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Hepatic Expression of Drug Metabolizing Enzyme in Diabetes

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당뇨병에서 간의 약물대사효소 발현변화

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요 약

간의 약물대사는 흡수된 외인성물질의 배설을 위한 중추적인 역할을 수행하며 이 반응은 일상대사와 이상대사효소로 구성된 약물대사효소계에 의해 매개된다. 약물대사효소의 발현과 활성은 외인성물질의 노출에 의해 유도되거나 억제되며 이 결과는 약물상호작용을 발생시키는 주요한 원인이다. 또한 당뇨, 비만, 영양실조, 음주, 염증반응 등의 병적인 생리상태는 간에서 약물대사효소의 발현과 활성을 조절하는 것으로 보고되고 있다. 이러한 변동은 치료약물 또는 환경오염물질에 대한 인체의 반응성에 영향을 미치며 결과적으로 예측하지 못한 부작용이나 독성을 발생시킬 수 있다. 본 논문에서는 당뇨병에서 약물대사효소의 발현변화를 정리하였다.

Key words : drug metabolizing enzyme, Cytochrome P450, drug interaction, diabetes

INTRODUCTION

Hepatic drug metabolism plays a critical role in metabolic clearance of xenobiotics, which mediated by xenobiotic, or drug, metabolizing enzymes divided classically into two groups, namely, phase I and phase II. Phase I reactions introduce functional groups into xenobiotics, which increases polarity (Kim *et al.*, 2005). Cytochrome P450 (CYP), the flavin-containing monooxygenase, xanthine oxidase, prostaglandin H synthase, amine oxidase, alcohol dehydrogenase, aldehyde dehydrogenase, microsomal epoxide hydrolase (mEH) and esterase can mediate phase I reactions. Phase II reactions include glucuronidation, sulfation, methylation, acetylation, glutathione conjugation and amino acid conjugation. These reactions, with the exception of methylation and acetylation, generally result in an increase in xenobiotic hydrophilicity and facilitate elimination via bile or urine.

Xenobiotics often change the expression or capacity of drug metabolizing enzymes and this response, known as induction or inhibition, is a tightly regulated process that is controlled at the levels of transcription, translation and/or posttranslation. Induction of drug metabolizing enzymes in a manner that

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is sensitive to repeated exposure of xenobiotics allows the animal to facilitate elimination of xenobiotics via drug metabolism. It is generally recognized that the expression of drug metabolizing enzymes may be altered in response to development, gender, genetic factors, nutrition, pregnancy and pathophysiological conditions such as diabetes, long-term alcohol consumption, inflammation, protein-calorie malnutrition. Although the mechanisms by which xenobiotics regulate drug metabolizing enzymes have been intensively studied, relatively less is known regarding the cellular mechanisms by which drug metabolizing enzymes are regulated in response to endogenous factors such as hormones, growth factors and cytokines. Recent findings, however, have revealed that hormones, growth factors and cytokines/chemokines play an important role in the regulation of drug metabolizing enzyme expression. Furthermore, several of the cellular signaling pathways involved in hormone- and growth factor-mediated regulation of drug metabolizing enzymes have been identified. The mechanism (s) by which the signaling pathway kinases and phosphatases regulate gene expression in response to agonists are being actively examined. In this review, an overview of hepatic expression of drug metabolizing enzyme in diabetes will be described.

1. Role of liver in glucose homeostasis and insulin signaling pathways

Diabetes is associated with a high risk of atherosclerosis and kidney, nerve, and tissue damage. Also a higher incidence of hepatic disease including hepatic cancer and non-alcoholic hepatitis has been reported to be associated with diabetes (Cherrington, 1999). Liver plays an important role in regulation of metabolic homeostasis and is one of major organ response to insulin and glucagon. Hepatic insulin level and cellular responsiveness are altered in diabetes. It is well established that, regardless of the degree of muscle insulin resistance, glucose levels in diabetic and non-diabetic individuals are determined by the rate of hepatic glucose production, which in turn is regulated by insulin. Disruption of insulin action in liver by tissue-specific knockout of the insulin receptor leads to severe glucose intolerance and resistance to the blood glucose-lowing effect of insulin. This provides evidence of a direct role of liver in postprandial glucose homeostasis, and suggests that a considerable portion of the decrease in blood glucose following insulin administration is due to a suppression of hepatic glucose production rather than an increase in muscle glucose uptake.

Insulin receptor mediates the numerous and varied biological functions of insulin. The insulin receptor belongs to the large family of receptor tyrosine kinase (RTK) cell surface receptors which possess intrinsic tyrosine kinase activity (Kim and Novak, 2007). Upon binding of corresponding agonist, this receptor undergoes autophosphorylation of tyrosine residues in the cytoplasmic tails and initiates a complex series of intracellular signaling cascades that ultimately results in diverse cellular responses. Insulin stimulates the recruitment of a family of lipid kinases known as class I phosphatidylinositol 3-kinases (PI3Ks) to the plasma membrane. There, the PI3Ks phosphorylate the glycerophospholipid phosphatidylinositol (PI) 4,5-bisphosphate ($PI(4,5)P_2$) at the D-3 position of the inositol ring, converting it to PI 3,4,5-triphosphate ($PI(3,4,5)P_3$). Recent evidence indicates that the 3-phosphoinositide-dependent protein kinase-1 (PDK1)-mediated activation of the downstream serine/threonine protein kinase B (Akt/PKB), mammalian target of rapamycin (mTOR), atypical protein kinase C (PKC) and p70 ribosomal protein S6 kinase (p70S6 kinase) mediate many of the downstream events controlled by PI3K. Activation of insulin receptor also leads to activation of the mitogen activated protein kinase signaling cascade. Following tyrosine phosphorylation of the cytoplasmic domain of the receptor, recruitment of adaptor proteins and Ras occurs. Ras is then activated by SOS, Son-of Sevenless, a guanine nucleotide exchange factor, which converts inactive Ras-GDP to activated Ras-GTP. The small guanosine triphosphatase G-protein Ras subsequently recruits and activates Raf, which leads to a

phosphorylation signaling cascade involving recruitment and activation of the MAPKs. RTK signaling is regulated not only by a cascade of phosphorylation via protein kinases but also by dephosphorylation via tyrosine and serine/threonine phosphatases and lipid phosphatases. The growth factor receptor binding protein 2 (Grb2) is constitutively associated with the SOS through binding of the SH3 domain of Grb2 to a SOS proline-rich region.

2. Expression of drug metabolizing enzymes in diabetes

Pathophysiological conditions such as diabetes, obesity, fasting and xenobiotic exposure, including excessive alcoholic consumption, result in altered expression/activity of hepatic drug metabolizing enzymes including CYP1A, 2B, 2C11, 3A, 4A, 2E1, mEH, UDP-glucuronosyltransferase (UGT) and sulfotransferases (Rubin and Lieber, 1968; Duvaldestin *et al.*, 1975; Abernethy *et al.*, 1983; Hong *et al.*, 1987; Bellward *et al.*, 1988; Thomas *et al.*, 1989; Barnett *et al.*, 1990; Song *et al.*, 1990; Donahue *et al.*, 1991; Raucy *et al.*, 1991; Badger *et al.*, 1993; Shimojo *et al.*, 1993; Van de Wiel *et al.*, 1993; Chaudhary *et al.*, 1993; Runge-Morris and Vento 1995; Irizar *et al.*, 1995; Clarke *et al.*, 1996; Visser *et al.*, 1996; Braun *et al.*, 1998; Roe *et al.*, 1999; Kardon *et al.*, 2000; Xiong *et al.*, 2002; Kim *et al.*, 2004; Cowpland *et al.*, 2006; Yoshinari *et al.*, 2006a, b). In contrast, research on expression and activity of the glutathione S-transferases (GSTs) during diabetes are inconclusive, with both increased and decreased GST expression being reported *in vivo* (Rouer *et al.*, 1981; Agius and Gidari, 1985; Grant and Duthie, 1987; Thomas *et al.*, 1989; Mukherjee *et al.*, 1994; Raza *et al.*, 1996). The reason for this discrepancy remains unknown. However, it may, in part, be associated with competing hormonal factors in vivo with variations in the mechanisms of inducing diabetes, and with variations in oxidative stress, usually observed in diabetes. It has been reported that transcriptional activation of some GST genes may be associated with changes in the redox status of the cell in conjunction with oxidative stress (Wasserman and Fahl, 1997; Kang *et al.*, 2001). In addition synthesis of glutathione (GSH), a cofactor for GST, is altered in response to pathophysiologic conditions, such as diabetes, protein-calorie malnutrition and alcohol consumption, through regulation of expression of gamma-glutamylcysteine ligase which is the rate-limiting step for catalysis of GSH synthesis, and by the availability of cysteine for GSH synthesis (Yoshida *et al.*, 1995; Lu *et al.*, 1999).

Diabetes may lead to chronic non-alcoholic liver diseases including nonalcoholic steatohepatitis (NASH) that may progress to hepatic cirrhosis and hepatocellular carcinoma. An increased risk factor for development of diabetes is associated with the metabolic syndrome, which is characterized by insulin resistance (Sanyal, 2005). Diabetes is associated with a 2-3-fold increase in the risk of hepatocellular carcinoma, regardless of the presence of other major hepatocellular carcinoma risk factors (Davila *et al.*, 2005). Insulin resistance is produced by a complex interplay of genetic and environmental factors, resulting in inhibition of insulin signaling/action in peripheral tissues, such as muscle, adipose tissue and liver. The resultant disequilibrium in lipid homeostasis causes triglycerides to accumulate in the liver. An increase in oxidative stress, defined as an imbalance between the production of highly reactive molecular species and antioxidant defenses, could be one mechanism by which the nonalcoholic fatty liver develops into nonalcoholic steatohepatitis (Videla *et al.*, 2004a). Insulin resistance in type 2 diabetes, cirrhosis and other hepatic diseases result in decreased insulin signaling and diminished signaling through downstream components, such as PI3Ks, Akt, mTOR and p70S6 kinase. Induction of CYP2E1 as well as depression of antioxidant system has been observed in NASH patients (Videla *et al.*, 2004b). From a pathological point of view, CYP2E1 is considered of particular interest due to its poor coupling with NADPH-cytochrome P450 reductase, with NADPH oxidase activity generating reactive oxygen species

(Lieber *et al.*, 1997). Leclercq *et al.* (2000) showed that CYP4A10 and CYP4A14 were upregulated in Cyp2e1 −/− mice and served as alternative initiators of oxidative stress in NASH. These results indicate that altered expression of xenobiotic metabolizing enzyme gene plays a progressive role in hepatic diseases.

Because pathophysiological states such as diabetes result in alteration of secretion and/or cellular response of hormone, including insulin, glucagon and growth hormone, these hormones may be etiologic factors affecting the expression of hepatic drug-metabolizing enzymes. It has been reported that insulin or growth hormone administration to chemically-induced or spontaneously diabetic rats restores drug-metabolizing enzyme activity and expression to control values (Dong *et al.*, 1988; Yamazoe *et al.*, 1989a, b; Thomas *et al.*, 1989; Donahue *et al.*, 1991; Tunon *et al.*, 1991; Runge-Morris and Vento 1995). Our laboratory and others have demonstrated that the activity and/or expression of hepatic drug metabolizing enzymes, such as CYP2B, CYP2E1, CYP2C11, CYP-2A5, GST alpha class, GST pi class, UGT and mEH are differentially regulated in response to insulin and glucagon (De Waziers *et al.*, 1995; Constantopoulos and Matsaniotis, 1978; Woodcroft *et al.*, 2002; Kim *et al.*, 2003a, b). These results indicate that changes in drug-metabolizing enzyme mRNA or protein levels observed in pathophysiological conditions, such as diabetes or inflammation, may be attributed to alterations in the efficiency of agonist activation of intracellular signaling pathways and components. Thus, it is of interest to identify which cellular signaling pathways are involved in regulating the expression of these genes in response to hormones and cytokines.

CONCLUSION

Endogenous factors including hormones, growth factors and cytokines play an important role in regulating drug metabolizing enzyme gene and protein expression in normal physiological conditions and well as in pathophysiological conditions. These results warrant studies for determining what signaling pathways and components are involved in endogenous factor-mediated regulation of drug metabolizing enzyme expression. Studies of cellular signal transduction events elicited by hormones and cytokines yield important insights into the regulation of drug metabolism in pathophysiological conditions. Consequently, understanding the role of signaling pathways and components in the regulation of xenobiotic metabolizing gene expression will advance our understanding of differences in xenobiotic metabolism with diseases, as well as the consequent effects on efficacy and safety of many therapeutics. In addition, understanding the signaling pathways and components that may regulate xenobiotic metabolizing enzyme gene expression will assist in understanding the progressive risk of an altered phenotype and xenobiotic metabolism and toxicity in the treatment of disease.

REFERENCES

Abernethy DR, Greenblatt DJ, Divoll M and Shader RI. Enhanced glucuronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen, J Lab Clin Med 1983; 101: 873-880.

Agius C and Gidari AS. Effect of streptozotocin on the glutathione S-transferases of mouse liver cytosol, Biochem Pharmacol 1985; 34: 811-819.

Badger TM, Ronis MJ, Lumpkin CK, Valentine CR, Shahare M, Irby D, Huang J, Mercado C, Thomas P, Ingelman-Sundberg M. and Crouch J. Effects of chronic ethanol on growth hormone secretion and hepatic cytochrome P450 isozymes of the rat, J Pharmacol Exp Ther 1993; 264: 438-447.

Barnett CR, Gibson GG, Wolf CR, Flatt PR and Ioannides C. Induction of cytochrome P450III and P450IV family proteins in streptozotocin-induced diabetes, Biochem J 1990; 268: 765-769.

Bellward GD, Chang T, Rodrigues B, McNeill JH, Maines S, Ryan DE, Levin W and Thomas PE. Hepatic cytochrome P-450j induction in the spontaneously diabetic BB rat, Mol Pharmacol 1988; 33: 140-143.

Braun L, Coffey MJ, Puskas F, Kardon T, Nagy G, Conley

AA, Burchell B and Mandl J. Molecular basis of bilirubin UDP-glucuronosyltransferase induction in spontaneously diabetic rats, acetone-treated rats and starved rats, Biochem J 1988; 336: 587-592.

Chaudhary IP, Tuntaterdtum S, McNamara PJ, Robertson LW and Blouin RA. Effect of genetic obesity and phenobarbital treatment on the hepatic conjugation pathways, J Pharmacol Exp Ther 1993; 265: 1333-1338.

Cherrington AD. Banting Lecture 1997. Control of glucose uptake and release by the liver in vivo, Diabetes 1999; 48: 1198-1214.

Clarke J, Snelling J, Ioannides C, Flatt PR and Barnett CR. Effect of vitamin C supplementation on hepatic cytochrome P450 mixed-function oxidase activity in streptozotocin-diabetic rats, Toxicol Lett 1996; 89: 249-256.

Constantopoulos A and Matsaniotis N. Augmentation of uridine diphosphate glucuronyltransferase activity in rat liver by adenosine 3,5′-monophosphate, Gastroenterology 1978; 75: 486-491.

Cowpland C, Su GM, Murray M, Puddey IB and Croft KD. Effect of alcohol on cytochrome p450 arachidonic acid metabolism and blood pressure in rats and its modulation by red wine polyphenolics, Clin Exp Pharmacol Physiol 2006; 33: 183-188.

Davila JA, Morgan RO, Shaib Y, McGlynn KA and El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study, Gut 2005; 54: 533-539.

De Waziers I, Garlatti M, Bouguet J, Beaune PH and Barouki R. Insulin down-regulates cytochrome P450 2B and 2E expression at the post-transcriptional level in the rat hepatoma cell line, Mol Pharmacol 1995; 47: 474-479.

Donahue BS, Skottner-Lundin A and Morgan ET. Growth hormone-dependent and -independent regulation of cytochrome P-450 isozyme expression in streptozotocin-diabetic rats, Endocrinology 1991; 128: 2065-2076.

Dong Z, Hong J, Ma Q, Li D, Bullock J, Gonzalez FJ, Park SS, Gelboin HV and Yang CS. Mechanism of induction of cytochrome P450ac (P450j) in chemically induced and spontaneously diabetic rats, Arch Biochem Biophys 1988; 263: 29-35.

Duvaldestin P, Mahu J-L and Berthelot P. Effect of fasting on substrate specificity of rat liver UDP-glucuronosyltransferase, Biochim Biophys Acta 1975; 384: 81-86.

Grant MH and Duthie SJ. Conjugation reactions in hepatocytes isolated from streptozotocin-induced diabetic rats, Biochem Pharmacol 1987; 36: 3647-3655.

Hong JY, Pan JM, Gonzalez FJ, Gelboin HV and Yang CS. The induction of a specific form of cytochrome P-450 (P-450j) by fasting, Biochem Biophys Res Commun 1987; 142: 1077-1083.

Irizar A, Barnett CR, Flatt PR and Ioannides C. Defective expression of cytochrome P450 proteins in the liver of the genetically obese Zucker rat, Eur J Pharmacol 1995; 293: 385-393.

Kang KW, Cho MK, Lee CH and Kim SG. Activation of phosphatidylinositol 3-kinase and Akt by tert-butylhydroquinone is responsible for antioxidant response element-mediated rGSTA2 induction in H4IIE cells, Mol Pharmacol 2001; 59: 1147-1156.

Kardon T, Coffey MJ, Banhegyi G, Conley AA, Burchell B, Mandl J and Braun L. Transcriptional induction of bilirubin UDP-glucuronosyltransrase by ethanol in rat liver, Alcohol 2000; 21: 251-257.

Kim MS, Wang S, Shen Z, Kochansky CJ, Strauss JR, Franklin RB and Vincent SH. Differences in the pharmacokinetics of peroxisome proliferator-activated receptor agonists in genetically obese Zucker and sprague-dawley rats: implications of decreased glucuronidation in obese Zucker rats, Drug Metab Dispos 2004; 32: 909-914.

Kim SK and Novak RF. The role of intracellular signaling in insulin-mediated regulation of drug metabolizing enzyme gene and protein expression, Pharmacol Ther 2007; 113: 88-120.

Kim SK, Woodcroft KJ and Novak RF. Insulin and glucagon regulation of glutathione S-transferase expression in primary cultured rat hepatocytes, J Pharmacol Exp Ther 2003a; 305: 353-361.

Kim SK, Woodcroft KJ, Kim SG and Novak RF. Insulin and glucagon signaling in regulation of microsomal epoxide hydrolase expression in primary cultured rat hepatocytes, Drug Metab Dispos 2003b; 31: 1260-1268.

Kim SK, Woodcroft KJ and Novak RF. Insulin and growth factor signaling in Drug Metabolism and Transport (Lash, L.H., Ed.). Humana Press, Totowa, 2005: pp. 49-83.

Leclercq IA, Farrell GC, Field J, Bell DR, Gonzalez FJ and Robertson GR. CYP2E1 and CYP4A as microsomal catalysts of lipid peroxides in murine nonalcoholic steatohepatitis, J Clin Invest 2000; 105: 1067-1075.

Lieber CS. Cytochrome P-4502E1: its physiological and pathological role, Physiol Rev 1997; 77: 517-544.

Lu SC, Huang ZZ, Yang JM and Tsukamoto H. Effect of ethanol and high-fat feeding on hepatic gamma-glutamylcysteine synthetase subunit expression in the rat, Hepatology 1999; 30: 209-214.

Mukherjee B, Mukherjee JR and Chatterjee M. Lipid peroxidation, glutathione levels and changes in glutathione-related enzyme activities in streptozotocin-induced dia-

betic rats, Immunol Cell Biol 1994; 72: 109-114.

Raucy JL, Lasker JM, Kraner JC, Salazar DE, Lieber CS and Corcoran GB. Induction of cytochrome P450IIE1 in the obese overfed rat, Mol Pharmacol 1991; 39: 275-280.

Raza H, Ahmed I, Lakhani MS, Sharma AK, Pallot D and Monague W. Effect of bitter melon (Momordica charantia) fruit juice on the hepatic cytochrome P450-dependent monooxygenases and glutathione S-transferases in streptozotocin-induced diabetic rats, Biochem Pharmacol 1996; 52: 1639-1642.

Roe AL, Howard G, Blouin R and Snawder JE. Characterization of cytochrome P450 and glutathione S-transferase activity and expression in male and female ob/ob mice, Int J Obes Relat Metab Disord 1999; 23: 48-53.

Rouer E, Mahu JL, Dansette P and Leroux JP. UDP-glucuronosyltransferase, epoxide hydrolase and glutathione S-transferase activities in the liver of diabetic mice, Biochim Biophys Acta 1981; 676: 274-277.

Rubin E and Lieber CS. Hepatic microsomal enzymes in man and rat: induction and inhibition by ethanol, Science 1968; 162: 690-691

Runge-Morris M and Vento C. Effects of streptozotocin-induced diabetes on rat liver sulfotransferase gene expression, Drug Metab Dispos 1995; 23: 455-459.

Sanyal AJ. Mechanisms of Disease: pathogenesis of nonalcoholic fatty liver disease, Nat Clin Pract Gastroenterol Hepatol 2005; 2: 46-53

Shimojo N, Ishizaki T, Imaoka S, Funae Y, Fujii S and Okuda K. Changes in amounts of cytochrome P450 isozymes and levels of catalytic activities in hepatic and renal microsomes of rats with streptozocin-induced diabetes, Biochem Pharmacol 1993; 46: 621-627.

Song BJ, Veech RL and Saenger P. Cytochrome P450IIE1 is elevated in lymphocytes from poorly controlled insulin-dependent diabetics, J Clin Endocrinol Metab 1990; 71: 1036-1040.

Thomas H, Schladt L, Knehr M and Oesch F. Effect of diabetes and starvation on the activity of rat liver epoxide hydrolases, glutathione S-transferases and peroxisomal beta-oxidation, Biochem Pharmacol 1989; 38: 4291-4297.

Tunon MJ, Gonzalez P, Garcia-Pardo LA and Gonzalez J. Hepatic transport of bilirubin in rats with streptozotocin-induced diabetes, J Hepatol 1991; 13: 71-77.

Van de Wiel JA, Fijneman PH, Teeuw KB, Van Ommen B, Noordhoek J and Bos RP. Influence of long-term ethanol treatment on rat liver biotransformation enzymes, Alcohol 1993; 10: 397-402.

Videla LA, Rodrigo R, Araya J and Poniachik J. Oxidative stress and depletion of hepatic long-chain polyunsaturated fatty acids may contribute to nonalcoholic fatty liver disease, Free Radic Biol Med 2004a; 37: 1499-1507.

Videla LA, Rodrigo R, Orellana M, Fernandez V, Tapia G, Quinones L, Varela N, Contreras J, Lazarte R, Csendes A, Rojas J, Maluenda F, Burdiles P, Diaz JC, Smok G, Thielemann L and Poniachik J. Oxidative stress-related parameters in the liver of non-alcoholic fatty liver disease patients, Clin Sci (Lond) 2004b; 106: 261-268.

Visser TJ, van Haasteren GA, Linkels E, Kaptein E, van Toor H and de Greef WJ. Gender-specific changes in thyroid hormone-glucuronidating enzymes in rat liver during short-term fasting and long-term food restriction, Eur J Endocrinol 1996; 135: 489-497.

Wasserman WW and Fahl WE. Functional antioxidant responsive elements, Proc Natl Acad Sci USA 1997; 94: 5361-5366.

Woodcroft KJ, Hafner MS and Novak RF. Insulin signaling in the transcriptional and posttranscriptional regulation of CYP2E1 expression, Hepatology 2002; 35: 263-273.

Xiong H, Yoshinari K, Brouwer KL and Negishi M. Role of constitutive androstane receptor in the in vivo induction of Mrp3 and CYP2B1/2 by phenobarbital, Drug Metab Dispos 2002; 30: 918-923.

Yamazoe Y, Murayama N, Shimada M, Yamauchi K and Kato R. Cytochrome P450 in livers of diabetic rats: Regulation by growth hormone and insulin, Arch Biochem Biophys 1989a; 268: 567-575.

Yamazoe Y, Murayama N, Shimada M, Imaoka S, Funae Y and Kato R. Suppression of hepatic levels of an ethanol-inducible P-450DM/j by growth hormone: relationship between the increased level of P-450DM/j and depletion of growth hormone in diabetes, Mol Pharmacol 1989b; 36: 716-722.

Yoshida K, Hirokawa J, Tagami S, Kawakami Y, Urata Y and Kondo T. Weakened cellular scavenging activity against oxidative stress in diabetes mellitus: regulation of glutathione synthesis and efflux, Diabetologia 1995; 38: 201-210.

Yoshinari K, Takagi S, Sugatani J and Miwa M. Changes in the expression of cytochromes P450 and nuclear receptors in the liver of genetically diabetic db/db mice, Biol Pharm Bull 2006a; 29: 1634-1638.

Yoshinari K, Takagi S, Yoshimasa T, Sugatani J and Miwa M. Hepatic CYP3A expression is attenuated in obese mice fed a high-fat diet, Pharm Res 2006b; 23: 1188-1200.