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Original Article

Alterations in proteins and transaminases activity induced by thioacetamide in albino rats

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Abstract
Thioacetamide (TAA) has been widely utilized in the development of animal models of hepatic damage by a number of researchers. The current investigation was designed to evaluate changes in tissue and serum total proteins and albumin along with urea, uric acid and serum transaminases activity after 12 and 24h of TAA administration in albino rats. Rats were randomly divided into three groups (n=3) namely control group, 12h group and 24h group. Each experimental group (12h and 24h) was administered 300 mg/ kg TAA intraperitoneally (i.p) while control received same volume of normal saline solution. Rats of 12h and 24h group were killed after 12 and 24h of TAA administration respectively. Blood was obtained; livers were excised and processed for protein profile and transaminases activity analysis. TAA injection resulted in significant alterations in serum proteins and transaminases levels. Significant hypoproteinemia and hypoalbuminemia were observed in sera as well as liver tissue of both experimental groups compared to control. Furthermore, transaminases activity was significantly increased for both; AST (P=0.0045) and ALT (P=0.0015) in both experimental groups when compared to control. Taking in account these results it can be concluded that TAA induces changes in the liver marker enzymes along with the change in the sera and tissue total protein contents specifically albumin.
Key words: Albumin, ALT, AST, Liver, Thioacetamide, Total proteins.

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INTRODUCTION

Liver fibrosis has been extensively studied employing various animal models (Caballero *et al.*, 2001; David *et al.*, 2002; Watanabe *et al.*, 2009). Thioacetamide (TAA) is a fungicide with potent hepatotoxic effects (Chilakapati *et al.*, 2005; Childs and Siegler, 1945). Concerning histological and biochemical changes, using different doses, times and routes of administration (Barker and Smuckler, 1972; Kim *et al.*, 2000; Shapiro *et al.*, 2005), TAA-induced rat models has been shown to resemble the human liver cirrhosis and serves to be suitable for studying the causes of human liver diseases (An *et al.*, 2006; Belanger and Butterworth, 2005; Gupta and Dixit, 2009; Li *et al.*, 2002; Manibur Rahman, 2001; Perez *et al.*, 2002; Rahman and Hodgson, 2003; Shapiro *et al.*, 2005; Stankova *et al.*, 2010). TAA not only affects liver but it also induces some pronounced alterations in structure and function of thymus (Barker and Smuckler, 1973), kidney (Barker and Smuckler, 1974; Caballero *et al.*, 2001), intestine (Caballero *et al.*, 2001; Ortega *et al.*, 1997), spleen, (al-Bader *et al.*, 2000) and lungs (Latha *et al.*, 2003). TAA provokes cellular damage generating free radicals, cytotoxic oxygen metabolites and other intermediate compounds resulting in lipid peroxidation, and certain other pathological effects like various cancers, aging and retinal deterioration as well (Caballero *et al.*, 2001; Perwez Hussain and Harris, 2007; Reznick *et al.*, 2006; Shapiro *et al.*, 2005). It is also involved in the alterations of key pathways of cellular respiration (Natarajan *et al.*, 2006; Osada *et al.*, 1993). Moreover, it leads to the formation of long-chain polyunsaturated fatty acids which alters

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lipoprotein metabolism (Moreira *et al.*, 1995). Furthermore, TAA induction interfere the action of ornithine aminotransferase and urea cycle resulting in an altered serum amino acid profile (Fontana *et al.*, 1996). Proteins are the integral constituents of the cells and regulate various key physiological functions of cell proliferation (Ladomery and Sommerville, 2005; Perbal, 2004), differentiation (Antic and Keene, 1997; Kratchmarova *et al.*, 2005) and death (Fesik, 2005; Liang and Fesik, 1997). Minor alterations in the structure and expression of proteins may influence its activity and lead to disease development. TAA when absorbed in body impairs many biochemical reactions and leads to an abnormal level of total serum profile, activities of hepatic enzymes (Fontana *et al.*, 1996) and bilirubin (Amin *et al.*, 2012). Denaturation and charge modifications of protein has been previously observed as TAA reacts extensively with proteins (Witzmann *et al.*, 1996), forming acetylimidolysine derivatives (Cheon Jeong *et al.*, 1999; Lee *et al.*, 2003) with injury of multiple protein systems (Shaker *et al.*, 2011) i.e. the one involved in stress response proteins e.g. heat shock proteins, that of endoplasmic reticulum and those responsible for mitochondrial respiration (Andres *et al.*, 2003; Toivola *et al.*, 2010). It also induces various histopathological alterations including gentle vascular clogging and modest inflammation characterized by change in nuclear size, jam-packed sinusoids and necrosis in the body (Wong *et al.*, 2012). So, the current research was planned to investigate the alterations in protein profile in sera and liver tissue and serum urea, uric acid and transaminases activities in albino rats induced by TAA after 12 and 24h of its administration.

MATERIALS AND METHODS

Preparation of thioacetamide

Stock solution of TAA was prepared by diluting the pure crystals of salt in distilled water. Rigorous stirring was performed to completely dissolve the crystals.

Experimental design

To induce liver damage, 300mg/kg TAA was administered intraperitoneally to albino rats of both experimental groups. Control rats received injections of normal saline (n=3). All the animals were housed in standard conditions (12: 12 light/ dark period; 22 ± 1°C). All the animals have a free access to water and food any time. Ketamine–distilled water mixture (1:1) was injected i.p. to anesthetize followed by killing the rats of 12h group and 24h group after 12 and 24h of TAA administration respectively. Livers were removed and processed for protein extraction. Blood was collected from control and treated animals into plain tube with activated gel and stored till further use.

Serum Quantitative Assessment

Blood samples were incubated at 4°C for clotting and were centrifuged at 2000g for about half an hour. Sera were removed in sterile circumstances for quantitative assessment of total proteins, albumin, urea, uric acid and transaminases activity via ready to use commercial kits. All the assessments were carried out according to the manufacturer's instructions.

Preparation of liver homogenate

1g liver tissues of all the experimental and control group were dissolved in 6N NaOH overnight at 40°C and homogenized using a tissue homogenizer. The resultant homogenates were centrifuged at 200× g for 20 minutes for clarifying the samples and for better solidity of the resulting pellet. The samples were avoided heating during extraction. To improve the separation of proteins from lipids, centrifugation step was repeated. The resulting supernatants were used for the assessment of total protein and albumin concentration as suggested by manufacturer using BCA protein assay reagent kit (Pierce, Bonn, Germany) with some modification in the protocol.

Statistical analysis

Prism Graph pad 5 software (San Diego, CA) was used in analysis of data. One-way analysis of variance (AONVA) and *Dunnett post hoc test* was utilized to calculate statistical significance. Significance was accepted at $P < 0.05$. Results are represented as Mean ±S.E.M (n=3).

RESULTS

Evaluation of serum aminotransferases activity

Administration of TAA to rats of experimental groups induced a statistically significant rise in serum activities of hepatic enzymes AST and ALT compared with the control ($P < 0.05$). A 131.5 and 157% increase in AST while 158 and

150% rise for ALT was noted for 12 and 24h, respectively compared to control (Figure 1a, b) which are indicative of hepatic injury.

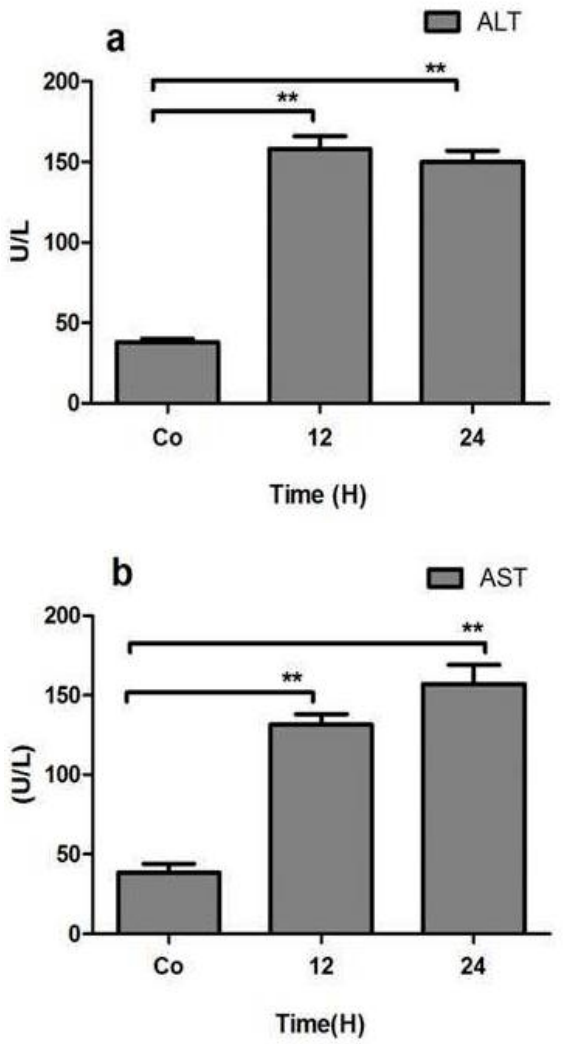

Figure 1: Serum level of transaminases after administration of TAA. (a) Serum level of ALT and (b) Serum level of AST were found to be increased significantly (P<0.05) in both experimental groups compared to control.

Changes in the sera and Liver tissue level of Total proteins and Albumin

Decrease in serum levels of both total proteins and albumin was noted after TAA injection to experimental animals. A significant decrease was noted in tissue total proteins level and serum albumin level after 12h. After 24h of TAA administration the total protein concentration in sera and tissue samples was declined ascompared to respective controls which are clear reflective of tissue damage. However, significant hypoalbuminemia was observed only in serum samples and not in tissue samples of both the experimental groups compared to control (Fig. 2a, b).

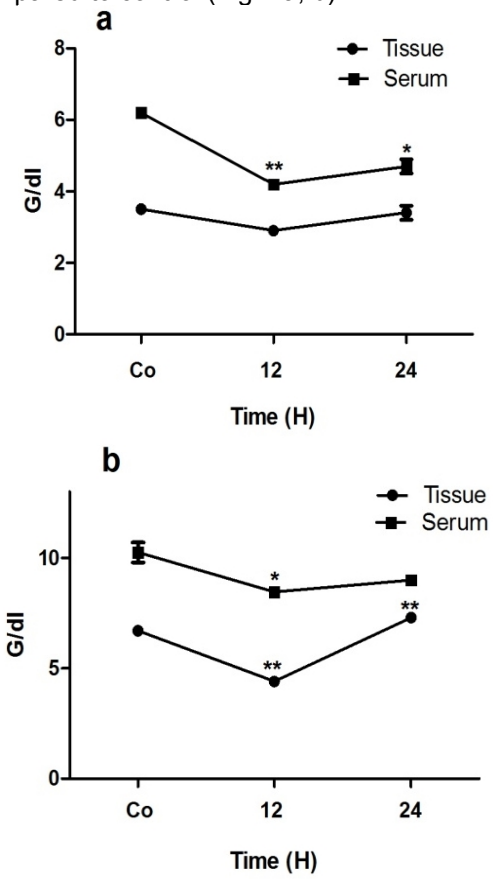

Figure 2: Changes in the serum and tissue albumin, and Total Protein. (a) A statistically significant decrease was noted in the level of albumin in sera samples of 12h and 24h groups compared to control. (b) In contrast to it, a significant decrease in total proteins of tissue samples was noted in both experimental groups compared to control. Statistically significant alterations (P<0.05) are marked with the help of asterisks (*P<0.05, **P<0.01, ***P<0.001).

Changes in the serum level of urea and uric acid

Serum levels of urea and uric acid showed a statistically significant positive and negative change, respectively after 24h in treated rats compared to control. A rise of 43.2% and decline of 25.84% was observed for

the said parameters respectively. Inter experimental group comparison in case of urea showed almost twice incremented value (P <0.05; Fig. 3).

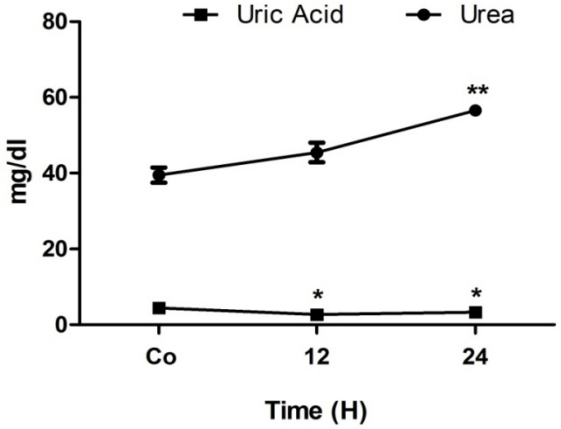

Figure 3: Alterations in concentration of urea and uric acid during 12 and 24h of intraperitoneal injection of TAA. A significant positive increase has been noted in serum urea level of 24h group compared to control. And a significant decrease in uric acid level was noted in both the experimental groups compared to control. Statistically significant changes are marked with the help of asterisks (*P<0.05, **P<0.01, ***P<0.001). Results from three animals for each time point (mean ± S.E.M.).

DISCUSSION

Liver diseases are one of the most common health concerns all over the world. A vast variety of chemicals, drugs, microbes especially viruses are investigated to cause severe liver damage (Stankova *et al.*, 2010). The mechanism of injury induced by drugs may involve free radical-associated damage (Muriel, 2009) and a series of inter related reactions including intracellular disruption, apoptosis or necrosis leading to provoked immune response (Lee *et al.*, 2003). Among all the reported hepatotoxicants, TAA is most potent among all because of its rapid removal and growing injury. Marked variability in serological and hematological parameters due to thioacetamide administration has been widely studied and reported (Al-Attar, 2011; Li *et al.*, 2002; Waters *et al.*, 2005).

In the present work, changes induced by TAA administration in total proteins, albumin, in the liver tissue and serum, together with changes in hepatic enzyme activities urea and uric acid in the sera were evaluated in albino rats after 12 and 24h. Estimation AST and ALT activity is a good marker for assessment of liver function (Balamurugan *et al.*, 2007). As a result of cellular damage and tissue necrosis which enhance the permeability of cell membranes, these enzymes are secreted into sera (Center, 2007), resulting in a raised level representing the type and degree of damage imposed (Flier *et al.*, 1993). The increased level of ALT (158%) in the current study peaked at 12h might be a suggestive of a brutal hepatic injury and other non-hepatic tissues as well, which is evident from raised serum level of AST (131.5%) in the same study point. A significantly increased level of both of these transaminases were found in the sera at both time points when compared to control and the ratio was quite high, which indicated the existence of severe liver damage or other organs. TAA intoxication induces ubiquitin-associated protein degradation which could be a leading cause of decline in the level of total proteins in plasma (Al-Attar, 2011; Galisteo *et al.*, 2006). A statistical negative change of 17.5 and 34.32% was observed after 12h in total proteins in serum and tissue, respectively. Hypoproteinemia, observed in our study perhaps occur due to inflammatory reaction or might be due to perturbed protein biosynthesis (Alshawsh *et al.*, 2011) and catabolism as a result of vasoconstriction or renal tubular necrosis (Cajone and Bernelli-Zazzera, 1984).

Regarding albumin in the serum and tissue, a decrease in concentration in the TAA-treated animals was detected at both time points. A reduction in albumin protein was highly significant after 12h, with 32.25 and 17.14% in tissue and serum, respectively. More or less, similar trend was observed after 24h. Occurrence of hypoalbuminemia might be a suggestive of liver disease, increased catabolism and nephritic syndrome due to TAA induction. Significance of albumin lies as it is the major/sole contributor and transporter of not only the plasma total proteins but also for a number of other substances including calcium, hormones, lipids and vitamins (Lloyd *et al.*, 1987; Moshage *et al.*, 1987). The decreased trend of protein values in the sera was usually

synchronized with decrease in level of albumin which is evident in the present study.

An elevation in urea concentration along with hypoproteinemia was observed in the current study. This elevation in urea might be due to enhanced protein catabolism or due to nephrotoxicity caused by TAA. Various drug induced findings were reported with increased serum level of urea particularly after carbon tetra chloride (CCl_4) induction (Bishayee *et al.*, 1995; Yousef *et al.*, 2008).

Conclusion

TAA is a powerful carcinogenic hepatotoxicant, whose intraperitoneal dose (300mg/kg B.W) leads to acute hepato-toxicity and initiate acute phase response which sets in a change in serum biochemical parameters especially total proteins particularly albumin as evident by marked hypoproteinemia and hypoalbuminemia in the current study. Moreover, elevated level of both hepatic transaminases in both of the experimental groups compared to control also reflects hepatic damage.

Competing interests:

The authors declare that there are no competing interests.

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