IMPACT OF INTENSIVE INSULIN THERAPY ON CRITICALLY ILL HYPERGLYCEMIC PATIENTS

Essay

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INTRODUCTION

Among a variety of physiologic targets in the modern management of critically ill patients, blood glucose control has become an important goal. Until recently, glycemic control in hospitalized patients has not been a major therapeutic focus, partly because of a lack of published targets and guidelines for their care and partly because evidence demonstrating improved outcomes as the result of improved glycemia was only just emerging. Hyperglycaemia is frequently found in critically ill patients even in the absence of diabetes and it is associated with a poor prognosis *(De La Rosa et al., 2008)*.

Critical illness induces counterregulatory hormones (glucagon, growth hormone, catecho-lamines, and glucocorticoids). In addition, several clinical interventions, such as corticosteroids, vasopressors, dextrose solutions, enteral or parenteral nutrition, and dialysis, further promote hyperglycemia. Moreover, changes in carbohydrate metabolism occur in critical illness, including increased peripheral glucose needs, enhanced hepatic

glucose production, insulin resistance, and relative insulin deficiency *(De Block et al., 2006)*.

Over the short term, hyperglycemia can adversely affect fluid balance and immune function, and it can promote inflammation. Hyperglycemia negatively affects many body systems, including the cardiovascular (acute myocardial ischemia, cardiogenic shock, arrhythmias), neuromuscular (polyneuropathy), immunologic (immunosuppression, nosocomial infections) and cerebral (ischemic stroke), and also impairs wound healing. In critically ill patients, besides maintaining euglycemia, insulin has beneficial multi-factorial actions in each of these body systems, as well as in wound healing *(Khoury et al., 2004)*.

Meanwhile, scientific experiments have clearly shown that strict blood sugar control in the range of 80-110 mg/dl significantly improves morbidity and mortality among critically ill patients *(Van Den Berghe et al., 2006)*.

Other recent don't and instead show increase hazards of hypoglycemia and no benefit over traditional glucose control *(Finfer et al., 2009)*.

AIM OF THE WORK

To discuss the problem of hyperglycemia in critically ill patients and role of intensive insulin therapy in its management.

Chapter 1

PHYSIOLOGY OF CARBOHYDRATE METABOLISM

Metabolism is the set of chemical reactions that happen in living organisms to maintain life. It is usually divided into two categories. Catabolism breaks down organic matter, for example to harvest energy in cellular respiration. Anabolism uses energy to construct components of cells such as proteins and nucleic acids *(Pace, 2001)*.

The chemical reactions of metabolism are organized into metabolic pathways, in which one chemical is transformed through a series of steps into another chemical, by a sequence of enzymes. Enzymes are crucial to metabolism because they allow organisms to drive desirable reactions that require energy and will not occur by themselves, by coupling them to spontaneous reactions that release energy. As enzymes act as catalysts they allow these reactions to proceed quickly and efficiently. Enzymes also allow the regulation of metabolic pathways in response to changes in the cell's environment or signals from other cells *(Smith and Morowitz, 2004)*.

Glucose molecule:

Carbohydrates are polyhydroxy aldehydes or ketones. Formulas representing dextro-glucose (D-glucose), the most common sugar in nature, are shown in Figure1.The middle figure is the open-chain form, and it shows the positions of the hydroxyl group on each of the asymmetric carbon atoms in the Fischer projection formula. The asymmetric hydroxyl group on carbon-5 (C5) forms a hemiacetal adduct with the carbonyl group on Cl, and a stable six-membered ring results. This generates another asymmetric carbon atom at position one. The hydroxyl group on Cl occurs with the alpha or beta configuration as shown. It is noteworthy that glucose with the beta configuration is one of the most stable sugar structures in nature. The six-membered ring is itself stable. The hydroxyl groups occupy equatorial positions and are as far apart from one another as possible *(Roskoski, 1993)*.

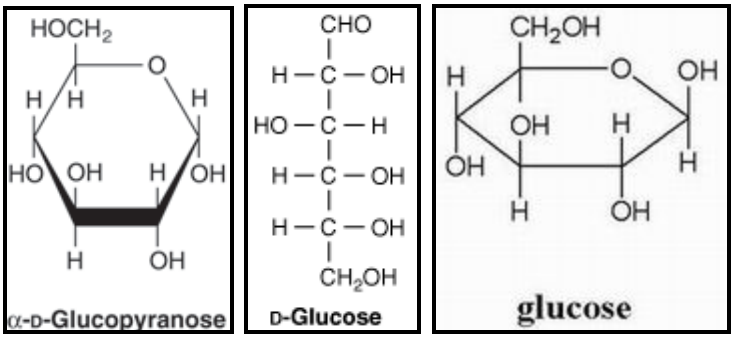

Fig. (1): Forms of glucose in aqueous solution *(Mayes and Bender, 2003)*.

Digestion of Dietary Carbohydrates

In the mouth:

Dietary carbohydrate enter the body in complex forms, such as disaccharides and the polymers **starch** and **glycogen**. The breakdown of polymeric sugars begins in the mouth. Saliva has a slightly acidic pH of 6.8 and contains lingual amylase that begins the digestion of carbohydrates *(Berg et al., 2007)*.

In the stomach

Once the food has arrived in the stomach, acid hydrolysis contributes to its degradation; specific gastric proteases and lipases aid this process for proteins and fats, respectively. The mixture of gastric secretions, saliva, and food, known collectively as **chyme**, moves to the small intestine *(Berg et al., 2007)*.

In the intestine:

The main polymeric-carbohydrate digesting enzyme of the small intestine is α-amylase. This enzyme is secreted by the pancreas and has the same activity as salivary amylase, producing disaccharides and trisaccharides. The latter are converted to monosaccharides by intestinal saccharidases. The resultant glucose and other simple carbohydrates are transported across the intestinal wall to the hepatic

portal vein and then to liver parenchymal cells and other tissues. There they are converted to fatty acids, amino acids, and glycogen, or else oxidized by the various catabolic pathways of cells *(Berg et al, 2007)*.

Glucose metabolic pathways (Embeden-Mayerhof glycolysis)

Glucose is oxidized to either lactate or pyruvate. Under aerobic conditions, the dominant product in most tissues is **pyruvate** and the pathway is known as **aerobic glycolysis**. When oxygen is depleted, as for instance during prolonged vigorous exercise, the dominant glycolytic product in many tissues is lactate and the process is known as **anaerobic glycolysis** *(Romano and Conway, 1996)*.

The Energy Derived from Glucose Oxidation

Aerobic glycolysis of glucose to pyruvate, requires two equivalents of adenosine triphosphate (ATP) to activate the process, with the subsequent production of four equivalents of ATP and two equivalents of reduced nicotinamide adenine dinucleotide (NADH). Thus, conversion of one mole of glucose to two moles of pyruvate is accompanied by the net production of two moles each of ATP and NADH *(Garrett and Grisham, 2005)*.

Glucose + 2 ADP + 2 NAD^+ + 2 P_i → 2 Pyruvate + 2 ATP + 2 NADH + 2 H^+

where:

ADP: Adinosine diphosphate

NAD: Nicotinamide adenine dinucleotide

NADH: reduced nicotinamide adenine dinucleotide

Pi: Inorganic phosphate.

H: Hydrogen.

The net yield from the oxidation of 1 mole of glucose is, therefore, either 6 or 8 moles of ATP. Complete oxidation of the 2 moles of pyruvate, through the tricarboxylic acid cycle (TCA) cycle, yields an additional 30 moles of ATP; the total yield, therefore being either 36 or 38 moles of ATP *(Garrett and Grisham, 2005)*.

Anaerobic Glycolysis:

Under anaerobic conditions and in erythrocytes under aerobic conditions, pyruvate is converted to lactate by the enzyme lactate dehydrogenase (LDH), and the lactate is transported out of the cell into the circulation *(Garrett and Grisham, 2005)*.

Regulation of Glycolysis

The reactions catalyzed by the enzymes; hexokinase, Phosphofructokinase-1 (PFK-1) and

Pyruvate kinase (PK) all are responsible for regulation of glycolysis. Pyruvate kinase (PK) is important for reversing glycolysis when ATP is high and activate gluconeogenesis. Phosphofructokinase-1 (PFK-1) is the rate limiting enzyme of glycolysis. PFK-1 is activated by adenosine monophosphate (AMP) and fructose 2,6-bisphosphate, (F2,6BP) and is inhibited by ATP and citrate . At high concentrations of ATP, PFK-1 is inhibited. The inhibition of PFK-1 by ATP is overcome by AMP. The most important allosteric regulator of both glycolysis and gluconeogenesis is fructose 2,6-bisphosphate, F2,6BP *(Berg et al., 2007)*.

When blood glucose levels drop, pancreatic insulin production falls, glucagon secretion is stimulated, and circulating glucagon is highly increased. Hormones such as glucagon bind to plasma membrane receptors on liver cells, activating membrane-localized adenylate cyclase leading to an increase in the conversion of ATP to cyclic adenosine monophosphate (cAMP). cAMP binds to the regulatory subunits of cAMP dependent protein kinase (PKA), leading to release and activation of the catalytic subunits. Under these conditions the liver stops consuming glucose and becomes metabolically gluconeogenic, producing glucose to reestablish normoglycemia *(Berg et al., 2007)*.

Regulation of glycolysis also occurs at the step catalyzed by pyruvate kinase, (PK). This enzyme is inhibited by ATP and acetyl-CoA and is activated by fructose 1,6-bisphosphate (F1,6BP). The liver enzyme is also controlled at the level of synthesis. Increased carbohydrate ingestion induces the synthesis of PK resulting in elevated cellular levels of the enzyme *(Berg et al., 2007)*.

A number of PK isozymes have been described. The liver isozyme (L-type), characteristic of a gluconeogenic tissue, is regulated via phosphorylation by PKA, whereas the M-type isozyme found in brain, muscle, and other glucose requiring tissue is unaffected by PKA. As a consequence of these differences, blood glucose levels and associated hormones can regulate the balance of liver gluconeogenesis and glycolysis while muscle metabolism remains unaffected *(Berg et al., 2007)*.

The Krebs Citric Acid Cycle

The bulk of ATP used by many cells to maintain homeostasis is produced by the oxidation of pyruvate in the TCA cycle. During this oxidation process, reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide ($FADH_2$) are

generated. The NADH and $FADH_2$ are principally used to drive the processes of oxidative phosphorylation, which are responsible for converting the reducing potential of NADH and $FADH_2$ to the high energy phosphate in ATP *(Koivunen et al, 2007)*.

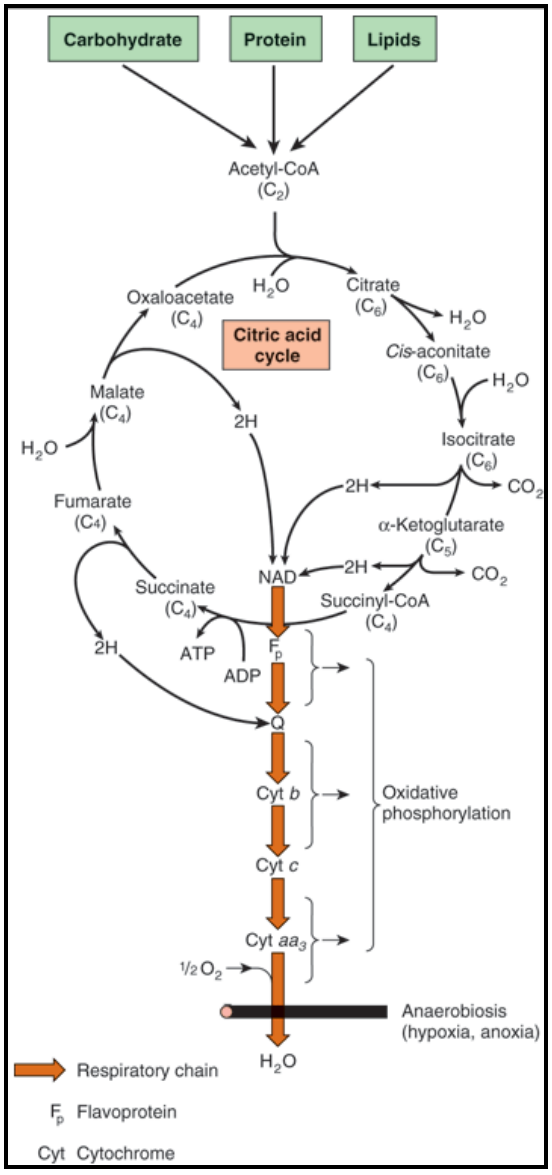

Fig. (2): Overview of the Krebs citric acid cycle *(Mayes and Bender, 2003)*.

The fate of pyruvate depends on the cell energy charge. In cells or tissues with a high energy charge pyruvate is directed toward gluconeogenesis, but when the energy charge is low pyruvate is preferentially oxidized to carbon dioxide (CO_2) and water (H_2O) in the TCA cycle, with generation of 15 equivalents of ATP per pyruvate. The enzymatic activities of the TCA cycle (and of oxidative phosphorylation) are located in the mitochondrion. When transported into the mitochondrion, pyruvate encounters two principal metabolizing enzymes: pyruvate carboxylase (a gluconeogenic enzyme) and pyruvate dehydrogenase (PDH), the first enzyme of the PDH complex. With a high cell-energy charge coenzyme A (CoA) is highly acylated, principally as acetyl-CoA, and able allosterically to activate pyruvate carboxylase, directing pyruvate toward gluconeogenesis. When the energy charge is low CoA is not acylated, pyruvate carboxylase is inactive, and pyruvate is preferentially metabolized via the PDH complex and the enzymes of the TCA cycle to CO_2 and H_2O. Reduced NADH and $FADH_2$ generated during the oxidative reactions can then be used to drive ATP synthesis via oxidative phosphorylation ***(Rich, 2003)***.

The first enzyme of the complex is PDH itself which oxidatively decarboxylates pyruvate. During the course of the reaction the acetyl group derived from decarboxylation of pyruvate is bound to thiamine pyrophosphate (TPP). The next reaction of the complex is the transfer of the two carbon acetyl group from acetyl-TPP to lipoic acid, the covalently bound coenzyme of lipoyl transacetylase. The transfer of the acetyl group from acyl-lipoamide to CoA results in the formation of 2 sulfhydryl (SH) groups in lipoate requiring reoxidation to the disulfide (S-S) form to regenerate lipoate as a competent acyl acceptor. The enzyme dihydrolipoyl dehydrogenase, with flavin adenine dinucleotide (FAD^+) as a cofactor, catalyzes that oxidation reaction. The final activity of the PDH complex is the transfer of reducing equivalents from the $FADH_2$ of dihydrolipoyl dehydrogenase to NAD^+. The fate of the NADH is oxidation via mitochondrial electron transport, to produce 3 equivalents of ATP:

The net result of the reactions of the PDH complex are:

$$\text{Pyruvate} + \text{CoA} + NAD^+ \rightarrow CO_2 + \text{acetyl-CoA} + \text{NADH} + H^+$$

The reactions of the PDH complex serves to interconnect the metabolic pathways of glycolysis, gluconeogenesis and fatty acid synthesis to the

ticarboxylic acid cycle (TCA) cycle. As a consequence, the activity of the PDH complex is highly regulated by a variety of allosteric effectors and by covalent modification. The importance of the PDH complex to the maintenance of homeostasis is evident from the fact that although diseases associated with deficiencies of the PDH complex have been observed, affected individuals often do not survive to maturity. Since the energy metabolism of highly aerobic tissues such as the brain is dependent on normal conversion of pyruvate to acetyl-CoA, aerobic tissues are most sensitive to deficiencies in components of the PDH complex *(Berg et al., 2002)*.

Regulation of the TCA Cycle

Regulation of the TCA cycle occurs at both the level of entry of substrates into the cycle as well as at the key reactions of the cycle. Fuel enters the TCA cycle primarily as acetyl-CoA. The generation of acetyl-CoA from carbohydrates is, therefore, a major control point of the cycle. This is the reaction catalyzed by the PDH complex.

The PDH complex is inhibited by acetyl-CoA and NADH and activated by non-acetylated CoA (CoASH) and NAD^+. The pyruvate dehydrogenase activities of