

INTESTINAL ZINC ABSORPTION IN DESFERROXAMINE-TREATED RATS

A. MERAT AND M. KARAMI

*From the Department of Biochemistry, School of Medicine,
Shiraz University of Medical Sciences, Shiraz,
Islamic Republic of Iran.*

ABSTRACT

Desferroxamine (Desferal) is used to chelate iron in thalassemia, a disease of very high prevalence in various parts of Iran. We have investigated intestinal zinc absorption in Desferal-treated rats which, in pilot experiments, showed low serum levels of both iron and zinc. Intraperitoneal administration of ten 0.5 g doses of Desferal (one injection every other day) to male rats produced severe iron deficiency accompanied by lower plasma zinc levels. An oral dose of 0.4 mg zinc sulfate, given to Desferal-treated rats, resulted in a higher increase in mucosal zinc absorption after 2 hours compared to normal controls. Similar results were obtained when the oral dose contained 0.4 mg each of ferrous sulfate and zinc sulfate. This suggests that the presence of iron has no effect on intestinal zinc absorption with the dose employed in this study. Zinc absorption increased with an oral zinc dose given to normal rats while iron absorption did not increase with an oral iron plus zinc dose given to normal rats, suggesting the absence of a regulatory mechanism for zinc absorption, similar to the one known to exist for iron absorption.

Keywords: Desferroxamine, Zinc absorption, Zinc deficiency.

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INTRODUCTION

Although the mechanisms of iron and zinc absorption are not yet fully understood, the intestinal zinc absorption processes are active, energy dependent and apparently mediated by specific zinc transport carriers.¹ For iron uptake, one regulatory mechanism is the synthesis of apoferritin by mucosal cells.² If little iron is required, a large amount of apoferritin is synthesized to trap iron within the mucosal cells. In a state of iron deficiency, virtually no apoferritin is synthesized so as not to compete against the transfer of iron

to the deficient host. A regulatory mechanism is suggested for the intestinal absorption of iron which functions through the expression of genes responsible for the synthesis of transferrin, transferrin receptor and ferritin.³ In iron deficiency there is a considerable increase in transferrin receptor m-RNA.³

Competitive interactions between iron and zinc were predicted some years ago. In chronically iron deficient rats, increased mucosal uptake of iron and zinc has been reported.⁴ Forth and Rummel⁵⁻⁷ found increased net absorption of zinc in chronically iron deficient rats. Conversely Hahn and Evans⁸ observed enhanced net absorption of both zinc and iron in zinc deficient rats.

In another study the effect of iron on zinc absorption in

Correspondence: A. Merat, Department of Biochemistry, Shiraz University of Medical Sciences, Shiraz P.O. Box 71345-1167, Islamic Republic of Iran. Fax: 71-59847.

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the rat was investigated by a single starch: sucrose test meal containing ^{65}Zn or ^{59}Fe by whole body counting.⁹ Zinc had no effect on iron absorption, but iron reduced zinc absorption when the sum of zinc plus iron reached 1.36 mg/body weight. Below this level, even a high Fe/Zn molar ratio (10:1) did not affect zinc absorption, probably since the transport mechanism for zinc had not reached full capacity.⁹

In the present investigation the mucosal uptake of zinc, in the presence and absence of iron, was studied in Desferal-treated rats.

MATERIALS AND METHODS

Animals

Male rats of Sprague Dawley strain weighing 250 to 300 g were divided in the following groups:

Group 1: consisting of 9 rats used for the measurement of normal plasma iron and zinc levels.

Group 2: twenty rats, each receiving 10 injections of 0.5g desferroxamine (Desferal, Ciba-Geigy, Switzerland) (in 1mL normal saline) intraperitoneally, one injection every other day. These animals were designated Desferal-treated rats. Five normal rats receiving normal saline served as controls. Oneday after the last injection, 5 of the rats were used for plasma iron and zinc determinations.

Group 3: seven rats from group 2 receiving an oral dose of 0.4 mg zinc sulfate, using a 1mL syringe connected to a flexible tubing, while the animals were slightly anesthetized.

Group 4: eight rats from group 2 receiving 0.4 mg each of iron sulfate and zinc sulfate orally.

Group 5: nine normal rats receiving the same oral dose as given to rats in group 3.

Group 6: nine normal rats receiving the same oral dose as given to rats in group 4.

Some animals were excluded from these groups due to various experimental conditions.

Methods

Oral doses of zinc sulfate and ferrous sulfate were fed to animals and elevations of plasma zinc concentrations were measured as an index of mucosal zinc absorption.

Blood samples were collected from the abdominal aorta. In animals receiving oral doses, blood specimens were collected 2 hours after mineral ingestion.

Plasma was analyzed for zinc by atomic absorption spectrophotometry (Shimatzu Model 670) on a 20:1 dilution of plasma in distilled deionized water according to the procedure given by Jacob and Tietz.¹ Plasma iron was measured according to the method of Fairbanks and Klee.¹⁰

RESULTS

Intraperitoneal administration of Desferal to normal rats resulted in significant decreases in plasma iron and zinc (Table I), almost with the same extent. At 2 hours after an oral zinc dose, given to both Desferal-treated rats and normal controls, the plasma zinc level increased more in

Table I. Comparison of plasma zinc and iron levels of control and Desferal-treated rats at zero time and at 2 h after ingestion of zinc and a combination of zinc and iron.

	Plasma iron ($\mu\text{g/dL}$)			Plasma zinc ($\mu\text{g/dL}$)		
	Normal controls	Desferal-treated	P-value*	Normal controls	Desferal-treated	P-value*
Zero time	135.0 \pm 6.3 n=7	100.2 \pm 6.6 n=5	<0.005	159.0 \pm 7.3 n=6	124.2 \pm 5.9 n=5	<0.005
2 h after Zn ingestion	128.5 \pm 6.6 n=7	106.0 \pm 4.9 n=9	<0.01	210.0 \pm 14.4 n=8	276.5 \pm 27.9 n=7	<0.025
P-value**	NS	NS		<0.005	<0.025	
2 h after Zn + Fe ingestion	138.5 \pm 5.0 n=7	207.0 \pm 14.0 n=6	<0.005	231.2 \pm 15.0 n=8	250.0 \pm 18.1 n=8	NS
P-value**	NS	<0.005		<0.005	<0.005	

Results are given as mean \pm SEM.

*P-values for Desferal-treated rats relative to the controls (Student's t-test).

** P-values for 2h postingestion levels relative to zero time (Student's t-test).

NS= not significant.

Desferal treated rats, as compared to normal controls. In Desferal treated rats, 2 hours after the oral zinc dose, plasma iron levels remained significantly lower compared to normal rats receiving the same oral zinc dose.

When zero time plasma levels of zinc were compared in control and Desferal-treated rats, with their post-ingestion values, there was a significant rise in plasma zinc levels in both groups and the rise was more than two-fold in the Desferal-treated group. Plasma iron levels remained unchanged in both groups.

When a combined oral dose of zinc and iron was given to both Desferal-treated and saline-treated control rats, the post-ingestion iron level was significantly higher in the Desferal-treated group compared to controls, while the post-ingestion zinc level was not significantly different in the two groups. However, there was a significant post-ingestion rise in plasma zinc in both groups. This rise exceeded two fold for the Desferal-treated group compared to their corresponding zero time values.

The iron levels for the Desferal-treated group, compared to their corresponding zero time values, showed an increase of more than two-fold, but remained unchanged in the control group.

DISCUSSION

From the present results, it is apparent that intraperitoneal administration of Desferal not only caused a severe iron deficiency but also made the rats severely zinc deficient. The lowering effect of Desferal on plasma zinc is presumably exerted by the same mechanism as that for plasma iron, since biological competition is common among chemically related metals of the transition metal series. It has been shown previously that iron deficient diets lower both plasma iron and zinc levels in rats.¹¹

Plasma zinc levels increased significantly by oral zinc administration with or without iron in both Desferal-treated and control rats. This increase exceeded two-fold for Desferal-treated rats. This is compatible with previous results showing increased mucosal zinc and iron absorption⁴ and increased net absorption of zinc^{5,9} in chronically iron deficient rats. However, the rats in the present investigation were deficient in both iron and zinc. The authors have previously studied the changes in serum zinc levels 5 hours after ingestion of 100 mg zinc sulfate in iron deficient women.¹² There was no difference in the percent increase of plasma zinc levels following the ingestion of oral zinc in both iron deficient and normal control women. The explanation for higher zinc absorption in Desferal-treated rats may be the presence of the deficiency of both iron and zinc in these rats, while the iron deficient women were not zinc deficient.

The present results are also in line with the reports on

increased net absorption of zinc in chronically iron deficient rats prepared by iron deficient diets.^{5,9} Zinc and iron uptake were also reported to be enhanced in zinc deficient rats³ as in the Desferal-treated animals in the present work.

The significant rise of plasma zinc in normal control rats, following an oral zinc dose, was of a similar magnitude when iron was also added to the oral zinc doses. Therefore in the present study with a dose of 0.4 mg ferrous sulfate or zinc sulfate and molar ratio of 1/1 (Fe/Zn), mucosal zinc absorption was not affected by the presence of iron 2 hours after the oral dose. This was also shown by Fairweather and Southon⁹ who reported no effect of zinc on iron absorption, so long as the sum of zinc and iron is less than 1.36 mg.

Following an oral dose of both zinc and iron, there was a significant increase in both plasma iron and zinc in Desferal-treated rats. In normal control rats, following oral zinc plus iron ingestion, the plasma zinc level increased significantly. However, plasma iron levels in these control rats, which were not iron deficient, remained unchanged. This is in line with the suggestion that intestinal iron absorption is under a regulatory system which restricts mucosal iron uptake, despite its abundance in the lumen.² Increased intestinal zinc absorption in the normal control rats that were not zinc deficient, suggests the absence of the same type of intestinal regulatory system for zinc absorption.

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