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Gluconeogenesis in patients with impaired liver function

Glukoneogenese bei Patienten mit eingeschränkter Leberfunktion

Summary This presentation gives an overview about the factors involved in the regulation of gluconeogenesis. Then, based on these regulatory principles, the changes seen in impaired liver function are discussed.

Gluconeogenesis from lactate and pyruvate is mediated through pyruvate carboxylase (PC) and phosphoenolpyruvate carboxykinase (PEPCK) activity. The PC mediated pathway depends on substrate supply and on the downregulation of the oxidative pathway for pyruvate. Both enzymes need ATP or GTP and, thus, depend on the cellular energy charge. Tissue anoxia can reduce the energy charge and limit the flow through the PEPCK pathway. Thus, one expects a coupling between reduced splanchnic blood flow, limited oxygen supply to the liver, resulting tissue anoxia, and reduced gluconeogenesis. Conditions are shown, where this coupling exists. Since gluconeogenesis is concentrated in the periportal region of the liver, the local oxygen tension is sufficient under many circumstances to maintain a high glucose production level. Also, the enzyme activity of PEPCK can compensate for long term anoxia. Thus, gluconeogenesis is sufficient in most cases, as seen in critically ill patients. However, this could be associated with a reduction in the perivenous oxygen tension, possibly below critical levels.

Beta-adrenergic stimulation increases gluconeogenesis. Examples are shown where this stimulation can overlay the dependency on the oxygen tension and substrate supply. Catecholamines are generally used to stabilize the hemodynamic system. This treatment could limit splanchnic bloodflow and, as a consequence, the oxygen supply to the liver with a simultaneous stimulation of gluconeogenesis and can cause severe anoxia in the perivenous region. These negative side effects of catecholamine treatment should be avoided and the ideal treatment should aim at improving splanchnic flow without stimulation of gluconeogenesis.

Zusammenfassung Die Präsentation gibt einer Übersicht über Faktoren, die die Glukoneogenese steuern. Es werden, basierend auf den dargestellten regulatorischen Prinzipien, Änderungen diskutiert, die bei eingeschränkter Leberfunktion sichtbar werden.

Die Glukoneogenese aus Laktat und Pyruvat wird über die Enzyme Pyruvat-Carboxylase (PC) und die Phosphoenolpyruvat-Carboxykinase (PEPCK) gesteuert. Der Fluß durch die PC hängt ab vom Substratangebot und von der Hemmung des oxidativen Abbauweges für Pyruvat. Beide Enzyme (PC und PEPCK) benötigen ATP oder GTP und hängen damit vom zellulären Energiestatus ab. Sauerstoffmangel kann den Energiestatus verschlechtern und den Fluß durch PEPCK einschränken. Deswegen könnte man vermuten, daß eine reduzierte Splanchnikus-Perfusion und Sauerstoffversorgung eine hepatische Anoxie induzieren und darüber die Glukoseproduktion hemmen. Die Existenz dieser Kopplung wird experimentell sowohl belegt als auch in Frage gestellt. Da die Glukoneogenese im periportalen Bereich der Leber stattfindet, sollte die Sauerstoffversorgung unter den meisten Umständen für eine hohe Glukoseproduktionsrate ausreichend sein. Darüber hinaus kann die Aktivität der PEPCK langanhaltende Hypoxien kompensieren. Daher sollte

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die Glukoseproduktion auch bei reduziertem Sauerstoffangebot unlimiertiert ablaufen können. Dies kann jedoch mit einer hepatisch perivenösen Hypoxie einhergehen, wie sie z.B. an der extrem niedrigen hepatovenösen O_2-Sättigung bei kritisch Kranken ersichtlich ist. Beta-adrenerge Stimulation steigert die Gluconeogenese. Katecholamine werden aber auch zur Stabilisierung des Hämodynamischen Systems eingesetzt. Damit könnte die Glukoseproduktion stimuliert und darüber eine Hypoxie im perivenösem Bereich induzieren werden. Diese negative Nebenwirkung sollte vermieden werden und ein ideales Behandlungsregime sollte darauf abzielen, den Splanchnikusfluß zu verbessern, ohne daß die Glukoseproduktion gesteigert wird.

Key words Gluconeogenesis – glucose – impaired liver functions – regulation – human

Schlüsselwörter Glukoneogenese – Glukose – Leberfunktionsstörungen – Regulation – Mensch

Introduction

We limit our study to impaired liver function found under critical illness like sepsis or trauma. Under these circumstances the contribution of glycogen breakdown to hepatic glucose production are small compared to gluconeogenesis. This justifies the assumption that the glucose production measured with stable isotopes reflects gluconeogenesis. This presentation gives an overview about the factors involved in the regulation of gluconeogenesis. Then, based on these regulatory principles, the changes seen in impaired liver function are discussed.

General regulatory principles

Gluconeogenesis is mainly regulated at the conversion of pyruvate to oxaloacetate, via the enzyme pyruvate-carboxylase (PC) and the subsequent conversion of oxaloacetate to phosphoenol pyruvate, via phosphoenolpyruvate-carboxykinase (PEPCK). The first step is regulated through supply of precursors like lactate or alanine. Both steps are further regulated through the activity of stress hormones, such as cortisol, glucagon or adrenaline. In addition, ATP or GTP are needed as cofactors for these steps. Tissue anoxia can reduce the energy charge, ATP content, and limit the flow through PEPCK. Thus, one expects a coupling between reduced splanchnic blood flow, limited oxygen supply to the liver, resulting tissue anoxia and reduced gluconeogenesis. In vivo rat experiments indicate that this is possible (1). However, gluconeogenesis is located in the periportal region of the liver; the region that has the best exposure to oxygen. This ensures that the local oxygen tension is sufficient under many circumstances to maintain a high production level. Thus, gluconeogenesis should not be limited by oxygen availability; it is rather one important factor which determines liver oxygen consumption in critically ill patients (2).

A variety of studies such as the one performed by Wilmore et al. (3) show that under sepsis or trauma gluconeogenesis is enhanced. Glucose production increases with the severity of the illness. However, at stages with high mortality such as severe sepsis, complicated with bacterial invasion, glucose production is reduced and is comparable to normal values. These stages are often associated with liver failure, and the question is, whether this fall in glucose production is due to an evolution of liver failure. What are the factors that lead to this biphasic behavior of glucose production? We analyse the following possibilities: a) the capacity for gluconeogenesis is rate limiting, b) insufficient nutrient supply to the liver, c) disintegration of liver cell function.

Capacity for gluconeogenesis

To what extent can the capacity for gluconeogenesis become rate limiting? For this liver cirrhosis is used as a model for a reduced capacity. Schricker et al. (4) showed that patients with advanced liver disease and diminished metabolically active cell mass have glucose production rates comparable to that of healthy subjects. In contrast to healthy subjects their glucose production can not be stimulated through adrenaline, indicating that their production is already at the maximal level. Nevertheless, the normal glucose production rate despite reduced active tissue mass implies that the liver has a substantial reserve for glucose production. The same study also showed that glucose production correlates with the stimulation of beta-adrenergic receptors. This demonstrates that adrenaline alone can stimulate glucose production. Similar results were found in healthy subjects (5).

In vivo dependency on nutrient supply to the liver

Can the oxygenation of the liver become rate limiting? The hepatic oxygen uptake depends on the oxygen supply to the liver, which indicates the oxygen supply is rate limiting (6). However, due to periportal location of glu-

coneogenesis, the oxygen supply for glucose production should be sufficient, and the question arises whether restriction in the flow to the liver could generate a rate limiting supply. Critically ill patients are mechanically ventilated. A generally used mechanical ventilation approach induces a positive pressure on the chest and abdomen. This pressure reduces the flow through the splanchnic bed. Träger et al. (7) describe a study, where the respiratory pressure was increased in septic patients in two steps, which should be associated with a stepwise decrease of the flow through the splanchnic bed. This study can be used as model to explore flow dependency in the splanchnic bed. The first step is linked with a slight increase of glucose production (from ca 4 to 5 mg/kg/min in surviving patients) and the next increase in pressure and reduction of flow is associated with sharp decline in glucose production from 5 to 3 mg/kg/min. Parallel to this the hepatic venous oxygen saturation is decreased dramatically from 60 to 45 %. This low oxygenation implies that oxygen availability becomes indeed rate limiting and is the primary cause for the reduced glucose production. It can be speculated that due to the reduced flow to the liver the oxygen tension decreases already in the periportal region to reach levels too low to maintain an adequate glucose production. These data also suggest that extreme conditions are required to obtain a supply to the liver that is rate limiting for glucose production.

Interaction with extrahepatic tissues

We focus again on the response to a first increase in the pressure on the chest and abdomen, induced by mechanical ventilation. Of interest is the associated increase of glucose production (from ca 4 to 5 mg/kg/min). It could be explained with an adrenergic stimulation of glucose production. Alterations in the abdominal pressure could stimulate catecholamine production. An alternative interpretation would be that the flow reduction in the splanchnic bed could lead to an imbalance between energy demand and nutrient supply. This imbalance is then compensated with increased glycolysis and hepatic glucose production. The notion that an extrahepatic imbalance between energy demand and nutrient supply stimulates hepatic glucose production is supported by the work of Bagley et al. (8). They described a study in which the microcirculation of septic patients was improved with an expansion of the circulatory blood volume as a first step. In a second step dopamine was given in addition to blood volume expansion. Septic patients, who were not treated for improved microcirculation showed a high glucose production rate. The stepwise improved microcirculation reduced the glucose production, whereas other parameters for liver metabolic activity improved. If the interpretation that tissue energy deficits stimulate glucose production holds, what are then the signals by which the liver is told to increase glucose production? A key candidate would be the flow of lactate to the liver. However, this is still controversial (9). The in vivo lactate load to the liver is difficult to assess because the intestinal lactate production is unknown and it's determination requires access to the portal vein, which is generally not given. Next to lactate other precursors can stimulate glucose production. Under sepsis the catabolism of muscle protein leads to an increased inflow of other substrates for glucose production. Thus, it might be the combined action of substrate supply and hormonal stimulation that leads to an increased production rate, even if this increase cannot be shown for a single factor alone.

The glucose production under a sepsis that is complicated with bacterial invasion and multi organ failure is lower than that found under less severe conditions (3). The oxygen supply to the liver seems to be sufficient as indicated by liver blood flow and hepatic venous saturation generally found under comparable conditions. Thus, the reduction in glucose production does not seem to be supply driven. It could be explained with the disintegration of the mitochondrial activity. In vitro experiments show structural changes in mitochondria to an extent that rule out functional respiratory chains (10).

The data and studies presented so far imply that under a sepsis, which is not associated with further complications, glucose production is increased. However, since this is an oxygen consuming process, other liver functions, which are located pericentral and perivenous, could be impaired due to local hypoxia. From this point of view we find increased glucose production rates at conditions where other liver functions are impaired.

Conclusion

Catecholamines are frequently used for the treatment of the hemodynamic system. This catecholamine treatment could further stimulate glucose production and could hereby induce or further increase of hypoxia in the perivenous region. From that point of view, it is necessary to further explore the interactions between catecholamines and glucose production under sepsis and develop treatments of the hemodynamic systems, which consider side effects on the metabolic function of the liver.

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