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Boron ameliorates fulminant hepatic failure by counteracting the changes associated with the oxidative stress

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Abstract

Boron has well-defined biological effects and may be of therapeutic benefit. In the current paper, the effect of boron in the form of borax was tested in experimental animal model of fulminant hepatic failure (FHF). The syndrome was induced in female Wistar rats by three consecutive daily intraperitoneal injections of thioacetamide (400 mg/kg). In the treatment groups, rats received borax (4.0 mg/kg) orally for three consecutive days followed by thioacetamide. The group administered with thioacetamide plus vehicle, and the borax alone treated rats served as controls. In all groups, rats were terminated 4 h after administering the last dose of thioacetamide, and the tissue/serum was used to measure hepatic levels of thiobarbituric acid reactive substances, reduced glutathione, and various enzymes associated with oxidative stress including peroxide metabolizing enzymes and xanthine oxidase. In thioacetamide treated group, many fold increase in the activity level of serum marker enzymes suggesting FHF was observed that could be brought down significantly in rats receiving boron. Modulation and a correlation in the activity level of oxidant generating enzyme and lipid peroxidation as well as hepatic glutathione level was also observed in rats receiving thioacetamide. In the group receiving boron followed by thioacetamide, these changes could be minimized moderately. The activity level of the peroxide metabolizing enzymes and the tripeptide glutathione, which decreased following thioacetamide treatment were moderately elevated in the group receiving boron followed by thioacetamide. The data clearly shows that borax partly normalizes the liver and offsets the deleterious effects observed in FHF by modulating the oxidative stress parameters.
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Keywords: Fulminant hepatic failure; Boron; Protection; Thioacetamide; Oxidative stress

1. Introduction

Fulminant hepatic failure (FHF) is one of the most intriguing and challenging conditions in the entire field of internal medicine [1]. It represents a clinical scenario that is associated with high morbidity and mortality, and very limited treatment options [2]. The syndrome encompasses a pattern of clinical symptoms and pathophysiological response associated with the rapid arrest of normal hepatic function [3], and is characterized by an acute onset of severe hepatic dysfunction in absence of pre-existing liver disease. The hallmarks of FHF are severe hepatocyte damage with massive necrosis that results in jaundice, hepatic encephalopathy, coagulopathy and prolonged prothrombin time. Viral infection and drug-induced hepatotoxicity are the most common causes of the syndrome [2,4,5]. Miscellaneous conditions such as Wilson's disease, Budd–Chiari syndrome, or ischemia are also considered among various causes of FHF [6–8]. Thioacetamide (TAA), a

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thiono-sulfur-containing compound with liver damaging activity, is often used to induce FHF in experimental animal models [9–11]. Shortly after administration, TAA undergoes extensive metabolism to acetamide and thioacetamide S-oxide by the mixed function oxidase system [12]. The monooxygenase system further metabolizes thioacetamide S-oxide to thioacetamide S-dioxide, which binds to cellular macromolecules and may be responsible for producing damage [13]. Recent studies have implicated reactive oxygen species (ROS) in TAA-induced liver injury [14,15], and therefore, oxidative stress may be implicated, in part, in the pathogenesis of FHF [16]. Oxidative stress affects many cellular functions by various mechanisms such as the alteration in gene expression through the activation of transcription factor, or the induction of permeability transition in mitochondria with fatal consequences. Trace elements such as Zn and Se have long been recognized as protectors of hepatic tissue damage [17,18]. This can be attributed either to the antioxidant properties of these elements or to their interaction with other trace elements/molecules in maintaining the cellular harmony [19–21]. In the present study, the efficacy of boron in protecting fulminant hepatic failure is examined.

Boron is a ubiquitous element widely distributed in nature in the form of borates at low concentrations in soils and rocks [22], and is released by the natural weathering processes in the form of boric acid, which is water soluble and biologically available. Being a dynamic trace element, boron has been observed to exert multiple effects [23]. The biological essentiality of the element in plants is well established since 1920s [24]. However, in animals, evidences have only recently been started accumulating suggesting the role of boron in diseased conditions [25–27]. Boron is distributed throughout soft tissues and fluids of animals and humans at concentrations mostly between 0.015 and 0.6 μg/g fresh tissue, and in a study in UK, serum boron concentration in 50 human blood samples ranged from 0.77 to 4.45 μmol/l (22.3 ng/ml) with a median of 2.06 μmol/l [28]. In animal systems, boron has been identified for its ability to strengthen the tissue antioxidant defenses [29] via a yet unidentified mechanism that may involve changes in oxidative metabolism [30]. Since the ROS is suggested to contribute to the pathogenesis of several forms of hepatic injury [14,15], suppression of ROS production or neutralization may reduce damage. Considering the assumption favoring the role of boron in counteracting the oxidative stress, boron was investigated in this study for its effect in FHF, which involves ROS in its pathogenesis. Borax is a commonly found compound of boron, which has been employed in this present study. It is completely absorbed when taken up by the oral route of exposure [31].

2. Materials and methods

2.1. Materials

Thioacetamide was procured from Sigma Chem. Co. (St. Louis, MO, USA). All other chemicals and kits used in this study were of highest purity grade purchased from standard commercial sources in India. Specific activities of all the enzymes measured in this study were determined by monitoring the change in the absorbance at respective wavelengths using a Perkin-Elmer Biolambda-20 spectrophotometer.

2.2. Animals

Adult female albino Wistar rats (weighing 150–200 g) were obtained from, and kept in the Central Animal House Facility of the institute in propylene cages in an environmentally controlled room with 12 h light/dark cycle. Each group consisted of six rats. Animals had free access to standard pellet diet and tap water ad libitum. Guidelines issued by the Animal Ethics Committee for the care and use of laboratory animals was strictly followed.

2.3. Induction of FHF and the experimental design

Fulminant hepatic failure was induced by three consecutive intraperitoneal injections of thioacetamide (400 mg/kg) at 24 h interval [9–11]. Supportive therapy by subcutaneous administration of 5% dextrose (25 ml/kg) and 0.9% sodium chloride with potassium (20 mequiv./l) was given every 12 h to avoid weight loss, hypoglycemia, and renal failure, as described by Geller [32]. Borax (4.0 mg/kg) was administered to rats orally for three consecutive days at an interval of 24 h followed by the administration of TAA, which was given an hour after the last dose of borax was administered. The dose level for boron for this study was selected on the basis of the studies in our laboratory, which showed that the protective response of boron reached its maximum at 4 mg/kg [27]. The group of rats given borax alone, and the group of rats receiving the intraperitoneal injections of thioacetamide alone, and the animals receiving injections of similar volumes of the vehicle (normal saline) served as controls. All animals were sacrificed at the same time and all the biochemical estimations were completed on the same day.

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