CYTOPROTECTIVE EFFECTS OF TAURINE AGAINST TOXICITY INDUCED BY ISONIAZID AND HYDRAZINE IN ISOLATED RAT HEPATOCYTES

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Isoniazid is one of the most commonly used drugs to treat tuberculosis. Its administration is associated with a high incidence of hepatotoxicity. The aim of this study was to establish the protective effects of taurine against cytotoxicity induced by isoniazid and its suspected toxic metabolite hydrazine in isolated rat hepatocytes by measuring reactive oxygen species (ROS) formation, lipid peroxidation, mitochondrial depolarisation, reduced glutathione (GSH), and oxidised glutathione (GSSG). Isoniazid caused no significant ROS formation in normal hepatocytes, but in glutathione-depleted cells it was considerable. Hydrazine caused ROS formation and lipid peroxidation in both intact and glutathione-depleted cells. Both isoniazid and hydrazine caused mitochondrial membrane depolarisation. Hydrazine lowered cellular GSH reserve and increased GSSG. Taurine (200 μmol L⁻¹) and N-acetylcysteine (200 μmol L⁻¹) effectively countered the toxic effects of isoniazid and/or hydrazine by decreasing ROS formation, lipid peroxidation, and mitochondrial damage. Taurine prevented depletion of GSH and lowered GSSG levels in hydrazine-treated cells. This study suggests that the protective effects of taurine against isoniazid and its intermediary metabolite hydrazine cytotoxicity in rat hepatocytes could be attributed to antioxidative action.

KEY WORDS: cytotoxicity, glutathione, lipid peroxidation, mitochondria, N-acetylcysteine, oxidative stress

Tuberculosis is a serious infectious disease affecting large population segments, especially in developing countries (1). Isoniazid is the most effective agent against tuberculosis and is used both for the treatment and the prophylaxis of this disease. Clinical use of isoniazid is associated with a high incidence of hepatotoxicity (2). The exact mechanism by which isoniazid affects the liver is not clear yet, but some authors point to oxidative stress in hepatocytes (3). The main culprit of hepatotoxic action, in fact, seems to be isoniazid metabolite hydrazine (4). Hydrazine is the product of cytochrome P450 metabolising activity (5) and is believed to induce oxidative stress (6). One of the consequences of oxidative stress is lipid peroxidation, as established in animal models treated with anti-tuberculosis drugs such as isoniazid (7) or hydrazine (8). Another consequence, established by Chowdhury et al. (9), is mitochondrial damage in hepatocytes.

Since oxidative stress is regarded as the major mechanism of isoniazid-induced hepatotoxicity, ROS scavengers or intracellular glutathione enhancers have been used to counteract isoniazid toxicity. One such agent, N-acetylcysteine (NAC) was reported to
effectively inhibit isoniazid hepatotoxicity in rats (10) or rat hepatocytes (11).

Taurine is a sulphur-containing amino acid that stabilises cell membrane and regulates cell ions, \( \text{Ca}^{2+} \) in particular (12). Moreover, hypotaurine, an intermediate in the biosynthesis of taurine, has been reported to scavenge free radicals in vivo (13). There are several reports on the protective effects of taurine against hepatotoxicity induced by chemicals (14,15) or xenobiotics (16, 17). Its protective effects seem to extend to other types of cells as well (18, 19), and have even been reported in clinical settings against diabetes (20) and pancreatitis (21).

The aim of our study was to evaluate the in vitro effects of taurine against toxicity induced by isoniazid and its metabolite hydrazine in freshly isolated rat hepatocytes.

MATERIALS AND METHODS

Chemicals

Taurine, 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (HEPES), triethanolamine, NAC, oxidised glutathione (GSSG), 1-bromoheptane (BHP), and 2-vinylpyridine were obtained from Acros (New Jersey, NJ, USA). Albumin bovine-type was purchased from Roche Diagnostics (Indianapolis, IN, USA). Rhodamine 123, isoniazid, 5,5’-dithio-bis(2-nitrobenzoic acid (DTNB), 2’,7’-dichlorofluoresceindiacetate (DCFDA), hydrazine hydrate, and collagenase from \( \text{C}l\text{ostridium histolyticum} \) were obtained from Sigma Aldrich (St. Louis, MO, USA). Ethyleneglycol-bis(\( p \)-aminoethyl-ether)-\( N,N,N',N' \)-tetra-acetic acid (EGTA), trichloroacetic acid (TCA), and Trypan blue were obtained from Merck (Darmstadt, Germany). Cimetidine was purchased from Medisca Pharmaceutique Inc. (Montreal, Canada). Thiobarbituric acid (TBA) was obtained from Serva (Heidelberg, Germany). All salts used for preparing buffer solutions were of analytical grade and obtained from Merck (Darmstadt, Germany).

Animals

Male Sprague-Dawley rats (weighing 250 g to 300 g) were obtained from the Tabriz University of Medical Sciences, Tabriz, Iran. The animals were fed standard chow diet and had free access to water. The animals were handled and used according to the animal handling protocol approved by the University’s ethics committee.

Isolation and incubation of hepatocytes

Hepatocytes were isolated by collagenase perfusion, as described previously (22). The cells (1x10⁶ mL⁻¹) were suspended in the Krebs-Henseleit buffer containing 12.5 mmol L⁻¹ HEPES and incubated under a stream of 95 % \( \text{O}_2 \) and 5 % \( \text{CO}_2 \) in continuously rotating round-bottomed flasks immersed in a water bath at 37 °C. Glutathione-depleted hepatocytes were obtained by pre-incubating hepatocytes with 0.2 mmol L⁻¹ 1-bromoheptane for 30 min (23). Cytochrome P450 was inactivated by preincubation of hepatocytes with cimetidine (2 mmol L⁻¹) 30 min before adding other agents (24).

To establish whether taurine offers effective protection against drug-induced toxicity, it was added to the incubation medium at 200 μmol L⁻¹ 30 min before isoniazid or hydrazine.

Untreated hepatocytes were used as controls in all experiments. Hepatocytes treated with NAC (200 μmol L⁻¹) were used as positive control, since its protective effects on isoniazid-induced hepatotoxicity have been proven in earlier studies (10).

Cell viability

Hepatocyte viability was assessed by plasma membrane disruption as determined using the Trypan blue uptake test (24). Cell viability was determined immediately after isolation and at scheduled time intervals following incubation. Approximately 85 % to 90 % of hepatocytes were viable at the time of isolation.

Determination of reactive oxygen species

Reactive oxygen species (ROS) was determined by measuring the fluorescence intensity of DCFDA, as explained previously (25). Briefly, 1.6 μmol L⁻¹ DCFDA was added to the incubation medium and 1 mL aliquots were drawn at different time points after incubation. These samples were centrifuged at 3000 g for 1 min. Fluorescence intensity was measured in supernatant using a Jasco® FP-750 fluorescence spectrophotometer (Jasco Corporation, Tokyo, Japan). Excitation and emission wavelengths were 490 nm and 520 nm, respectively.

Determination of lipid peroxidation in hepatocytes

Hepatocyte lipid peroxidation was determined by measuring the amount of thiobarbituric acid reactive substances (TBARS) formed during the decomposition of lipid hydroperoxides. After treating a 1.0 mL aliquot
of hepatocyte suspension (10^6 cells mL\(^{-1}\)) with TCA (70 %) and boiling the supernatant with TBA (0.8 %) for 20 min, the absorbance of developed colour was measured at 532 nm in an Ultraspec2000® spectrophotometer (Pharmacia Biotech, Cambridge, England) (24).

Mitochondrial membrane potential assay

Fluorescent dye rhodamine 123 accumulates in intact mitochondria by facilitated diffusion. When a mitochondrion is damaged and its membrane potential reduced, diffusion is no longer facilitated and the amount of rhodamine 123 in supernatant is increased. At different time points, we took 2 mL samples of cell suspension and centrifuged them at 1000 \(g\) for 1 min. The cell pellet was then resuspended in 2 mL of Krebs-Henseleit buffer containing 1.5 \(\mu\)mol L\(^{-1}\) rhodamine 123, and gently shaken in a 37 °C water bath for 10 min. Hepatocytes were separated by centrifugation at 3000 \(g\) for 1 min, and the amount of rhodamine 123 appearing in the incubation medium was measured fluorimetrically using a Jasco® FP-750 fluorescence spectrophotometer at 490 nm excitation and 520 nm emission wavelengths. The capacity of mitochondria to take up rhodamine 123 was calculated as the difference in fluorescence intensity between control and treated cells (22).

Determination of hepatocyte GSH/GSSG content

Hepatocyte GSH and GSSG content was determined using the enzymatic recycling method (26). For GSH, we took 1 mL aliquots of cell suspension (10^6 cells), added 2 mL of 5 % TCA, and centrifuged. Then we added 0.5 mL of Ellman’s reagent (0.0198 % DTNB in 1 % sodium citrate) and 3 mL of phosphate buffer (pH 8.0). The absorbance of developed colour was determined at 412 nm using an Ultraspec® 2000 spectrophotometer. To assess hepatocyte GSSG level, cellular GSH content was first covalently bonded to 2-vinylpyridine. Then the excess of 2-vinylpyridine was neutralised with triethanolamine, and GSSG reduced to GSH using glutathione reductase and NADPH. The amount of GSH formed was measured as described for GSH using the Ellman’s reagent (0.0198 % DTNB in 1 % sodium citrate).

Statistical analysis

Results represent mean values [±standard error (SE)] of at least three independent experiments. Statistical significance of difference between control and treatment groups was determined using the one-way analysis of variance (ANOVA) followed by a Tukey’s post hoc test. Significance was set at \(P<0.05\).

RESULTS

Isoniazid toxicity to rat hepatocytes was concentration-dependent (Figure 1) and its LC\(_{50}\) (causing death to 50 % of the cells after two hours of incubation) was 10 mmol L\(^{-1}\) (Figure 1). Cell death rate induced by concentrations lower than 5 mmol L\(^{-1}\) was not significantly higher than control. Hydrazine was more cytotoxic than the parent drug and its LC\(_{50}\) was 8 mmol L\(^{-1}\) (Figure 2).

In glutathione-depleted cells isoniazid and/or hydrazine-induced cell death rate was dramatically higher than in normal cells (Table 1). N-acetylcysteine reduced this rate significantly. In control hepatocytes, taurine and/or NAC attenuated the toxicity induced by isoniazid and/or hydrazine. However, in glutathione-depleted cells taurine showed no protective effect (data not shown).

Incubation with enzyme-inhibitory agents such as cimetidine reduced the rate of cell death induced by isoniazid (Table 1). The effect of cimetidine on isoniazid-induced toxicity is in line with previous investigations in this field (27) and might indicate the role of reactive metabolites such as hydrazine in isoniazid-induced hepatotoxicity.

There was no significant difference between isoniazid-treated and control hepatocytes in ROS formation levels (Figure 3), but when cellular glutathione reserves were depleted, a significant amount of ROS was formed (Figure 4). N-acetylcysteine effectively reduced ROS formation in isoniazid-treated glutathione-depleted cells (Figure 4). Hydrazine increased ROS formation in both normal and glutathione-depleted cells (Figures 3 and 4). Pretreatment with taurine reduced ROS formation induced by hydrazine (Figure 3) and so did NAC in normal or glutathione-depleted hepatocytes (Figure 3).

Figure 5 compares lipid peroxidation in hepatocytes. Normal cells incubated with isoniazid showed no increase in lipid peroxidation, but glutathione-depleted cells were more susceptible to isoniazid effects. Hydrazine caused higher formation of TBARS in normal cells and an outstanding formation in glutathione-depleted cells. N-acetylcysteine effectively reduced lipid peroxidation in either normal or
Figure 1  Dose response relationship for isoniazid in isolated rat hepatocytes
At different time points, 1 mL $(10^6$ cells) was taken and their viability was evaluated using Trypan blue exclusion test microscopically. The $LC_{50}$ (the dose which caused 50% cell death after 2 h) for isoniazid was found 10 mmol L$^{-1}$. Data are given as mean±SE for three independent experiments.

* Significantly higher as compared to control $(P<0.05)$.

Figure 2  Hydrazine-induced cytotoxicity in isolated rat hepatocytes
The samples were taken at mentioned time intervals and cell death was assessed by Trypan blue exclusion method. Data are shown as mean±SE for at least three separate experiments.

* Significantly higher than control group $(P<0.05)$.

Table 1  Cytotoxicity of isoniazid and hydrazine in isolated rat hepatocytes and the counter effects of protective agents

| Incubation time / min | Control hepatocytes | + 1-Bromohexane 200 μmol L$^{-1}$ | + Cimetidine 2 mmol L$^{-1}$ | + Isoniazid 10 mmol L$^{-1}$ | + Taurine 200 μmol L$^{-1}$ | + NAC 200 μmol L$^{-1}$ | + 1-Bromohexane 200 μmol L$^{-1}$ | + NAC 200 μmol L$^{-1}$ | + Hydrazine 8 mmol L$^{-1}$ | + Taurine 200 μmol L$^{-1}$ | + NAC 200 μmol L$^{-1}$ | + 1-Bromohexane 200 μmol L$^{-1}$ | + NAC 200 μmol L$^{-1}$ |
|----------------------|--------------------|---------------------------------|-----------------------------|-----------------------------|----------------------------|-----------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| 60                   | 20±2               | 22±2                           | 19±2                        | 41±2 $^a$                   | 25±2 $^b$                  | 20±2 $^b$                   | 20±2 $^b$                  | 50±4 $^{a,c}$              | 30±2 $^b$                   | 46±2 $^a$                   | 30±3 $^d$                   | 70±6 $^{a,c}$              | 50±3 $^d$                   |
| 120                  | 23±2               | 24±1                           | 24±2                        | 53±1 $^a$                   | 33±3 $^b$                  | 29±2 $^b$                   | 28±2 $^b$                  | 71±4 $^{a,c}$              | 40±2 $^b$                   | 56±3 $^a$                   | 37±3 $^d$                   | 100 $^{a,c}$               | 77±5 $^d$                   | 100 $^{a,c}$               |
| 180                  | 28±3               | 31±2                           | 30±3                        | 72±5 $^a$                   | 45±2 $^b$                  | 40±2 $^b$                   | 35±2 $^b$                  | 90±3 $^{a,c}$              | 45±2 $^b$                   | 67±4 $^a$                   | 50±2 $^d$                   | 100 $^{a,c}$               | 94±5                       | 100 $^{a,c}$               |

Trypan blue exclusion test was used to assess cell death rate induced by isoniazid. Data are given as mean±SE for at least three independent experiments.

NAC: N-acetylcysteine

$^a$ Glutathione-depleted hepatocytes were prepared with incubating cells with 1-bromohexane (200 μmol L$^{-1}$), 30 min before other agents.

$^b$ Enzyme-inhibited hepatocytes were prepared by incubating rat hepatocytes with cimetidine (2 mmol L$^{-1}$), 30 minutes before other agents.

$^c$ Significantly higher than control group $(P<0.05)$.

$^d$ Significantly lower than isoniazid-treated cells $(P<0.05)$.

$^e$ Significantly higher than hydrazine-treated cells $(P<0.05)$.

$^f$ Significantly lower than hydrazine-treated cells $(P<0.05)$.
Since the cytotoxicity of isoniazid and its metabolite was more severe in glutathione-depleted hepatocytes, we measured cellular glutathione reserves to see if isoniazid or hydrazine affected cellular glutathione content. Our findings confirmed that they significantly reduced cellular GSH (Figure 6). Taurine in turn counteracted this reduction in cellular GSH to an extent.

The decrease in cellular GSH content was accompanied by an increase in GSSG in hydrazine-treated hepatocytes (Figure 7), indicating that GSH depletion was mainly due to its oxidation to GSSG. Treating rat hepatocytes with taurine significantly reduced GSSG in hydrazine-treated cells. Isoniazid caused no significant elevation in cellular GSSG content.

Figure 8 shows changes in respect to mitochondrial membrane potential. Isoniazid and hydrazine caused mitochondrial depolarisation, and taurine and/or NAC counteracted their action in normal hepatocytes. As expected, in glutathione-depleted cells isoniazid/hydrazine effects were even more damaging, and only NAC counteracted them significantly.

DISCUSSION

Taurine showed no significant effect against isoniazid and/or hydrazine in glutathione-depleted cells. Aruoma et al. (13) have already suggested that taurine is a poor antioxidant and reacts slowly with reactive intermediates such as hydroxyl radical (OH•). This points to a limitation of our experiment, as may have not allowed sufficient time for taurine to show better protective effects against chemicals-induced toxicity as in other in vivo experimental models, such as the one described by Dinçer et al. (28). Furthermore, some taurine precursors such as hypotaurine and cysteamine showed better radical scavenging and antioxidant properties (13) and may act better than taurine against chemical-induced cell injury in different situations.

In our study, the effects of isoniazid and hydrazine on ROS formation, lipid peroxidation, and mitochondrial depolarisation were dose-dependent and were even more pronounced in glutathione-depleted rat hepatocytes. However, taurine did protect normal rat liver cells against isoniazid and hydrazine-induced toxicity. These protective effects are associated with the scavenging of free radicals and prevention of GSH depletion (29,30), which might explain why it was not as effective in glutathione-
Figure 5  Lipid peroxidation in hepatocytes exposed to isoniazid and hydrazine
To prepare glutathione-depleted hepatocytes, cells were treated with 1-bromohexane for 30 min before adding other agents. Mean±SE for three experiments is shown as measured after 120 min of incubation time. BHP: 1-bromohexane.

- Significantly higher than control group (P < 0.05).
- Significantly higher than hydrazine-treated group (P < 0.05).
- Higher than BHP-treated group (P < 0.05).
- Lower than isoniazid + BHP (P < 0.01).
- Lower than hydrazine + BHP (P < 0.001).

TBARS – thiobarbituric acid reactive substances

Figure 6  Effect of isoniazid and hydrazine on cellular reduced glutathione (GSH) content and the role of taurine
Data are shown as mean±SE for three separate experiments.

- Significantly lower than control group (P < 0.001).
- Significantly higher than “b” (P < 0.05).
- Significantly higher than “a” (P < 0.05).

Figure 7  Effect of isoniazid and hydrazine on cellular oxidised glutathione (GSSG) formation
Data are shown as mean±SE for three separate experiments.

- Significantly higher than control group (P < 0.001).
- Significantly lower than hydrazine-treated group (P < 0.001).

Figure 8  Mitochondrial depolarization induced by isoniazid and hydrazine
Data represent Mean±SE for at least three independent experiments as assessed after 90 min of incubation.

- Significantly lower than control group (P < 0.001).
- Significantly higher than isoniazid-treated group (P < 0.05).
- Significantly higher than isoniazid-treated group which is depleted of glutathione (P < 0.01).
- Significantly higher than hydrazine-treated group (P < 0.01).
- Significantly higher than hydrazine-treated group which is glutathione-depleted (P < 0.001).
depleted cells. Another reason for its ineffectiveness in glutathione-depleted cells is that the duration of treatment with taurine was not sufficient to upregulate antioxidant enzymes in these cells. As we expected, the cytotoxicity of isoniazid and hydrazine in glutathione-depleted cells increased dramatically (Table 1), which suggests that clinical conditions such as malnutrition increase the risk of isoniazid hepatotoxicity.

ROS formation induced by hydrazine confirmed earlier findings (6). To establish whether taurine could efficiently counteract oxidative damage caused by isoniazid and hydrazine in rat hepatocytes, we compared its effects with the well-known cytoprotective agent N-acetylcysteine. Its protective effects on isoniazid-induced hepatotoxicity have been proven in earlier investigations (10) and generally they could be attributed to its direct effect in scavenging ROS (31). The protective effects of taurine have been reported by Redmond et al. (32), who found that it attenuates nitric oxide- and reactive oxygen intermediate-dependent hepatocyte injury (32), while Kerai et al. (33) observed its protective properties against lipid peroxidation in rats poisoned with ethanol. The results of our study suggest that the protective effects of taurine against isoniazid and/or its metabolite might also be related to attenuation of oxidative stress in isolated rat hepatocytes.

The ability of hydrazine and isoniazid to produce ROS in GSH-depleted cells was further confirmed by the measurements of TBARS, whose levels point to the increased amount of lipid peroxides. Our results suggest that taurine efficiently prevents lipid peroxidation induced both by isoniazid and its reactive metabolite. This is in line with earlier studies (17, 33), which propose that taurine prevents lipid peroxidation through free-radical scavenging.

Another point that should be discussed is increased cellular glutathione content, which may reflect oxidative stress. We found that hydrazine (but not the parent compound isoniazid) increased cellular GSSG content in hepatocytes. Taurine lowered GSSG in hydrazine-treated cells, which could be attributed to its anti-oxidant properties. It is possible that lowered cellular glutathione content reflects the conjugation of reactive metabolites with GSH or oxidation of GSH to GSSG (oxidised glutathione) (34).

Greater mitochondrial damage caused by isoniazid and hydrazine in glutathione-depleted than in normal cells once again confirms the importance of glutathione. What seems to be protecting functional proteins in mitochondria from reactive metabolites is GSH conjugation and therefore GSH depletion makes these targets more vulnerable.

Ozden et al. (35) have reported that the protective properties of taurine against chemical-induced toxicity effect are related to its effects on antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. In our study, however, taurine did not show significant protective effects in glutathione-depleted cells. Perhaps the reason was the insufficient time for taurine to upregulate antioxidant enzymes. In normal hepatocytes, taurine reduces oxidative stress by regulating cellular ions such as Ca²⁺, stabilising cellular membrane, and scavenging reactive species (36), but in glutathione-depleted cells where cellular defence mechanisms are interrupted and isoniazid causes more dramatic toxic effect, this amino acid is unable to protect the hepatocytes. On the other hand, being a glutathione precursor and a more potent radical scavenger than taurine (37), NAC has shown superior protective properties against isoniazid and hydrazine in both intact and glutathione-depleted cells.

CONCLUSION

Regardless of its shortcomings, our study suggests that taurine has a promising protective potential against drug-induced liver injury in rats, and we hope that future studies will address its potential use in more detail.

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Declaration of interest

We report no conflicts of interest and are alone responsible for the content and the writing of this paper.

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Sažetak

CITOPROTEKTIVNO DJELOVANJE TAURINA NA TOKSIČNOST IZONIAZIDA I HIDRAZINA U IZOLIRANIM STANICAMA ŠTAKORA

Izoniazid je jedan od najčešćih lijekova za tuberkulozu, ali se njegova primjena povezuje s veoma učestalom hepatotoksičnosti. Cilj je ovog istraživanja bio ocijeniti djelotvornost taurina u zaštiti izoliranih hepatocita štakora od citotoksičnosti izazvane izoniazidom i njegovim toksičnim metabolitom hidrazinom. U tu smo svrhu utvrdili razine reaktivnih kisikovih spojeva (ROS), lipidnu peroksidaciju, depolarizaciju mitohondrija, reducirani glutation (GSH) te oksidirani glutation (GSSG). Izoniazid nije doveo do značajnoga nastanka ROS-a u normalnih hepatocita, ali je zato bio značajan u stanica osiromašenih glutationom. I izoniazid i hidrazin doveli su do depolarizacije membrane mitohondrija. Hidrazin je smanjio staničnu rezervu GSH i povećao razinu GSSG. Taurin (200 μmol L⁻¹) i N-acetilcistein (200 μmol L⁻¹) uspješno su zaštitili od toksičnoga djelovanja izoniazida i/ili hidrazina, smanjivši nastanak ROS-a, lipidnu peroksidaciju i oštećenje mitohondrija. Taurin je spriječio potpuni gubitak GSH-a te snizio razine GSSG-a u stanica tretiranih hidrazinom. Rezultati našeg istraživanja upućuju na to da se zaštitno djelovanje taurina od stanične toksičnosti izoniazida i hidrazina može pripisati njegovu antioksidacijskom djelovanju.

KLIJUČNE RIJEČI: citotoksičnost, glutation, lipidna peroksidacija, mitohondriji, N-acetilcistein, oksidativni stres

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