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Effects of Dietary Vitamin E and Selenium on Aspartate Aminotransferase and Alanine Aminotransferase Activities in Rats Treated with High Doses of Glucocorticoid

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Abstract: The effects of dietary intake of vitamin E and selenium on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities in rats treated with high doses of prednisolone were investigated. Rats were divided into 5 groups. Groups 3, 4 and 5 received a daily supplement in their drinking water of 20 mg vitamin E, 0.3 mg Se and a combination of vitamin E and Se, respectively, for 30 days. For 3 days subsequently, the control group (group 1) was given a placebo and the remaining 4 groups were injected intramuscularly with 100 mg kg^{-1} body weight prednisolone. After the last administration of prednisolone, 10 rats from each group were killed at 4, 8, 12, 24 and 48 h and the activities of aspartate aminotransferase and alanine aminotransferase enzymes in their tissues were measured. In the group, treated with prednisolone alone, AST activity in the liver was not affected, the ALT activity was significantly decreased at 12 h only. AST and ALT activities in the kidneys were significantly decreased by prednisolone at all time periods. AST activity in the heart also decreased in the prednisolone group between 4 and 24 h, significantly at 12 h. Significant decreases were found at 4, 8 and 12 h in the heart ALT activity of the prednisolone administered group. AST activity in the liver, kidneys and heart was lower in vitamin E and Se supplemented groups than control and prednisolone groups. In the combination group, compared to both the control and prednisolone groups, AST activity in the kidneys and heart was decreased, but increased in liver. Vitamin E and Se alone or in combination had a preventive effect on the decrease of ALT activity in the liver and kidneys caused by prednisolone. ALT activity in the heart tissue of the vitamin E supplemented group was found to be increased at all time periods, however, it reduced in the Se and combination groups compared to the prednisolone group. Therefore, the present study demonstrates that vitamin E and Se alone or in combination may prevent the decrease in ALT activity in the liver and kidneys caused by high doses of prednisolone.

Key words: Glucocorticoid, aspartate aminotransferase, alanine aminotransferase, vitamin E, selenium

INTRODUCTION

Aspartate aminotransferase (AST; E.C. 2.6.1.1) and alanine aminotransferase (ALT; E.C. 2.6.1.2) widely distribute in animal tissues. AST catalyses the reversible conversion of L-aspartate and α-ketoglutarate to oxaloacetate and L-glutamate. ALT catalyses the reversible conversion of L-alanine and α-ketoglutarate to pyruvate and L-glutamate. These transamination reactions have an important role in amino acid synthesis and degradation, as well as in the link between the urea and tricarboxylic acid cycles. Moreover, these enzymes participate in gluconeogenesis since they catalyze the production of oxaloacetate and pyruvate, which can then enter the gluconeogenic pathway (Mathews and Holde, 1990).

Vitamin E provides homeostasis in living cells (Gallo-Torres, 1980). The importance of selenium in animal nutrition and its close metabolic interrelationship with vitamin E was first suggested by the observation that it could replace vitamin E in the prevention of dietary liver necrosis in the rat (Schwarz and Folz, 1957). Vitamin E and selenium have the protective effect against chronic liver damage and cirrhosis. Vitamin E and selenium significantly decrease both hepatocellular damage and elevation in the plasma AST and ALT activities caused by hepatocellular damage (Merrick *et al*., 1986; Geetha *et al*., 1990; Lee and Clemens, 1992; Nagamatsu and Hasegawa, 1993; Naziroglu *et al*., 1999).

An increase of the activity of several hepatic enzymes, which are involved in gluconeogenesis and in

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the metabolism of amino acids is a recognized consequence of administration of glucocorticoids (Rosen and Nichol, 1963). It has been established that glucocorticoids increase activities of liver ALT (Bellamy and Leonard, 1964; Freedland *et al*., 1968; Lefauconnier *et al*., 1973; Befort *et al*., 1976) and AST (Bhargava and Sreenivasan, 1968; Freedland *et al*., 1968; Herzfeld and Greengard, 1971; Greengard, 1975) in rat.

To our knowledge, there are no other data in the literature concerning how high-dose prednisolone treatment affects AST and ALT activities in the liver. Therefore, in the present study, we examined the effect of high-dose prednisolone treatment on AST and ALT activities in the liver and the protective effect of dietary vitamin E and Se on probable increase in the enzyme activities.

MATERIALS AND METHODS

The experiment was carried out on 210, 2-3-month-old clinically healthy adult male Wistar Albino rats weighing 250±25 g, which were housed, 5 rats to a cage, at a room temperature of 20°C. During a 14 days adaptation period, the animals were given a basic diet (Table 1) and tap water *ad libitum*. At the end of this period, the rats were divided into 5 groups (50 rats-group, except for the 1st group with 10 rats). The 1st and 2nd groups were maintained on the diet mentioned above and the 2nd, 4th and 5th groups were also given daily doses of vitamin E (20 mg dl-alpha-tocopheryl acetate dissolved in 0.2 mL of corn oil), Se (as 0.3 mg Na_2SeO_3 prepared in 0.9% NaCl solution) and a combination of vitamin E and Se (20 mg dL^{-1} -α-tocopheryl acetate and 0.3 mg Na_2SeO_3), respectively, with drinking water for 30 days. At the end of this period, 100 mg kg^{-1} body weight (bw) prednisolone was intramuscularly injected for 3 days to all the groups, except the 1st group, which was given the same amount of a placebo and served as a control group. Ten rats from each of the groups other than control were killed by decapitation at the indicated times (4, 8, 12, 24 and 48 h) after the last prednisolone administration. The liver, kidney and heart samples were then excised, rinsed in cold saline (0.9% NaCl) and kept frozen at -30°C until analysis.

The frozen tissues were weighed and homogenized with 10 volumes of 10 mM Tris-HCl buffer pH (7.4) in a glass Potter Elvehjem homogenizer in an ice bath. The homogenates were centrifuged at 20,000 g for 10 min at 4°C. The supernatants were used for the AST and ALT assay. AST and ALT activities were measured by the method of Reitman and Frankel (1957). One unit of AST and ALT activities was expressed as the amount of enzyme catalyzing the formation of 4.82×10^{-4} μmole of glutamate min^{-1} at 25°C and pH 7.5.

Table 1: Diet composition

Ingredients	(%)
Wheat	10.0
Corn	23.0
Barley	15.0
Wheat bran	8.0
Soybean	26.0
Fish flour	8.0
Meat-bone flour	4.0
Pelted	5.0
Salt	0.8
Vitamin mineral mix*	0.2

*Vit. A, D_3, E, K_3, B_1, B_2, B_6 and B_{12}, nicotinamide, folic acid, biotin, Mn, Fe, Zn, Cu, I, Co, Se, antioxidants (butylhydroxytoluol) and Ca

Statistical analysis: Results were expressed as mean±SEM. Analysis of variance (ANOVA) followed by Duncan test was used to determine whether there were significant differences among the groups. Differences were considered as significant when $p<0.05$.

RESULTS

AST activity in the liver was not affected by the administration of prednisolone alone, but it significantly decreased in the groups supplemented with vitamin E and Se between 4 and 24 h, it increased significantly in the combination group at all time periods (Table 2).

The hepatic ALT activity of the prednisolone group significantly decreased at 12 h only. Compared to prednisolone group, ALT activity in the liver was significantly increased in the vitamin E administered group at 8, 12 and 24 h and ALT activity in the liver was increased from 8-48 h in the Se administered group, significantly at 12 and 48 h. Compared to both the control and prednisolone groups, ALT activity in the liver was increased in the combination group at all time periods, significantly at 24 and 48 h. The significant decrease in ALT activity due to prednisolone was prevented by vitamin E and Se alone or in combination (Table 3).

AST activity in the kidneys significantly decreased in the prednisolone group at all time periods and reduced approximately 45% of that of the control group at 12 h. AST activity in the heart also decreased in the prednisolone group between 4 and 24 h, significantly at 12 h. Compared to both the control and prednisolone groups, AST activities in both kidneys and heart were significantly decreased in the vitamin E and Se alone or in combination groups. Vitamin E or Se alone caused more decrease than vitamin E and Se in combination in AST activity in kidneys and heart (Table 4 and 5).

ALT activity in the kidneys was decreased by the administration of prednisolone alone at all time periods. Compared to prednisolone group, ALT activity in the kidneys was decreased in the vitamin E administered group between 4 and 12 h, significantly increased and

Table 2: Effect of dietary intake vitamin E and Se on AST activity (U) in the liver of rats treated with prednisolone

Control (at time 0)	Time after treatment (h)	Treatment	Vitamin E	Se	Combination	p-value
187.2±11.1[a]	4	176.1±6.50[a]	124.8±6.8[b]	126.7±10.1[b]	214.3±11.2[c]	<0.001
	8	182.4±9.50[a]	134.8±7.8[b]	148.0±4.5[b]	337.9±10.2[c]	<0.001
	12	186.2±12.5[a]	148.1±7.9[b]	139.6±6.9[b]	343.2±15.9[c]	<0.001
	24	183.7±24.4[a]	128.1±7.0[b]	138.9±6.9[b]	268.8±16.4[c]	<0.001
	48	169.5±6.30[a]	158.8±9.7[a]	162.9±8.7[a]	326.4±26.4[b]	<0.001

Table 3: Effect of dietary intake vitamin E and Se on ALT activity (U) in the liver of rats treated with prednisolone

Control (at time 0)	Time after treatment (h)	Treatment	Vitamin E	Se	Combination	p-value
253.6±33.3[ab]	4	231.7±19.7[ab]	321.1±38.7[a]	173.7±27.9[b]	276.0±23.3[a]	<0.050
253.6±33.3[ab]	8	191.0±20.1[a]	331.1±34.3[b]	206.1±16.5[a]	320.6±26.9[ab]	<0.001
253.6±33.3[a]	12	179.1±9.50[b]	261.6±14.6[a]	284.8±18.8[a]	305.2±30.7[a]	<0.010
253.6±33.3[ab]	24	185.0±18.6[a]	277.6±14.9[b]	251.2±12.1[ab]	350.4±31.5[c]	<0.001
253.6±33.3[a]	48	247.5±26.2[a]	302.6±15.8[ab]	339.5±20.4[bc]	379.3±26.6[c]	<0.010

Table 4: Effect of dietary intake vitamin E and Se on AST activity (U) in the kidneys of rats treated with prednisolone

Control (at time 0)	Time after treatment (h)	Treatment	Vitamin E	Se	Combination	p-value
230.1±10.0[a]	4	164.2±4.4[b]	44.4±2.0[c]	71.7±5.1[d]	144.3±6.0[e]	<0.001
	8	134.5±4.3[b]	63.6±6.5[c]	68.0±6.1[c]	117.2±8.8[b]	<0.001
	12	104.6±4.4[b]	98.4±5.4[b]	73.6±5.6[c]	101.7±13.6[b]	<0.001
	24	149.4±7.9[b]	59.0±2.5[c]	90.2±1.2[d]	93.8±3.6[d]	<0.001
	48	156.9±8.4[b]	69.3±4.3[c]	72.7±6.8[c]	120.7±5.9[d]	<0.001

Table 5: Effect of dietary intake vitamin E and Se on AST activity (U) in the heart of rats treated with prednisolone

Control (at time 0)	Time after treatment (h)	Treatment	Vitamin E	Se	Combination	p-value
214.0±21.8[a]	4	175.6±9.6[ac]	111.1±15.2[b]	115.0±12.2[b]	141.4±10.8[bc]	<0.001
	8	199.2±25.0[a]	87.8±2.2[b]	80.1±2.5[b]	147.7±21.9[c]	<0.001
	12	130.1±8.0[b]	99.0±5.7[b]	98.9±7.2[b]	106.3±17.8[b]	<0.001
	24	178.8±21.6[ad]	118.6±11.7[b]	94.4±4.9[bc]	161.1±10.0[cd]	<0.001
	48	217.2±22.0[a]	118.0±13.1[b]	104.3±7.2[b]	142.5±15.0[b]	<0.001

Table 6: Effect of dietary intake vitamin E and Se on ALT activity (U) in the kidneys of rats treated with prednisolone

Control (at time 0)	Time after treatment (h)	Treatment	Vitamin E	Se	Combination	p-value
12.7±0.7[a]	4	9.1±0.4[b]	7.3±0.7[b]	17.9±0.9[c]	20.7±0.9[d]	<0.001
	8	10.1±0.7[b]	6.8±0.6[c]	16.7±0.8[d]	13.4±0.7[a]	<0.001
	12	10.7±0.7[ab]	9.8±1.2[b]	17.3±0.6[c]	11.2±0.3[ab]	<0.001
	24	9.4±0.4[b]	15.5±1.7[ac]	20.1±0.9[d]	11.9±0.7[ab]	<0.001
	48	8.9±0.3[b]	16.3±2.4[ac]	18.9±1.0[c]	13.8±0.3[a]	<0.001

Table 7: Effect of dietary intake vitamin E and Se on ALT activity (U) in the heart of rats treated with prednisolone

Control (at time 0)	Time after treatment (h)	Treatment	Vitamin E	Se	Combination	p-value
19.5±1.0[a]	4	14.3±0.9[b]	41.2±3.5[c]	8.2±0.5[d]	4.0±0.1[d]	<0.001
	8	14.2±0.7[b]	31.2±3.7[c]	9.7±4.4[bd]	6.4±0.4[d]	<0.001
	12	11.9±0.9[b]	35.0±3.9[c]	9.4±0.4[bd]	5.7±0.4[d]	<0.001
	24	16.7±1.2[a]	46.6±4.3[b]	8.5±0.7[c]	5.8±0.1[c]	<0.001
	48	17.7±0.7[a]	45.3±3.0[b]	8.8±0.3[c]	5.8±0.2[c]	<0.001

Values with different superscripts within the same line, were statistically significant ($p<0.05$)

recovered to the control level at 24 and 48 h. Compared to the control and prednisolone groups, ALT activity in the kidneys was increased significantly in the Se administered group all time periods. In the combination group, it recovered to the control level after 4 h (Table 6).

Significant decreases were found at 4, 8 and 12 h in the heart ALT activity of the prednisolone administered group. Compared to both the control and prednisolone groups, ALT activity in the heart was significantly increased in the vitamin E administered group at all time periods, whereas it was significantly decreased in the Se administered group and in the combination group (Table 7).

DISCUSSION

Hormones, which modify the developmental formation of an enzyme in one organ may have no effect, or the opposite effect, on the same enzyme in other tissues of the same animal. Even in the same tissue the response of the enzyme depends on age, sex and physiological state of the animal (Herzfeld and Greengard, 1971). The response to glucocorticoid hormones of ALT and AST enzymes in liver tissue has also been increased or no affected according to age, sex and physiological state of the animal (Harding *et al*., 1961; Herzfeld and Greengard, 1971; Patnaik and Kanungo, 1974; Greengard, 1975; Greengard and Cayanis, 1983).

ALT activity in the liver of male rats given a single dose of hydrocortisone (6 mg/100 g bw) was not altered after 2 and 4 h, whereas it was significantly increased (40%) in rats received injections of hydrocortisone (6 mg/100 g bw) daily for 15 days (Lefauconnier *et al*., 1973b). A single dose of dexamethasone (10 mg/100 g bw) slightly increased AST and ALT activity in the liver of male rats after 12 h, whereas 3 repeated injections of same dose significantly increased ALT activity (Befort *et al*., 1976). A single dose of hydrocortisone (2.5 mg/100 g bw) did not altered the level of AST in liver after 18 h. But the same dose of hydrocortisone given for 5 consecutive days caused a doubling of the level of the enzyme in males, though not in females (Herzfeld and Greengard, 1971). In a study, it was demonstrated that increasing of cortisol dose (2.5, 5, 10, 20 mg) caused a reduced lag period without affecting the rate of increase of ALT activity (Bellamy and Leonard, 1964). It has been shown that glucocorticoids induce the synthesis of both the enzymes by stimulating the transcription of AST and ALT mRNAs in the liver (Patnaik and Kanungo, 1974; Pave-Preux *et al*., 1988; Aggerbeck *et al*., 1993).

On the contrary to the literature and our expectation, we found that AST activity in the liver did not change after treatment with high doses of prednisolone, but ALT activity significantly decreased at 12 h only. Similarly, it has been found that ALT activity in liver slightly decreased but not significantly after 48 h injection of cortisol (2.5 mg/100 g bw) (Greengard and Cayanis, 1983). In female rats, ALT activity in liver was not induced after 4 h injection of cortisol (a single dose or daily for 15 days, 6 mg/100 g bw) (Lefauconnier *et al*., 1973a). Assays done 2 days after the cortisol injection (1.25 mg/10 g bw) also did not reveal any changes in the AST activity in male rat liver (Greengard, 1975).

We suggest according to our data and other literatures that dose and sort of glucocorticoids as well as age, sex and physiological state of animal may be the effective on the response to glucocorticoid hormones of ALT and AST enzymes. For instance, cortisol administration increased liver transaminases while cortisol sulfate treatment had no effect on hepatic AST and ALT activities (Miyabo *et al*., 1972).

In recent years, it has been shown that prednisolone therapy improved liver injury in patient with hepatitis (Iwai *et al*., 2003; Arakawa *et al*., 2004; Mohamadnejad *et al*., 2005) and also had the protective effects towards ischaemia-reperfusion-related liver injury (Wang *et al*., 2001; Glanemann *et al*., 2004). The increased plasma AST and ALT activities in patient with hepatitis recovered to normal level after administration of prednisolone (Iwai *et al*., 2003; Arakawa *et al*., 2004; Mohamadnejad *et al*., 2005). Present study indicates that prednisolone may be use hormonal therapy for the treatment of various liver disorders in which the level of this enzyme shows great variations, due to AST and ALT activities in the liver were not changed after treatment with high doses of prednisolone.

AST and ALT activities were increased by 32% and 52% in kidney cortex from cortisone treated rats (5 mg daily for 5 days) (Joseph and Subrahmanyam, 1972). A single dose of cortison acetate (4 mg/100 g bw) leaded an increase in both liver and kidneys AST activity at 4-6 h after injection (Bhargava and Sreenivasan, 1968). Hydrocortisone (5 mg/100 g bw, twice daily for 4 days) increased the AST activity in both liver and kidneys of male rats, but not affected in heart and brain (Pave-Preux *et al*., 1988). Assays done 2 days after the cortisol injection (1.25 mg/10 g bw) did not reveal any changes in the AST activity in male and female rat kidneys and heart (Greengard, 1975). We found that AST and ALT activities in the kidneys were significantly decreased after administration of prednisolone, but in the heart significant decrease was detected at 12 h. No change or decrease in AST and ALT activities may be due to the appearance of repressor of AST and ALT genes towards this dose of prednisolone.

It has been evidenced that vitamin E and Se mitigate the effects of liver disorders and protect the liver against hepatotoxic substance-induced liver damage and also decrease the elevation in the plasma AST and ALT activities caused by hepatocellular damage (Merrick *et al*., 1986; Geetha *et al*., 1990; Lee and Clemens, 1992; Nagamatsu and Hasegawa, 1993; Naziroglu *et al*., 1999).

Decrease in hepatic AST and ALT activities of cadmium-treated rats has been minimised by vitamin E administration (El-Demerdash *et al*., 2004). In present study, also was demonstrated that vitamin E had an important effect on the decrease in ALT activity of liver, kidneys and heart caused by high doses prednisolone. Whereas, AST activities in these tissues were reduced under the values in both the control and prednisolone groups by vitamin E administration.

Dietary intake of Se prevented the increase in hepatic AST and ALT activities in CCl_4-induced liver injury in mice (Chen *et al*., 2005). In present study, Se supplementation prevented the decrease in ALT activity in the liver and kidneys caused by prednisolone. Whereas, AST activities in liver, kidneys and heart were reduced under the values in both the control and prednisolone groups by Se administration.

CONCLUSION

In conclusion, prednisolone administration caused decrease in AST and ALT activities in tissues of rats. Vitamin E and Se alone or in combination may prevent the decrease in ALT activity in the liver and kidneys caused by high doses of prednisolone. However, dietary intake of vitamin E and Se does not have a positive effect on the changes in AST activity caused by high doses of prednisolone.

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