arginine, isoproterenol, and theophylline: evidence for a preferential effect on glucagon secretion. *Endocrinology* 96:749-754
6. Patzelt C, Schiltz E 1984 Conversion of proglucagon in pancreatic alpha cells: the major endproducts are glucagon and a single peptide, the major proglucagon fragment, that contains two glucagon-like sequences. *Proc Natl Acad Sci U S A* 81(16):5007-5011
7. Conlon JM 1980 The glucagon-like polypeptides - order out of chaos? *Diabetologia* 18(2):85-88
8. Weir G 1981 Glucagon in normal physiology and diabetes mellitus. In: Brownlee E, ed. *Diabetes Mellitus*. New York: Garland STPM Press; 207-259
9. Jaspan JB, Rubenstein AH 1977 Circulating glucagon. Plasma profiles and metabolism in health and disease. *Diabetes* 26(9):887-904
10. Brockman RP, Manns JG, Bergman EN 1976 Quantitative aspects of secretion and hepatic removal of glucagon in sheep. *Can J Physiol Pharmacol* 54(5):666-670
11. Rojdmarm S, Bloom G, Chou MC, Jaspan JB, Field JB 1978 Hepatic insulin and glucagon extraction after their augmented secretion in dogs. *Am J Physiol* 235(1):E88-E96
12. Emmanouel D, Jaspan J, Rubenstein A, Huen A, Fink E, Katz A 1978 Glucagon metabolism in the rat: contribution of the kidney to the metabolic clearance rate of the hormone. *J Clin Invest* 62:6-13
13. Jaspan JB, Huen AH, Morley CG, Moossa AR, Rubenstein AH 1977 The role of the liver in glucagon metabolism. *J Clin Invest* 60(2):421-428
14. Rojdmarm S, Bloom G, Chou MC, Field JB 1978 Hepatic extraction of exogenous insulin and glucagon in the dog. *Endocrinology* 102(3):806-813
15. Blackard W, Nelson N, Andrews S 1974 Portal and peripheral vein immunoreactive glucagon concentrations after arginine or glucose infusions. *Diabetes* 23:199-202
16. Felig P, Gusberg R, Hendler R, Gump F, Kinney J 1974 Concentrations of glucagon and the insulin : glucagon ratio in the portal and peripheral circulation. *Proc Soc Exp Biol Med* 147:88-90
17. Dencker M, Hedner P, Holst J, Tranberg K 1975 Pancreatic glucagon response to an ordinary meal. *Scand J Gastroenterol* 10:471-474
18. Kuku S, Jaspan J, Emmanouel D, Zeidler A, Katz A, Rubenstein A 1976 Heterogeneity of plasma glucagon: circulating components in normal subjects and patients with chronic renal failure. *J Clin Invest* 58:742-750
19. Noe BD, Bauer GE, Steffes MW, Sutherland DE, Najarian JS 1975 Glucagon biosynthesis in human pancreatic islets: preliminary evidence for a biosynthetic intermediate. *Horm Metab Res* 7(4):314-322
20. Weir GC, Horton ES, Aoki TT, Slovick D, Jaspan J, Rubenstein AH 1977 Secretion by glucagonomas of a possible glucagon precursor. *J Clin Invest* 59(2):325-330
21. Valverde I, Lemon HM, Kessinger A, Unger RH 1976 Distribution of plasma glucagon immunoreactivity in a patient with suspected glucagonoma. *J Clin Endocrinol Metab* 42(5):804-808
22. Recant L, Perrino PV, Bhathena SJ, Danforth DN, Jr., Lavine RL 1976 Plasma immunoreactive glucagon fractions in four cases of glucagonoma: increased "large glucagon-immunoreactivity". *Diabetologia* 12(4):319-326
23. Tasaka Y, Inoue S, Hirata Y, Hanyu F, Endo M 1981 Time course of content of insulin, glucagon and pancreatic polypeptide in human pancreatic tissue obtained by surgery. *Endocrinol Jpn* 28(3):261-264
24. Rastogi GK, Sinha MK, Dash RJ 1973 Insulin and proinsulin content of pancreases from diabetic and nondiabetic subjects. *Diabetes* 22(11):804-807
25. Carpentier JL, Malaisse-Lagae F, Muller WA 1977 Glucagon release from rat pancreatic islets. A combined morphological and functional approach. *J Clin Invest* 60(5):1174-1182
26. Gerich J, Charles M, Grodsky G 1976 Regulation of pancreatic insulin and glucagon secretion. *Ann Rev Physiol* 38:353-388

27. Toyota T, Sato SI, Kudo M, Abe K, Goto Y 1975 Secretory regulation of endocrine pancreas: Cyclic AMP and glucagon secretion. *J Clin Endocrinol Metab* 41(1):81-89
28. Bokvist K, Olsen HL, Hoy M, Gotfredsen CF, Holmes WF, Buschard K, Rorsman P, Gromada J 1999 Characterisation of sulphonylurea and ATP-regulated K⁺ channels in rat pancreatic A-cells. *Pflugers Arch* 438(4):428-436
29. Carpentier JL, Sawano F, Ravazzola M, Malaisse WJ 1986 Internalization of 3H-glibenclamide in pancreatic islet cells. *Diabetologia* 29(4):259-261
30. Grodsky GM, Epstein GH, Fanska R, Karam JH 1977 Pancreatic action of the sulfonylureas. *Fed Proc* 36(13):2714-2719
31. Hoy M, Olsen HL, Bokvist K, Buschard K, Barg S, Rorsman P, Gromada J 2000 Tolbutamide stimulates exocytosis of glucagon by inhibition of a mitochondrial-like ATP-sensitive K⁺ (KATP) conductance in rat pancreatic A-cells. *J Physiol* 527 Pt 1:109-120
32. Fisher M, Sherwin RS, Hendler R, Felig P 1976 Kinetics of glucagon in man: effects of starvation. *Proc Natl Acad Sci U S A* 73(5):1735-1739
33. Alford F, Bloom S, Nabarro J 1976 Glucagon metabolism in man: studies on the metabolic clearance rate and the plasma acute disappearance time of glucagon in normal and diabetic subjects. *J Clin Endo & Metab* 42:830-838
34. Sherwin R, Fisher M, Bessoff J, Snyder N, Hendler R, Conn H, Felig P 1978 Hyperglucagonemia in cirrhosis: altered secretion and sensitivity to glucagon. *Gastroenterology* 74:1224-1228
35. Sherwin R, Bastl C, Finkelstein F, Fisher M, Black H, Hendler R, Felig P 1976 Influence of uremia and hemodialysis on the turnover and metabolic effects of glucagon. *J Clin Invest* 57:722-731
36. Lefebvre P, Luyckx A, Nizet A 1974 Renal handling of endogenous glucagon in the dog: comparison with insulin. *Metabolism* 23:753-760
37. Bastl C, Finkelstein F, Sherwin R, Hendler R, Felig P, Hayslett J 1977 Renal extraction of glucagon in rats with normal and reduced renal function. *Am J Physiol* 233:67-71
38. Emmanouel D, Jaspan J, Kuku S, Rubenstein A, Katz A 1976 Pathogenesis and characterization of hyperglucagonemia in the uremic rat. *J Clin Invest* 58:1266-1271
39. Gerich J, Charles M, Grodsky G 1974 Characterization of the effects of arginine and glucose on glucagon and insulin release from the perfused rat pancreas. *J Clin Invest* 54:833-841
40. Mitrakou A, Ryan C, Veneman T, Mokan M, Jenssen T, Kiss I, Durrant J, Cryer P, Gerich J 1991 Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol* 260:E67-E74
41. Rocha DM, Faloona GR, Unger RH 1972 Glucagon-stimulating activity of 20 amino acids in dogs. *J Clin Invest* 51(9):2346-2351
42. Gerich J, Langlois M, Schneider V, Karam J, Noacco C 1974 Effects of alterations of plasma free fatty acid levels on pancreatic glucagon secretion in man. *J Clin Invest* 53:1284-1289
43. Goberna R, Tamarit J, Jr., Osorio J, Fussganger R, Tamarit J, Pfeiffer EF 1974 Action of B-hydroxy butyrate, acetoacetate and palmitate on the insulin release in the perfused isolated rat pancreas. *Horm Metab Res* 6(4):256-260
44. Gerich J, Karam J, Forsham P 1973 Stimulation of glucagon secretion by epinephrine in man. *J Clin Endocrinol Metab* 37:479-481
45. Iversen J 1973 Effect of acetyl choline on the secretion of glucagon and insulin from the isolated, perfused canine pancreas. *Diabetes* 22(5):381-387
46. Marliss EB, Girardier L, Seydoux J, Wollheim CB, Kanazawa Y, Orci L, Renold AE, Porte D, Jr. 1973 Glucagon release induced by pancreatic nerve stimulation in the dog. *J Clin Invest* 52(5):1246-1259
47. Kaneto A, Kosaka K, Nakao K 1967 Effects of stimulation of the vagus nerve on insulin secretion. *Endocrinology* 80(3):530-536
48. Unger RH, Ketterer H, Dupre J, Eisentraut AM 1967 The effects of secretin, pancreozymin, and gastrin on insulin and glucagon secretion in anesthetized dogs. *J Clin Invest* 46(4):630-645
49. Pederson RA, Brown JC 1978 Interaction of gastric inhibitory polypeptide, glucose, and arginine on insulin and glucagon secretion from the perfused rat pancreas. *Endocrinology* 103(2):610-615
50. Santeusano F, Faloona GR, Unger RH 1972 Suppressive effect of secretin upon pancreatic alpha cell function. *J Clin Invest* 51(7):1743-1749
51. Goldfine ID, Kirshteins L, Lawrence AM 1972 Excessive glucagon responses to arginine in active acromegaly. *Horm Metab Res* 4(2):97-100
52. Wise JK, Hendler R, Felig P 1973 Influence of glucocorticoids on glucagon secretion and plasma amino acid concentrations in man. *J Clin Invest* 52(11):2774-2782
53. Seino Y, Goto Y, Taminato T, Ikeda M, Imura H 1974 Plasma insulin and glucagon responses to arginine in patients with thyroid dysfunction. *J Clin Endocrinol Metab* 38(6):1136-1140
54. Marliss E, Aoki T, Unger R, Soeldner J, Cahill G 1970 Glucagon levels and metabolic effects in fasting man. *J Clin Invest* 49:2256-2270
55. Lewis S, Wallin J, Kane J, Gerich J 1977 Effect of diet composition on metabolic adaptations to hypocaloric nutrition: comparison of high carbohydrate and high fat isocaloric diets. *Am J Clin Nutr* 30:160-170
56. Kalkoff R, Gossain V, Maktute M 1973 Plasma glucagon in obesity. *N Engl J Med* 289:465-467
57. Cryer P 1996 Glucagon and glucose counterregulation. In: Lefebvre P, ed. *Glucagon I*. Berlin: Springer-Verlag; 149-158
58. Carlson MG, Snead WL, Campbell PJ 1993 Regulation of free fatty acid metabolism by glucagon. *J Clin Endocrinol Metab* 77(1):11-15
59. Exton J, Park C 1972 Interaction of insulin and glucagon in the control of liver metabolism. In: Steiner D, Freinkel

- N, eds. *Endocrine Pancreas*, Section 7, *Handbook of Physiology*. Baltimore: Williams and Wilkins; 437-455
60. Gerich J, Schneider V, Dippe S, Langlois M, Noacco C, Karam J, Forsham P 1974 Characterization of the glucagon response to hypoglycemia in man. *J Clin Endocrinol Metab* 38:77-82
 61. Galbo H, Holst JJ, Christensen NJ 1975 Glucagon and plasma catecholamine responses to graded and prolonged exercise in man. *J Appl Physiol* 38(1):70-76
 62. Wilmore DW, Lindsey CA, Moyland JA, Faloona GR, Pruitt BA, Unger RH 1974 Hyperglucagonaemia after burns. *Lancet* 1(7847):73-75
 63. Rocha DM, Santeusano F, Faloona GR, Unger RH 1973 Abnormal pancreatic alpha-cell function in bacterial infections. *N Engl J Med* 288(14):700-703
 64. Willerson JT, Hutcheson DR, Leshin SJ, Faloona GR, Unger RH 1974 Serum glucagon and insulin levels and their relationship to blood glucose values in patients with acute myocardial infarction and acute coronary insufficiency. *Am J Med* 57(5):747-752
 65. Gerich J, Davis J, Lorenzi M, Rizza R, Bohanan N, Karam J, Lewis S, Kaplan S, Schultz T, Cryer P 1979 Hormonal mechanisms of recovery from insulin-induced hypoglycemia in man. *Am J Physiol* 236:E380-E385
 66. Rizza R, Cryer P, Gerich J 1979 Role of glucagon, catecholamines, and growth hormone in human glucose counterregulation. Effects of somatostatin and combined α - and β -adrenergic blockade on plasma glucose recovery and glucose flux rates after insulin-induced hypoglycemia. *J Clin Invest* 64:62-71
 67. Garber A, Cryer P, Santiago J, Haymond M, Pagliara A, Kipnis D 1976 The role of adrenergic mechanisms in the substrate and hormonal response to insulin-induced hypoglycemia in man. *J Clin Invest* 58:7-15
 68. Feldman J, Plonk J, Bivens C 1975 The role of cortisol and growth hormone in the counterregulation of insulin-induced hypoglycemia. *Horm Metab Res* 7:378-381
 69. Lecavalier L, Bolli G, Cryer P, Gerich J 1989 Contributions of gluconeogenesis and glycogenolysis during glucose counterregulation in normal humans. *Am J Physiol* 256:E844-E851
 70. Ohneda A, Watanabe K, Horigome K, Sakai T, Kai Y, Oikawa S 1978 Abnormal response of pancreatic glucagon to glycemic changes in diabetes mellitus. *J Clin Endocrinol Metab* 46(3):504-510
 71. Shah P, Vella A, Basu A, Basu R, Schwenk WF, Rizza RA 2000 Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 85(11):4053-4059
 72. Shah P, Basu A, Basu R, Rizza R 1999 Impact of lack of suppression of glucagon on glucose tolerance in humans. *Am J Physiol* 277:E283-E290
 73. Dinneen S, Alzaid A, Turk D, Rizza R 1995 Failure of glucagon suppression contributes to postprandial hyperglycaemia in IDDM. *Diabetologia* 38:337-343
 74. Mitrakou A, Kelley D, Mookan M, Veneman T, Pangburn T, Reilly J, Gerich J 1992 Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. *N Engl J Med* 326:22-29
 75. Baron A, Schaeffer L, Shragg P, Kolterman O 1987 Role of hyperglucagonemia in maintenance of increased rates of hepatic glucose output in type II diabetics. *Diabetes* 36:274-283
 76. Ahren B, Larsson H 2001 Impaired glucose tolerance (IGT) is associated with reduced insulin-induced suppression of glucagon concentrations. *Diabetologia* 44(11):1998-2003
 77. Felig P, Wahren J, Hendler R 1975 Influence of oral glucose ingestion of splanchnic glucose and gluconeogenic substrate mechanism in man. *Diabetes* 24:468-475
 78. Kelley D, Mitrakou A, Marsh H, Schwenk F, Benn J, Sonnenberg G, Archangeli M, Aoki T, Sorensen J, Berger M, Sonksen P, Gerich J 1988 Skeletal muscle glycolysis, oxidation, and storage of an oral glucose load. *J Clin Invest* 81:1563-1571
 79. Gerich J, Lorenzi M, Karam J, Schneider V, Forsham P 1975 Abnormal pancreatic glucagon secretion and postprandial hyperglycemia in diabetes mellitus. *JAMA* 234:159-165
 80. Miles J, Rizza R, Haymond M, Gerich J 1979 Effects of acute insulin deficiency and administration on ketone body and glucose turnover in man. *Clin Res* 27:658
 81. Witters LA, Trasko CS 1979 Regulation of hepatic free fatty acid metabolism by glucagon and insulin. *Am J Physiol* 237(1):E23-E29
 82. McGarry J, Takabayashi Y, Foster D 1978 The role of malonyl-CoA in the coordination of fatty acid synthesis and oxidation in isolated rat hepatocytes. *J Biochem* 253:8294-8300
 83. Schade DS, Eaton RP 1975 Modulation of fatty acid metabolism by glucagon in man. I. Effects in normal subjects. *Diabetes* 24(5):502-509
 84. Rodbell M 1983 The actions of glucagon at its receptor. In: Lefebvre P, ed. *Glucagon I*. Berlin: Springer-Verlag; 263-290
 85. Baetens D, Malaisse-Lagae F, Perrelet A, Orci L 1979 Endocrine pancreas: three-dimensional reconstruction shows two types of islets of langerhans. *Science* 206(4424):1323-1325
 86. McGarry J, Foster D 1983 Glucagon and ketogenesis. In: Lefebvre P, ed. *Glucagon I*. Berlin: Springer-Verlag; 383-398
 87. Unger RH, Orci L 1976 Physiology and pathophysiology of glucagon. *Physiol Rev* 56(4):778-826
 88. Unger R 1978 Role of glucagon in the pathogenesis of diabetes: the status of the controversy. *Metabolism* 27:1691-1709
 89. Muller WA, Faloona GR, Aguilar-Parada E, Unger RH 1970 Abnormal alpha-cell function in diabetes. Response to carbohydrate and protein ingestion. *N Engl J Med* 283(3):109-115
 90. Wahren J, Felig P, Hagenfeldt L 1976 Effect of protein ingestion on splanchnic and leg metabolism in normal man and in patients with diabetes mellitus. *J Clin Invest* 57:987-999
 91. Unger RH 1973 Normal and abnormal alpha cell function. *Annu Rev Med* 24:303-308
 92. Seino Y, Ikeda M, Kurahachi H, Taminato T, Sakurai H, Goto Y, Inoue Y, Kadowaki S, Mori K, Imura H 1978 Failure to suppress plasma glucagon concentrations by orally administered glucose in diabetic patients after treatment.

Diabetes 27(12):1145-1150

93. Raskin P, Fujita Y, Unger RH 1975 Effect of insulin-glucose infusions on plasma glucagon levels in fasting diabetics and nondiabetics. *J Clin Invest* 56(5):1132-1138

94. Gerich J, Langlois M, Noacco C, Karam J, Forsham P 1973 Lack of glucagon response to hypoglycemia in diabetes: evidence for an intrinsic pancreatic alpha-cell defect. *Science* 182:171-173


95. Barnes A, Bloom S 1976 Pancreatectomized man: a model for diabetes without glucagon. *Lancet* 1:219-221

96. Asplin C, Paquette T, Palmer J 1981 In vivo inhibition of glucagon secretion by paracrine beta-cell activity in man. *J Clin Invest* 68:314-318


97. Gerich J, Schultz T, Tsalikian E, Lorenzi M, Lewis S, Karam J 1977 Clinical evaluation of somatostatin as a potential adjunct to insulin in the management of diabetes mellitus. *Diabetologia* 13:537-544

98. Cryer P 2002 Hypoglycaemia: The limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 45:937-948

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