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Role of Liver in Glucose Metabolism

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Introduction

Liver is the primary organ for glucose metabolism. Apart from expressing the enzymes involved in glucose metabolism and regulation, liver possesses numerous enzymes involved in detoxification and toxicity enhancement (Phase I and Phase II). Also, most substances, upon entry into the body are primarily subjected to metabolism in the liver. Reports dealing with the effects of high glucose on liver are discussed in the following sections of this mini-review.

Liver Damage in Diabetes

Several studies have shown that significant oxidative stress and liver damage occurs in diabetes. A study using Non- Obese Diabetic (NOD) mice showed elevated serum enzymes associated with liver damage and apoptosis as indicated by marked DNA fragmentation and all these changes were decreased with selenium treatment [1]. Another study indicated that Streptozotocin (STZ)-induced diabetic rats (animal model for Type I diabetes) exhibited increased lipid peroxidation and decreased levels of antioxidant enzymes- catalase, glutathione peroxidase and Superoxide Dismutase (SOD) in liver which were reversed with aucubin [2]. The protein expression of the antioxidant enzymes, SOD and catalase which are involved in the detoxification of Reactive Oxygen Species (ROS) were found to be decreased in the STZ-induced diabetic rat liver tissues and vitamin C or lipoic acid treatments elevated their levels [3]. STZ mediated hyperglycemia decreased glutathione peroxidase, catalase, glucose-6-phosphate dehydrogenase and transketolase activities in liver tissue of diabetic rats and although treatment with melatonin slightly elevated the levels of the antioxidant enzymes, it markedly reversed the activities of glucose-6-phosphate dehydrogenase and transketolase [4].

Another study reported that glucose levels as indicated by glucose oxidase, glycated haemoglobin, an indicator of glycative stress, and the 8-oxo-2'- deoxyguanosine (8-oxodG) content of DNA, an indicator of oxidative DNA damage, in the liver of STZ-diabetic rats were much higher compared with control rats [5]. Similar observations were reported in another study showing that the nuclear and mitochondrial DNA levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), another biomarker for oxidative DNA damage increased several fold in STZ treated rats and these changes were reversed with rice bran oil treatment [6]. Liver 8-OHdG levels in STZ treated rats were significantly decreased by combined treatment with insulin and antioxidant (probucol or vitamin E), but not by insulin treatment alone [7].

STZ induced diabetes led to the increased expression of liver and hepatocyte inducible Nitric Oxide Synthase (iNOS) [8]. The activation of Peroxisome Proliferator Activated Receptor alpha (PPAR alpha) was shown to protect STZ treated mice against the toxicity of acetaminophen, a potent hepatotoxicant [9]. Another study observed disparate effects of alpha lipoic acid on the decreased liver SOD and Glutathione (GSH) levels and increased lipid peroxidation in STZ treated rats [10]. The livers of STZ treated rats showed increased oxidation of GSH, lipoperoxides and activity of xanthine oxidase, a superoxide-generating enzyme [11]. Impaired proteosome activity needed to degrade oxidized proteins was observed in the cytosol of STZ treated rats [12]. Livers from STZ treated rats have been shown to exhibit increased levels of gamma-glutamyltranspeptidase, a premalignant marker [13].

Liver mitochondria from STZ-diabetic rats exhibited less susceptibility to oxidative damage (induced by Fe^{3+}/Adenosine 5'-diphosphate (ADP) xanthine/xanthine oxidase), compared to normal rats [14]. Increase in apoB-48 lipoproteins was observed, due to significantly less sulfate incorporation into heparan sulfate proteoglycans in livers of STZ-treated rats [15]. Fatty Aldehyde Dehydrogenase (FALDH), a key component of the detoxification pathway of aldehydes arising from lipid peroxidation events was decreased in two models of insulin-resistant mice: db/db and high fat diet mice and STZ-treated rats, suggesting that FALDH dysregulation occurs both in hyperinsulinemic insulin-resistant state and hypoinsulinemic type 1 diabetes models [16].

Non-alcoholic fatty liver disease, a spectrum of liver damage that ranges from relatively benign hepatic steatosis to potentially fatal cirrhosis is very closely associated with Type 2 diabetes. The clearance of 4-hydroxynonenal, a major product of lipid peroxidation, by the enzymes Glutathione-S-Transferase (GST), Aldehyde Dehydrogenase (ALDH), and Alcohol Dehydrogenase (ADH) was impaired in liver microsomes and mitochondria of BB/WOR diabetic rats [17]. An elevation of both alpha- tocopherol and Coenzyme Q content-antioxidant enzymes, which may be involved in the elimination of mitochondrially generated ROS and decreased susceptibility of liver mitochondria to oxidative damage, was observed in Goto-Kakizaki (12-month-old diabetic) rats, a model of non-insulin dependent diabetes mellitus than in the mitochondria from normal rats [18]. Further, the mRNA expression of Heme Oxygenase-1 (HO-1), an important sensitive marker of the stress response was found to be increased in spontaneously diabetic rats [19]. Lipoperoxidative aldehydes were shown to accumulate in liver microsomes and mitochondria at a higher rate in spontaneously diabetic BB/WOR rats than in control non-diabetic animals [20].

The Cytochrome P450 (CYP) enzymes which play a significant role in hepatotoxicity - CYP2A6, 2E1, and 3A4/5 were found to be increased in hepatocytes of patients with fatty liver due to obesity or diabetes [21]. Due to the limited availability of liver samples from humans and the tedious process of liver biopsy, the study of effect of high glucose in human liver has been restricted to very few reports.

Studies have also stressed upon the use of herbal preparations in protecting against liver damage in diabetes. A new thiazolidinedione analog was found to be effective in alleviating oxidative stress in alloxan treated rats [22]. Another study observed that tetrahydrocurcumin, one of the active metabolites of curcumin lowered oxidative stress in livers of STZ- nicotinamide induced diabetic rats [23]. An aqueous

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extract of Albizzia lebbeck was effective in decreasing oxidative stress in alloxan treated rats [24]. A bark extract of Helicteres isora exhibited hypoglycemic and hepatoprotective activity in STZ induced diabetic rats [25]. The antioxidant effect of an aqueous extract of Scoparia dulcis, was observed in rats with STZ-induced diabetes [26]. Similarly, a few more studies have explored the hepatoprotective effects of Indian medicinal plants in diabetes [27-30].

Use of Hepatocytes to Investigate the Effects of High Glucose

In vitro studies using hepatocytes and HepG2 cells have provided valuable insights into the mechanisms of glucose toxicity in liver. Glycolytic enzymes- glucokinase and phosphofructokinase-2/ fructose bisphosphatase-2 were found to play coordinate roles in the elevated hepatic glycolysis observed in hepatocytes obtained from in insulin-resistant Zucker fa/fa rats [31]. Human hepatocyte cell lines, Huh7 treated with high glucose alone or in combination with proinflammatory cytokines, were found to exhibit increased levels of the transcription factor Nuclear Factor kappa-B (NF-kappaB) and enhanced coagulation-related gene expression and the effects were mediated, at least partly, by the generation of oxidative stress [32]. Hepatocytes from Zucker fa/fa rats were found to show increased sensitivity of glycogen synthesis to phosphorylase-a and impaired expression of the glycogen-targeting protein R6 [33]. Carbohydrate response element binding protein was found to directly promote lipogenic enzyme gene transcription in hepatocytes isolated from wild type mice and exposed to high concentration of glucose [34]. A study using mouse Hepatocytes (HEP6-16) reported that decreased ATP content downregulated mitochondrial uncoupling Protein 2 (UCP2) expressions, thus affecting the energy metabolism [35].

However, the use of hepatocytes for a long period proves to be difficult due to the unstable expression of differentiated functions, low cell survival and rapid cell senescence.

Use of Hepatoma Cell Lines, Hepg2 to Investigate the Effects of High Glucose

The human hepatoma cell lines, HepG2 have been used extensively to study hyperglycemia *in vitro*. The expression of hepatic Scavenger Receptor class B type I (SR-B1) which binds High Density Lipoprotein (HDL) particles that mediate reverse cholesterol transport and thus lowers the risk of atherosclerosis was observed to be suppressed in HepG2 cells exposed to high glucose [36]. In primary rat Hepatocytes and in HepG2 cells, the transcription of the human apolipoprotein (apo) A-II gene was upregulated by glucose [37]. High glucose up regulated the transcription of human Phospholipids transfer protein which plays an important role in human plasma HDL metabolism and increased mRNA levels for several genes that are functionally important in HDL metabolism, including human ATP-binding cassette transporter A1, Apo A-1, SR- B1, and hepatic lipase in HepG2 cells [38]. High glucose led to the decrease of mitochondrial DNA content and inhibition of mitochondrial function in HepG2 cells [39]. The effects of a high concentration of glucose on the insulin receptor-down signaling were investigated in HepG2 cells to delineate the molecular mechanism of insulin resistance under glucose toxicity and high concentration of glucose caused phosphorylation of IRS-1, leading to selective attenuation of metabolic signaling of insulin [40]. Further, the phosphorylation of IRS-1 with high glucose treatment was blocked only by Protein Kinase C (PKC) inhibitors. The surface binding of asialo- orosomucoid, a well-documented ligand for hepatic receptor for asialoglycoproteins, increased significantly with increasing glucose concentrations in HepG2 cells [41].

Thus, as evidenced through the above studies utilizing in vivo animal models and invitro models of hepatocytes and HepG2 cells, metabolism of high concentrations of glucose in liver may impair several cellular processes thus leading to injury.

References

1. Hwang D, Seo S, Kim Y, Kim C, Shim S, et al. (2007) Selenium acts as an insulin-like molecule for the down-regulation of diabetic symptoms via endoplasmic reticulum stress and insulin signalling proteins in diabetes-induced non-obese diabetic mice. J Biosci 32: 723-735.
2. Jin L, Xue HY, Jin LJ, Li SY, Xu YP (2008) Antioxidant and pancreas-protective effect of aucubin on rats with streptozotocin-induced diabetes. Eur J Pharmacol 582: 162-167.
3. Sadi G, Yilmaz O, Güray T (2008) Effect of vitamin C and lipoic acid on streptozotocin-induced diabetes gene expression: mRNA and protein expressions of Cu-Zn SOD and catalase. Mol Cell Biochem 309: 109-116.
4. Sudnikovich EJ, Maksimchik YZ, Zabrodskaya SV, Kubyshin VL, Lapshina EA, et al. (2007) Melatonin attenuates metabolic disorders due to streptozotocin-induced diabetes in rats. Eur J Pharmacol 569: 180-187.
5. Andican G, Burçak G (2005) Oxidative damage to nuclear DNA in streptozotocin-diabetic rat liver. Clin Exp Pharmacol Physiol 32: 663-666.
6. Hsieh RH, Lien LM, Lin SH, Chen CW, Cheng HJ, et al. (2005) Alleviation of oxidative damage in multiple tissues in rats with streptozotocin-induced diabetes by rice bran oil supplementation. Ann N Y Acad Sci 1042: 365-371.
7. Park KS, Kim JH, Kim MS, Kim JM, Kim SK, et al. (2001) Effects of insulin and antioxidant on plasma 8-hydroxyguanine and tissue 8-hydroxydeoxyguanosine in streptozotocin-induced diabetic rats. Diabetes 50: 2837-2841.
8. Madar Z, Kalet-Litman S, Stark AH (2005) Inducible nitric oxide synthase activity and expression in liver and hepatocytes of diabetic rats. Pharmacology 73: 106-112.
9. Shankar K, Vaidya VS, Corton JC, Bucci TJ, Liu J, et al. (2003) Activation of PPAR-alpha in streptozotocin-induced diabetes is essential for resistance against acetaminophen toxicity. FASEB J 17: 1748-1750.
10. Dinçer Y, Telci A, Kayali R, Yilmaz IA, Cakatay U, et al. (2002) Effect of alpha-lipoic acid on lipid peroxidation and anti-oxidant enzyme activities in diabetic rats. Clin Exp Pharmacol Physiol 29: 281-284.
11. Desco MC, Asensi M, Márquez R, Martínez-Valls J, Vento M, et al. (2002) Xanthine oxidase is involved in free radical production in type 1 diabetes: protection by allopurinol. Diabetes 51: 1118-1124.
12. Portero-Otín M, Pamplona R, Ruiz MC, Cabiscol E, Prat J, et al. (1999) Diabetes induces an impairment in the proteolytic activity against oxidized proteins and a heterogeneous effect in nonenzymatic protein modifications in the cytosol of rat liver and kidney. Diabetes 48: 2215-2220.
13. Hemmings SJ, Pekush RD (1994) The impact of type I diabetes on rat liver gamma-glutamyltranspeptidase. Mol Cell Biochem 139: 131-140.
14. Sukalski KA, Pinto KA, Berntson JL (1993) Decreased susceptibility of liver mitochondria from diabetic rats to oxidative damage and associated increase in alpha-tocopherol. Free Radic Biol Med 14: 57-65.
15. Ebara T, Conde K, Kako Y, Liu Y, Xu Y, et al. (2000) Delayed catabolism of apoB-48 lipoproteins due to decreased heparan sulfate proteoglycan production in diabetic mice. J Clin Invest 105: 1807-1818.
16. Demozay D, Rocchi S, Mas JC, Grillo S, Pirola L, et al. (2004) Fatty aldehyde dehydrogenase: potential role in oxidative stress protection and regulation of its gene expression by insulin. J Biol Chem 279: 6261-6270.
17. Traverso N, Menini S, Odetti P, Pronzato MA, Cottalasso D, et al. (2002) Diabetes impairs the enzymatic disposal of 4-hydroxynonenal in rat liver. Free Radic Biol Med 32: 350-359.
18. Santos MS, Santos DL, Palmeira CM, Seiça R, Moreno AJ, et al. (2001) Brain and liver mitochondria isolated from diabetic Goto-Kakizaki rats show different susceptibility to induced oxidative stress. Diabetes Metab Res Rev 17: 223-230.
19. Cosso L, Maineri EP, Traverso N, Rosatto N, Pronzato MA, et al. (2001) Induction of heme oxygenase 1 in liver of spontaneously diabetic rats. Free Radic Res 34: 189-191.

20. Traverso N, Menini S, Odetti P, Pronzato MA, Cottalasso D, et al. (1999) Lipoperoxidation in hepatic subcellular compartments of diabetic rats. Free Radic Biol Med 26: 538-547.

21. Niemelä O, Parkkila S, Juvonen RO, Viitala K, Gelboin HV, et al. (2000) Cytochromes P450 2A6, 2E1, and 3A and production of protein-aldehyde adducts in the liver of patients with alcoholic and non-alcoholic liver diseases. J Hepatol 33: 893-901.

22. Chaudhry J, Ghosh NN, Roy K, Chandra R (2007) Antihyperglycemic effect of a new thiazolidinedione analogue and its role in ameliorating oxidative stress in alloxan-induced diabetic rats. Life Sci 80: 1135-1142.

23. Murugan P, Pari L (2006) Antioxidant effect of tetrahydrocurcumin in streptozotocin-nicotinamide induced diabetic rats. Life Sci 79: 1720-1728.

24. Resmi CR, Venukumar MR, Latha MS (2006) Antioxidant activity of Albizzia lebbeck (Linn.) Benth. in alloxan diabetic rats. Indian J Physiol Pharmacol 50: 297-302.

25. Kumar G, Murugesan AG, Rajasekara Pandian M (2006) Effect of Helicteres isora bark extract on blood glucose and hepatic enzymes in experimental diabetes. Pharmazie 61: 353-355.

26. Pari L, Latha M (2005) Antidiabetic effect of Scoparia dulcis: effect on lipid peroxidation in streptozotocin diabetes. Gen Physiol Biophys 24: 13-26.

27. Singh N, Kamath V, Rajini PS (2005) Attenuation of hyperglycemia and associated biochemical parameters in STZ-induced diabetic rats by dietary supplementation of potato peel powder. Clin Chim Acta 353: 165-175.

28. Prakasam A, Sethupathy S, Pugalendi KV (2004) Influence of Casearia esculenta root extract on protein metabolism and marker enzymes in streptozotocin-induced diabetic rats. Pol J Pharmacol 56: 587-593.

29. Sabu MC, Kuttan R (2004) Antidiabetic activity of Aegle marmelos and its relationship with its antioxidant properties. Indian J Physiol Pharmacol 48: 81-88.

30. Gupta S, Kataria M, Gupta PK, Murganandan S, Yashroy RC (2004) Protective role of extracts of neem seeds in diabetes caused by streptozotocin in rats. J Ethnopharmacol 90: 185-189.

31. Payne VA, Arden C, Lange AJ, Agius L (2007) Contributions of glucokinase and phosphofructokinase-2/fructose bisphosphatase-2 to the elevated glycolysis in hepatocytes from Zucker fa/fa rats. Am J Physiol Regul Integr Comp Physiol 293: R618-625.

32. Iwasaki Y, Kambayashi M, Asai M, Yoshida M, Nigawara T, et al. (2007) High glucose alone, as well as in combination with proinflammatory cytokines, stimulates nuclear factor kappa-B-mediated transcription in hepatocytes in vitro. J Diabetes Complications 21: 56-62.

33. Arden C, Green AR, Hampson LJ, Aiston S, Härndahl L, et al. (2006) Increased sensitivity of glycogen synthesis to phosphorylase-a and impaired expression of the glycogen-targeting protein R6 in hepatocytes from insulin-resistant Zucker fa/fa rats. FEBS J 273: 1989-1999.

34. Ishii S, Iizuka K, Miller BC, Uyeda K (2004) Carbohydrate response element binding protein directly promotes lipogenic enzyme gene transcription. Proc Natl Acad Sci U S A 101: 15597-15602.

35. Cheng G, Polito CC, Haines JK, Shafizadeh SF, Fiorini RN, et al. (2003) Decrease of intracellular ATP content downregulated UCP2 expression in mouse hepatocytes. Biochem Biophys Res Commun 308: 573-580.

36. Murao K, Yu X, Imachi H, Cao WM, Chen K, et al. (2008) Hyperglycemia suppresses hepatic scavenger receptor class B type I expression. Am J Physiol Endocrinol Metab 294: E78-87.

37. Sauvaget D, Chauffeton V, Dugué-Pujol S, Kalopissis AD, Guillet-Deniau I, et al. (2004) In vitro transcriptional induction of the human apolipoprotein A-II gene by glucose. Diabetes 53: 672-678.

38. Tu AY, Albers JJ (2001) Glucose regulates the transcription of human genes relevant to HDL metabolism: responsive elements for peroxisome proliferator-activated receptor are involved in the regulation of phospholipid transfer protein. Diabetes 50:1851-1856.

39. Palmeira CM, Rolo AP, Berthiaume J, Bjork JA, Wallace KB (2007) Hyperglycemia decreases mitochondrial function: the regulatory role of mitochondrial biogenesis. Toxicol Appl Pharmacol 225: 214-220.

40. Nakajima K, Yamauchi K, Shigematsu S, Ikeo S, Komatsu M, et al. (2000) Selective attenuation of metabolic branch of insulin receptor down-signaling by high glucose in a hepatoma cell line, HepG2 cells. J Biol Chem 275: 20880-20886.

41. Weiss P, Ashwell G, Morell AG, Stockert RJ (1994) Modulation of the asialoglycoprotein receptor in human hepatoma cells: effect of glucose. Hepatology 19: 432-439.