REVIEW ARTICLE

Regulation of Glucose Production With Special Attention to Nonclassical Regulatory Mechanisms: A Review

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Hepatic glycogenolysis and gluconeogenesis are essential processes for the prevention of hypoglycemia during short-term starvation. As has been calculated from stable isotope studies, gluconeogenesis accounts for approximately 35% to 50% of total basal glucose production, glycogenolysis for the other 50% to 65%. In long-term starvation, the kidney also contributes to glucose production by gluconeogenesis. Glucose production is regulated by the interaction of different regulatory mechanisms, eg, by glucoregulatory hormones, glucose itself, and gluconeogenic substrates. In the last decades, more insight has been gained into the importance of the autonomous nervous system and the existence of an extensive paracrine network in the liver that seems to exert a potent glucoregulatory role as well. This review is focused on the regulation of hepatic glucose production by the autonomous nervous system and the paracrine network, with special emphasis on studies carried out in human subjects.

MAINTAINANCE OF A constant blood glucose level is essential for normal physiology in the body, particularly for the central nervous system. The brain can neither synthesize nor store the amount of glucose required for normal cellular function.[1] In the postabsorptive state, glucose is the obligatory fuel for the brain and provides more than 90% of the energy needed for brain function.[2] In the postabsorptive state, maintenance of plasma glucose concentration depends on a delicate balance between endogenous glucose production and glucose utilization. When glucose production ceases in the presence of unabated use in the postabsorptive state, the blood glucose concentration is halved in approximately 40 minutes.[3-5] Glucose is produced mainly by the liver and in smaller but substantial quantities by the kidney. The liver produces glucose by glycogenolysis and gluconeogenesis and the kidney by gluconeogenesis because it does not store glycogen.[6] Gluconeogenesis is limited to the liver and the kidney because other tissues lack glucose-6-phosphatase.[7-9]

After absorption of the last meal, endogenous glucose production gradually increases to prevent hypoglycemia. Liver glycogen stores, as measured by liver biopsy, are limited to approximately 70 to 150 g after an overnight fast[10,11]; the kidney does not store glycogen.[6] Consequently, glucose production during more prolonged starvation depends on hepatic and renal gluconeogenesis.

Renal gluconeogenesis becomes important in prolonged fasting and glucose counterregulation.[12,13] Reports on the individual contributions of the liver and the kidney to gluconeogenesis are not conclusive,[14,15] probably because of differences in experimental protocols. To assess the individual contribution of the liver and the kidney, which both simultaneously take up and release glucose, a combination of net balance of glucose across the specific organ and overall isotopic rate of release of glucose into the circulation must be used.[16] The contribution of the kidney to total postabsorptive gluconeogenesis differs from 5%[17] to 30% to 50%,[14,15] probably because of differences in study design, such as insertion of the catheter in the left[17] or right[16] renal vein. Because the left renal vein involves the contribution of the left testicle, this could lead to underestimation of renal glucose release. Otherwise, the differences in the reported renal contribution to gluconeogenesis may reflect compounded experimental errors caused by relying on such small concentration differences, as is the case when measurements are performed across the kidney, with its relatively high blood flow.

In maintaining glucose homeostasis, the liver and kidney are dependent on the interaction of different regulatory mechanisms, such as the classical glucoregulatory hormones, glucose itself, and gluconeogenic substrate supply. In the last decades it has become clear that paracrine mediators and the autonomous nervous system also exert a potent regulatory role. Pathophysiologic changes in different parts of this network will disturb glucose metabolism (eg, in liver disease or diabetes mellitus). There are some major differences in the effects of these regulatory systems on hepatic and renal glucose production. Although hepatic and renal glucose production are both inhibited by insulin[18,19] and stimulated by catecholamines,[20-24] cortisol,[25,26] and growth hormone,[25,27] glucagon has only documented stimulatory effects on hepatic glucose production.[28-30] The major stimulus for renal gluconeogenesis seems to come from α_1-adrenergic stimulation.[31] Thyroid hormone and vasopressin, hormones less known for their glucoregulatory effects, only stimulate hepatic glucose production, whereas parathyroid hormone has documented stimulatory effects only on renal glucose production.[32] Although lactate and glycerol are common substrates for both organs, alanine conversion to glucose takes place almost exclusively in the liver, whereas glutamine conversion to glucose occurs predominantly in the kidney.[13]

This review gives an overview of the regulation of basal glucose production with emphasis on hepatic glucose production. Traditionally, most attention has focused on the regulation

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of basal hepatic glucose production by the classical glucoregulatory hormones, glucose itself, and substrates for glucose production. In this review we focus on the importance of the autonomous nervous system and on the importance of an extensive paracrine network within the liver that seems to play an important role in glucoregulation.

METHODS USED TO MEASURE GLUCONEOGENESIS IN HUMANS

There are different techniques to quantitate gluconeogenesis (Table 1). Endogenous glucose production consists of 2 components: glycogenolysis and gluconeogenesis. In the past decades, several methods have been developed to measure the contribution of these 2 components to total glucose production. These methods involve the infusion of different radioactive and stable isotope-labeled precursors of gluconeogenesis,[33-38] measurement of arteriovenous differences across the splanchnic area,[39,40] and methods using liver biopsies[10,11] or nuclear magnetic resonance (NMR) technology to quantify changes in hepatic glycogen.[41,42]

The application of radioactive and stable isotopes for the measurement of gluconeogenesis is attractive because of the simple and noninvasive study design. Whole-body glucose production is measured after an overnight fast and a standardized carbohydrate-rich diet the 3 to 4 days before the experiments using 3^3H-, 6^3H-, or $6,6^2H_2$-glucose. However, tracer dilution techniques do not discriminate between hepatic and renal gluconeogenesis. To assess the individual contributions of the liver and the kidney, a combination of net balance of glucose across the specific organ and overall isotopic rate of release of glucose into the circulation must be used.[16] In addition, conceptual problems in the application of these isotopes for this purpose have been recognized for many years. The application of labeled gluconeogenic precursors such as alanine, pyruvate, and lactate[37,38] suffer from the limitation that these tracers are diluted in the relatively rapidly turning-over oxaloacetate pool, before conversion to glucose. Moreover, in the calculation of gluconeogenesis, the enrichment of the precursor pool for gluconeogenesis, the oxaloacetate pool, which cannot be measured directly, must be taken into account.[43] Isotopic exchanges in the oxaloacetate pool result in dilution of the labeling.[44] Consequently, these isotope approaches are limited by the assumptions regarding enrichment of the oxaloacetate pool.

In recent years, 2 different stable isotope methods for the quantification of gluconeogenesis have been described that bypass the problems of the oxaloacetate precursor pool enrichment, namely mass isotopomer distribution analysis (MIDA) based on infusion of [2-^{13}C]glycerol or [U-^{13}C]glucose and the deuterated water method. Using these different stable isotope techniques, postabsorptive gluconeogenesis in humans has been calculated to account for approximately 35% to 50% of total endogenous glucose production (Table 1). Hellerstein and Neese[45] infused [2-^{13}C]glycerol and measured the enrichment and mass isotope distribution of ^{13}C in glucose. In this method, enrichment of the precursor pool of gluconeogenesis, the triose phosphate pool, was derived by the principles of the MIDA.[45] Questions have been raised about the validity of MIDA to measure gluconeogenesis because of metabolic zonation in the liver with concomitant decreases in concentration and enrichment of glycerol across the liver lobule.[46,47] Homogeneity of the precursor pool is a key condition of validity for the MIDA technique because enrichment of the precursor must be the same in all cells that synthesize the calculated biopolymer, in this case glucose. Another method to quantify gluconeogenesis by MIDA, based on the use of [U-^{13}C]glucose, was published by Tayek and Katz.[36] According to Landau et al,[48] however, this method underestimated gluconeogenesis because underlying assumptions apparently could not be fulfilled and the contribution of gluconeogenesis from glycerol and amino acids was ascribed to glycogenolysis. Recently, Katz and Tayek[49] presented and discussed their questioned approach by publishing a theoretical analysis of recycling and concluded that their method was correct. Nevertheless, again Landau,[50] Kelleher,[51] and Radziuk and Lee[52] questioned the presentation and stated that this approach was invalid. The administration of ^2H_2O according to the method of Landau measures the enrichment of deuterium in specific positions in glucose, namely C2 and C5.[33] Because the exchange of deuterium between the gluconeogenic precursors and body water occurs after passing through the oxaloacetate pool, this method also does not involve the limitations of the unknown enrichment of this pool.

Table 1. Methods Used to Quantitate Gluconeogenesis in Healthy Humans

Method	% GNG in Basal State	% GNG After Prolonged Fasting	References
Stable isotopes			
^2H_2O	~50%	93% after 42 hours	33
^{13}C-lactate	39-50%	NM	34
2-$^{13}C_1$-glycerol	36%	84% after 60 hours	35, 45
U-$^{13}C_6$-glucose	47%	NM	36
Radioactive isotopes			
3-^{14}C-lactate	17%	NM	38
3-^{13}C-alanine	17%	NM	38
2-^{14}C-acetate	28%	97% after 66 hours	37
Liver biopsy	~30%	NM	10, 11
Splanchnic catherization	~20%	72% after 72 hours	39, 40
^{13}C-NMR	50-65%	96% after 64 hours	41

Abbreviations: GNG, gluconeogenesis; NM, not measured.

From studies using liver biopsies,[10,11] and splanchnic catherization,[39,40] gluconeogenesis was estimated to account for ~20% to 30% of total hepatic glucose production in the postabsorptive state; the rest (~70% to 80%) was the result of hepatic glycogenolysis.

Rothman et al measured hepatic glycogenolysis by ^{13}C-NMR spectroscopy.[41,42] The net rate of gluconeogenesis was calculated by subtracting the rate of net hepatic glycogenolysis (measured by NMR measurement of liver glycogen content in combination with liver volume) from the rate of glucose production in the whole body as measured with 6^3H-glucose glucose. In their study, it was calculated that gluconeogenesis accounted for 50% to 65% of total hepatic glucose production in the postabsorptive state.

In studies using liver biopsies,[10,11] liver volume[10] was not measured and was assumed to be 1.8 L in the postabsorptive state, which is ~30% higher than the mean volume measured by Rothman et al[41] in a comparable group of subjects. This will result in overestimation of total glycogenolysis and thus of the contribution of glycogenolysis to total hepatic glucose release, as taken from the splanchnic catherization studies.[39,40] In the splanchnic catherization studies,[39,40] in which gluconeogenesis is calculated by multiplying the arterial-hepatic venous difference in concentration of gluconeogenic substrates by hepatic flow (measured by infusion of indocyanine green), hepatic uptake of substrate formed within the splanchnic bed (eg, gut release of lactate or amino acids[53]) is not taken into account, nor do these studies allow for splanchnic extrahepatic glucose use and the contribution of the kidney to glucose production.[54] Thus, differences in the quantification of gluconeogenesis, and therefore in the estimation of the relative contributions of gluconeogenesis and glycogenolysis to total hepatic glucose production are attributable to methodologic limitations of the different techniques.

Because postabsorptive liver glycogen content is limited to 70 to 150 g[10,11] and glucose consumption occurs at a rate of approximately 225 g/d, it is obvious that hepatic glycogen stores decrease quickly during progression of a fast. As shown in dogs, during fasting glycogen deposition can occur at the same time as glycogen breakdown.[55] Liver biopsy samples obtained after a 24- to 48-hour fast in healthy subjects show virtually total disappearance of glycogen, which persists as fasting continues.[10,11] In accordance, Rothman et al[41] showed that after 64 hours of fasting, gluconeogenesis accounted for approximately 96% of hepatic glucose production. Values of 84-93% were found in the isotope dilution studies.[33,35]

In conclusion, in the postabsorptive state, total hepatic glucose production is the sum of glycogenolysis and gluconeogenesis. Data from liver biopsies, splanchnic catherization studies, NMR, and stable isotope studies show that after an overnight fast, gluconeogenesis accounts for 20% to 65% of total hepatic glucose production. During progressive starvation, the relative contribution of gluconeogenesis to total glucose production increases, whereas that of glycogenolysis decreases. At present a gold standard for the measurement of gluconeogenesis is lacking. Therefore, it is difficult to test the validity of the underlying assumptions of the different approaches to quantitate gluconeogenesis.

FACTORS AFFECTING HEPATIC GLUCOSE PRODUCTION

The factors affecting hepatic glucose production are shown in Table 2.

Substrates

The gluconeogenic substrates are lactate, glycerol, and the gluconeogenic amino acids. Lactate is produced by anaerobic glycolysis from stored or circulating glucose. It is produced not only by tissues with obligatory anaerobic glycolysis, but also under physiologic conditions by tissues such as muscle and brain.[56] In normal humans, the contribution of lactate (the Cori-cycle) is estimated to be ~15% of total glucose production in the postabsorptive state.[48,57-59] However, the exact quantification of the contribution of lactate to glucose production in humans in vivo is hampered by the complex kinetics of lactate and pyruvate tracers.[60] Conversion of gluconeogenic amino acids, of which alanine makes the largest contribution, accounts for 6% to12% of total glucose production in the postabsorptive state.[59,61] The predominance of alanine in the outflow of amino acids from muscle[61-63] and the evidence of its synthesis from glucose-derived pyruvate[61-65] has led to recognition of the glucose-alanine cycle[61-65] analogous to the Cori cycle. In the kidney, glutamine is the predominant substrate accounting for 5% to 8% of total glucose production.[15,66,67]

Glycerol is derived from hydrolysis of triglycerides in adipose tissue. Postabsorptive glucose production from glycerol is estimated to be limited (~2%).[60] Glycerol becomes quantitatively more important when lipolysis is accelerated, such as after prolonged fasting[68] and in diabetes.[69]

The effects of free fatty acids (FFAs) on gluconeogenesis in humans is still controversial. In animals, the effects of FFAs on gluconeogenesis seem to be species specific. Stimulatory ef-

Table 2. Mechanisms Involved in the Regulation of Glucose Production

Mechanism	In Vitro Effect	In Vivo Effect
Hormones		
Insulin	↓ 94,95	↓ 18,19,87-89,91,96
Glucagon	↑ 9,94,98,99	↑ 29,31,92,101,102,104
Catecholamines	↑ 20	↑ 21-24,106-108
Cortisol	↑ 111,112	↑ 25,26
Growth hormone	↑ 25,27	↑ 25,113,114
Substrates		
Amino acids	↑ 63,260-262	↑ 59,61-67
Lactate	↑ 265	↑ 57,58
Glycerol	↑ 261,263	↑ 60,68,69
FFA	↑ 70	↑ 73-76, ↓ 72,75
Glucose	↓ 119,120,126,127	↓ 121-124,129
Paracrine mediators		
Adenosine	↑ 142,143, ↓ 144	↑ 147
Prostaglandins	↑ 166-174	↓ 191
Cytokines		
TNF	= 203	↑ 196-202
IL-1	↑ 214,215	↑ 202, ↓ 217
IL-6	↑ 215,230	↑ 228,229
Autonomous nervous system		
Parasympathetic nerves	↓ 237	↓ 236,241,264, = 244,245
Sympathetic nerves	↑ 237	↑ 236,241,242

fects have been reported in rats,[70,71] whereas inhibitory effects have been reported in dogs, cats, and guinea pigs.[72] In humans, FFA stimulated postabsorptive gluconeogenesis from alanine and lactate[73,74] but decreased gluconeogenesis from alanine in healthy humans fasted 4 days.[75] By use of ^2H_2O, a method to quantitate gluconeogenesis from all precursors instead of from 1 or at most 2 precursors,[73-75] it was shown that FFAs increase gluconeogenesis.[76]

The role of substrate supply in maintaining glucose production is limited in the postabsorptive state and during short-term fasting (<86 hours). During 86 hours of fasting, glucose production could not be stimulated by increased precursor supply.[77-82] Conversely, glucose production decreases only when precursor supply is decreased to unphysiologically low levels.[77] Therefore, maintenance of glucose production during short-term fasting is not dependent on precursor supply. After prolonged fasting, however, replenishing gluconeogenic precursor supply resulted in an increase in glucose production.[12,83,84]

Glucoregulatory Hormones

The classical hormones involved in the regulation of hepatic glucose production are insulin and the counterregulatory hormones glucagon, epinephrine, norepinephrine, cortisol, and growth hormone. Besides their specific effects, all glucostimulatory hormones act by increasing cytosolic free calcium levels, either directly or by stimulation of IP3 synthesis. Increasing calcium levels is sufficient by itself to stimulate gluconeogenesis.[85,86]

Insulin

Shortly after the discovery of insulin, it was shown that insulin inhibits hepatic glucose production and stimulates peripheral glucose uptake.[87-89] After an overnight fast, insulin concentrations decrease to basal levels (~5 μU/mL, equivalent to ~35 pmol/L). This results in a major decrease in glucose uptake by insulin-dependent tissues such as resting muscle and adipose tissue, which can use FFAs for their energy supply instead of glucose. Consequently, glucose is available for non–insulin-dependent tissues such as the brain, blood cells, and renal medulla, which depend strongly on glucose for their energy supply.[90]

Basal insulin restrains basal glucose production.[91,92] Somatostatin infusion in postabsorptive dogs, together with intraportal infusion of glucagon to create selective insulin deficiency, results in a rapid increase in glucose production as a result of increased glycogenolysis.[92,93] Insulin inhibits both glycogenolysis and gluconeogenesis. Insulin directs glucose-6-phosphate to glycogen by increasing the activity of glycogen synthase and decreasing the activity of glycogen phosphorylase (which stimulates the breakdown of glycogen to glucose). In addition, insulin inhibits gluconeogenesis by inhibiting the transcription of the gene of one of the main gluconeogenic enzymes, phosphoenolpyruvate carboxykinase (which converts oxaloacetate into 2-phosphoenolpyruvate),[94] and by increasing the transcription of the gene of one of the main glycolytic enzymes, pyruvate kinase (which converts 2-phosphoenolpyruvate into pyruvate).[95] Insulin also indirectly decreases gluconeogenesis by inhibiting peripheral release of gluconeogenic precursors.[96] Glycogenolysis seems to be more sensitive than gluconeogenesis to inhibition by small increments in insulin secretion.[19] The decrease in plasma insulin from postprandial to basal concentrations is crucial for the stimulation of hepatic glycogenolysis.[97]

Glucagon

Infusion of pharmacologic doses of glucagon was shown to increase both hepatic glycogenolysis and gluconeogenesis.[28] Glucagon stimulates glycogenolysis by activation of glycogen phosphorylase, the rate-limiting enzyme for glycogenolysis in the liver.[98] Glucagon regulates gluconeogenesis by decreasing hepatic fructose 2,6-biphosphate, thereby increasing the conversion of fructose 1,6-biphosphate to fructose 6-phosphate, thus activating gluconeogenesis.[9,99] In addition, glucagon increases gene transcription of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (which converts oxaloacetate into 2-phosphoenolpyruvate)[94] and inactivates pyruvate kinase.[9] Glucagon in the liver is lipolytic, resulting in increased concentrations of FFAs and glycerol, thereby contributing to gluconeogenesis.[95] The gluconeogenic effect of the hormone is brought about solely by its hepatic action because glucagon did not increase peripheral release of any of the major gluconeogenic substrates.[100] In addition to the above-mentioned effects of glucagon on glycogenolytic and gluconeogenic enzymes, glucagon also increases hepatic alanine uptake, suggesting an effect on the aminoacid transporter,[101] and increases the proportion of extracted alanine that is converted to glucose, suggesting an action of the hormone on the enzymes within the hepatocyte.[29]

It has been shown in dogs that glucagon infusion only transiently stimulates the glycogenolytic component of hepatic glucose production (in contrast to sustained stimulation of the gluconeogenic component), even when counterregulatory insulin secretion was prevented by somatostatin infusion and basal insulin was replaced. This effect of glucagon waned even under circumstances in which the plasma glucose level was maintained at either euglycemic or hyperglycemic levels,[102] excluding a regulatory effect of changes in plasma glucose concentration. Administration of Bay-R3401, a glycogen phosphorylase inhibitor, to fasted dogs, resulted in a decrease in basal and glucagon-stimulated glycogenolysis but no change in total hepatic glucose production as a result of a reciprocal increase in gluconeogenesis.[103] In accordance, a transient effect of glucagon on hepatic glucose production was also found in human studies.[104,105] This suggests the existence of a reciprocity between glycogenolysis and gluconeogenesis or, alternatively, the existence of another inhibitory feedback system within the liver maintaining total glucose ouput by the liver on a certain level.

Catecholamines

Catecholamines stimulate hepatic glycogenolysis and hepatic gluconeogenesis during fasting,[20-23] eg, by activation of pyruvate carboxylase.[20] Part of the stimulatory response is caused by stimulation of glucagon secretion by epinephrine. In dogs and humans, physiologic hyperepinephrenemia causes sustained suppression of glucose clearance. In contrast, epi-

nephrine infusion causes only a transient increase in the glycogenolytic component of hepatic glucose production (in contrast to the sustained increase in gluconeogenesis). The transient effect of epinephrine appeared not be caused by glycogen or substrate depletion and occurred without changes in plasma insulin or glucagon,[21,22] suggesting that, analoguous to glucagon, an increase in epinephrine levels elicits one or more opposing forces to restore hepatic glucose production. Like epinephrine, physiologic hypernorepinephrinemia in healthy subjects suppresses glucose clearance and transiently stimulates hepatic glucose output.[106-108] Catecholamines normally do not play an essential role in maintaining plasma glucose concentration during fasting. However, enhanced secretion of catecholamines compensates and prevents hypoglycemia when the glucagon secretion is deficient.[109]

Corticosteroids

During progressive fasting, serum cortisol and urinary cortisol excretion increase as a result of an increase in the amplitude of pulses of serum cortisol without a change in duration or number of pulses per 24 hours.[110] Corticosteroids are known to activate gluconeogenic enzymes,[111,112] to augment the transfer of free amino acids to the liver,[25] and to induce hepatic resistance to insulin.[26] In contrast to the acute stimulatory effect of glucagon and catecholamines on hepatic glucose production, the stimulatory effect of cortisol on hepatic glucose production takes several hours to occur.[25]

Growth Hormone

Like cortisol, growth hormone may increase hepatic glucose production by inducing hepatic resistance to insulin,[113] altering substrate availability,[25,114] or promoting enzyme induction.[25] Progressive starvation enhances growth hormone secretion by combined frequency and amplitude modulation.[115] Like cortisol, the stimulatory effect of growth hormone on hepatic glucose production takes several hours to occur.[25]

Of all classical hormones described above, studies in which endogenous insulin and glucagon secretion was inhibited by somatostatin[116] show that the ratio between the basal levels of insulin and glucagon seems to be the main determinant of basal glucose production. Somatostatin infusion in postabsorptive dogs resulted in a decrease of ~80% of portal vein insulin and glucagon levels. This was associated with a decrease of ~40% in hepatic glucose production, indicating that effects of glucagon normally override the effects of insulin after an overnight fast and that ~40% of basal glucose production is glucagon dependent. In human studies, in which somatostatin was infused systemically instead of intraportally, in contrast to studies in dogs, hepatic glucose production decreased only transiently and then returned to the basal rate,[117] indicating that in humans other mechanisms must be operative that maintain basal glucose production besides insulin and glucagon, traditionally viewed as the major regulators of basal glucose production.

Plasma Glucose Concentration

The concept that hepatic glucose output is regulated by the prevailing plasma glucose concentration is well established.[118] This process, frequently referred to as autoregulation, has received support from many in vivo and in vitro studies.

Increased glucose concentrations inhibit in vitro glucose release from rat hepatocytes and isolated perfused liver in rats[119,120] and inhibit in vivo glucose production in pigs and humans independent of changes in glucoregulatory hormones.[121-124] In the postabsorptive state, reduction in hepatic glycogenolysis and enhancement of glucose cycling between glucose and glucose-6-phosphatase are the primary mechanisms by which the autoregulatory response occurs. After a more prolonged fast, when hepatic glycogen concentrations have been reduced to a stable minimum, reduction in the gluconeogenic rate becomes the predominant mechanism of the autoregulatory response.[125] This could well be attributable to stimulation of glycogen synthetase by increased levels of glucose-6-phosphate[126] or inhibition of glucose-6-phosphatase by high concentrations of glucose.[127]

Decreased glucose concentrations in the media of liver preparations of rats resulted in increased glucose release.[128] During a physiologic decrease in plasma glucose in humans from 5.3 mmol/L (glucose infusion) to 3.6 mmol/L (glucose infusion stopped), induced by clamping insulin at ~14 μU/mL (basal concentrations ~6 μU/mL) by infusion of somatostatin together with insulin, glucose production increased without changes in concentrations of glucagon, cortisol, or growth hormone. This increase in hepatic glucose production could be prevented totally by combined α- and β-adrenergic blockade, indicating that hepatic autoregulation does not contribute to an increase in glucose production during a physiologic decrement in plasma glucose.[129] However, severe hypoglycemia (plasma glucose concentrations clamped at 1.6 mmol/L), induced by physiologic hyperinsulinemia during neurohumoral blockade (somatostatin, propanolol, phentolamine, metyrapone), resulted in doubling of hepatic glucose production compared with euglycemia in the presence of comparable insulin concentrations and neurohumoral blockade. Both glycogenolysis and gluconeogenesis contribute to the autoregulatory response. The data show that when very low glucose levels are reached, the glucose signal can 'escape' and override the insulin signal. The same was found by Cherrington et al. in dogs with denervated livers (to interrupt neural pathways between the liver and the brain).[125] These observations suggest that activation of hepatic autoregulation may become important as an emergency system to prevent further decreases in plasma glucose concentrations and thus to protect the brain from hypoglycemic damage.[130] The mechanism by which glucose production becomes activated during hypoglycemia independent of neurohumoral influences is unclear. However, the results of this study[130] and other, in vitro studies suggest a direct intrahepatic mechanism.[128]

In conclusion, increases in plasma glucose concentrations, even at euglycemic concentrations, inhibit hepatic glucose production both in vitro in rats and in vivo in humans, partly by unknown (most likely intrahepatic) mechanisms. Decreases in plasma glucose concentrations increase hepatic glucose production in vitro in rats and in vivo in humans (only when severe hypoglycemic exists), partly by unknown (most likely intrahepatic) mechanisms.

Paracrine Mediators

Adenosine

Adenosine has emerged as an important modulator of many physiologic processes. For instance, adenosine inhibits lipolysis in vivo and in vitro.[131-134] From in vitro studies, it is known that adenosine is formed and released in many tissues, including the liver, by 3 different mechanisms: dephosphorylation of adenosine monophosphate (AMP), hydrolysis of S-adenosylhomocysteine, and release from both adrenergic and cholinergic nerve endings.[135-137] On rat liver plasma membranes, adenosine receptors activating adenylate cyclase have been identified.[128,139] In cultured hepatocytes, adenosine stimulates basal glycogenolysis by stimulation of phosphorylase a activity,[140,141] the effect being transient with a duration of ~5 minutes, probably because of its rapid removal by adenosine deaminase.[141] Both stimulatory[142,143] and inhibitory[143,144] effects of adenosine on gluconeogenesis in isolated rat hepatocytes were reported. Stimulation of gluconeogenesis by adenosine is obtained by metabolism of adenosine through adenosine deaminase and inhibition of gluconeogenesis by metabolism of adenosine through adenosine kinase.[143] In healthy human subjects, pentoxifylline infusion, which blocks the adenosine receptor,[145,146] resulted in a transient decrease in hepatic glucose production. Because there was no change in plasma concentrations of glucoregulatory hormones,[147] a stimulatory role for adenosine on hepatic glucose production is suggested.

Prostaglandins and Thromboxane A2

Endogenous prostaglandins can be formed by virtually all tissues and cells in response to a variety of stimuli, produce a wide range of effects, and are involved in the regulation of virtually all functions.[148,149] The half-life of prostaglandins in the circulation is short. Approximately 97% of an intravenous dose of PGE_2 is eliminated from the plasma within 90 seconds.[150,151] Prostaglandin degradation enzymes are widely distributed in the body, with highest activities in lung, kidney, spleen, adipose tissue, and intestine. Prostaglandins are readily inactivated by enzymatic conversion to 15-ketometabolites[152,153] and are further metabolized by β and ω oxidation. The characteristics of prostaglandin metabolism indicate that prostaglandins may be important at the side of production rather than at distant sides.

In the liver, the major producers of prostaglandins are the Kupffer cells.[154] The main prostaglandins produced by these cells are PGD_2, PGE_2, and $PGF_{2\alpha}$.[155] Only a small contribution to hepatic prostaglandin production is derived from the sinusoidal endothelial cells.[156]

Prostaglandin synthesis by Kupffer cells can be stimulated by extracellular mechanisms (phorbol ester, lipopolysaccharide, tumor necrosis factor [TNF]α),[155,157] or intracellular mechanisms (eg, increased calcium levels).[155] Mechanisms that operate both extracellularly and intracellularly (nucleotides like adenosine triphosphate and adenosine) were also found to stimulate prostaglandin synthesis from perfused animal livers.[158,159] Prostaglandins are interpreted as paracrine factors with a short range of action.[160] Thus, inactivation of the signals is a necessary feature of their actions. Rapid uptake and degradation of Kupffer cell–derived prostaglandins is accomplished by hepatocytes; prostaglandins do not accumulate and are not stored within liver cells.[161]

Prostaglandins, produced by Kupffer cells, exert their effects in the Kupffer cell itself by stimulation of second messenger systems, or they can leave the cell and modulate the function of neighbor cells. The parenchymal cells of the liver (hepatocytes) contain receptors for prostaglandins.[162,163] The PGE_2 receptor is coupled to adenylate cyclase by a G protein.[164]

It has been shown recently that prostaglandins are able to stimulate glycogenolysis in perfused rat liver[165-167] and in isolated rat hepatocytes.[166-174] Glycogenolysis is stimulated by PGE_1, PGE_2, and $PGF_{2\alpha}$ by activation of glycogen phosphorylase and deactivation of glycogen synthase.[172-174] Prostaglandins are also thought to mediate the effects of effectors such as phorbol esters, zymosan particles, arachidonic acid, or platelet-activating factor that seem to activate glycogenolysis in liver parenchymal cells by stimulating the synthesis of prostaglandins such as PGD_2, PGE_2, or $P1F_{2\alpha}$ from nonparenchymal cells.[166,171,175,176] In contrast to its stimulating effects on glycogenolysis per se, PGE_2 was found to inhibit both cAMP-dependent (glucagon)[177-181] and cAMP-independent (epinephrine) stimulated glycogenolysis in isolated hepatocytes.[179] With respect to the latter effect, epinephrine-induced glycogenolysis in normal rat liver is largely mediated by Ca^{2+} and independent of cAMP.[182] Because prostaglandins stimulate Ca^{2+} release,[166] the inhibition of epinephrine-stimulated glycogenolysis seems to take place distal from Ca^{2+} in the pathway. Gluconeogenesis has been reported to be inhibited by PGE_1[183] and $PGF_{2\alpha}$[184] in perfused liver of fasted rats. One study reported an inhibitory effect of PGE_2 on glucagon-induced hepatic gluconeogenesis.[185]

No data are available on the effects of prostaglandins on glycogenolysis or gluconeogenesis in human liver preparations or in humans in vivo. Interpretation of the effects of prostaglandins on hepatic glucose production in vivo in animals and humans is difficult because infusion of prostaglandins results in increased hepatic glucose production associated with increased levels of glucagon and epinephrine.[186-189] Therefore, direct effects of these prostaglandins on hepatic glucose production cannot be deduced from these studies. We showed that indomethacin in a dose that has been shown to inhibit prostaglandin synthesis[190] increases hepatic glucose production in healthy subjects without changes in concentrations of glucoregulatory hormones.[191] This points to an inhibitory influence of prostaglandins on hepatic glucose production. Thromboxane, another eicosanoid, was also shown to stimulate glycogenolysis in perfused rat livers, although not in isolated hepatocytes. This glycogenolytic effect of thromboxane A2 seems to be an indirect effect, via vasoconstriction-induced hypoxia within the liver.[192]

Cytokines

In addition to other tissues and blood (especially monocytes, lymphocytes, neutrophils, platelets), the liver produces mediators like TNF-α, interleukin (IL) 1, and IL-6, cytokines with overlapping biologic properties.[155,194,195] Within the liver, Kupffer cells are the most potent producers of cytokines.[132] However, cytokines are also produced by other cells like en-

dothelial cells.[155] Cytokines usually act in picomolecular concentrations through specific, high-affinity cell surface receptors. In contrast to the classical hormones, they act mainly in a paracrine and autocrine manner, although they can also act in an endocrine manner on distant cells. Most of what we know about the effects of cytokines is related to inflammatory events; very little is known about functions of cytokines under normal physiologic conditions. However, evidence accumulates that cytokines are not only important in pathofysiological conditions but also in physiology.

TNF-α. TNF-α, discovered in 1985, is a 17-kd polypeptide, secreted mainly by monocytes and macrophages, among them the Kupffer cells.[155,194,195] In mice, Kuppfer cells were shown to produce high levels of TNF-α spontaneously (without stimulation).[195]

In healthy humans, a bolus injection of TNF induces an increase in glucose production of ~10%.[196] In rats, dogs, and lambs, TNF has also been reported to enhance glucose production.[197-202] This stimulatory effect of TNF on glucose production was associated with increased levels of glucocounterregulatory hormones.[196-202] It is unlikely that TNF exerts a direct effect on the liver because TNF does not affect either gluconeogenesis or glycogenolysis in isolated rat hepatocytes in vitro.[203] Although TNF increases substrate availability for gluconeogenesis in vivo,[204-210] this is not a likely way to influence hepatic glucose production because, as mentioned above, increased substrate availability is not a major regulator of basal hepatic glucose production.[80-89]

In conclusion, TNF stimulates hepatic glucose production in vivo. Because no effect was found in vitro in isolated rat hepatocytes, this effect of TNF seems to be indirect, eg, through secretion of glucocounterregulatory hormones.

IL-1β. IL-1 is produced by a wide variety of cells, mainly monocytes and macrophages (Kupffer cells included).[155,211-213] There are no data on the effects of IL-1 on hepatic glucose production in humans. Data on the in vivo and in vitro effects of IL-1 in animals are not concordant, probably partly because of differences in experimental design and interspecies differences. For instance, Flores et al[202] reported that infusion of IL-1β (10 ηg/kg bolus; 10 ηg/kg in 4 hours) into rats resulted in an increase in hepatic glucose production and peripheral glucose uptake, the mean plasma glucose being increased. The increase in glucose production was associated with an increase in glucagon.[202] In accordance with this in vivo study, Il-1α and IL-1β increased glycogenolysis in isolated rat hepatocytes.[214,215] Therefore, Il-1 may increase hepatic glucose production in rats directly and/or indirectly,[216] eg, by interaction with the effect of glucoregulatory hormones. Kanemaki et al[216] showed that IL-1β inhibited insulin-stimulated glycogen deposition in primary cultured rat hepatocytes most likely by inhibiting glycogen synthase. Although hepatic glucose production itself was not measured, del Rey and Besedovsky[217] reported that injection of recombinant IL-1β in mice (dose, 0.04 to 80 g/kg) induced a dose-dependent hypoglycemia. The hypoglycemia induced by IL-1β in mice occurred independent of changes in insulin levels. This could be related to inhibition of phophoenolpyruvate carboxykinase (PEPCK) by IL-1β, one of the rate-controlling enzymes of gluconeogenesis, in mice.[218]

In conclusion, interspecies differences exist for the effects of IL-1 on glucose production. In rats, IL-1 seems to stimulate basal hepatic glucose production and to inhibit insulin-stimulated glycogen deposition, whereas it inhibits glucose production in mice. Furthermore, it remains unclear whether the effects of IL-1 on glucose production are direct, indirect, or both.

IL-6. IL-6, discovered in 1980, is a 26-kilodalton protein produced by a variety of cells, mainly monocytes and macrophages (including Kupffer cells),[155,219-222] after stimulation by endotoxin, TNF, and IL-1[155,219,223,224] and spontaneously.[225] IL-6 binds to a specific receptor,[226] which is expressed in many different cells, including hepatocytes.[227]

IL-6 infusion into humans induced a moderate increase in hepatic glucose production and plasma glucose, concomitant with an increase in glucose counterregulatory hormones.[228,229] In accordance, IL-6 was shown to inhibit insulin-stimulated glycogen deposition[216] and to stimulate glycogenolysis and gluconeogenesis in isolated rat hepatocytes.[215,230]

Thus, although reports on the effects of IL-6 on hepatic glucose production are scarce, they point to a stimulatory effect of IL-6 on hepatic glucose production.

Interactions between paracrine mediators. There are complex interactions between the various mediators within the liver on one hand and between these mediators and the classical hormones on the other hand. This is one of the reasons it is extremely difficult to unravel the direct effects of these mediators, especially in vivo. For instance, adenosine induces prostaglandin biosynthesis in tissues, including the liver.[158] Because TNF can act as an autacoid, it can, after its production by rat Kupffer cells, activate these cells to produce PGE_2, IL-1, and IL-6.[155,194] IL-1, which also acts as an autacoid, induces PGE_2, TNF, and IL-6 production.[155,213] Besides mediating certain effects of TNF, IL-6 suppresses macrophage TNF and IL-1 production,[138,214,231] and PGE_2, which suppresses production of TNF-α (at the transcriptional level),[232,233] of IL-1 (at the translation level),[234] and of IL-6,[235] thereby participating in an autoregulatory pathway to form a self-limiting regulatory cycle. The suppressive effect of PGE_2 on TNF production is remarkable for its specificity; other prostaglandins (eg, PGD_2 and $PGF_{2\alpha}$) are ineffective.[233]

In conclusion, a complex paracrine signaling system seems to operate between Kuppfer cells, hepatic endothelial cells, and hepatocytes. Because these substances have many interactions with the classical hormones and with each other, it is difficult to unravel the effects of the individual paracrine substances on hepatic glucose production.

The Autonomous Nervous System

The liver is richly innervated by the sympatic and parasympatic nervous system.[236-240] The sympatic fibers are derived from the splanchnic nerves, which are connected to the ventromedial hypothalamus. Their postganglionic fibers originate in the celiac ganglia and plexus. The parasympatic fibers are derived from the vagus nerves, which project to the lateral hypothalamus, and the respective ganglion cells are located close to the liver. Remarkably, each hepatocyte is directly innervated. Electron microscopic studies have shown nerve terminals making direct contact with hepatocytes, indicating that these liver cells are subjected to direct neural control

through both the sympatic and parasympatic nerves.[239,240] In animal models, it has been found that the functions of the ventromedial hypothalamus/sympatic and lateral hypothalamus/parasympatic system in the regulation of carbohydrate metabolism in the liver seem to be reciprocal. Activation of the ventromedial hypothalamus produces hyperglycemia by increasing glycogenolysis and gluconeogenesis. These effects appear to be mediated via efferent nerve supply (sympatic fibers) to the liver and by release of adrenaline and glucagon in a complex, integrated neurohormonal response.[237,241,242] Direct activation of hepatic sympatic nerves rapidly increases glucose output from the liver by Ca^{2+}-mediated stimulation of glycogen phosphorylase.[237-239] Stimulation of the lateral hypothalamus leads to a rather slow and small decrease in plasma glucose by activation of hepatic glycogen synthase and inhibition of PEPCK.[239] Direct activation of the parasympatic fibers enhances the activity of hepatic glycogen synthase, resulting in a decrease in hepatic glucose output.[239,243] Changes in gluconeogenic enzymes occur after 2 to 4 hours, in contrast to the rapid response of enzymes controlling glycogen metabolism.[239,243] We found no change in hepatic glucose production in postabsorptive humans after truncal vagotomy, which involves complete parasympathetic denervation of the liver,[244,245] indicating that withdrawal of parasympathetic tone does not appear to be an important glucoregulatory process in humans in the postabsorptive state.

Glucose sensors have been detected not only in the brain,[246-250] especially in the ventromedial and lateral hypothalamus, but in the portal vein as well.[250-253] These sensors are extremely important in case of hypoglycemia.[251,252] Although the mechanism of portal glucose sensing remains to be fully elucidated, it does appear that these portal glucose-sensitive afferents, which seem to be linked to the glucose sensors in the hypothalamus, are part of a portal-sympathetic glucoregulatory reflex.[253,254] Cherrington et al recently demonstrated that in response to a carbohydrate-rich meal, the negative arterial-portal glucose gradient produces a portal signal that rapidly stimulates net hepatic glucose uptake.[255-258] Indirect evidence that the portal signal interacts with the autonomous nervous system is suggested by the fact that augmentation of hepatic glucose uptake produced by the portal signal is abolished in dogs that have undergone complete hepatic surgical denervation.[259]

In conclusion, animal data show that hepatic nerves are involved in the regulation of hepatic glucose production. Glucose sensors are present both in the hypothalamus and in the portal vein, effectively sensing hypoglycemia. These latter afferent sensors seem to be linked to the sensors within the hypothalamus, thereby forming a hepatoglucoregulatory reflex. Sympatic efferents in functional relation with different hypothalamic nuclei stimulate hepatic glucose production, whereas parasympatic efferents have an inhibitory influence on hepatic glucose output.

SUMMARY AND CONCLUSIONS

Glucose production, which is essential for postabsorptive glucose homeostasis, is regulated by the delicate interaction between different glucoregulatory mechanisms that exert their influence on glycogenolysis by the liver and gluconeogenesis by the liver and kidney. Traditionally most attention has focused on the regulation of postabsorptive glucose production by powerful blood-derived mediators, such as hormones. In addition, there are indications for small substrate-driven effects of hepatic glucose production. In the past years, evidence has accumulated on the importance of the autonomous nervous system on the regulation of hepatic glucose production. In this respect, it is highly remarkable that each hepatocyte is in close contact with the autonomous nervous system. Finally, circumstantial evidence exists for an extensive paracrine network within the liver that seems to exert a potent glucoregulatory role as well. All of these systems seem to have both direct and indirect effects by interacting with each other.

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