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Alcoholism and Its Relation to Hypoglycemia – An Overview

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Abstract Alcohol (ethanol) is metabolized in the liver by enzymes alcohol dehydrogenase and aldehyde dehydrogenase to acetate, which is spontaneously broken down to CO_2 and H_2O utilizing NAD^+ and Cytochrome P_{450} E_1 (CYPE1). Thus alcohol metabolism decreases NAD^+ / NADH ratio(redox state). Gluconeogenesis, the synthetic pathway of glucose from non-carbohydrate sources(propionate, lactate, aminoacids, glycerol, alanine) predominantly takes place in liver. The significance of gluconeogenic pathway is that it helps in maintaining blood glucose levels in fasting or starvation conditions. Alcoholism (>120ml /day) leads to an increase in the ratio of NAD^+ / NADH, and since the gluconeogenic pathway is dependent on the NAD^+ / NADH ratio, increased ratio slows down the pathway leading to hypoglycemia. There is enhanced ketone body metabolism due to hypoglycemia, leading to the accumulation of beta hydroxy butyrate resulting in alcoholic ketosis. Thus alcoholic hypoglycemia and alcoholic ketosis are associated with each other and gross change in liver can be seen after chronic alcoholism with malnutrition. Further studies are required to better understand how liver is able to maintain the redox states longer even during alcoholism.

Keywords: *alcoholism, alcoholic hypoglycemia, alcoholic ketosis, redox state*

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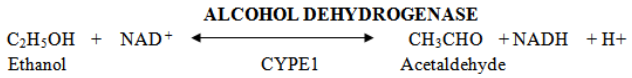
1. Introduction

1.1. Alcohol Metabolism

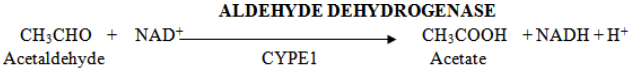
Alcohol i.e., ethanol is metabolized in the liver by alcohol dehyrogenase to acetaldehyde, it reduces nicotinamide adenine dinucleotide (NAD^+) to NADH facilitated by cytochrome P450 E1(CYPE1).

First step:



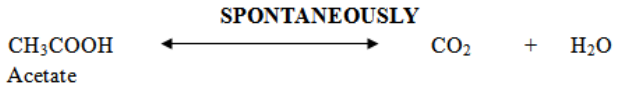
The acetaldehyde is metabolized by aldehyde dehyrogenase to produce acetic acid, here also NAD^+ gets reduced to NADH + H^+ (second step). This step also takes place in liver and is facilitated by CYPE1.

Second step:



The acetate produced from breakdown of ethanol leaves the liver for its metabolism in extra hepatic tissues such as skeletal muscle. The acetate is spontaneously broken down to CO_2 and H_2O.

Third step:



Thus, alcohol metabolism significantly decreases the hepatic NAD^+/NADH ratio [1].

1.2. Gluconeogenesis

The pathway of glucose synthesis from non-carbohydrate sources (propionate, lactate, aminoacids, glycerol, alanine) is called gluconeogenesis. This pathway predominantly takes place in liver and the significance of this pathway is that it maintains blood glucose levels during fasting or starvation conditions (Figure 1). The gluconeogenic pathway is reversible pathway of glycolysis, and the irreversible steps are catalysed by the enzymes as shown in Figure 1. The glycolysis (glucose breakdown) and gluconeogenic pathways (glucose synthesis) are reciprocally regulated i.e,. when one pathway is active other pathway gets inactivated [2]. This requires a specific NAD^+/NADH ratio for the reductive synthesis of glucose [3].

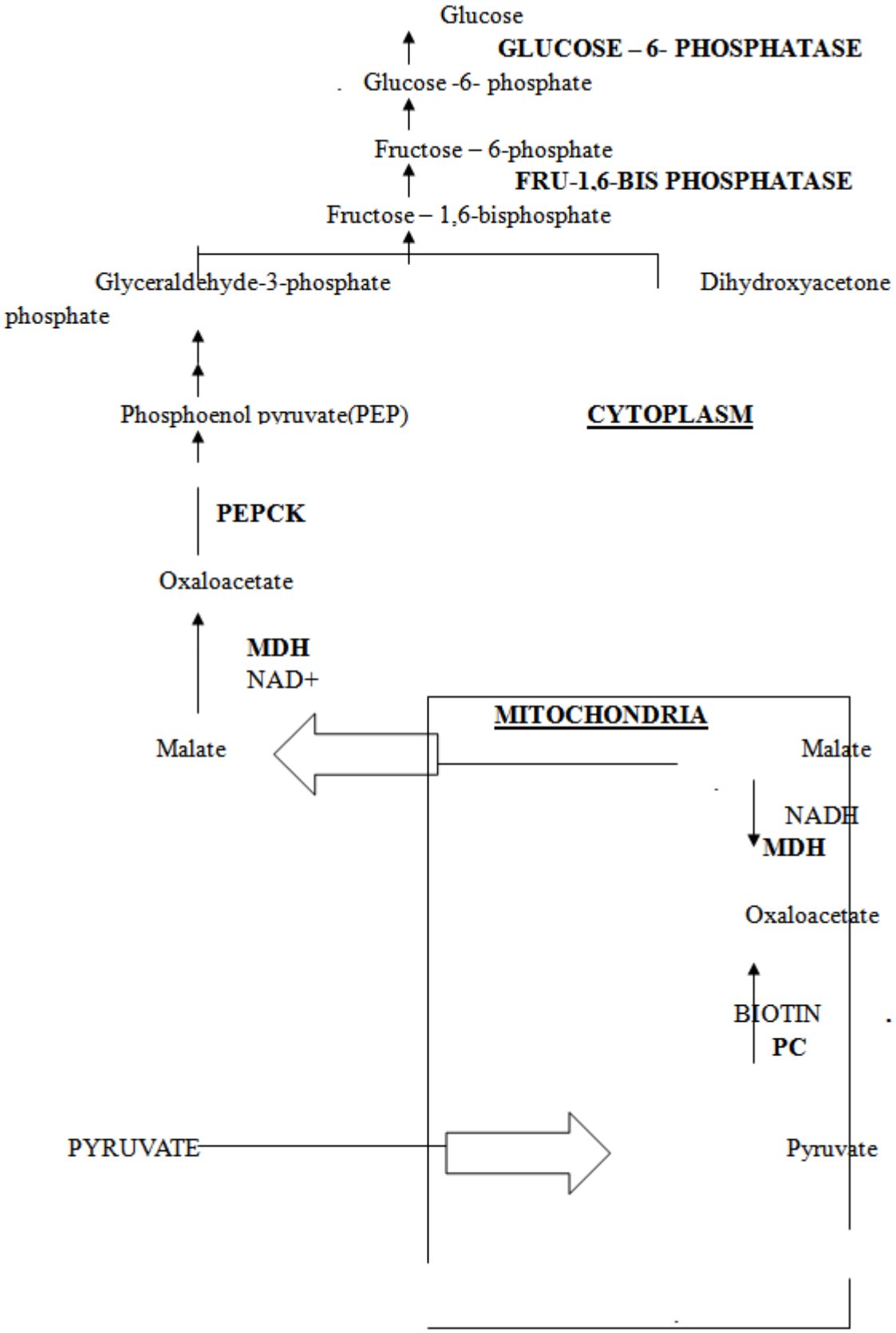


Figure 1. Flow chart of gluconeogenesis

PEPCK- Phosphoenolpyruvate carboxy kinase
MDH – Malate dehydrogenase
PC - Pyruvate carboxylase

2. Alcohol Metabolism, Gluconeogenesis & NAD^+/NADH Ratio

During the metabolism of ethanol there is elevated levels of NADH, which affect a number of critical dehydrogenases in the liver required for gluconeogenesis [4]. The high NADH inhibits conversion of lactate to

pyruvate by Lactate dehydrogenase, malate to oxaloacetate by Malate dehydrogenase, which decreases the availability of pyruvate and oxaloacetate for gluconeogenesis. Alanine produced in muscle via cori cycle (Figure 2) produces glucose but increased NADH by ethanol oxidation causes conversion of pyruvate to lactate. Thus, ethanol consumption increases blood lactate concentration, while decreasing the level of glucose. In experimental studies conducted on rats to know the effect of ethanol on the hepatic redox state (NAD^+/NADH), freeze – clamping of liver is done and then change in redox state is observed. There is a change in redox state from 700/1 to 200/1 [5]. This change in redox state has profound effect on metabolic processes in the liver, since both alcohol metabolism and gluconeogenesis occur in this tissue, and both metabolic processes alter NAD^+/NADH ratio [6].

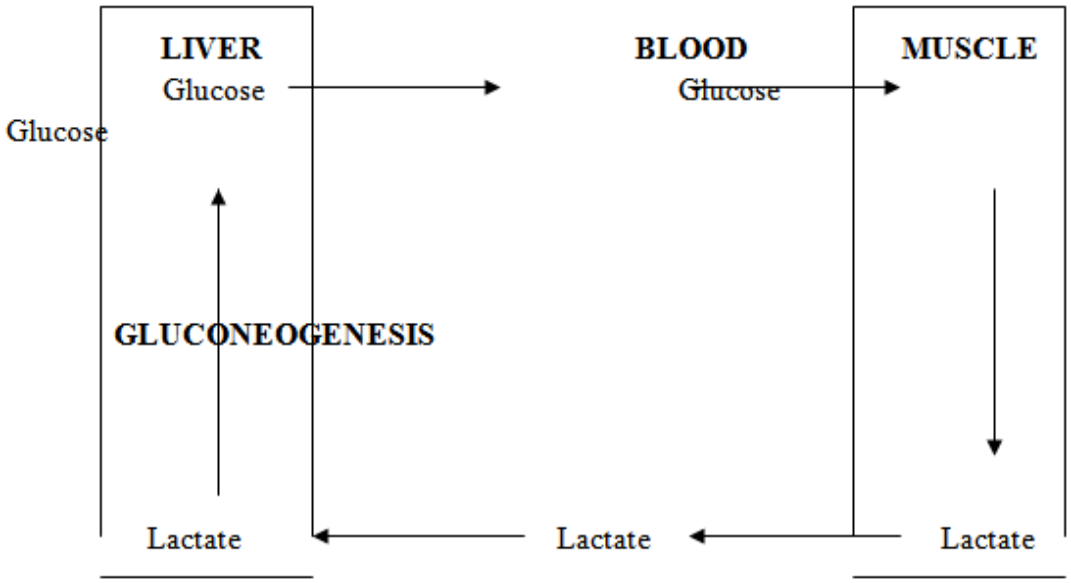


Figure 2. THE CORI - CYCLE

3. Alcoholism & Hypoglycemia

Alcoholism is the enhanced consumption of ethanol (> 120ml/day) and hypoglycemia is a condition where there is decreased blood glucose levels (<50mg/dl or 2.8mmol/L) [7]. Enhanced ethanol oxidation raises NADH levels which inhibit key or regulatory enzymes of gluconeogenesis thus blocks release of glucose from liver leading to hypoglycemia [8]. Alcohol exerts substantial influences on pancreatic microcirculation by evoking a massive redistribution of pancreatic blood flow from exocrine into endocrine(insulin-producing) part via mechanisms mediated by the messenger molecule nitric oxide and the vagus nerve, augmenting late phase insulin secretion leading to hypoglycemia [9]. Both lipolytic and ketogenic pathways are important to prevent hypoglycemia by providing substrates like glycerol, free fatty acids (FFA), ketone bodies for gluconeogenesis which helps in maintaining blood glucose levels. if these substrates or pathways fail to produce glucose during fasting state it aggravates the risk of hypoglycemia. Chronic malnutrition is also noticed in alcoholics that in turn inhibits release of FFA from adipose tissue and decreases the gluconeogenesis [10].

4. Alcoholic Hypoglycemia & Ketosis

Alcoholic hypoglycemia occurs as a result of prolonged fasting and excess alcohol intake, when the hepatic glycogen store becomes depleted and alcohol inhibits gluconeogenesis [11,12]. Ethanol also causes structural abnormalities in the liver mitochondria which leads to ketosis superimposed by starvation, chronic malnutrition [13,14]. When ethanol is infused into starved rats' liver it was observed that the ratio of beta hydroxy butyrate, acetoacetate rises in the effluent [15]. The ethanol content in tissues of alcoholic ketotic patients disappears apparently [16]. Thus, alcoholic hypoglycemia and alcoholic ketoacidosis are associated with excess consumption of alcohol, food deprivation and increased ratio of NAD^+/NADH. The increased NADH levels favours accumulation of hydroxyl butyrate thus leading to ketosis [17].

5. Conclusion

Alcoholic hypoglycemia is due to inhibition of gluconeogenesis by ethanol and alcoholic ketosis is due to accumulation of beta hydroxy butyrate by increased concentrations of NADH. Thus alcoholic hypoglycemia and alcoholic ketosis are the sequential events occurring one after another in alcoholism and liver can replenish its function on supply of glucose and the most salient feature of liver is that changes in liver can be seen only after chronic alcoholism associated which is also with malnutrition. Further research is required to know the mechanism in liver that helps to maintain the reduced hepatic redox state during alcoholism longer than expected.

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