INTRODUCTION

The human body is programmed to maintain constant homeostasis of all body system through a complex neuro-endocrine and autonomic network. Critical illness alters this homeostasis through various exaggerated autonomic and cytokine responses ***(Van den Berghe et al., 2001)***.

The hyper metabolic stress response that usually follows any type of major trauma or acute illness is associated with hyperglycemia and insulin resistance, often referred to as stress diabetes or diabetes of injury. In critically ill patients, even in those who were not previously diagnosed with diabetes, glucose uptake is reduced in peripheral insulin sensitive tissues, where as endogenous glucose production is increased ***(Thorell et al., 1999; McCowen et al., 2001)***.

Although intensive insulin therapy reduces incidence of hyperglycemia, mortality and morbidity in certain patients, little is known regarding the pathophysiology of acute insulin resistance following injury and infection. Studies suggest that acute insulin resistance is complex and might differ in a tissue specific manner, involving multiple causative factors and intracellular signaling pathway.Therefore, the advantages of insulin therapy might not be uniform to all injuries or critical illness. The controversy over how to treat these patients in ICU and the varying mechanisms by which insulin resistance develops in different tissues is still attracting the interest of researchers **(*Simkova et al., 2007)***.

AIM OF THE WORK

To shed light on the pathogenesis of glucose metabolism disorder and insulin resistance in critically ill patients in ICU.

GLUCOREGULATION IN THE HUMAN BODY

Carbohydrate Metabolism

Carbohydrates present in diet are in the form of monosaccharides (glucose, galactose and fructose), disaccharides (maltose, lactose and sucrose) or polysaccharides (starch and cellulose) ***(Karam, 1997)***.

Glucose oxidation is a major source of energy for many cells of the body. Since cell membranes are impermeable to hydrophilic molecules such as glucose, all cells require carrier proteins to transport glucose across the lipid bilayers into the cytosol. While the intestine and kidney have an energy dependant Na-glucose co-transporter, all other cells have non energy dependant transporters that facilitate diffusion of glucose from a higher concentration to a lower concentration across cell membranes ***(Karam, 1997)***.

Glucose is the required metabolic fuel for the brain under physiologic conditions. Other organs, however, can use both glucose and fatty acids to generate energy. The process of glucose homeostasis maintains plasma glucose level within a narrow range, usually between 60 and 150 mg/dl (3.3 and 8.3 mmol/L) ***(Guyton and Hall, 2004)***.

Carbohydrates are polyhydroxy aldehydes or ketones. Formulas representing D-glucose, the most common sugar in nature, are shown in Figure-1 ***(Mayes and Bender, 2003)***.

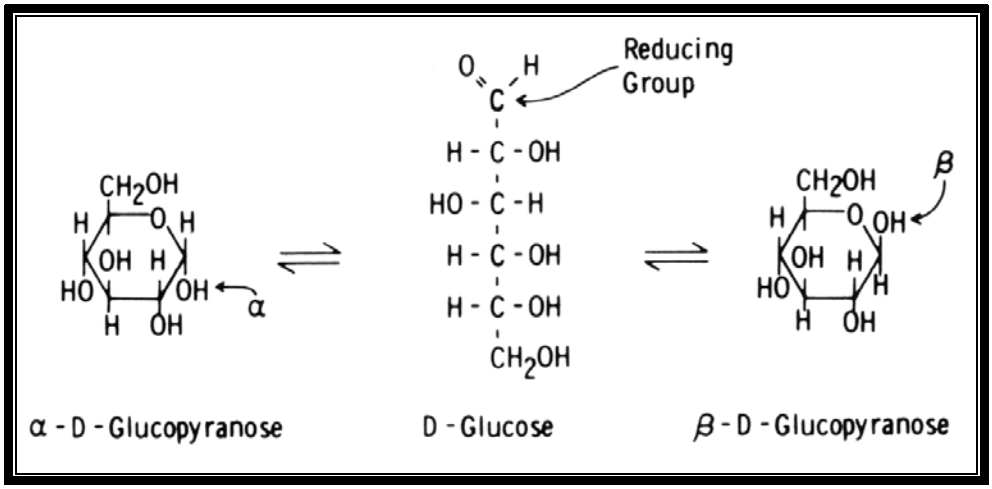

Fig. (1): Forms of glucose in aqueous solution ***(Mayes and Bender, 2003)***.

Metabolism of glucose is the main mechanism to produce energy for energy-requiring reactions in cells. When blood glucose increases in blood stream, glucose is rapidly metabolized to produce ATP, a high energy end product. Because of the high demand for ATP, glucose is oxidized through a large series of reactions that extract the greatest amount of energy possible from it. The first phase in the series of reactions is known as glycolysis in the cytoplasm of the cell. The next phase of glucose metabolism is the Citric Acid Cycle (TCA or Krebs cycle). The citric acid cycle occurs in mitochondria and is also the site of oxidative phosphorylation.

Glucose is then stored as glycogen in the liver through Glycogenesis ***(Nelson and Cox, 2004)***.

When blood glucose decreases, free glucose formed is released to the blood, as the main function of liver glycogen is to maintain blood glucose level especially during fasting or carbohydrate deficiency. This is done through Gluconeogenesis and Glycogenolysis ***(Smith and Campbell, 1994)***.

I. Oxidation of glucose:

The major pathways of glucose oxidation which are mainly for energy production are:

A. Glycolysis.

B. Citric acid cycle (Kreb's cycle).

A. Embden-Meyerhof Glycolysis:

Glycolysis is a series of biochemical reactions by which glucose is converted to pyruvate in aerobic condition or converted to lactate in anaerobic condition ***(Guyton and Hall, 2004)***.

Under aerobic conditions one molecule of glucose gives 8 adenosine tri-phosphate (ATP) molecules +2 pyruvate molecules which enter citric acid cycle. Under anaerobic condition one molecule of glucose gives 2 ATP molecules + 2 lactate molecules. Also amino acids are produced from

intermediates of glycolysis, so glycolysis has great importance ***(Srere, 1988)***.

Pyruvate Fructo-Kinase (PFK) is the rate limiting enzyme of the pathway and also the main regulatory enzyme. PFK is activated by adenosine monophosphate (AMP) and fructose-2, 6-biphosphate and inhibited by ATP and citrate. One function of glycolysis is to generate chemical energy as ATP. When cellular concentrations of ATP are high, glycolysis is inhibited. When ATP levels fall, ADP and AMP are formed and AMP activates phospho-fructokinase. During conditions where fatty acids are used as source of energy, citrate levels increase and glycolysis decreases ***(Srere, 1988)***.

Glycolysis occurs by 10 successive chemical reactions. Each step is catalyzed by at least one specific protein enzyme (fig.2).

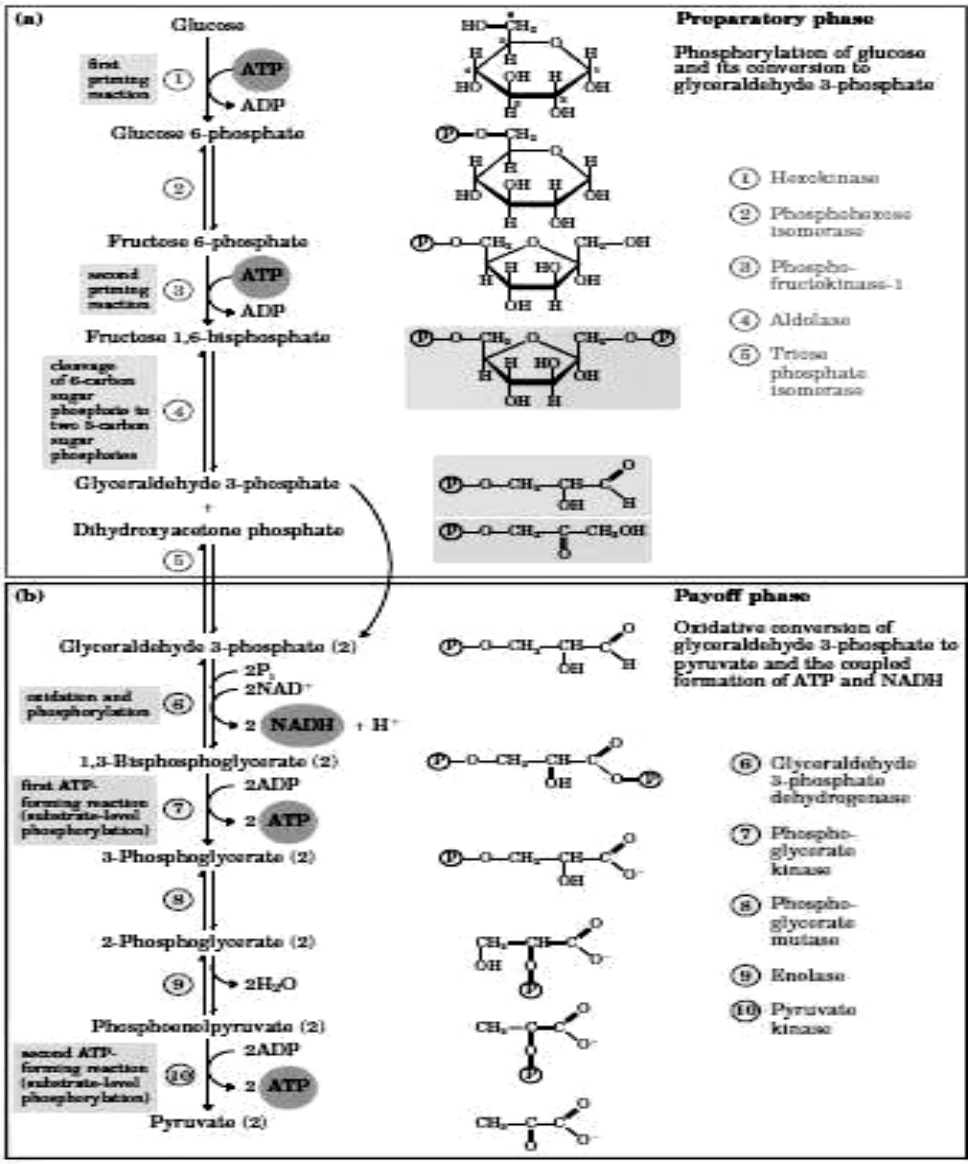

Fig. (2): Embden Meyerhof pathway of glycolysis
(Nelson and Cox, 2004).

B. The Krebs Citric Acid Cycle:

The Krebs citric acid or tri-carboxylic acid cycle is often called the final common pathway of metabolism. The

catabolism of glucose and fatty acids yields acetyl-CoA. The citric acid cycle provides a pathway for the oxidation of acetyl-CoA (fig.3). The reactions occur in the mitochondria of eukaryocytes. The pathway includes eight discrete steps. Seven of the enzyme activities are found in the mitochondrial matrix; the eighth is associated with the electron transport chain within the inner mitochondrial membrane ***(Mayes and Bender, 2003).***

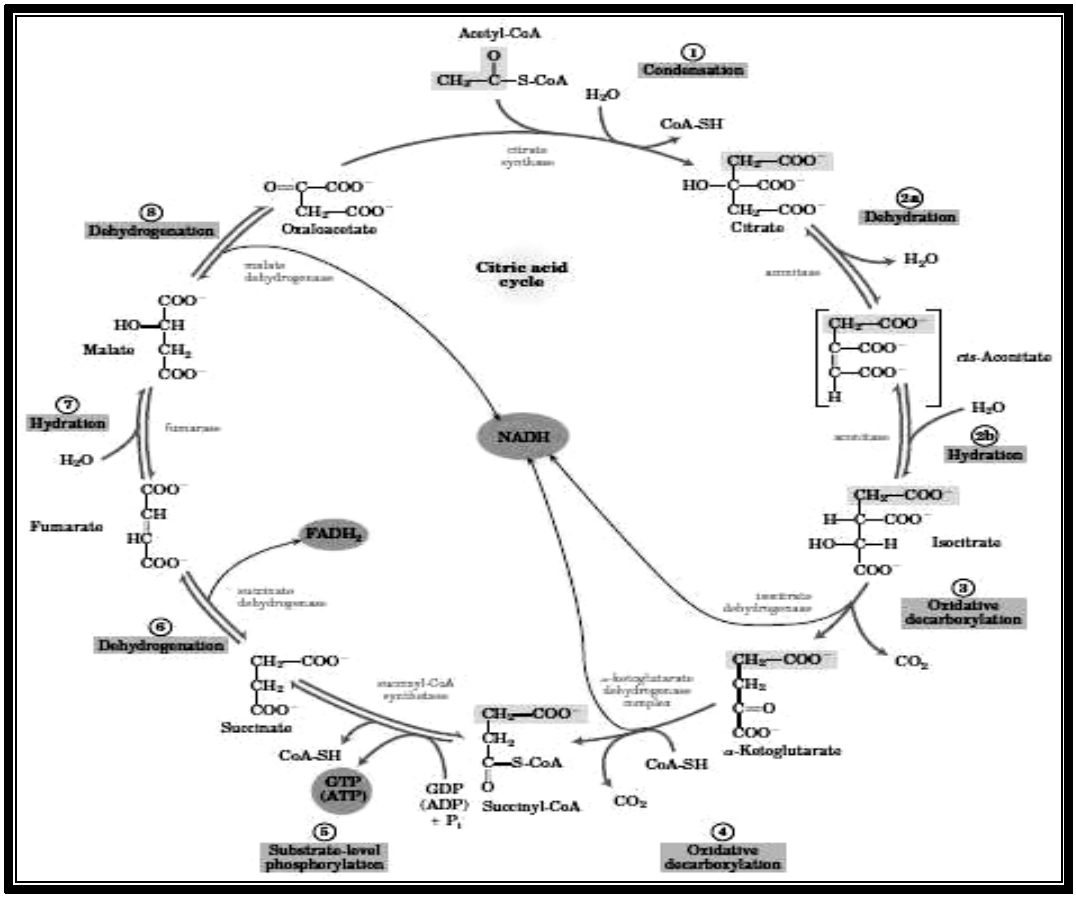

Fig. (3): Overview of the Krebs citric acid cycle ***(Nelson and Cox, 2004)***.

The net reaction catalyzed during each revolution of the tri-carboxylic acid cycle can be depicted as follows:

Acetyl - COA + $2H_2O$ + 3 NAD+ + FAD + GDP + Pi $\rightarrow$ COA + $2CO_2$ + 3 NADH+ + 3 H + $FADH_2$ + GTP

The CO_2 is an end product of metabolism. Coenzyme A can be reutilized for a variety of reactions. Guanosine triphosphate (GTP) is formed by substrate-level phosphorylation and is bioenergetically equivalent to ATP and serves a variety of functions. The production of 11ATP equivalents by oxidative phosphorylation and 1GTP by substrate level phosphorylation is noted ***(Mayes and Bender, 2003)***.

II. Glycogenesis:

Glycogenesis is the synthesis of glycogen from glucose. It occurs mainly in the cytosol of liver cells and muscles by glycogen synthetase which is the key enzyme of glycogenesis. It is present in two forms "a" and "b":

1) The "a" form is active and de-phosphorylated. It is allosterically inhibited by accumulated glycogen.
2) The "b" form is inactive and phosphorylated. It becomes active on the presence of high concentration of Glucose-6-phosphate (Allosteric activator).

Conversion of "a" form to "b" form is catalyzed by the enzyme Protein Kinase A, which is activated by cAMP. The conversion of "b" form to "a" form is catalyzed by Protein Phosphatase 1 ***(Cryer, 1999)***.

Insulin causes activation of phosphodiesterase, which decreases cAMP and causes inactivation of protein kinase A. At the same time, insulin activates the protein phosphatase 1. These effects lead to the conversion of "b" form to "a" form of glycogen synthetase and activation of glycogenesis in both liver and muscles.

Glucagon (in liver) and epinephrine (in liver and muscles) produce activation of adenyl cyclase through activation of G protein which increase cAMP level. This produces activation of cAMP dependent protein kinase A, which converts the glycogen synthetase "a" to "b" form. Accordingly glucagon and epinephrine decrease the rate of glycogenesis.

Growth hormone and glucocorticoids may stimulate Glycogenesis by allosteric activation of glycogen synthetase b by elevated levels of glucose-6-phosphate. The latter is produced by stimulation of Gluconeogenesis ***(Cryer, 1999)***.

III. Glycogenolysis:

It is the breakdown of glycogen to form glucose-1-phosphate. Glycogenolysis involves four enzymes:

1- Glycogen Phosphorylase. 2- Debranching enzymes.

3- Phosphoglucomutase. 4- Glucose -6-phosphatase.

In muscle; glucose-6-phosphate is oxidized by glycolysis to provide energy. In liver; due to presence of the enzyme glucose-6-phosphatase and glucose-6-phosphate, glycogen is mainly converted to glucose. Free glucose formed is released to the blood, as the main function of liver glycogen is to maintain blood glucose level especially during fasting or carbohydrate deficiency ***(Smith and Campbell, 1994)***.

Glycogen phosphorylase is the key enzyme for Glycogenolysis. It is present in two forms. The active form "a" is phosphorylated, while the inactive form "b" is dephosphorylated. Conversion of the "b" to "a" form is catalyzed by the active phosphorylase kinase. The conversion of "a" to "b" form is catalyzed by the protein phosphatase-1. Phosphorylase kinase is also present in two forms. The active form "a" is phosphorylated and the inactive form "b" is de-phosphorylated. Conversion of the inactive "b" to active "a" form is catalyzed by cAMP dependent protein kinase A, this reaction is reversed by the protein phosphatase -1 ***(Smith and Campbell, 1994)***.

IV. Gluconeogenesis:

Gluconeogenesis is the process responsible for converting lactate (produced by red blood cells, muscle, and other tissues), glycerol (produced from lipolysis or triglyceride catabolism), pyruvate, and intermediates of the tricarboxylic acid cycle (derived from amino acid catabolism) into glucose ***(Guyton and Hall, 2004)***.

Approximately 25 per cent of the liver's glucose production during fasting is from Gluconeogenesis, helping to provide a steady supply of glucose to the brain. During prolonged fasting, the kidneys also synthesize considerable amounts of glucose from amino acids and other precursors and phosphogluconate reactions, thus allowing free sugar to the brain ***(Guyton and Hall, 2004)***.

The main importance of gluconeogenesis is the maintenance of blood glucose especially in fasting, starvation, stress, prolonged exercise and dietary carbohydrate deficiency. Glycolysis and gluconeogenesis are reciprocally controlled ***(Guyton and Hall, 2004)***.

Regulation of Glucose Metabolism

The concentration of glucose in the blood is normally tightly regulated despite a significant fluctuation in supply and demand, this occurs via alterations in the removal of glucose from and addition of glucose to the circulation ***(Baron et al.,***

2001). The control of blood glucose concentration occurs via an interaction:

- Hormonal.
- Neural.
- Hepatic autoregulatory mechanisms.

I. Hormonal regulation:

A. Insulin Hormone:

Insulin is secreted by the B-cells of pancreatic islets in response to elevation in blood glucose levels. It is a protein consisting of 51 amino acids contained within two peptide chains; α chain and β chain. The chains are connected by two disulphide bridges (figure 4). In addition, there is an intra-chain disulphide bridge that links positions 6 and 11 in the (α) chain. The molecular weight of human insulin is 5808 ***(Eckel et al., 2005)***.

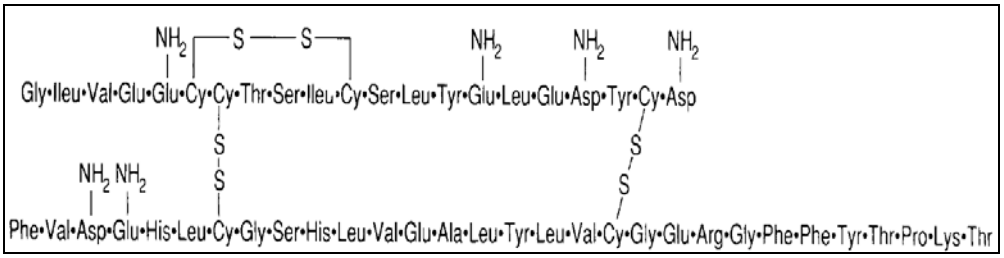

Fig. (4): Human insulin molecule ***(Guyton and Hall, 2006)***.

Insulin Secretion:

When insulin is secreted into the blood, it circulates almost entirely in an unbound form; it has a plasma half-life that averages only about 6 minutes, so that it is mainly cleared from the circulation within 10 to 15 minutes. Except for that portion of the insulin that combines with receptors in the target cells, the remainder is degraded by the enzyme insulinase mainly in the liver, to a lesser extent in the kidneys and muscles, and slightly in most other tissues ***(Guyton and Hall, 2006)***.

The human pancreas secretes 40-50 units of insulin per day in normal adults. The basal concentration of insulin in the blood of fasting human averages 10 Mu/ml (0.4ng/ml). In normal subjects, insulin seldom rises above 100Mu/ml after standard meals. The increase in peripheral insulin concentration begins 8-10 minutes after ingestion of food and reaches peak concentration in peripheral blood by 30-45 minutes (figure 5). This is followed by a rapid decline in postprandial blood glucose level, which returns to baseline values by 90-120 minutes ***(Karam, 1997)***.

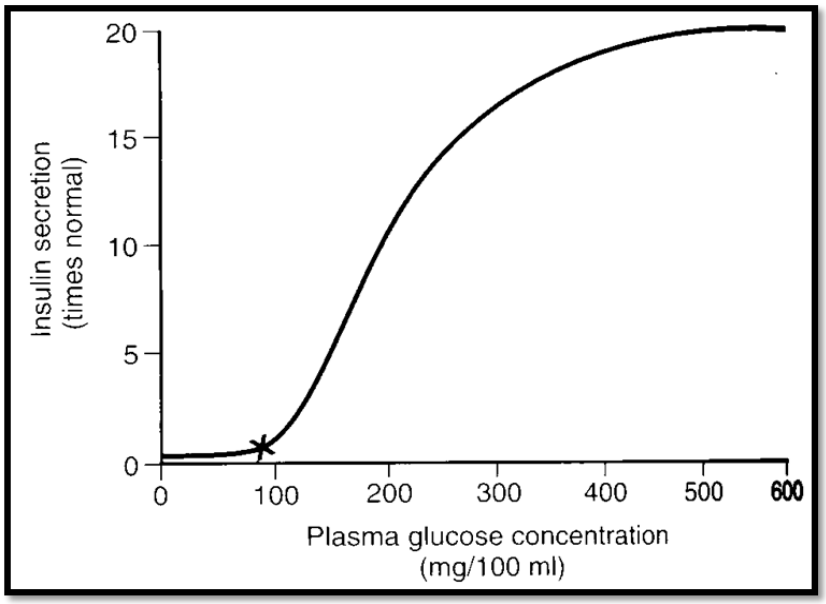

Fig. (5): Approximate insulin secretion at different glucose levels ***(Guyton and Hall, 2006)***.

Glucose is known to enter β-pancreatic cells by diffusion, which is facilitated by a specific membrane protein termed glucose transporter-2. By virtue of its relatively low affinity for glucose, this protein more effectively facilitates transport of glucose during hyperglycemia than at the lower levels of blood glucose as during fasting state ***(Goldfine and Pilch, 1992)***.

Factors involved in regulation of insulin secretion, can be divided into three categories (table 1): Direct stimulants, which are known to stimulate insulin release directly. Amplifiers, which appear to potentiate the response of the β-cell to glucose and inhibitors of insulin release. The action of the amplifier substances, many of which are gastrointestinal hormones stimulated by ingestion of meals, explains the observation that