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The Hormones of Glucose Metabolism

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Abstract: Like every other process that is crucial to homeostasis, glucose metabolism is regulated by the endocrine system. There are many hormones that impact this metabolism indirectly due to their roles in key processes such as circulation, appetite, or stress response; however, this paper will examine the hormones that directly regulate or impact glucose metabolism. Additionally, an overview of glycemic disorders is provided.

Key Words: Glucose metabolism, endocrine glucose regulators, endocrinopathies of glucose metabolism.

GLUCOSE

Glucose is a simple carbohydrate that is the human body's primary source of energy [1]. Circulating glucose is in the monosaccharide form, but is stored in the polysaccharide form as glycogen. Although the body can use other sources, such as fats and proteins, to produce energy, these alternative energy sources cannot substitute for glucose in red blood cells or brain cells [2]. Glycogen, however, has recently been proven to serve as a glucose equivalent within the brain, acting as a reserve energy source in the event of hypoglycemic states [3].

To understand glucose metabolism, it is important to first recognize that it is not a singular process, nor is there a common starting point. In fact, it is continuous activity with multiple sources, mechanisms, locations, and triggers [4]. There are four pathways of glucose metabolism: glycolysis, gluconeogenesis, glycogenesis, and glycogenolysis. By understanding each of these processes, one can get a better picture of the roles of each pertinent hormone and their relationship to one another.

GLYCOLYSIS

The process by which glucose is broken down into usable energy forms is called glycolysis. Within cellular cytoplasm, each glucose molecule is cleaved and then converted into pyruvate, creating adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NADH) by the glycolysis reactions. This is a lengthy process involving several enzymes, but regulation of the glycolytic flux depends on the three enzymes that catalyze the irreversible steps: hexokinase, phosphofructokinase, and pyruvate kinase [5]. The relationship is direct—glycolytic activity increases and decreases in relation to the fluctuations in these enzyme levels.

GLUCONEOGENESIS

Gluconeogenesis is the synthesis of glucose from non-carbohydrate forms. The primary location for this synthesis is typically the liver, with minimal synthesis occurring in the kidneys [6]. The enzymatic reactions of gluconeogenesis are mostly the reverse of glycolytic steps, with substitutions of glucose-6-phosphatase, fructose-1,6-biphosphatase, and phosphoenolpyruvate carboxykinase for (respectively) hexokinase, phosphofructokinase, and pyruvate kinase [7]. These mechanisms inhibit one another, thus preventing them from reacting simultaneously and forming a futile cycle [8].

GLYCOGENESIS

When glucose is converted to its storable form glycogen, this process is called glycogenesis. In a properly

functioning metabolic system, glycogenesis occurs in the liver and muscle cells in response to excess circulating glucose without increased energy demand [9]. Glycogen then lies in storage until glucose levels fall, or there is an increased demand for glucose that is not otherwise being met within the body. Once this need arises, the process of glycogenolysis takes place.

GLYCOGENOLYSIS

In the liver and muscle cells, stored glycogen is broken down into glucose-1-phosphate. Skeletal muscle is technically capable of generating glucose from glucose-1-phosphate, which could then enter the bloodstream. However, the abundance of hexokinase in these cells immediately phosphorylates any free glucose before it can do so and it enters the glycolytic pathway instead. In the liver, glucose-1-phosphate is further converted to glucose-6-phosphate by phosphoglucomutase [10]. This is then either distributed for use in energy production, or further converted into glucose for dispersion to the tissues unable to utilize the phosphorylated form.

HORMONAL REGULATORS OF GLUCOSE METABOLISM

The previously described metabolic pathways are regulated and/or influenced by several hormones. Epinephrine, cortisol, growth hormone, thyroid hormones, somatostatin, and ACTH are all implicated in glucose metabolism. They express their effects on metabolic pathways directly by affecting components or steps of the pathway, indirectly through influences on insulin and/or glucagon, or a combination of these routes [11]. However, the primary hormones responsible for maintaining glucose homeostasis are the pancreatic hormones insulin and glucagon.

INSULIN

A peptide hormone synthesized from proinsulin by the pancreas, insulin is the most widely recognized glucose-mediating hormone. It is secreted continuously to maintain circulating glucose levels, and secreted in increased amounts in response to exogenous stimuli [12]. When the β-cells of the islets of Langerhans detect elevated circulating glucose, they secrete insulin. This response appears as though secretion is happening purposely in two separate bursts; however, recent research indicates that the immediate peak is caused by the rapid release of stored insulin. The subsequent drop and secondary peak is caused by the depletion of stores followed by the secretion of newly created insulin [13].

There are several mechanisms by which insulin produces its glucose-lowering effects, and these actions take place in several different organs and tissues. In the liver, insulin stimulates glycogen synthesis by activating hexokinase. This promotes storage of glucose (as glycogen), thus lowering circulating glucose levels. It also inhibits the ketogenesis and gluconeogenesis by disrupting enzymes involved in each process [12]. By inhibiting gluconeogenesis, circulating glucose levels are prevented from increasing.

Adipose tissue—the fatty tissue—is another area that involves significant levels of insulin activity. Adipose tissue is comprised of triglycerides, and it is these triglycerides that are the object of the insulin effects [14]. Insulin prompts lipoprotein lipase production, which in turn hydrolyzes triglycerides from circulating lipoproteins allowing the fatty acids to enter adipose cells. Additionally, insulin enhances α-glycerol phosphate availability, which is used to esterify free fatty acids into triglycerides inside the adipose cells. Lipolysis of stored triglycerides requires lipase whose intracellular production is inhibited by insulin. The result of all of these mechanisms is increased triglyceride storage and reduced circulating fats.

Insulin activity within muscle tissue is more diverse than that of adipose tissue, primarily due to the complexity of muscle composition and action. As in the liver, insulin promotes glycogen synthesis. In the muscle, this is achieved as a result of three insulin actions: glycogen phosphorylase inhibition, glycogen synthase enhancement, and increased transport of glucose. Intracellular glucose transporters are otherwise inactive until insulin binds to receptors [15].

There are multiple glucose transporter proteins (i.e. GLUT 1 through GLUT 4) with different affinities for glucose and a time lag following binding insulin to the receptor during which the transporter protein translocates to the cell membrane. The difference in the affinities allows preferential release of glucose to brain and muscle tissue (i.e. GLUT 2 has low affinity for glucose and this causes decreased uptake and storage by hepatic cells during fasting. Another example would be when GLUT 4 is sequestered in intracellular compartments of cells and is not able to function as a transporter until it receives the signal from insulin binding to its cell membrane receptor, at which time GLUT 4 translocates to the cell membrane

[12]. Insulin also increases protein synthesis within the muscle tissue. This effect is due to insulin's combined increases in ribosomal proteins production and amino acid transportation.

GLUCAGON

Glucagon, like insulin, is a peptide hormone synthesized in the pancreas. It is also responsible for glucose homeostasis, but its role is the exact opposite of insulin. Secreted by the α-islets in response to low circulating glucose, glucagon prompts several actions that result in an increase in circulating glucose [16]. Glucagon secretion is also stimulated by various amino acids and catecholamines independent of glucose levels. It is primarily inhibited by glucose, but insulin and somatostatin's inhibition of α-islet cells also reduces glucagon secretion [17].

Like insulin, glucagon's actions take place in a variety of organs and tissues. The liver holds the largest concentrations of glucagon receptors, which results in the majority of glucagon activity impacting hepatic mechanisms. Glucagon binds to adenylyl cyclase receptors, inducing gluconeogenesis [18]. When amino acid precursors are depleted, glucagon stimulates enzymatic break down of stored glycogen [19]. When glycogen stores are depleted, ketogenesis is prompted in the form of acetoacetate, β-hydroxybutyrate, and acetone [20].

Glucagon receptors also exist in adipose tissue, kidneys, the heart, pancreas, gastrointestinal tract, thyroid, and central nervous system [21]. In the kidneys, glucagon stimulates cyclic adenosine monophosphate production [22]. Additionally, glucagon increases amino acid concentration of glomerular tissue, inducing glomerular enlargement. As a result of these two actions, vasodilation and increased glomerular filtration rates occur [23], prompting a decrease in blood pressure.

In adipose tissue, glucagon increases lipolysis [24] by triggering the release of fatty acids from triglycerides. In the gastrointestinal tract, glucagon produces an anti-spasmolytic effect [25], and relaxes smooth muscle of the upper and lower tracts [26]. Glucagon increases both the rate and force of cardiac contractions [27], as a result of glucagon's stimulation of cyclic adenosine monophosphate production and calcium channel activity.

PATHOLOGIES OF ENDOCRINE IRREGULARITIES

Abnormalities of the aforementioned hormones, either in function or amount, will result in imbalances of circulating and/or stored glucose. These glucose homeostasis disorders can be divided into three classifications: hyperglycemia, hypoglycemia, or congenital defect of metabolism. Humans require constant sources of energy, which is primarily derived by the metabolism of glucose and disruption of this metabolism can result in severe and devastating effects.

HYPERGLYCEMIC DISORDERS

Chronic hyperglycemia is most commonly caused by diabetes mellitus, which is a syndrome of deficient or ineffective insulin. This disorder is divided into two classifications (type 1 and type 2), and is further defined by dependence on insulin intervention. Diagnosis is prompted after investigation of the etiology for persistently elevated serum glucose levels. Patient symptoms usually result in the medical practitioner's order of blood glucose, insulin and ketone testing. However, Type 2 may remain asymptomatic for several years [28], with diagnosis resulting from the detection of hyperglycemia during routine laboratory testing.

Type 1 diabetes mellitus.

Type 1 diabetes mellitus is the more severe of the two diabetes types, causing critical long- and short-term complications. It is characterized by the failure of the pancreatic beta cells to secrete insulin in response to circulating glucose. Prognosis improves the earlier it is detected and treated. Long-term complications to vascular, retinal, renal, and immune system function are related to the success and consistency of glycemic control [29]. Left untreated, the resulting production and accumulation of ketones is inevitably fatal. Treatment involves a combination of diet (low sugar) and insulin injections.

Pancreatic dysfunction of type 1 diabetes has several idiopathic and immune-mediated origins, but the most prevalent cause is genetic mutation [30]. Several genes have been identified that contribute to its onset, with various confounding factors increasing risk. The mutations implicated in diabetes disturb immune system

function, resulting in autoimmune destruction of pancreatic β-cells [31]. Mutations of insulin receptors also are rarely implicated. The implicated mutations are not a guarantee that type 1 diabetes will develop, but isolating the specific gene mutation (or combination of gene mutations) helps determine the susceptibility. As such, genetic mapping of children with familial history of type 1 diabetes can serve as an essential early intervention strategy [32]. By identifying the potential for type 1 diabetes development early, immunosuppressant therapy can prevent autoimmune destruction of the pancreatic cells.

Type 2 diabetes mellitus.

As with type 1 diabetes, type 2 diabetes mellitus is characterized by chronic and persistent hyperglycemic states. Elevated glucose levels are caused by insulin resistance, as opposed to insulin deficiency [12]. Several mechanisms associated with insulin resistance have been identified, but the underlying cause of these mechanisms remains undefined. Risk factors include obesity, diet, gender, and race; additionally, several gene mutations increasing susceptibility have been identified [33].

Pharmacological management of type 2 diabetes involves medications that lower blood glucose. Medications that stimulate insulin production and secretion, or inhibit enzymatic carbohydrate metabolism may be added if insulin sensitizers are inadequate [34]. Insulin injection is used in cases where hypoglycemic oral agents fail, but combined therapies in early disease management have gained popularity [35] due to insulin's protective effects on β-cells [36].

Modification of diet and exercise can reverse insulin resistance in many type 2 diabetics, especially in obese patients [37]. In pre-diabetic patients, diet and exercise can also prevent development of type 2 diabetes [38]. Non-obese type 2 diabetics, who compose up to 40% of the type 2 population, are also typically responsive to diet and exercise. However, exercise-induced insulin improvements of non-obese patients are strictly short-term and relative to consistency [39] whereas obese patients can see long-term improvements due to decreased body fat.

Diagnosis of diabetes mellitus.

Laboratory findings of fasting glucose levels greater than 126 mg/dL (7.0 mmol/L), diabetic symptoms combined with glucose levels greater than 200 mg/dL (11.1 mmol/L), or 2-hour glucose measurement during a glucose tolerance test (GTT) greater than 200 mg/dL (11.1 mmol/L) are definitive diagnostic criteria. Most type-1 diabetes patients become symptomatic, and are therefore diagnosed, in childhood. However, in the event of uncertainty, presence of islet cell autoantibodies can conclusively differentiate between type 1 and type 2 [40]. Additional laboratory findings of diabetes mellitus also include glucosuria, hyperlipidemia, ketonuria, proteinuria, and microalbuminuria.

HYPOGLYCEMIC DISORDERS

Hypoglycemia can be caused by a wide variety of diseases, disorders, physiological states, and pharmaceutical reactions. True hypoglycemic disorders are differentiated by the absence of an external cause (known as reactive hypoglycemia), and can be broadly classified as hyperinsulinemic or non-hyperinsulinemic [40]. Inadequate glucose causes nausea, vomiting, cognitive impairment, and emotional lability. Left untreated, hypoglycemic patients will progress into unconsciousness, coma, and eventually death.

Hyperinsulinemic hypoglycemia.

Excess insulin has an obvious effect of lowering circulating glucose levels to a hypoglycemic state. Upon presentation of hypoglycemia and hyperinsulinemia, the etiology of the excess insulin must be determined. In the absence of a chronic disease, the sudden occurrence of hypoglycemia in an adult is most commonly due to an insulin secreting tumor of the pancreas [12]. If exogenous causes of hyperinsulinemia have been ruled out, autoantibodies to insulin should be considered.

Several drugs can induce hypoglycemia, and the sudden onset of hypoglycemia in an otherwise healthy adult is most commonly drug-related [41]. Patients presenting with a seemingly spontaneous hypoglycemic event warrant a complete investigation of prescription and over-the-counter medications. Sulfonylurea drugs are one of the most commonly implicated, and are especially prevalent in patients with renal insufficiency [42].

Non-hyperinsulinemic hypoglycemia.

The cause of hypoglycemia without a corresponding elevation in insulin requires an extensive examination of clinical presentation and laboratory findings, as there are

numerous possible causes. Dietary and pharmaceutical intake, environmental factors, extra-pancreatic endocrine disorders, renal or liver disease, and carbohydrate or fatty acid metabolism disorders can all induce hypoglycemia [43]. Traumatic injury and severe illness, primarily of the liver, kidneys, or pancreas can also cause hypoglycemia. Symptom severity varies relative to glucose levels, but gradual and chronic onset may result in lack of patient awareness of the symptoms [44].

As mentioned earlier, the liver plays a vital role in glucose homeostasis. Understanding this, the dysfunction or inhibition of the liver is the mechanism of hypoglycemia in many etiologies. Ethanol and salicylates are hepatotoxic, resulting in inhibited gluconeogenesis [45]. Diseases of the liver and kidneys also inhibit gluconeogenesis, resulting in lowered circulating glucose. Extra-pancreatic endocrine disorders that induce hypoglycemia are those that result in deficiencies of growth hormone, adrenal insufficiency, hypopituitarism, and thyroid dysfunction. The presence of symptoms that can't be explained by hypoglycemia (such as stunted growth) help identify the appropriate etiology.

Carbohydrate and amino acid metabolism disorders (also called inborn errors of metabolism) are predominantly found in newborns and infants. Glycogen storage disorders, caused by defects or deficiencies in enzymes of the glycogenesis pathway are characterized by suppressed insulin secretion and elevated glucagon levels [40]. Galactosemia and fructose intolerance are caused by enzyme irregularities that inhibit the breakdown of, respectively, galactose and fructose. Glucose synthesis is diminished or absent, and accumulations of galactitol in tissues results in irreversible optic, hepatic, and neurologic damage [46].

Diagnosis of hypoglycemic disorders.

Unlike the hyperglycemic states, the diagnosis of hypoglycemic disorders is not dependent on the presentation of hypoglycemic symptoms. Neonatal screening for inborn errors of metabolism as a result of an increased understanding of their importance has resulted in earlier diagnosis – often before clinical symptoms even appear [47]. The more thorough investigations of neonates with family history of metabolic disease have improved early diagnosis rates [48]. In the absence of a previously identified metabolic disorder, fasting evaluations are performed. Patients are required to fast and serial blood glucose testing is performed at specified intervals. The urine output also is tested for ketones during the fasting period. Upon presentation of either hypoglycemic symptoms or glucose levels below 45 mg/dL (2.5 mmol/L), insulin levels are tested in conjunction with the glucose measurements. Intravenous glucagon is administered at the termination of the fast, and blood is drawn every 10-15 minutes post-administration for glucose testing [40].

Evaluation of the insulin concentration in relation to the glucose levels at the same time serve as the first step in determining etiology of hypoglycemic states [49]. If insulin levels are elevated, C-peptide levels—using samples from the same timeframe—are then used to differentiate between exogenous and endogenous insulin sources [50, 43]. Once this is determined, more specific tests such as insulin autoantibodies, sulfonylurea, β-hydroxybutyrate, and free fatty acids can be utilized to identify the source of disproportionately elevated insulin. When clinical symptoms are consistent with hyperinsulinemic hypoglycemia without an elevated insulin-to-glucose ratio, care should be taken to exclude the possibility of insulin-like substances, especially in the absence of urine ketones [40].

Diagnostic investigations that follow hypoglycemia *without* corresponding hyperinsulinemia are first distinguished by the presence of ketones (or lack thereof) and free fatty acids. If free fatty acids are elevated but ketones remain normal or are suppressed, disorders of fatty acid metabolism are the likely culprit [51]. When ketones are also elevated, endocrinopathies, liver or renal disease, ingested substances, and inborn carbohydrate and amino acid metabolism disorders should be considered. Laboratory evaluations to rule out or confirm suspected causes will vary, as the patient's symptoms lead to the narrowing of possible etiologies.

Other causes, such as substrate inhibition or increased utilization, may also be the origin of the hypoglycemia. Hypoglycemia caused by sepsis is apparent when evaluating blood counts in connection to hypoglycemia, although such observations are viewed as a marker of disease severity [52]. In some of these causes, the clinical assessment can be more definitive than laboratory findings. For example, severe malnutrition or excessive physical exertion is easily discernible to the practitioner, but may result in a variety of laboratory results that fail to point to an obvious cause [53]. Severe dehydration resulting from gastrointestinal illness may also prompt hypoglycemia with an electrolyte imbalance as the only other demonstrated laboratory abnormality [54].

Treatment for hypoglycemia often involves regulation of the timing, type (carbohydrate, lipid, protein) and volume of food intake.

In conclusion, a knowledge of the hormones involved in glucose regulation and access to clinical testing for these hormones is essential for the correct diagnosis of hyper and hypoglycemic disorders. Additionally, genetic mapping and genetic engineering can lead to early and more successful therapeutic interventions.

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