INTRODUCTION

During drug research and development, primarily healthy young adult animals are used for preclinical toxicology studies conducted according to Good Laboratory Practice (GLP) standards and other regulatory agency guidances. They are easily obtained and randomized for GLP toxicology studies and they produce stable data with small inter-animal variability that can be analyzed easily and accurately.

Drug-induced toxicities are dependent not only on the characteristics of the drug per se, but also on various factors of the patients. One of the most important of these factors is disease conditions which are well known to alter drug absorption, distribution, metabolism, and excretion as well as a patient’s susceptibility to a drug (Groeningen et al., 2000; Kulmatycki et al., 2001; Jones et al., 2003). Such alterations can lead to different types and levels of toxicities that are completely unexpected from standardized preclinical toxicology studies using healthy young adult animals. In today’s modern society, the population of people with lifestyle-related diseases such as obesity, diabetes, hypertension, and hyperlipidemia is growing rapidly. Such disease conditions possibly may change the drug-induced toxicities, which, in turn, may cause a medication-related health crisis. Therefore, preclinical investigations into the alterations in drug-induced toxicities using appropriate disease animal models are very important. This paper reviews the reported data related to the effects of diabetes and hypertriglyceridemia, common lifestyle-related diseases in a modern society, on acetaminophen (APAP)-induced hepatotoxicity and nephrotoxicity in rats and mice. It has generally been reported that diabetes protects rats and mice from APAP-induced hepatotoxicity and there are several reports that help to speculate on the effects of diabetes on APAP-induced nephrotoxicity. In fructose-induced hypertriglyceridemic rats, hepatotoxicity of APAP becomes apparently less severe, whereas nephrotoxicity of APAP becomes significantly more severe. The mechanisms of alteration of APAP-induced hepatorenal toxicity under diabetic and hypertriglyceridemic conditions are also discussed in this paper.

Key words: Acetaminophen, Diabetes, Hepatorenal toxicity, Hypertriglyceridemia, Mouse, Rat

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Mechanisms of APAP-induced hepatorenal toxicity

At therapeutic dosages, APAP is converted mostly to inactive compounds via Phase II metabolism by conjugation with sulfate and glucuronide (Jollow et al., 1974). As the APAP dosage increases, those Phase II metabolism pathways become saturated and more APAP metabolism is diverted to cytochrome P-450 pathways, a minor metabolic pathway that converts APAP to a highly-reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI) (Dahlin et al., 1984; Harbison et al., 1988; Zaher et al., 1998). Under normal condition, NAPQI is detoxified by conjugation with glutathione (GSH), but at sufficiently high doses, GSH becomes depleted (Lucas et al., 2000), leaving NAPQI free to covalently bind to critical cellular proteins, causing hepatocyte necrosis (Mitchell, 1973; Dahlin et al., 1984; Hazelton et al., 1986; Liu et al., 2006). Experiments using knockout mice showed that CYP2E1 and CYP1A2 are mainly involved in NAPQI formation (Zaher et al., 1998). Although covalent binding of NAPQI has been shown to correlate well with toxicity, enhanced oxidative stress (Corcoran et al., 1985; Bajt et al., 2004; Dambach et al., 2006), intracellular leakage of hydrolytic enzymes such as cathepsins (Limaye et al., 2003, 2005), and delayed and/or suppressed cell division and liver tissue repair (Shankar et al., 2003a), have also been shown to occur and are likely important in the initiation of and recovery from toxicity. Recently, Sumioka et al. (2004) reported that the level of expression of hepatic HSP25 may be a crucial determinant of the fate of mice exposed to APAP insult, and Tolson et al. (2006) reported that increased HSP70I expression in response to APAP acts to limit the extent of tissue injury in mice. Abdel-Zaher et al. (2007) pointed out that overproduction of nitric oxide and subsequent depression of intracellular GSH levels are also involved in the induction of APAP hepatotoxicity. Liu et al. (2006) reported that following the hepatocellular initiation events, pro- and anti-inflammatory cascades of the innate immune system are simultaneously activated, and this pro-/anti-inflammatory balance plays a major role in determining the progression and severity of APAP-induced hepatotoxicity.

In Fischer 344 (F344) rats, nephrotoxicity of APAP is due, in part, to the cytochrome P-450-independent N-deacetylation of APAP to p-aminophenol (PAP) (Newton et al., 1985). In mice, intrarenal biotransformation of APAP to a reactive electrophile significantly contributes to APAP covalent binding within the kidneys and subsequent nephrotoxicity (Harts et al., 1994). Hoivik et al. (1995) have shown that renal, rather than hepatic, biotransformation of APAP to a toxic electrophile is central to APAP-induced nephrotoxicity. Recently, Stern et al. (2005a, 2005b) reported that APAP-induced renal injury may involve the APAP-GSH conjugate, or a metabolite derived from it, because disruption of GSH conjugate transport or metabolism pathways protects CD-1 mice from APAP nephrotoxicity, but not hepatotoxicity and that APAP-cysteine, a conjugate product of γ-glutamyl pathway, depletes renal but not hepatic GSH.

In 2001, Bessem and Vermeulen reviewed the APAP-induced hepatorenal toxicities in detail, but the mechanism of APAP-induced hepatorenal toxicity had not been fully clarified yet.

Effects of diabetes on APAP-induced hepatorenal toxicity

Diabetic patients have a nearly 2-fold higher risk of acute liver failure, chronic liver failure, and hepatocarcinogenesis compared with non-diabetic patients (El-Serag and Everhart, 2002; Huerta et al., 2002; El-Serag et al., 2004).

It has generally been reported that diabetes protects rats and mice from APAP-induced hepatotoxicity (Price and Jollow, 1982; Gaynes and Watkins, 1989; Jeffery et al., 1991; Sawant et al., 2006). Price and Jollow (1982) reported that hepatoprotection in insulin-deficient diabetic male rats are due to increased capacity to eliminate the drug as nontoxic glucuronide and sulfate conjugates and to increased GSH-dependent detoxification capacity. They suggested that the most striking effect of diabetes on APAP metabolism is a marked enhancement of the glucuronidation capacity, possibly as a result of diabetes-related acceleration of uridine diphosphate glucuronic acid (UDPGA) formation (Price and Jollow, 1981; Sweeney et al., 1981). In contrast to these reports, decreased levels of GSH have been observed in blood of diabetic patients (Ilting et al., 1951; Lal and Kumar, 1967; Awadallah et al., 1978). In streptozotocin (STZ)-induced diabetic Sprague Dawley (SD) rats, an additional mechanism of hepatoprotection may be higher rates of biliary excretion of the APAP-cysteine brought about by an increased activity of...
γ-glutamyl transpeptidase in the livers of these animals (Watkins et al., 1998). Shankar et al. (2003a) reported that the resistance of STZ-induced diabetic mice against APAP hepatotoxicity appears to be mediated by a combination of enhanced APAP clearance and robust compensatory tissue repair. It is also said that hepatoprotection in type 1 diabetic mice is dependent on peroxisome proliferator receptor (PPAR)-α activation (Shankar et al., 2002). Recently, Sawant et al. (2006) reported that GSH conjugation may not be underlying mechanisms of the hepatoprotective effects in type 2 diabetic mice since type 2 diabetes does not change GSH status of the liver.

Although liver microsomal cytochrome P-450 changes have been reported in diabetic animal models, the results have been varied and inconclusive. In STZ-induced type 1 diabetic rats, liver microsomal CYP2E1 protein expression and enzyme activity are markedly increased (Sakuma et al., 2001; Wang et al., 2000), whereas in type 1 diabetic mice a small but statistically significant decrease occurs (Sakuma et al., 2001; Shankar et al., 2003a). In type 2 diabetic rats (Sawant et al., 2004) and mice (Sawant et al., 2006) including type 2 ob/ob mice and Zucker rats (Novak and Wooderoff, 2000), CYP2E1 protein and mRNA are not significantly changed. In this connection, in type 2 diabetic patients, contradictory evidence of increased CYP2E1 (Wang et al., 2003) and unchanged CYP2E1 protein and activity (Lucas et al., 1998) has been reported. Collectively, Sawant et al. (2006) suggest that decreased bioactivation and increased detoxification are unlikely to explain diabetes-induced protection from APAP-induced hepatotoxicity.

Mitochondrial damage is an early event after APAP overdosage (Qiu et al., 1998; Ruepp et al., 2002), leading to decreased oxidative phosphorylation and energy production (Meyers et al., 1988; Vendemiale et al., 1996). Liver mitochondria from diabetic animals are less susceptible to oxidative damage (Sukalski et al., 1993; Ferreira et al., 1999; Santos et al., 2001) and have a higher antioxidant capacity (Elangovan et al., 2000), which is critical in the elimination of mitochondrially generated reactive oxygen species.

Sawant et al. (2006) reported that advancement of cells in the cell division cycle and higher tissue repair protect type 2 diabetic mice by preventing progression of APAP-initiated liver injury that normally leads to mortality. It appears that the greater number of cells in G2 phase in the diabetic mice provide the stimulus for early onset of tissue repair (Shanker et al., 2003a). Diabetic mice also exhibit markedly higher levels of circulating growth hormone which may play a role in this increased repair response. This is supported by the report of Shimizu et al. (2001) that carbon tetrachloride-induced hepatotoxicity is enhanced in the Mini rat model, a Wistar-derived transgenic rat in which the expression of growth hormone is suppressed by the presence of an antisense transgene.

In addition to the above-mentioned APAP-induced hepatotoxicity, several studies have established the critical role of liver cell division and compensatory tissue repair in determining the ultimate outcome of various hepatotoxic exposures, viz. survival or death (Mehendale, 1995; Dalu and Mehendale, 1996; Rao et al., 1996; Soni and Mehendale, 1998). Type 1 diabetic mice exhibit early onset of liver tissue repair as well as lower bioactivation of thioacetamide (TA) and are resistant to TA-induced hepatotoxicity (Shanker et al., 2003b), while type 1 diabetic rats are sensitive to TA-induced hepatotoxicity due to induced CYP2E1 (Wang et al., 2000) and inhibited compensatory tissue repair (Sawant et al., 2006). It was also reported that modulation of carbon tetrachloride-induced hepatotoxicity was different between diabetic rats and diabetic mice (Gaynes and Watkins, 1989; Watkins et al., 1998). Moreover, unlike type 2 diabetic rats, type 2 diabetic mice are resistant to carbon tetrachloride and bromobenzene (Sawant et al., 2006). The cause of such species difference in the sensitivity to hepatotoxicant between diabetic rats and diabetic mice is not clear.

In humans, diabetes is associated with a predisposition to renal disease including nephropathy and renal failure (Hollenberg, 2004; Jaw et al., 2006). Although there are no reports directly dealing with the effects of diabetes on APAP-induced nephrotoxicity, the following evidence is helpful in speculating its effect. Diabetes is associated with hyperlipidemia, an elevation of triglyceride and cholesterol levels that is one of the primary causes of a majority of diabetic complications (Saad and Naijar, 2005). Hypertriglyceridemic rats showed enhanced APAP-induced nephrotoxicity (Ishida et al., 1995) and a greater sensitivity to the nephrotoxic effect of cyclosporine A (Bohdancecká et al., 1999), suggesting that diabetes might have similar effects. Diabetes is also associated with increased blood glucose which leads to systemic oxidative stress in diabetes (Hunt and Wolff, 1991). In addition, changes in the antioxidant enzymatic systems activity occur in various tissues including the kidney (Kedziora-Kornatowska et al., 2003) together with significant reduction of total nitric oxide in the kidney (Hoshiyama et al., 2003) and with unchanged or decreased GSH levels (Mukherjee et al., 1994; Watkins et al., 1998). The diabetic state also enhances the clearance of APAP from plasma irrespective of the level of liver injury (Shankar et al., 2003a), perhaps due to diabetes-related changes in renal morphology and function.
reported in diabetes such as polyuria, glucosuria, and glomerular hypertrophy (Sharma et al., 1999). These conditions may influence APAP-induced nephrotoxicity.

Experimental diabetes has been shown to protect against the nephrotoxic effects of several compounds including cyclosporine A, gentamicin, cisplatin, mercuric chloride and cephaloridine (Vaamonde et al., 1984; Elliott et al., 1985; Valentovic et al., 1991; Cacini et al., 1993; Grover et al., 2002; Saad and Naijar, 2005). Challenge with nephrotoxicants is known to stimulate a compensatory tissue repair response in the kidney (Dobyan et al., 1980; Haagsma and Pound, 1980; Laurent et al., 1988; Korrapati et al., 2005), suggesting that such repair mechanisms underlie this diabetes-induced protection. Dnyanmote et al. (2000) reported that diabetes-induced replacement of S-phase cells in the kidney is critical in mitigating the progression of renal injury initiated by 1,2-dichlorovinyl-cysteine by upregulating tissue repair, resulting in acute renal failure avoidance and survival. On the other hand, Valentovic et al. (2006) reported that STZ-induced diabetic rats showed increased susceptibility to benzo(a)pyrene-mediated renal damage following repeated treatment for 5 weeks when compared to age-matched normoglycemic rats, although the mechanism is unclear.

Effects of hypertriglyceridemia on APAP-induced hepatorenal toxicity

Although alteration of the developmental mode of APAP-toxicity has been reported in diabetic rats and mice and spontaneous hyperlipidemic rats as mentioned above, their disease conditions are too complex to clarify the major factor which causes an alteration in the mode of APAP-toxicity. In contrast, as mentioned later, fructose-induced hypertriglyceridemic rats showed only an increase in plasma triglyceride level, and they are considered to be of great benefit in the examination of the effects of hypertriglyceridemia on the mode of toxicity of various chemicals including APAP (Ishida et al., 1995).

Like diabetic rats, fructose-pretreated hypertriglyceridemic rats have less severe APAP-induced hepatotoxicity, but significantly more severe nephrotoxicity (Fig. 1).

Fructose induces hypertriglyceridemia both by overproduction of very-low-density lipoprotein (VLDL) triglyceride and by impaired removal rate of VLDL triglyceride from the blood (Iwata et al., 1990; Mazur et al., 1992; Yoshino et al., 1992; Ishida et al., 1997b). Liver and kidney are important sites of fructose disposal (Bjorkman and Felig, 1982). In this regard, it is reported that the treatment of sucrose, olive oil, glycerol and Triton WR-1339 also induce hypertriglyceridemia in rats (Nikkila and Ojala, 1964; Lindall et al., 1971; Steiner et al., 1984), however, like glucose, not all of these compounds induce changes in APAP-toxicity similar to that seen in fructose-pretreated hypertriglyceridemic rats. Pretreatments of fructose, sucrose and glycerol which enhance fructose metabolism along with triglyceride overproduction in the liver and kidney cause clear modifications of APAP-induced hepatorenal toxicity. In contrast, glucose, olive oil and Triton WR-1339, which do not produce enhanced fructose metabolism or triglyceride overproduction in the liver and kidney, have no effect on the mode of APAP-toxicity, similar to glucose. This suggests that enhancement of fructose metabolism in conjugation with overproduction of triglyceride in both liver and kidney is responsible for the modification of APAP-induced hepatorenal toxicity in fructose-induced hypertriglyceridemic rats. The contrast in triglyceride production between fructose and glucose treatments may reflect a difference in the amount of lipogenic substrates available in the liver (Herzberg and Rogerson, 1982; Spence and Pitot, 1982). Neither hyperglycemia nor hyperinsulinemia can account for changes in APAP-toxicity in diabetic animal models since both fructose and glucose pretreatments produce both conditions...
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(Kazumi et al., 1986), but only fructose pretreatment produces hypertriglyceridemia and changes in APAP-toxicity (Ishida et al., 1995).

It was previously shown that fructose was partially efficient in preventing hypoxic and APAP-induced damage to hepatocytes, and that its protective effect was related to its ability to provide glycolytic ATP (Anundi and DeGroot, 1989; Mourelle et al., 1991). ATP produced glycolytically may be primarily used for maintenance of membrane functions and Ca2+-uptake by endoplasmic reticulum promoting the survival of the cell (McDonald et al., 1971; Jones and Mason, 1978; Weiss and Lamp, 1987). It has been demonstrated that other carbohydrates such as glucose, xylitol and mannitol do not have the same ability to increase ATP levels as fructose does (Sols et al., 1964). Price and Jollow (1989) showed that administration of glucose and glucronic substrates did not reverse the fasting-induced potentiation of APAP-induced hepatotoxicity and that the rate-determining step for UDP-GA synthesis for glucuronidation of hepatotoxic doses of APAP was prior to UDP-glucose formation. Thus even though equivalent concentrations of APAP and/or metabolites are distributed in the livers of both control and fructose-pretreated rats, it is possible that the latter show less severe hepatic lesions. In addition, the possibility remains that the protective effect of fructose against cell injury demonstrated in vitro system (Anundi and DeGroot, 1989; Mourelle et al., 1991; Beales and McLean, 1995), enhancement of non-toxic metabolic pathways (glucuronidation) by increased hepatic glycogen concentration (Hjelle, 1986; Price and Jollow, 1989; Howell and Klaassen, 1991) and stimulation of cell division and hepatic tissue repair by enhanced fructose metabolism in hepatocytes (Chanda et al., 1995) could contribute to a reduction of APAP-induced hepatotoxicity.

On the other hand, Hojo et al. (2000) described that co-administration of APAP and sucrose resulted in marked liver injury as detected by increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities. This sucrose-associated increase in serum ALT and AST activities was APAP-selective and not detected with carbon tetrachloride, D-galactosamine or alpha-naphthyl isothiocyanate. They also suggested that the involvement of high-dose sucrose is at a step(s) occurring after the metabolic activation of APAP and that fructose has a primary role in the sucrose enhancement of APAP-toxicity in rats. This contradiction with the above-mentioned results reported by Ishida et al. (1995) (reduction of APAP hepatotoxicity by fructose) may be due to differences in treatment regimens between those two studies. In the study conducted by Hojo et al. (2000), rats received a single oral administration of extremely high doses of sucrose (1.8 to 3.4 g/kg) concomitant with oral APAP. In contrast, rats received a single ip injection of APAP after 3 or 5 weeks of pretreatment with fructose in drinking water ad libitum in the studies reported by Ishida et al. (1995, 1997a).

Ishida et al. (1997d) also reported that renal APAP-concentrations during the early phase (15 and 30 min after APAP-administration) were significantly greater in fructose-pretreated rats than those in normal ones and plasma and hepatic APAP concentrations in fructose-pretreated rats were greater than those in normal ones only at the later phase (plasma: 6 hr; liver: 6 and 12 hr after APAP-administration). On the other hand, there were no significant differences in the APAP-induced depletion of hepatic and renal GSH nor in the basal hepatic and renal cytochrome P-450 contents between fructose-pretreated and control rats. Fructose-pretreated rats were also more susceptible to PAP, a nephrotoxic metabolite of APAP (Newton et al., 1985), than normal rats. Therefore, they indicated that enhanced susceptibility to APAP-induced nephrotoxicity in fructose-pretreated rats may be due, at least in part, to increased renal APAP concentration and increased susceptibility to its nephrotoxic metabolite. In addition, partial hepatectomy (70% or 90%) did not potentiate APAP-induced nephrotoxicity or renal APAP concentration, and fructose-pretreated rats showed more severe renal lesions and greater renal APAP concentration than non-pretreated rats irrespective of partial hepatectomy, indicating that an increase in renal APAP concentration in the fructose-pretreated rats is not related to an alteration in hepatic metabolic capacity of APAP (Ishida et al., 1997c).

F344 rats have two toxic metabolic pathways involving cytochrome P-450-dependent oxidation of APAP to NAPQI and P-450-independent deacetylation of APAP to PAP (Fig. 2) (McMurty et al., 1978; Newton et al., 1985; Emeigh Hart et al., 1991; Mugford and Tarloff, 1995). In contrast, in SD rats, which are more resistant to APAP nephrotoxicity than F344 rats, this deacetylation pathway does not significantly contribute to the bioactivation of APAP (Mugford and Tarloff, 1995). Ishida et al. (1997a) reported that the inhibition of APAP oxidation by piperonyl butoxide, a cytochrome P-450 inhibitor, or inhibition of deacetylation by bis(p-nitrophenyl)phosphate, carboxylesterase inhibitor, did not alter APAP-induced renal lesions in the non-pretreated SD rats while these inhibitors protected fructose-pretreated SD rats from APAP nephrotoxicity. These results indicate that the enhancement of APAP-induced nephrotoxicity in fructose-pretreated SD rats is due not only to cytochrome P-450-
mediated oxidation of APAP but also to its cytochrome P-450-independent deacetylation which is not responsible for APAP-induced nephrotoxicity in normal SD rats. In addition, since there were no differences in the severity of gentamicin- (Tarloff and Goldstein, 1994), chloroform- (Pohl et al., 1977; Kluwe and Hook, 1981), or 45 min-ischemia/reperfusion-induced renal lesions (Arnold et al., 1986; Shapiro et al., 1987, 1989; Mourelle et al., 1991) between the non-pretreated and the fructose-pretreated rats (Ishida et al., 1997a), alterations in APAP-specific pharmacokinetics and metabolism may play an important role in enhancement of APAP nephrotoxicity in fructose-pretreated rats.

From the above-mentioned experiments, Ishida et al. (1997a) concluded that the enhancement of APAP-induced nephrotoxicity observed in the fructose-pretreated SD rats is attributable to at least the following two factors: 1) an increase in renal APAP concentration at the early phase (15 and 30 min after APAP dosing) and 2) enhanced bioactivation of APAP via two metabolic pathways: cytochrome P-450-mediated oxidation of APAP to NAPQI and cytochrome P-450-independent deacetylation of APAP to PAP which is not responsible for nephrotoxicity in normal SD rats (Figs. 2 and 3). Similar changes in the severity of nephrotoxicity caused by hyperlipidemia have been reported in several animal models with various nephrotoxicants. In hypercholesterolemic rabbits, an increase in plasma cholesterol levels modifies amphotericin B pharmacokinetics and renal toxicity following multiple intravenous doses of deoxycholate-amphotericin B and amphotericin lipid complex (Ramaswamy et al., 2001). Bohdanecká et al. (1999) reported that rats with hereditary hypertriglyceridemia showed greater sensitivity to the nephrotoxic effect of cyclosporine A than control rats, and Yang et al. (2004) reported that hypertriglyceridemia aggravated contrast media-induced nephrotoxicity through reduced production of nitric oxide.

Ishida et al. (1998) reported that enhancement of APAP-induced nephrotoxicity by fructose pretreatment is sex-dependent. Namely, fructose pretreatment markedly potentiates APAP-induced nephrotoxicity in male rats while it has minimal effect in female rats. Furthermore, the enhanced APAP-induced nephrotoxicity was reduced by castration and estradiol treatment in males, but potentiated by ovariectomy in females, indicating that the enhancement of APAP-induced nephrotoxicity is dependent on sex hormones. In addition, it has been reported that the susceptibility to APAP-induced hepatorenal toxicity, fructose metabolism, and fructose-induced hypertriglyceridemia are also sex-dependent (Hart et al.,...
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![Metabolic pathways of acetaminophen in the liver and kidney of fructose-pretreated hypertriglyceridemic rats.](image)

**Fig. 3.** Metabolic pathways of acetaminophen in the liver and kidney of fructose-pretreated hypertriglyceridemic rats.

1982; Raheja *et al.*, 1983; Cohen, 1986; Mugford and Tarloff, 1995; Tarloff *et al.*, 1996). These reports support the assumption that mixed function oxidase activities (Kuo and Fook, 1980), glutathione conjugation (Potter *et al.*, 1974), and non-toxic metabolic pathways, (i.e. glucuronidation and sulfation) (Linscheer *et al.*, 1980; Raheja *et al.*, 1982), are also sex-dependent.

**Conclusion**

Many reports indicate that diabetes can change the mode of APAP-induced hepatotoxicity in rats and mice through several different mechanisms. Diabetes is also considered to alter the mode of APAP-induced nephrotoxicity judging from the reports of the effects of diabetes on other chemicals-induced nephrotoxicity, although there are no reports directly dealing with the effects of diabetes on APAP-induced nephrotoxicity. In addition, there are very interesting reports that in fructose-induced hypertriglyceridemic rats, as compared with normal ones, hepatotoxicity of APAP is apparently less severe, whereas nephrotoxicity of APAP is significantly more severe. The mechanisms of alteration of APAP-induced hepatorenal toxicity under hypertriglyceridemic condition are well discussed by Ishida *et al.* (1997a, 1997b and 1997d) Differing from diabetic animals, fructose-induced hypertriglyceridemic rats show only an increase in plasma triglyceride level, and so they are considered to be of great benefit for examination of the effects of hypertriglyceridemia, which is a representative lifestyle-related disease in a modern society, on the mode of toxicity of various chemicals.

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**REFERENCES**


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Ther., 237, 750-756.


are protected from acetaminophen hepatotoxicity. Toxicol. Sci., 73, 220-234.


