

Prior administration of a low dose of thioacetamide protects type 1 diabetic rats from subsequent administration of lethal dose of thioacetamide

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Abstract

Previously, we reported that an ordinarily non-lethal dose of thioacetamide (TA, 300 mg/kg) causes 90% mortality in type 1 diabetic rats due to inhibited liver tissue repair, whereas 30 mg TA/kg allows 100% survival due to stimulated although delayed tissue repair. Objective of this investigation was to test whether prior administration of a low dose of TA (30 mg/kg) would lead to sustainable stimulation of liver tissue repair in type 1 diabetic rats sufficient to protect from a subsequently administered lethal dose of TA. Therefore, in the present study, the hypothesis that preplacement of tissue repair by a low dose of TA (30 mg TA/kg, ip) can reverse the hepatotoxicant sensitivity (autoprotection) in type 1 diabetic rats was tested.

Preliminary studies revealed that a single intraperitoneal (ip) administration of TA causes 90% mortality in diabetic rats with as low as 75 mg/kg. To establish an autoprotection model in diabetic condition, diabetic rats were treated with 30 mg TA/kg (priming dose). Administration of priming dose stimulated tissue repair that peaked at 72 h, at which time these rats were treated with a single ip dose of 75 mg TA/kg. Our results show that tissue repair stimulated by the priming dose enabled diabetic rats to overexpress, calpastatin, endogenous inhibitor of calpain, to inhibit calpain-mediated progression of liver injury induced by the subsequent administration of lethal dose, resulting in 100% survival. Further investigation revealed that protection observed in these rats is not due to decreased bioactivation. These studies underscore the importance of stimulation of tissue repair in the final outcome of liver injury (survival/death) after hepatotoxicant challenge. Furthermore, these results also suggest that it is possible to stimulate tissue repair in diabetics to overcome the enhanced sensitivity of hepatotoxicants.

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1. Introduction

Type 1 as well as type 2 diabetes are known to potentiate the hepatotoxicity of numerous structurally and mechanistically diverse hepatotoxicants such as thioacetamide (TA), CHCl₃, and CCl₄ (El-Hawari and Plaa, 1983; Hanasono et al., 1975; Sawant et al., 2004, 2006).

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A large prospective cohort study indicates that diabetic patients are at two times higher risk of acute liver failure compared to non-diabetic patients (El-Serag and Everhart, 2002). To what extent, if any, drug treatments affect liver in diabetic patients was not investigated. Collectively, however these studies suggest that diabetics suffer from higher sensitivity to numerous drugs and hepatotoxicants. Previously, our laboratory reported that a normally non-lethal dose of TA (300 mg/kg, ip) causes acute liver failure and 90% mortality in type 1 diabetic rats (Wang et al., 2000a) due to inhibited S phase DNA synthesis and inhibited liver tissue repair (Wang et al., 2000a,b, 2001). On the other hand, diabetic rats receiving a 10-fold lower dose (30 mg TA/kg, ip) exhibited delayed but stimulated tissue repair (S phase DNA synthesis peaked at 72 h after TA administration), resulting in delayed recovery as compared to TA treated non diabetic rats and 100% survival (Wang et al., 2000a). Detailed investigation of the molecular mechanisms revealed that cyclin D1-retinoblastoma signaling pathway was inhibited in diabetic rats receiving 300 mg TA/kg, explaining inhibited tissue repair in these rats (Devi and Mehendale, 2005a,b, 2006). In contrast, diabetic rats receiving a 10-fold lower dose of TA (30 mg/kg) exhibited only a delay in cyclin D1-retinoblastoma signaling, explaining delayed tissue repair. These studies established that impaired tissue repair in diabetic rats plays a determinant role in the potentiation of TA-induced hepatotoxicity.

Therefore, it was of interest to investigate, whether it is possible to stimulate sufficient liver tissue repair in diabetic rats to protect from a subsequently administered lethal dose. Previous work had shown that a low dose of TA (30 mg/kg) stimulates tissue repair (peak at 72 h). Therefore, the objective of this investigation was to test whether prior administration of a low dose of TA (30 mg/kg) to diabetic rats would lead to sustainable stimulation of liver tissue repair sufficient to protect from a subsequently administered lethal dose of TA. We hypothesized that preplacement of tissue repair by the low dose of TA (30 mg TA/kg, ip) can reverse (autoprotection) the hepatotoxicant sensitivity in type 1 diabetic rats.

Autoprotection is a phenomenon whereby prior exposure to a small dose of a chemical results in protection against a subsequently administered lethal dose of the same compound (Mehendale et al., 1994). A well known example of autoprotection is the protection provided by a small dose of carbon tetrachloride against a high dose of the same compound administered 24 h later (Mehendale et al., 1994; Thakore and Mehendale, 1991). In these experiments, neither bioactivation nor the metabolism and disposition of CCl₄ were affected

(Rao and Mehendale, 1993). The lower dose of CCl₄ stimulates tissue repair resulting in augmented and sustained hepatocellular division and tissue repair, which enables the autoprotected rats to overcome the same level of massive injury, which is ordinarily irreversible and leads to hepatic failure followed by animal death. Autoprotection has been established with several other structurally and mechanistically dissimilar toxicants such as TA, 2-butoxyethanol, S-(1-2-dichlorovinyl)-L-cysteine (DCVC) in various tissues such as liver, blood, lung, and kidney (Barton et al., 2000; Mangipudy et al., 1995a; Sivarao and Mehendale, 1995; Vaidya et al., 2003). The mechanism for TA autoprotection is also stimulated cell division and tissue repair by the priming dose of TA (Mangipudy et al., 1995a). The mechanism of 2-butoxyethanol autoprotection is the appearance of newly formed red blood cells which are resistant to hemolysis (Sivarao and Mehendale, 1995; Sawant et al., 1999). Autoprotection against α -naphthylthiourea is due to stimulated alveolar epithelial cell division (Barton et al., 2000). Recently, autoprotection has been observed in kidney with DCVC and the molecular mechanisms upregulated by the priming dose appear to explain stimulated cell division and renal tissue repair (Korrapati et al., 2005; Korrapati et al., 2006; Vaidya et al., 2003). Therefore, work with structurally diverse model toxicants known to inflict tissue injury by equally diverse mechanisms points to the critical importance of priming dose-stimulated tissue repair in the recovery from even massive tissue injury.

We report here that administration of a low dose of TA (30 mg/kg) stimulates liver tissue repair in diabetic rats, offering protection against a high dose due to sustained hepatic cell division and tissue repair. These findings indicate that even though promitogenic and tissue repair signals are downregulated upon exposure to liver toxicants in diabetic rats, pharmacological intervention may be possible to upregulate such signals to avert drug-induced liver failure encountered due to hepatotoxic sensitivity in diabetes.

2. Materials and methods

2.1. Induction of diabetes

Type 1 diabetes was induced in male Sprague-Dawley rats as described previously (Wang et al., 2000a). Briefly, male Sprague-Dawley rats (250–300 g) were obtained from our central animal facility. The rats received commercial rodent chow (Teklad rodent diet # 7002, Harlan Teklad, Madison, WI) and water *ad libitum* and were housed under controlled temperature ($21 \pm 1^\circ\text{C}$), humidity ($50 \pm 10\%$), and a 12 h photoperiod. Animal care and use were in accordance with the NIH Guide

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