Toxic effect of streptozotocin (STZ) on the hepatobiliary function: Oxidative stress and inflammation may contribute to the hepatic complications during STZ-induced insulin-dependent diabetes

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Streptozotocin (STZ: 2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose) is synthesized by Streptomycetes achromogenes and is used to induce both insulin-dependent and non-insulin-dependent diabetes mellitus (IDDM and NIDDM, respectively). The single intravenous dose most frequently used in adult rats to induce IDDM is between 40 and 60 mg/kg b.w., but higher doses are also used. STZ is also efficacious after intraperitoneal administration of a similar or higher dose. Streptozotocin action on B cells is accompanied by characteristic alterations in the blood levels of insulin and glucose. Two hours after injection, hyperglycemia is observed together with a concomitant drop in blood insulin. About six hours later, hypoglycemia occurs with high levels of blood insulin. Finally, hyperglycemia develops and blood insulin levels decrease. These changes in the blood levels of glucose and insulin reflect abnormalities of B cell function. STZ impairs glucose oxidation and decreases insulin biosynthesis and secretion. The liver plays an important role in the metabolism and excretion of STZ. At first, we analyzed the direct effect of STZ on the hepatobiliary function. The effect of streptozotocin on hepatobiliary function was studied in rats on the 1<su>st</su>, 7<su>th</su> and 15<su>th</su> days after treatment. Serum glucose significantly increased on the 1st day, and remained high onwards. Bile flow and the bile acids output were significantly decreased on the 1<su>st</su> day of treatment. Also, the biliary excretion of sulfobromophthalein (BSP, a substance used for evaluating the function of the liver) was significantly decreased on the first day of treatment. All parameters tested, except for serum glucose, tended to normalize at 7<su>th</su> day after treatment. The results suggested a transient

toxic effect of STZ on the hepatocyte. It is known that bile flow (BF) is determined by two fractions: the bile acid dependent flow (BADF) and the bile acid independent flow (BAIF). We analyzed both fractions and demonstrated that STZ itself, and not its diabetogenic effect, produced a diminution in BF at the expense of both BAIF and BADF. In a second stage, we used STZ to induce insulin-dependent diabetes in rats. It is known that the liver is a central regulator of carbohydrate homeostasis and it releases glucose according to metabolic demand. Besides, in the last years, liver injury has been recognized as a major complication of diabetes mellitus (DM). We analyzed the contribution of oxidative stress and Tumor Necrosis Factor alpha (TNF-?) intracellular pathway in the development of apoptosis in the liver of streptozotocin- induced diabetic animals. In this review, we describe the role of upstream mediators of the interaction between TNF? and its receptor, TNFR1, by assessing the ability of the in vivo treatment with etanercept (TNF-? blocking antibody) to protect against TNF-?-induced apoptosis. Also, we studied the role of iNOS-induction in the TNF-? pathways of liver apoptosis in IDDM, by treatment of diabetic rats with aminoguanidine (selective iNOS inhibitor), which blocked the induction of apoptosis. Interestingly, iNOS inhibition significantly reduced TNF-? levels, thus evidencing an interaction between TNF-? and iNOS activity. On the other hand, we found that the administration of antioxidants/hydroxyl radical scavengers (Tempol and Desferal) prevented oxidative stress by reducing the effects of hydroxyl radical production and both LPO levels and apoptosis. Taken together, our studies support the notion that, at least in part, the hydroxyl radical acts as a reactive intermediate, which leads to liver apoptosis in a model of STZ-mediated hyperglycemia. The present review bears two major insights: First, it provides evidence for a transient toxic effect of STZ on the hepatobiliary function. This toxic effect becomes relevant for the study, at short time, of hepatic metabolism in the experimental diabetes induced by STZ. Second, it provides further knowledge about the mechanisms which may contribute to the disease process in the liver during the course of an inflammatory process as is IDDM. Regulation of hepatic oxidative stress and TNF-o levels in the diabetic state could be of therapeutic relevance for the improvement or delay of the hepatic complications linked to chronic hyperglycemia.

Apoptosis

Bile flow

Diabetes mellitus

Hydroxyl radical

Inflammation

iNOS

Liver

NO

Oxidative stress

Streptozotocin

TNF-?