Effects of Dietary Tin and Copper on Rat Hepatocellular Antioxidant Protection (43130)

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Abstract. **The effects of dietary tin on copper status and on enzymes and metabolites involved in hepatocellular antioxidant protection were measured in rats fed copper-adequate or copper-deficient diets with glucose or fructose. Rats became copper-depleted after 4 weeks on diets containing <0.5 μg of copper/g as evidenced by significant decreases in liver copper and serum ceruloplasmin. Signs of copper deficiency occurred in copper-depleted rats fed diets containing 100 μg of tin/g. Significant effects of tin on liver glutathione peroxidase and superoxide dismutase activities and on liver iron and total glutathione concentrations were observed. Interactions between copper and tin on liver copper and iron and on liver superoxide dismutase and malondialdehyde production are reported. Adverse effects of feeding diets containing 100 μg of tin/g include (i) copper depletion in rats fed copper-adequate diets, (ii) accelerated development of copper deficiency in rats fed copper-deficient diets, and (iii) reduction in hepatocellular antioxidant protection.** [P.S.E.B.M. 1990, Vol 195]

Several enzyme systems protect cellular membranes from oxidative damage. The activity of two of these systems is dependent upon essential dietary trace minerals: the copper metalloenzyme, superoxide dismutase (SOD) and the selenoenzyme, glutathione peroxidase (GSH-Px). Dietary copper deficiency has been shown to decrease both SOD and GSH-Px activity in rat liver (1–3). The extent to which copper deficiency impairs these antioxidant enzyme systems is increased when the dietary carbohydrate source is fructose rather than glucose or starch (1). This influence of a specific dietary carbohydrate on copper deficiency is well recognized (1, 4). We recently reported that ingestion of dietary tin also has significant effects on copper status (5).

The United States population ingests inorganic tin primarily from foods in which it is present as a result of processing and/or leaching from unlacquered cans or tin foils used in packaging. Ingestion of tin from typical Western diets has been reported to be 1–38 mg daily (see ref. 6 for review). Daily human intakes of tin have not generally been considered hazardous, but several recent reports have shown that levels of 100–200 μg of tin/g diet can alter the metabolism of essential minerals such as copper and zinc in rats (5, 7, 8).

Interactions among essential dietary trace minerals, carbohydrates, and tin present in food may increase the risk of impairment of crucial cellular protective mechanisms. The objective of the present study was to determine whether copper depletion resulting from the ingestion of moderate levels of tin affects the enzymes or metabolites involved in hepatocellular antioxidant protection.

Materials and Methods

Experimental Diets. Diet compositions were based upon that of diet AIN-76A (9, 10). Diets contained (%) protein (casein), 20; choline bitartrate, 0.2; DL-methionine, 0.3; cornstarch, 15; corn oil (Mazola), 5; fiber (cellulose), 5; AIN-76A mineral mix, 3.5; AIN-76A vitamin mix, 1; and glucose, 50, or fructose, 50. Minerals added to copper-adequate diets included (mg/kg diet) calcium, 5100; phosphorus, 3910; sodium, 1090; potassium, 3600; magnesium, 500; iron, 35.8; zinc, 32.2; copper, 5.5; iodine, 0.21; selenium, 0.11; and chromium, 2.0. Copper carbonate was omitted from mineral mixes used to prepare copper-deficient diets. Stannous chloride (Sigma Chemical Co., St. Louis, MO) was included at 100 μg of tin/g diet. Diet components were obtained from Teklad Test Diets, Madison, WI. Salts used in mineral mix preparation were Baker-analyzed reagent grade (J. T. Baker Co., Phillipsburg, NJ).

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Animals.[1] Weanling male Long-Evans rats (22 days, 44 ± 8 g, mean ± SD) were obtained from Blue Spruce Farms, Altamont, NY. Rats were housed individually in suspended stainless steel cages. Distilled deionized water was provided *ad libitum* in glass bottles with polyethylene stoppers and stainless steel sipper tubes. Powdered diets were provided *ad libitum* (except as noted below) in ceramic food bowls with stainless steel lids and food followers. Animals were weighed daily and food consumption was measured weekly except as follows. Food consumption of rats in Group 7 was measured daily and a mean value calculated. Rats in Group 5 were fed the mean amount of food consumed by rats in Group 7. Rats were euthanized after 4 weeks and the livers were removed, weighed, and frozen in liquid nitrogen. The livers were stored at <−70°C. Blood was collected by cardiac puncture. Serum was prepared and stored at <−70°C until analyzed.

Analytical Procedures. Serum ceruloplasmin was measured by the method of Schosinsky *et al.* (11) using *o*-dianisidine dihydrochloride as the substrate. Hemoglobin was measured with Sigma Diagnostics kit no. 525 (Sigma Chemical Co.). Serum cholesterol was measured enzymatically using Sigma Diagnostics kit no. 352.

Portions of the livers and aliquots of the diets were weighed and wet-digested in mixtures of nitric, perchloric, or nitric, perchloric, and sulfuric acids (12). Care was taken throughout the digestion procedure to prevent charring of the samples. Copper, iron, and tin were analyzed by inductively coupled argon plasma-atomic emission spectrometry (ICP-AES) using a sequential Perkin-Elmer Plasma II system (Norwalk, CT). Portions of the National Institute of Standards and Technology (formerly National Bureau of Standards) Reference Material Bovine Liver 1577 were digested and analyzed for copper and iron. Values fell within ±6% of certified values for these elements. There are no certified reference materials for tin. Validation was based upon analysis of tin in diet samples spiked with tin prior to digestion. Duplicate analysis of each of three independent subsamples of each diet gave the following mean results for copper and tin, respectively (μg/g): Diet 1: 5.6, < detect.; Diet 2: 5.5, 96; Diet 3: 0.3, < detect.; Diet 4: 0.4, 97; Diet 5: 5.4, < detect.; Diet 6: 5.4, 88; Diet 7: 0.3, < detect; and Diet 8: 0.1, 93. Levels of tin in Diets 1, 3, 5, and 7 were at the detection limit for analysis by ICP-AES. When tin in control diets was determined by hydride generation atomic absorption spectrometry (13), values of <1 μg of tin/g diet were routinely obtained.

Portions of livers were weighed while frozen, homogenized in appropriate buffers, and centrifuged according to the methods referenced for each assay. Total liver glutathione was determined according to an enzymatic recycling assay based upon glutathione reductase (14). Liver GSH-peroxidase (GSH-Px) was determined according to the spectrophotometric method of Paglia and Valentine (15). Liver SOD was assayed according to a method using the inhibition of the autooxidation of pyrogallol (16). Liver malondialdehyde (MDA) production was determined according to the method of Levine (17). Liver homogenate supernatant protein was assayed using the Bio-Rad protein reagent (Bio-Rad, Richmond, CA).

Statistical Procedures. Data were subjected to a 2 × 2 × 2 analysis of variance. Differences in means were determined by Duncan's multiple range test (18).

Results

Rats fed copper-adequate tin-containing diets (Groups 2 and 6) gained significantly more weight than did those fed corresponding tin-free diets (Groups 1 and 5, respectively) (Table I). Rats fed copper-deficient diets with fructose grew less well than did those fed copper-deficient diets with glucose regardless of the dietary tin content. Relative heart weight was increased only in rats fed copper-deficient diets containing tin.

Hemoglobin values were significantly reduced compared with respective control groups in rats fed copper-deficient diets with fructose but not copper-deficient diets with glucose (Table II). Addition of tin reduced hemoglobin in rats fed copper-deficient diets with glucose and in those fed copper-adequate or copper-deficient diets with fructose.

Serum ceruloplasmin was significantly reduced in rats fed copper-deficient diets with either glucose or fructose. Addition of tin reduced ceruloplasmin in rats fed copper-adequate glucose-containing diets. Cholesterol was increased when tin was added to copper-adequate and copper-deficient diets with glucose and to copper-deficient diets with fructose.

Total liver glutathione decreased significantly in rats fed tin in copper-deficient diets with glucose and copper-adequate diets with fructose (Table III). Liver GSH-Px was significantly higher in rats fed copper-adequate diets with fructose than in those fed copper-adequate diets with glucose. GSH-Px activity was significantly lower in rats fed copper-deficient diets with fructose than in those fed copper-adequate diets with fructose. Addition of tin significantly increased GSH-Px activity in rats fed copper-adequate and copper-deficient diets containing glucose.

Liver copper decreased significantly in rats fed copper-deficient diets with glucose or fructose for 4 weeks (Fig. 1). Liver copper decreased significantly in rats fed tin in copper-adequate or copper-deficient diets with glucose and in copper-deficient diets with fructose. The pattern of change for liver SOD was similar to that observed for liver copper. Concentrations of iron in

[1] The studies reported herein were conducted according to the principles set forth in the Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal resources, National Research Council, NIH Publication No. 86-23, 1986.

Table I. Weight Gain, Food Consumption, and Relative Heart Weight in Rats Fed Tin in Copper-Adequate and Copper-Deficient Diets with Glucose and Fructose[a]

	Dietary			Weight gain	Food consumption	Heart weight
	Carbohydrate	Copper (μg/g)	Tin	(g)	(g)	(% of body wt)
1	Glucose	5.5	0	136 ± 13b	308 ± 35b,c	0.37 ± 0.03b
2	Glucose	5.5	100	160 ± 25a	365 ± 47a	0.37 ± 0.03b
3	Glucose	<0.5	0	136 ± 13b	323 ± 41b	0.37 ± 0.04b
4	Glucose	<0.5	100	140 ± 14b	339 ± 33a,b	0.48 ± 0.06a
5	Fructose	5.5	0	139 ± 16b	313 ± 24b,c	0.35 ± 0.03b
6	Fructose	5.5	100	161 ± 20a	344 ± 40a,b	0.38 ± 0.03b
7	Fructose	<0.5	0	115 ± 18c	281 ± 28c	0.37 ± 0.03b
8	Fructose	<0.5	100	110 ± 32c	280 ± 36c	0.50 ± 0.09a

ANOVA (2 × 2 × 2):	Weight gain ($P <$)	Food consumption ($P <$)	Heart weight ($P <$)
Copper	0.0001	0.0056	0.0001
Carbohydrate	0.0169	0.0014	NS
Tin	0.0156	0.0022	0.0001
Copper/carbohydrate	0.0023	0.0131	NS
Tin/carbohydrate	NS	NS	NS
Copper/tin	0.0087	0.0343	0.0001
Copper/carbohydrate/tin	NS	NS	NS

[a] Values are mean ± SD, 10/group. Means with the same letter are not significantly different, $P \leq 0.05$.

Table II. Hemoglobin, Serum Ceruloplasmin and Cholesterol in Rats Fed Tin in Copper-Adequate and Copper-Deficient Diets with Glucose or Fructose[a]

	Dietary			Hemoglobin	Serum	
	Carbohydrate	Copper (μg/g)	Tin	(g/dl)	Ceruloplasmin (units/liter)	Cholesterol (mg/dl)
1	Glucose	5.5	0	8.5 ± 1.3c,d	83 ± 33a	81 ± 20b,c
2	Glucose	5.5	100	9.8 ± 1.1b,c	18 ± 27c,d	123 ± 34a
3	Glucose	<0.5	0	9.1 ± 0.9c	45 ± 50b,c	62 ± 12c
4	Glucose	<0.5	100	7.2 ± 1.1e	2 ± 4d	117 ± 30a
5	Fructose	5.5	0	11.9 ± 1.7a	82 ± 48a	96 ± 25b
6	Fructose	5.5	100	10.7 ± 1.6b	67 ± 48a,b	95 ± 17b
7	Fructose	<0.5	0	9.7 ± 1.3b,c	29 ± 37c,d	83 ± 15b,c
8	Fructose	<0.5	100	7.6 ± 1.7d,e	1 ± 1d	119 ± 16a

ANOVA (2 × 2 × 2):	Hemoglobin ($P <$)	Ceruloplasmin ($P <$)	Cholesterol ($P <$)
Copper	0.0001	0.0001	NS
Carbohydrate	0.0001	NS	NS
Tin	0.0019	0.0001	0.0001
Copper/carbohydrate	0.0108	0.0508	NS
Tin/carbohydrate	0.0303	0.0505	0.0026
Copper/tin	0.0015	NS	0.0113
Copper/carbohydrate/tin	NS	NS	NS

[a] Values are mean ± SD, 10/group. Means with the same letter are not significantly different, $P \leq 0.05$.

liver were not significantly different among groups of rats fed Diets 1, 2, 3, 5, 6, and 7 (Fig. 2). Significant increases in liver iron and MDA were found in rats fed tin in copper-deficient diets containing glucose or fructose.

Discussion

Observations of adverse effects of tin on the metabolism of copper, zinc, iron, selenium, and calcium vary with the chemical form of tin, dose, route of administration, and duration of exposure (6, 19, 20). For example, hypertrophy of the gastrointestinal tract and increased loss of zinc occurs in rats fed high levels of tin (approximately 2000 μg/g diet) (21). Absorption of zinc is depressed in rats fed moderate levels of tin (approximately 200 and 500 μg/g diet) (21). In general, growth depression in rats occurs when dietary tin levels

Table III. Total Hepatic Glutathione Concentration and GSH-Px Activity in Rats Fed Tin in Copper-Adequate and Copper-Deficient Diets with Glucose or Fructose[a]

	Dietary			Liver	
	Carbohydrate	Copper (μg/g)	Tin	Glutathione (μmol/g)	GSH-Px (units/min/mg protein)
1	Glucose	5.5	0	4.52 ± 0.37a,b	11.1 ± 4.5b,c,d
2	Glucose	5.5	100	4.28 ± 0.45a,b	18.1 ± 3.8a
3	Glucose	<0.5	0	4.82 ± 0.38a	8.5 ± 2.7d
4	Glucose	<0.5	100	4.18 ± 0.53b	14.6 ± 3.2a,b
5	Fructose	5.5	0	4.14 ± 0.66b	18.0 ± 3.5a
6	Fructose	5.5	100	3.43 ± 0.77c	17.8 ± 3.5a
7	Fructose	<0.5	0	3.95 ± 0.92b,c	10.1 ± 4.9c,d
8	Fructose	<0.5	100	3.95 ± 0.61b,c	13.8 ± 5.1b,c

ANOVA (2 × 2 × 2):	Glutathione ($P <$)	GSH-Px ($P <$)
Copper	NS	0.0001
Carbohydrate	0.0001	0.0557
Tin	0.0061	0.0001
Copper/carbohydrate	NS	NS
Tin/carbohydrate	NS	0.0111
Copper/tin	NS	NS
Copper/carbohydrate/tin	NS	NS

[a] Values are mean ± SD, 9–10/group. Means with the same letter are not significantly different, $P \leq 0.05$.

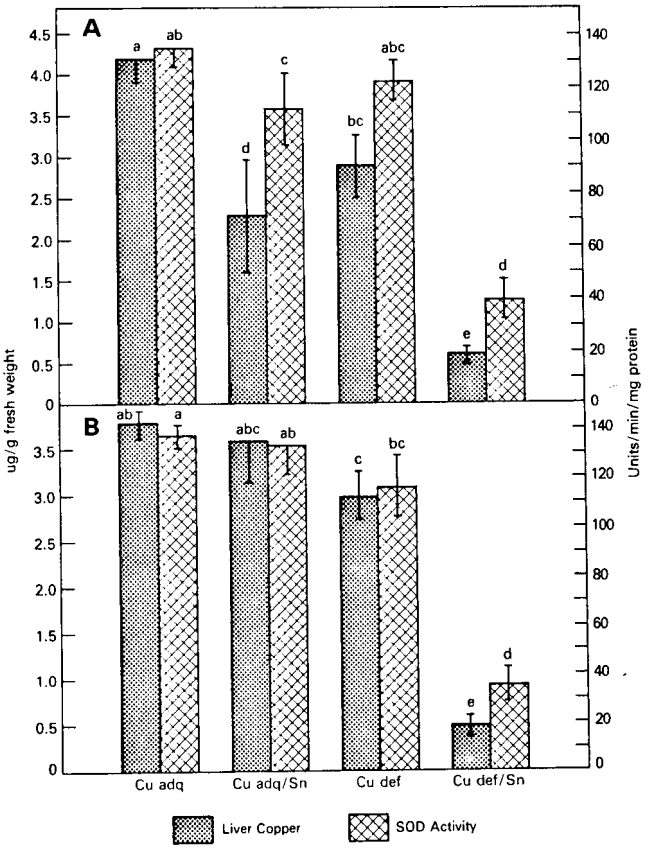

Figure 1. Liver copper levels and SOD activity in glucose (A)- and fructose (B)-fed rats 4 weeks after initiation of diet treatment. Values represent mean ± SD of 8–10 observations/group. Bars without common letters are significantly different ($P \leq 0.05$).

ANOVA (2 × 2 × 2):	Liver copper ($P <$)	Liver SOD ($P <$)
Copper	0.0001	0.0001
Carbohydrate	NS	NS
Tin	0.0001	0.0001
Copper/carbohydrate	NS	NS
Tin/carbohydrate	0.0136	NS
Copper/tin	0.0001	0.0001
Copper/carbohydrate/tin	0.0262	NS

exceed 300–500 μg/g diet. Levels of copper in plasma, liver, and kidney are significantly decreased in rats fed 500 and 2000 μg of tin/g (8). Kidney copper in rats fed 200 μg of tin/g are reduced compared with values in rats fed control diets (7). We pursued studies using diets containing 100 μg of tin/g since this level significantly decreased tissue copper but did not affect growth during 4-week feeding studies (5).

In the present study, rats fed diets containing 0.1–0.4 μg of copper/g, with glucose or fructose as the primary carbohydrate source, became copper-depleted after 4 weeks. The copper-depleted state, characterized by significant decreases in liver copper and serum ceruloplasmin, is distinguishable from a state of severe copper deficiency by the absence of changes in indices known to be associated with the latter. Fields *et al.* (22) observed severe copper deficiency characterized by increased relative heart weight, increased total liver lipid, increased liver iron, and increased serum cholesterol in rats maintained on diets containing 0.86–0.92 μg of copper/g for 9 weeks.

Significant interactions between copper and carbohydrate on weight gain, food consumption, and hemoglobin, but not on relative heart weight, ceruloplasmin, and cholesterol were observed in our copper-depleted rats. The development of severe copper deficiency would be expected if the rats had been maintained on the diets for an additional 4–6 weeks. Rats fed fructose-containing diets in the present study were more severely affected by the feeding of copper-deficient diets than were rats fed copper-deficient diets with glucose. These observations are consistent with those of Fields *et al.* (22) who reported that rats fed diets with <1 μg of copper/g generally exhibited a more severe copper deficiency when fructose rather than starch or glucose was the carbohydrate source.

The copper-depleted status of the young rats in the present study increased their sensitivity to dietary tin. The appearance of signs of copper deficiency such as increased relative heart weight, decreased hemoglobin, increased serum cholesterol, and increased liver iron when tin was included in the copper-deficient diets and the findings of significant interactions between tin and copper on these parameters suggest that tin accelerated copper depletion in these rats.

Fields *et al.* (23) fed weanling rats purified diets containing starch, glucose, or fructose and 1.2 μg of

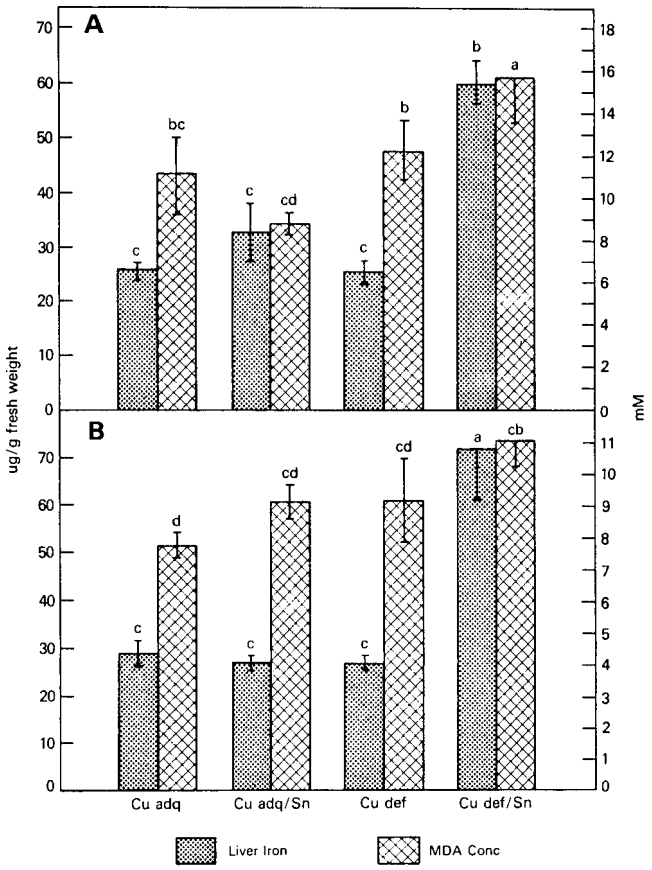

Figure 2. Liver iron and MDA concentrations in glucose (A)- and fructose (B)-fed rats 4 weeks after initiation of diet treatments. Values represent mean ± SD of 8–10 observations/group. Bars without common letters are significantly different ($P \leq 0.05$).

ANOVA (2 × 2 × 2):	Liver iron ($P <$)	Liver MDA ($P <$)
Copper	0.0001	0.0001
Carbohydrate	NS	0.0001
Tin	0.0001	NS
Copper/carbohydrate	0.0310	NS
Tin/carbohydrate	NS	NS
Copper/tin	0.0001	0.0139
Copper/carbohydrate/tin	NS	0.0477

copper/g diet for 11 weeks and observed significant decreases in GSH-Px activity in groups fed copper-deficient diets with fructose but not glucose or starch. We observed a similar decrease in GSH-Px activity in our copper-depleted fructose-fed groups. Liver SOD activity decreased significantly in all fed copper-deficient diets regardless of the carbohydrate source. The greatest percentage of reduction in SOD activity was found in copper-deficient rats fed diets containing fructose (23). Allen *et al.* (3) fed weanling rats purified diets containing 72% sucrose and <0.2 μg of copper/g diet for 51 days and observed significant increases in total hepatic glutathione and GSH concentrations and significant decreases in liver GSH-Px and SOD activities. These authors proposed that the increased GSH concentration observed may represent a compensatory change in response to reduced antioxidant capacity caused by decreases in GSH-Px and SOD activities (3). Significant increases (170%) in hepatic GSH concentrations were reported by Zidenberg-Cherr *et al.* (24) in mice maintained on diets containing 0.2 μg of copper/g for 6 weeks. Copper concentrations in liver decreased to a mean value of 1.2 μg of copper/g in the copper-deficient mice. This value is markedly lower than the liver copper values of 2.4–3.2 μg of copper/g observed in our copper-depleted rats.

We observed significant effects of copper on hepatic GSH-Px and SOD activities but not on total glutathione levels. The observed changes in GSH-Px and SOD are not as large as those reported by others (3, 23) and the differences may be due to the copper-depleted rather than copper-deficient status of our animals.

The observed alterations in antioxidant enzyme systems produce an impairment of hepatocellular antioxidant protection. This impairment, which favors peroxidation of fatty acids, may lead to increased MDA production. The administration of tin tartrate to sham-operated and partially hepatectomized rats has been reported to result in hepatic GSH depletion and an increase in lipid peroxide formation (25). In the present study, total liver iron and MDA concentration were increased in rats fed tin in copper-deficient diets containing glucose or fructose. At this time, it is not possible to estimate the relative contributions of liver iron accumulation or reduced antioxidant protection to the increased production of MDA in the tin-treated rats.

Significant interactions between copper and tin were observed with SOD activity and MDA production. In the case of SOD activity, the interaction results from significant effects of both copper and tin on SOD activity, whereas in the case of MDA production, the affect of copper is primary.

Estimates of daily intakes of tin by human populations have not been as extensively reported as have those of other minerals. Foods from nonlacquered or partially lacquered cans may contain 50–150 μg of tin/g, with levels of >650 μg of tin/g measured in such foods following storage at refrigerator temperatures for 7 days in their opened containers (6). Consumption of diets containing a high proportion of canned vegetables, fruits, or juices from unlacquered cans could result in daily intakes of 50 to >200 mg of tin (6). The levels of tin used in these studies are within the range of values reported for tin present in foods from unlacquered cans. The sensitivity of copper status to tin indicates that effects of chronic ingestion of tin may need to be reexamined.

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