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# Lidocaine metabolism in isolated perfused liver from streptozotocin-induced diabetic rats

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## Abstract

Insulin deficiency can trigger not only an altered glucose metabolic state but may also affect drug metabolism. The formation rate of the major lidocaine metabolite monoethylglycinxylidide (MEGX) has been shown to reflect the activity of CYP3A2 and CYP1A2. In the present study the effects of streptozotocin-induced diabetes on lidocaine elimination and MEGX formation in a model of isolated, non-recirculated, perfused rat liver with constant flow was evaluated. The parameters describing hepatic lidocaine elimination studied 10 days after streptozotocin administration, i.e. hepatic extraction coefficient ($E_H$), hepatic clearance ($Cl_H$) and elimination rate ($V_L$), were significantly decreased in diabetic livers in comparison with the controls. The $E_H$ in the controls varied between $0.88 \pm 0.07$ and $0.93 \pm 0.06$, whereas in diabetic livers it was markedly reduced to between $0.27 \pm 0.15$ and $0.39 \pm 0.23$. The $Cl_H$ dropped to $8.04 \pm 4.12 - 11.66 \pm 2.99$ mL min$^{-1}$ in diabetic rats in comparison to $26.29 \pm 2.07 - 27.94 \pm 0.92$ mL min$^{-1}$ in the control animals. The $V_L$ was estimated to be $128.08 \pm 18.60 - 136.44 \pm 17.59$ $\mu$g mL$^{-1}$ in the controls and from $40.87 \pm 28.31$ $\mu$g mL$^{-1}$ to $56.83 \pm 22.16$ $\mu$g mL$^{-1}$ in diabetic perfused livers. The major lidocaine metabolite, i.e. MEGX, concentrations were significantly decreased in diabetic rats compared to the controls. The observed changes indicate an impairment of N-deethylation metabolic pathway in streptozotocin-induced diabetic rats, i.e. a possible decrease in the enzymatic activity of CYP3A2 and CYP1A2.

## Introduction

Diabetes mellitus, a disease with wide prevalence in humans, involves many complications, including micro- and macroangiopathy as well as neuropathy, which in turn lead to increased mortality (Sullivan & Feldman 2005; Renard & Van Obberghen 2006). Besides those diabetes-related pathologies, it is believed that possible diabetes-induced alterations in the hepatic biotransformation of pharmaceutical agents could also pose an additional health risk because of the dangerous side-effects of drug toxicity (Cheng & Morgan 2001). Although diabetes is known to involve profound alterations in intracellular metabolism in most tissues, little definitive data are available concerning the effects of diabetes on hepatic drug metabolism (Dixon et al 1961; Dajani & Saheb 1974; Klaassen & Watkins 1984; Watkins & Dykstra 1987). Moreover, the results of those studies are not univocal and are often contradictory. In one of the first studies on drug metabolism in streptozotocin-induced diabetes, inhibition of the rates of hexobarbital and aniline metabolism were observed by Ackerman & Leibman (1977). However, Warren et al (1983) reported no alterations in the protein distribution in the cytochrome P450 region, and no changes in benzopyrene hydroxylase activity and an increase in aniline hydroxylase activity in the same model of diabetes. Further studies in streptozotocin-induced diabetes in rats by Knodell et al (1984) revealed a significant increase in cytochrome P450 content and enzyme activity (evaluated as meperidine demethylation and pentobarbital hydroxylation). The data on the activity of other metabolic pathways during streptozotocin-induced diabetes are also contradictory, e.g. the activity of testosterone hydroxylase was reported to be significantly increased (Vega et al 1993) or not affected (Warren et al 1983) and glucuronidation impairment (Emudianughe et al 1988) and increase were seen (Lin et al 1989).

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Taking into consideration the number of diabetic patients and the paucity of available data on drug pharmacokinetics in diabetics it is important to characterize the kinetics of drugs, especially those metabolized in the liver. A representative of these drugs is lidocaine, whose hepatic metabolism is well documented both in animals and humans. The drug is mostly eliminated via biotransformation in the liver in two main pathways i.e. N-deethylation and hydroxylation with formation of monoethylglycinxylidide (MEGX) and its metabolite glycinxylidide (GX) as well as 3- and 4-hydroxylidocaine, respectively (Pang et al 1986; Nakamoto et al 1997). It has been shown that MEGX formation rate is a sensitive indicator of hepatic dysfunction, and in the case of rats reflects the activity of CYP3A2 and CYP1A2 (Nakamoto et al 1997). Thus, lidocaine can be used as a model substance to assess the activity of CYP3A2 (the rat counterpart of human CYP3A4) and CYP1A2. The aim of this study was to evaluate the effect of experimental streptozotocin-induced diabetes on lidocaine metabolism and MEGX formation using the isolated perfused liver model. The perfused liver model with constant perfusate flow enables the elimination of other potentially confounding factors, e.g. liver blood flow or protein binding, which could affect lidocaine metabolism. Thus, the results of the study could give an insight into the activity of some hepatic metabolic pathways in diabetes mellitus.

## Materials and Methods

### Animals

The study was carried out in male Wistar rats (280–380 g) kept under standard laboratory conditions. The animals were randomly divided into two experimental groups: group I, control animals (six rats); group II, streptozotocin-induced diabetic rats (six animals). The animals were made diabetic with a single intravenous injection of streptozotocin, 60 mg $kg^{-1}$ bw (Sigma). The streptozotocin was dissolved in 0.9% saline containing 0.01 M sodium citrate (pH adjusted to 4.5), and then 1 mL per rat was injected via the tail vein within 30 min of its preparation. The diabetic state was assessed by measurement of non-fasting plasma glucose exceeding 200 mg $dL^{-1}$, evaluated 10 days after streptozotocin administration (Ackerman & Liebman 1977; Fein et al 1980). Glucose concentration was measured using an Olympus AU 560 analyser (Bio-Merieux). The protocol of the study was approved by the local Ethics Committee for Animal Studies (Szczecin, Poland)

### Isolated liver perfusion

The liver was isolated 10 days after streptozotocin administration and perfused as described by Miller et al (1951). Each rat was anesthetized with urethane (1 g $kg^{-1}$ ip), heparinized and cannulated into the bile duct, portal vein and superior vena cava. The liver was perfused in situ with oxygenated Krebs–Ringer solution buffer with composition (in mM) 118.0 NaCl, 4.75 KCl, 2.54 $CaCl_2$, 1.2 $MgSO_4$, 1.0 $NaH_2PO_4$, 25.0 $NaHCO_3$ and 11.1 glucose, and constantly gassed with 95%$O_2$/5%$CO_2$ by a non-recirculating method at a constant flow rate of 30 mL $min^{-1}$. The temperature of the liver perfusion system was kept at 37°C. The liver was allowed to equilibrate for about 10 min before the addition of lidocaine. Lidocaine was dissolved in perfusate (final concentration 5 mg $L^{-1}$) and the isolated liver was perfused for 30 min. Perfusion solution and perfusate samples were collected at timed intervals 5, 10, 15, 20, 25 and 30 min after the perfusion onset for lidocaine and MEGX assays. During the experiment perfusate $pO_2$, $pCO_2$ and pH were monitored, and the liver oxygen consumption was calculated. Perfusate samples were stored at −20°C until analysis.

The concentrations of lidocaine and its metabolite, MEGX, were determined by the HPLC method of Chen et al (1992a, b). Based on lidocaine and MEGX concentrations the following parameters related to hepatic lidocaine elimination were evaluated:

$$\text{hepatic extraction coefficient } E_H = (C_{in} - C_{out})/C_{in}$$
$$\text{hepatic clearance } Cl_H = E_H \times Q_H$$
$$\text{elimination rate } V_L = Q_H \times (C_{in} - C_{out})$$

where $C_{in}$ is the lidocaine concentration in the perfusate container ($\mu$g $L^{-1}$), $C_{out}$ is the lidocaine concentrations in perfusate leaving the liver ($\mu$g $L^{-1}$) and $Q_H$ is the perfusate flow rate (mL $min^{-1}$).

### Statistical analysis

The results obtained are given as mean ± s.d. Statistical analysis was performed using the Friedman's test to compare lidocaine and MEGX perfusate concentrations, and in the case of lidocaine hepatic elimination parameters the Friedman's test was followed by the Mann–Whitney U-test, with a $P$ value of $< 0.05$ being statistically significant.

## Results

The body weight of the animals measured 10 days from the study onset was similar in both study groups, and did not change significantly from initial values, i.e. in the controls it increased by 4.88%, whereas in rats with streptozotocin-induced diabetes it decreased by 18.53%. Plasma glucose concentrations measured 10 days from the onset of the study were significantly increased in animals given streptozotocin, 388.4 ± 164.4 mg $dL^{-1}$ as compared with the controls, 102.8 ± 31.1 mg $dL^{-1}$ ($P < 0.01$).

The present study demonstrated that experimental streptozotocin-induced diabetes results in a significant increase in perfusate lidocaine concentrations at all study points up to 30 min from the liver perfusion onset (Figure 1). However, in diabetic rats, when compared to the controls, the major lidocaine metabolite (MEGX) concentrations decreased throughout the observation period. At all measurement points the differences were statistically significant ($P < 0.01$).

The parameters describing hepatic lidocaine elimination, i.e. the hepatic extraction coefficient ($E_H$), hepatic

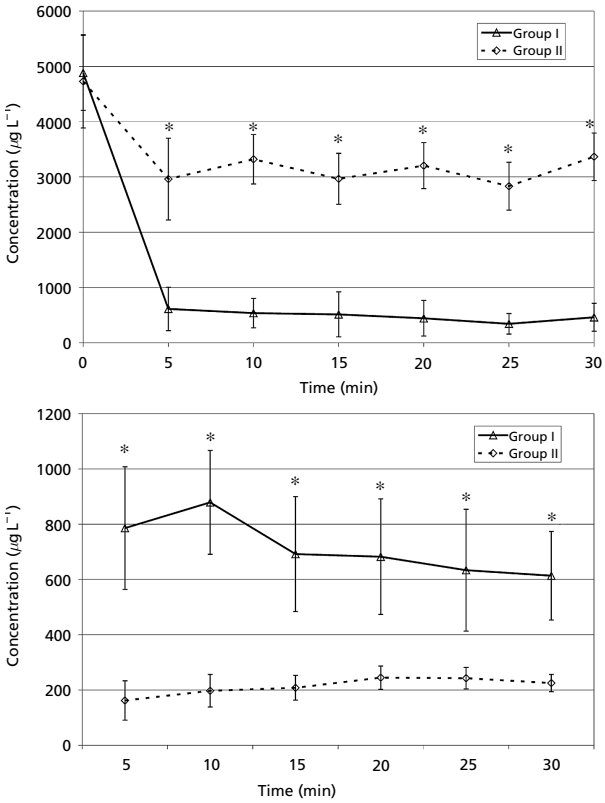


**Figure 1** Lidocaine (upper panel) and MEGX (lower panel) perfusate concentrations from livers of streptozotocin-induced diabetic rats (group II, n = 6) and control animals (group I, n = 6). *$P < 0.01$.

clearance ($Cl_H$) and elimination rate ($V_L$), were significantly decreased when evaluated at all time points analysed (Table 1). In the case of all the parameters the reduction was homogenous at the analysed time points, and ranged between 30 and 40%. The $E_H$ in the controls varied between $0.88 \pm 0.07$ and $0.93 \pm 0.06$, whereas in diabetic livers it was markedly reduced from $0.27 \pm 0.15$ to $0.39 \pm 0.23$. Similar changes were noted for $Cl_H$ and $V_L$. The $Cl_H$ dropped to $8.04 \pm 4.12 - 11.66 \pm 2.99\,mL\,min^{-1}$ in diabetic rats in comparison to $26.29 \pm 2.07 - 27.94 \pm 0.92\,mL\,min^{-1}$ in the control animals. The $V_L$ was estimated to be $128.08 \pm 18.60 - 136.44 \pm 17.59\,\mu g\,mL^{-1}$ in healthy rats and from $40.87 \pm 28.31\,\mu g\,mL^{-1}$ to $56.83 \pm 22.16\,\mu g\,mL^{-1}$ in diabetic perfused livers.

## Discussion

Lidocaine is almost exclusively eliminated by hepatic biotransformation, with renal excretion of the unmodified drug accounting for only 2 to 3% of the elimination of an intravenous dose. It is postulated that two isoforms of CYP P450 are implicated in lidocaine metabolism, i.e. CYP3A4 and CYP1A2 in humans and CYP3A2 and CYP1A2 in rats (Bargetzi et al 1989; Wang et al 1999; Orlando et al 2004). However, lidocaine is a drug with a medium to high extraction ratio and therefore its clearance also significantly depends on liver blood flow (Tucker & Mather 1979). The contribution of both metabolism and liver blood flow to drug elimination does not enable the discrimination between the aforementioned factors to overall drug elimination in vivo. In our previous studies in streptozotocin-induced diabetic rats we found enhanced lidocaine elimination accompanied by an increased MEGX formation rate in vivo after intravenous administration (Gawronska-Szklarz et al 2003a), whereas in-vitro studies in liver microsomes demonstrated an impairment of the drug metabolism (Gawronska-Szklarz et al 2003b). To complement former studies and gather more detailed data on the interplay between liver blood flow and drug metabolism in lidocaine elimination in streptozotocin-induced diabetic rats, a model of isolated perfused liver with constant flow rate was applied.

Streptozotocin-induced diabetes is one of the most popular models of experimental, insulin-dependent diabetes. The study time point (10 days from streptozotocin administration) reflects an acute phase of insulin-dependent diabetes, contrary to more remote time points (20 days up to 3 months), which are a counterpart of chronic diabetes in humans (Skett & Joels 1985). An increased activity of CYP1A2, CYP2E1, CYP4A2 and CYP4A3 in microsomes of streptozotocin-induced diabetic rats has been reported (Kim et al 2005). However, the activity of CYP2C11 in those animals was reduced (Shimojo et al 1993). Reports on the activity of CYP3A2, a counterpart

**Table 1** Lidocaine hepatic elimination parameters (mean ± s.d.) in diabetic livers (group II) and controls (group I)

| | Parameter (units) | Time (min) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 15 | 20 | 25 | 30 |
| Group I | $E_H$ (L/L) | 0.876 ± 0.069 | 0.892 ± 0.042 | 0.898 ± 0.071 | 0.912 ± 0.056 | 0.931 ± 0.062 | 0.905 ± 0.044 |
| Group II | | 0.356 ± 0.188* | 0.275 ± 0.149* | 0.359 ± 0.130* | 0.299 ± 0.149* | 0.388 ± 0.231* | 0.267 ± 0.137* |
| Group I | $Cl_H$ (mL min$^{-1}$) | 26.29 ± 2.07 | 26.79 ± 1.30 | 26.95 ± 2.16 | 27.37 ± 1.68 | 27.94 ± 0.92 | 27.16 ± 1.33* |
| Group II | | 10.69 ± 5.67* | 8.26 ± 4.49* | 10.77 ± 3.81* | 8.98 ± 4.49* | 11.66 ± 2.99* | 8.04 ± 4.12* |
| Group I | $V_L$ ($\mu g\,mL^{-1}$) | 128.08 ± 18.60 | 130.33 ± 15.66 | 131.04 ± 13.55 | 136.44 ± 17.59 | 136.14 ± 17.38 | 132.58 ± 18.91 |
| Group II | | 52.97 ± 31.35* | 42.24 ± 27.84* | 52.97 ± 23.04* | 45.67 ± 28.31* | 56.83 ± 22.16* | 40.87 ± 28.31* |

*$P < 0.01$.

of human CYP3A4, in rats with experimental diabetes are contradictory. Thummel & Schenkman (1990) noted an increase in the enzyme activity in vivo, whereas Shimojo et al (1993) demonstrated a decrease in activity in diabetic rats. Some of the discrepancies may rely on the gender of the animals studied because in streptozotocin-induced diabetic rats a suppression of CYP3A2 was noted in males whereas an induction was observed in females (Thummel & Schenkman 1990).

In the present study male rats were used in the model of experimental diabetes since Meftah & Skett (1989) noted sex differences in the metabolism of lidocaine in the rat. However, the same authors reported that induction of diabetes in the male rat abolished those sex-related differences. During the study a significant reduction in the enzymatic activity of the cytochrome P450 N-deethylation pathway activity, measured as lidocaine hepatic extraction coefficient ($E_H$), hepatic clearance ($Cl_H$) and elimination rate ($V_L$), was demonstrated in streptozotocin-induced diabetic rats. The observed changes indicate an impairment of N-deethylation, i.e. a possible decrease in the enzymatic activity of CYP3A2 and CYP1A2, which are the major enzymes catalysing this reaction.

Analysing our data in streptozotocin-induced diabetic rats from the present study, i.e. decreased metabolic lidocaine elimination under constant perfusate flow in isolated perfused liver model, as well as previous ones, i.e. inhibition of lidocaine metabolism in isolated liver microsomes (Gawronska-Szklarz et al 2003b) and enhanced elimination in vivo (Gawronska-Szklarz et al 2003a), one can conclude that streptozotocin-induced diabetes not only affects liver enzymatic activity but also influences liver blood flow. However, in otherwise healthy rats treated with pentobarbital, Nakamoto et al (1997) revealed accelerated lidocaine elimination and metabolism evaluated in two experimental models, i.e. in vivo as well as in isolated hepatic microsomes. There is no available information on the hepatic blood flow in streptozotocin-induced diabetic rats. Lucas & Foy (1977) reported an increased proportion of cardiac output received by the kidneys and gastrointestinal tract in streptozotocin-induced diabetic rats as compared to control animals. It is therefore possible that increased blood flow in those animals can contribute to accelerated hepatic elimination of high extraction ratio drugs, such as lidocaine. Further studies are required to elucidate the mechanisms underlying hepatic drug elimination in diabetes.

Another factor in the present study that might be implicated in lidocaine metabolism is urethane anaesthesia. Studies in rats administered a single dose of urethane (Loch et al 1995; Meneguz et al 1999) indicated that urethane increased the activity of CYP1A by 91.5 and 40% and reduced CYP3A activity by 37 and 40.5%, respectively. However, both groups in the study were administered urethane in the same protocol so its effects were comparable in the control and diabetic rats.

The detailed mechanisms, e.g. effects of hypoinsulinaemia or hyperglycaemia, underlying altered drug metabolism in diabetes are not completely elucidated. Ackerman & Leibman (1977) revealed that hyperglycaemia produced by glucose infusion did not affect the metabolism of hexobarbital in vitro, whereas treatment of animals with streptozotocin, which produces an insulin-deficient state, caused inhibition of the rate of hexobarbital metabolism associated with prolongation of hexobarbital sleeping times. Similarly, Reinke et al (1978) found an increase in aniline hydroxylase activity and cytochrome P450 content in streptozotocin-induced diabetic rats. Insulin treatment of diabetic animals antagonized all physical and biochemical abnormalities of the diabetic state. Furthermore, administration of methyl analogues of streptozotocin did not produce a diabetic state and resulted in no changes in aniline hydroxylase activity and cytochrome P450 content. These findings are in keeping with the observations of Lin et al (1989), who observed correction of increased diflunisal elimination following insulin administration, and Shimojo et al (1993), who found that insulin administration restored the catalytic activities of aniline hydroxylation, testosterone 2-$\beta$-, 6-$\beta$-, 7-$\alpha$, 16-$\beta$-hydroxylation. Those observations suggest that insulin deficiency primarily influences the drug metabolism of diabetic animals.

## Conclusions

Summarizing the results of the present study it can be stated that streptozotocin-induced diabetes reduces lidocaine elimination along with a decrease in the formation rate of the major lidocaine metabolite (MEGX). The observed changes indicate an impairment of the N-deethylation metabolic pathway in streptozotocin-induced diabetic rats, i.e. a possible decrease in the enzymatic activity of CYP3A2 and CYP1A2, which are the major enzymes catalysing this reaction. Extrapolating these data to humans suggests that diabetes mellitus may affect the metabolism of drugs that are metabolised through CYP3A4 (the human counterpart of rat CYP3A2) and CYP1A2. Inhibition of the hepatic metabolism of drugs may precipitate an increased risk of medication-related toxicity or drug–drug interactions in diabetic patients.

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