Bioavailability of *all-trans* and *cis*-Isomers of Lycopene

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Lycopene, the predominant carotenoid in tomatoes, is among the major carotenoids in serum and tissues of Americans. Although about 90% of the lycopene in dietary sources is found in the linear, *all-trans* conformation, human tissues contain mainly *cis*-isomers. Several research groups have suggested that *cis*-isomers of lycopene are better absorbed than the *all-trans* form because of the shorter length of the *cis*-isomer, the greater solubility of *cis*-isomers in mixed micelles, and/or as a result of the lower tendency of *cis*-isomers to aggregate. Work with ferrets, a species that absorbs carotenoids intact, has demonstrated that whereas a lycopene dose, stomach, and intestinal contents contained 6–18% *cis*-lycopene, the mesenteric lymph secretions contained 77%-*cis* isomers. The ferret studies support the hypotheses that *cis*-isomers are substantially more bioavailable then *all-trans* lycopene. *In vitro* studies suggest that *cis*-isomers are more soluble in bile acid micelles and may be preferentially incorporated into chylomicrons. The implications of these findings are not yet clear. Rats appear to accumulate lycopene in tissues within the ranges reported for humans, suggesting that they can be used to study effects of lycopene isomers on disease processes. Investigations are underway to determine whether there are biological differences between *all-trans* and various *cis*-isomers of lycopene regarding its antioxidant properties or other biological functions. Exp Biol Med 227:914–919, 2002

Lycopene, the red pigment in tomatoes, is a C40, open-chain hydrocarbon carotenoid (Fig. 1). Rotation of any of its 11 conjugated double bonds allows for the formation of a number of *cis*-geometrical isomers, which may have implications regarding the biological action of this carotenoid. Although the potential health-promoting effects of lycopene have been known since the late 1950s (1), much of the recent interest in lycopene bioavailability (BV) is a result of Giovannucci *et al.*'s publication (2) associating a significant, 35% reduction in prostate cancer risk in men in the upper quartile of tomato intake. Because tomatoes account for over 80% of the lycopene in American diets, a hypothesis was generated suggesting that lycopene was responsible for this reduction in cancer risk. To determine the biological plausibility that lycopene was the protective component of tomatoes, Clinton and colleagues (3) analyzed the lycopene content of the human prostate. Using newly developed C30 column HPLC technology, these investigators were the first to have demonstrated that indeed lycopene is found in the human prostate and, interestingly, it was found there as 15-18 *cis* geometrical isomers despite dietary lycopene sources being mainly *all-trans* lycopene. The possibility that specific isomers perform unique biological functions has led to the investigation of factors that determine the isomeric composition of both foods and tissues.

Digestion and Absorption of Lycopene

The matrix in which lycopene is found in foods appears to be an important determinant of its BV (4), and release of lycopene from this matrix is the first step in the absorptive process (5). The process of cooking usually makes lycopene more bioavailable by its release from the matrix into the lipid phase of the meal. Food processing also has been shown to increase BV. Tomato paste (6) and tomato puree (7) have been shown to be more bioavailable sources of lycopene than are uncooked food sources such as a raw tomato.

The uptake of lycopene into intestinal mucosal cells is aided by the formation of bile acid micelles (Fig. 2). Because bile production is stimulated by dietary fat, consuming fat with a lycopene-containing meal increases the efficiency of absorption (8). Data from human studies in India have suggested that a minimum of 5–10 g of fat in a meal is required for the absorption of carotenoids (9). Conversely, a number of other investigators have found that carotenoids are absorbed from lower-fat meals. The amount of fat needed may depend upon the carotenoid in question (10). Regardless, it is generally accepted that the amount of fat (40% of calories) in a typical American diet is ample to provide for optimal lycopene absorption.

Factors such as certain fibers (11–13), fat substitutes (14), plant sterols (15), and cholesterol lowering drugs (16)

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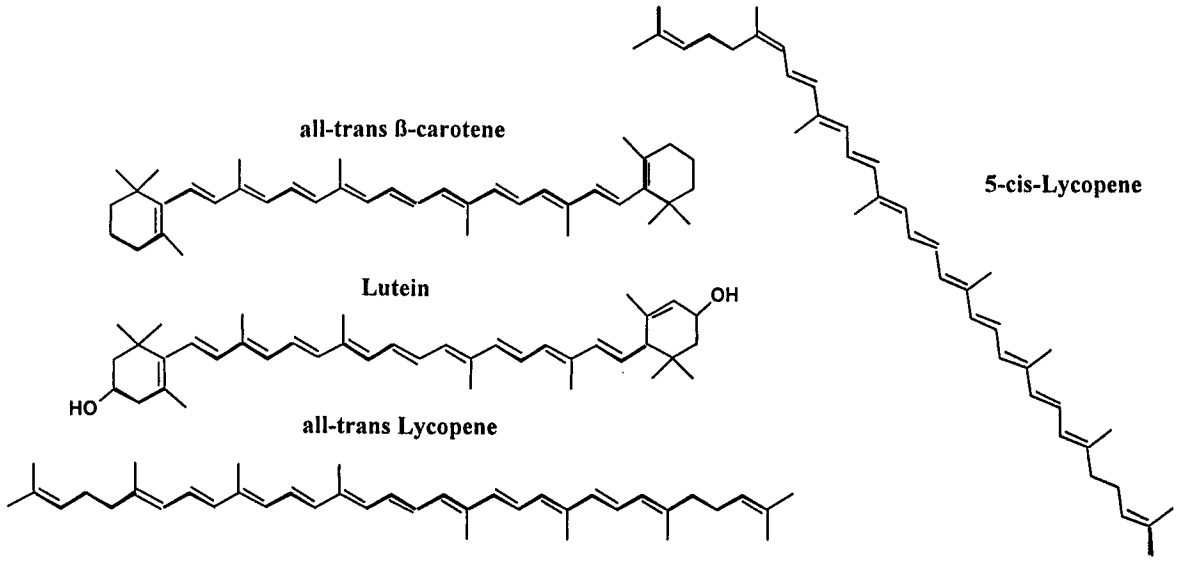

Figure 1. Structures of common carotenoids found in human serum and tissues. Lycopene lacks the β-ionone ring end structure of βC and lutein and does not contain any hydroxyl groups. *Cis*-geometrical isomers are formed by the introduction of a *cis* double bond in the polyene chain. *all-trans* and 5-*cis*-lycopene are the two most common isomers found in human and animal tissues.

that interfere with the incorporation of lycopene into micelles can potentially decrease the efficiency by which this carotenoid is absorbed. Certain fat substitutes may also create a hydrophobic sink in the lumen of the small intestine, binding lycopene and thereby making it unavailable for uptake.

The uptake of lycopene by the brush border membrane of the intestinal mucosal cell is thought to be by passive diffusion, and little is known about the intra-mucosal processing of lycopene (Fig. 2). It remains to be elucidated whether lycopene is transported intracellularly by specific proteins or whether it migrates in lipid droplets (17). Within the enterocyte, β-carotene (βC) and other pro-Vitamin A (VA) carotenoids such as α-carotene and β-cryptoxanthin can be metabolized to vitamin A or retinol by a specific enzyme, βC-15,15′ dioxygenase (18, 19). Unlike βC, lycopene is not metabolized to VA but oxidative metabolites of lycopene have been found in human serum although little is known about the sites and mechanisms involved in their formation (20).

Lycopene exits the mucosal cell in chylomicrons, which are secreted via the mesenteric lymph system into the blood (Fig. 2). Through the action of lipoprotein lipase on chylomicrons, lycopene and other carotenoids have the potential to be taken up passively by various tissues, including adrenals, kidney, adipose, spleen, lung, and reproductive organs before clearance of chylomicron remnants by the liver via the chylomicron receptor. Carotenoids can accumulate in the liver or can be repackaged into very low-density lipoprotein (VLDL) and sent back into the blood. Uptake of carotenoids into tissues from VLDL and LDL is thought to occur via the LDL receptor, and the tissues with the highest concentrations of carotenoids (liver, adrenal, testes) tend to have high LDL receptor activity. Lycopene is a predominant carotenoid in the human liver, adrenals, adipose tissue, testes, and prostate (3, 21–24).

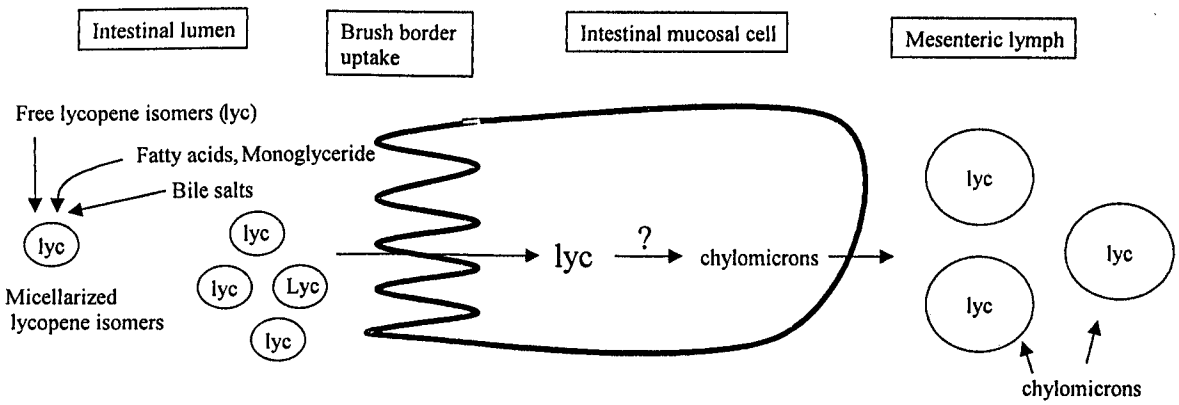

Figure 2. Critical events in the intestinal uptake of lycopene isomers. Free lycopene isomers from dietary sources are incorporated into mixed micelles, taken up by the mucosal brush border membrane, and packaged into chylomicrons for secretion into lymph tissue. Very little is known (?) about the intra-mucosal transport and metabolism of lycopene isomers and mechanisms by which they are incorporated into chylomicrons.

Sources of *cis*-Lycopene Isomers

Lycopene Isomers in Foods. Although lycopene exists in human and animal tissues mainly as *cis*-isomers, lycopene is found in most food sources primarily as the *all-trans* isomer (80–97% *all-trans*; Table I). As noted above, heated and processed food products contain more BV sources of lycopene than uncooked sources. Clearly the release of lycopene from the matrix is one important factor modulating lycopene BV, but it has also been suggested that formation of *cis*-isomers also increases BV. Several studies have investigated the possibility that food processing and cooking results in the isomerization of *all-trans* lycopene to *cis*-isomers. Nguyen and Schwartz (25) demonstrated that, unlike βC, little isomerization of *all-trans* lycopene to *cis*-lycopene was noted with thermal processing (Table II). Similarly, Schierle *et al.* (26) found that heating tomato paste for up to 3 hr in either water or oil resulted in only small increases in *cis*-isomers. Even dehydration, which is performed at high heat over relatively long periods of time, only results in small increases in *cis*-lycopene isomers in tomato products (Table II). These studies suggest that thermal treatment and processing result in only small increases (<10%) in *cis*-lycopene content of foods and it is clear that other physiological processes are responsible for the large differences in *cis: trans* ratios observed between foods and tissues.

Lycopene isomerization in the stomach. The hypothesis that lycopene is isomerized in the stomach as a result of low pH has recently been investigated. Re *et al.* (27) performed *in vitro* incubations with lycopene from commercially available capsules (The Boots Company, Nottingham, UK) or tomato puree and with either a commercially available simulated gastric juice (Sigma-Aldrich Chemical, St. Louis, MO) or human gastric juice obtained at endoscopy. Their results indicated that the percent *cis*-isomers in both lycopene sources increased after incubation with gastric juices, but the capsules increased more than the puree suggesting a stabilizing effect of food matrix (Table III).

The development of animal models whose absorption of carotenoids mimics that of humans has aided in understanding factors that affect BV of lycopene isomers (28). Of the laboratory animals that appear to absorb carotenoids similarly to humans, gerbils and ferrets are the best characterized and most frequently studied.

Our *in vivo* studies in ferrets support modest gastric isomerization of lycopene. In ferrets orally dosed with lycopene, the percentage of lycopene *cis*-isomers increased from 6.2% in stomach contents to 17.5% in the intestinal contents (29; Fig. 3). Thus it appears that both thermal processing and exposure to the low pH of the stomach result in small increases in *cis*-lycopene isomers, but this isomerization cannot explain the observation that intestinal mucosal cells contained 58.8% *cis*-lycopene.

Preferential Absorption of Lycopene Isomers. Stahl and Sies were among the first to suggest that *cis*-lycopene isomers are preferentially absorbed compared with the *all-trans* isomer. They observed that despite tomato juice dose having only about 20% *cis*-isomers, the serum was composed of about 50% *cis*-isomers after consumption of tomato juice by healthy volunteers (8). Using HPLC with C18 column separations these investigators identified four isomers of lycopene, with *all-trans* being the predominant, but the three other *cis* isomers (9-, 13-, 15-*cis*) accounting for the most lycopene.

More recent studies conducted in our laboratory (3) and other laboratories (6, 26, 30) have supported the hypothesis that *cis*-lycopene isomers preferentially accumulate in tis-

Table I. Isomer Composition of Tomato Products

Product	Percent *trans*	Reference
Raw tomato	90	(3)
Tomato soup	79	
Tomato paste	91	
Raw tomato	95	(6)
Tomato paste	97	
Tomato paste	93	(25)
Tomato juice	94	
Ketchup	94	
Pizza sauce	96	
Tomato paste	96	(26)
Canned tomatoes	84	
Red palm oil	16	

Table II. Influence of Processing on Lycopene Isomerization in Foods

Lycopene source	Percent *trans*	Reference
Fresh tomato	100	(36)
Vac-dried	89.9	
Air-dried	84.4	
Fresh tomato	95.8	(25)
Fresh tomato, heated 200°C, 45 min	89.3	
Tomato paste	92.6	(26)
Tomato paste, heated 70°C, 3 hr	83.4	

Table III. Influence of Gastric Juices on Isomerization of Lycopene From Capsules or Tomato Puree After 1-min or 3-hr Incubations

Sample	1-min incubation percent *trans*	3-hr incubation percent *trans*
Capsule	82	79
Capsule+HCl[a]	59	63
Capsule+SGJ[b]	55	61
Capsule+HGJ[c]	59	56
Tomato Puree	94	91
Tomato Puree + SGJ	83	83
Tomato Puree + HGJ	89	89

[a] Data from (27).
[b] HCl = hydrochloric acid.
[c] SGJ = simulated gastric juice.
[d] HGJ = human gastric juice.

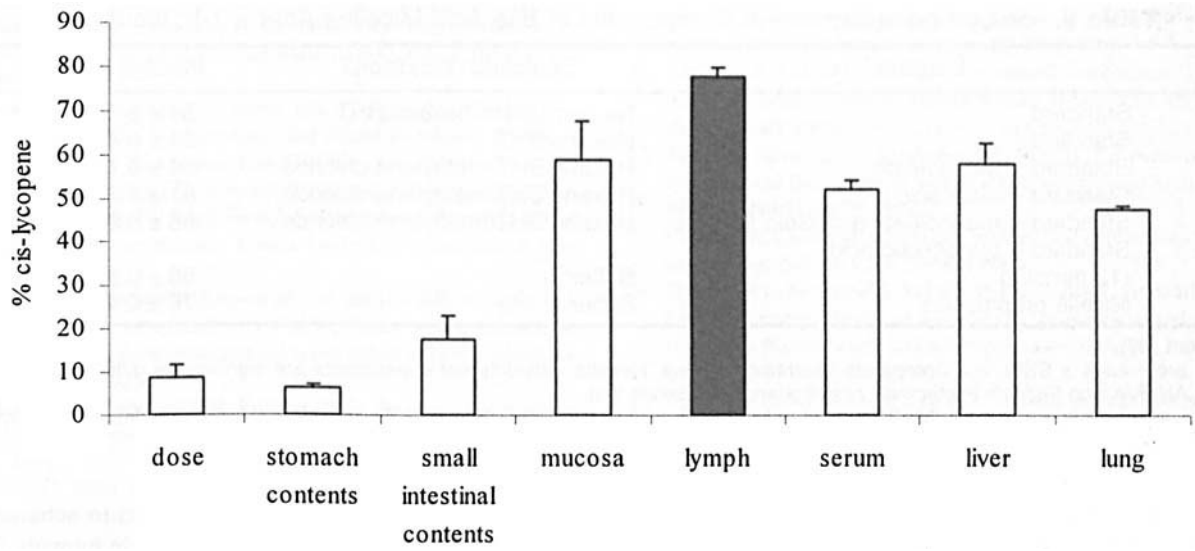

Figure 3. Percentage of lycopene as cis-isomers in ferret tissues after an oral lycopene dose (40 mg of lycopene/kg body weight as Lycored™ mixed in soybean oil). Ferrets were killed after a 2-hr lymph collection and all digestive and tissue fractions were analyzed by HPLC with separations performed on a C30 column.

sues and serum. Using HPLC and newly developed C30 column technology, our laboratory has demonstrated that lycopene exists in human prostate and serum in as many as 18 different isomeric forms. The most abundant isomeric forms in human tissue and blood are the *all-trans* and 5-*cis* isomers, with the sum of *cis*-isomers accounting for the majority (58–88%) of the total lycopene (Table IV).

Our laboratory (29) dosed ferrets orally with lycopene and collected small intestine, lymph, and several tissues to determine *cis:trans*-isomer ratios. It was observed that despite the dose containing only 9% *cis*-isomers, mucosa (58.8%), lymph (77.4%), blood (52%), and tissues contained significantly more *cis*-lycopene isomers than stomach (6%) or intestinal content (17.5%; Fig. 3). Because the mucosal cells contained 41% more *cis*-lycopene isomers than intestinal contents, we further examined the uptake of lycopene isomers by bile acid micelles *in vitro*. Indeed, results suggested that *cis*-lycopene isomers are more readily taken up by micelles making them more easily absorbed (Table V). These data support the hypothesis that *cis*-lycopene isomers are more efficiently taken up into the mucosal cells and absorbed into lymph than *all-trans* lycopene.

Table IV. Lycopene Isomers in Human and Rat Blood and Tissues

Species, tissue	Isomer (%)	Reference
Human blood[a]		
all-trans	27–42	(3)
Total *cis*	58–73	
Human prostate[a]		
all-trans	12–21	(3)
Total *cis*	79–88	
Human blood		
all-trans	41	(26)
5-*cis*	28	
9-*cis*	2	
13- + 15-*cis*	12	
Other *cis*	16	
Rat liver[b]		
all-trans	18–37	(35)
5-*cis*	44–60	
Other-*cis*	19–22	
Rat blood[b]		
all-trans	26–41	(35)
Total *cis*	59–74	

[a] Range of lycopene isomers in 25 men who underwent prostatectomy for localized prostate cancer.
[b] Range of lycopene isomers in intact male rats fed lycopene-containing (0.05, 0.50, and 5.0 g lycopene/kg diet) diet for 8 weeks.

The mechanisms responsible for the selective incorporation of *cis*-isomers into micelles are poorly understood. Because the introduction of one or more *cis* double bonds into a lycopene molecule reduces its length it has been hypothesized that isomerization allows the molecules to "fit" into micelles with greater ease. Alternatively, it has been suggested that linear *all-trans* isomers may more readily aggregate within the intestine and form crystals, greatly reducing their uptake by micelles (31). The recent development of an *in vitro* model to study the cellular and physiochemical events involved in carotenoid digestion and intestinal uptake may aid in the further understanding of the BV of *cis*-lycopene isomers (32).

Accumulation of Lycopene Isomers in Rodent Tissues

Few studies have examined the tissue distribution of lycopene in laboratory animals commonly used to study disease processes. Mathews-Roth *et al.* (33) have shown the liver to be the major site of lycopene accumulation in the rat after a single dose of ^{14}C lycopene. Zhao and co-workers (34) demonstrated in a dose–response feeding trial that lycopene accumulated in liver and extrahepatic tissues of male and female F344 rats in a dose–response manner when

Table V. *cis*-Lycopene Isomers in Components of Bile Acid Micelles After a 1-hr Incubation

Fraction	Sonication conditions	Percent *cis*[a]
Standard	No sonication; hexane/BHT	54 ± 2.7[1]
Standard	Hexane/BHT	54 ± 0.4[1]
Standard + monooleate	Hexane/BHT/methylene chloride	56 ± 0.1[1]
Standard + oleic acid	Hexane/BHT/methylene chloride	61 ± 3.3[1,2]
Standard + monooleate and oleic acid	Hexane/BHT/methylene chloride	66 ± 5.3[1,2]
Standard + taurocholic acid (12 mmol/L)	Buffer[b]	56 ± 0.5[1]
Micelle preparation	Buffer	76 ± 0.4[3]

[a] Data from (29).
[b] Values are means ± SEM, $n = 3$ separate incubations/group. Results with different superscripts are significantly different ($P < 0.05$) by one-way ANOVA and Fisher's Protected Least-Squares Difference test.
[c] Buffer = 100 mM mannitol, 5 mM $CaCl_2$, 0.1 mM $MgSO_4$, 100 mM NaCl, 25 mM KCl, and 10 mM *N*-tris[hydroxymethyl]-methyl-2-aminoethanesulfonic acid.

fed in the diet for 10 weeks. Liver was found to be the major site of lycopene accumulation, but lung, prostate, mammary glands and serum were also found to accumulate significant amounts of lycopene. Other laboratories have documented similar lycopene tissue distributions (39).

Our laboratory further demonstrated that rats could be used as a model to study biological actions of lycopene isomers (35). Male F344 rats fed lycopene-containing diets for 8 weeks achieved lycopene tissue concentrations and isomer patterns similar to those observed for humans (Tables IV & VI). We have also demonstrated that castrated rats accumulate more total lycopene and more lycopene as *cis*-isomers than intact rats despite eating less total lycopene (Table VII). Additionally, the percentage of lycopene as *cis*-isomers increased as dietary lycopene concentrations increased (Table VII). These results suggest that hormonal and other physiological factors may also regulate the isomeric ratio of lycopene in tissues.

It appears that the rat may be a useful model to study lycopene metabolism and mechanisms by which lycopene modifies biological processes such as cancer. However, since rats inefficiently absorb lycopene, relatively high dietary lycopene concentrations are needed to achieve tissue concentrations similar to those observed in humans. The rat is not the preferred model to study lycopene bioavailability from foods. The gerbil or ferret would be a better model for this type of study (28).

Conclusions

Although the predominant form of lycopene in foods is *all-trans*, human blood and tissues contain mainly *cis*-isomers. The potential role for specific lycopene *cis*-isomers in disease processes has stimulated interest in their sites of formation and BV. It appears that food processing and thermal treatment of foods results in only modest increases in the percentage of *cis*-lycopene isomers. Studies in humans and animal models support a hypothesis that *cis*-lycopene isomers are preferentially absorbed. *In vitro* studies indicate that *cis*-isomers are more easily taken up by mixed micelles in the intestine and hence are more bioavailable. Further work is necessary to determine other factors influencing the BV of lycopene isomers and their importance in health and disease.

Table VI. Lycopene Concentrations of Human and Rat Tissues

Species & tissue	Lycopene concentration[a] (nmol lycopene/g tissue)	References
Human		
Liver	0.1–20.7	21,37
Adrenal	0.2–21.6	21, 22
Blood	0.26–0.90[b]	38
Prostate	0.0–1.7	3, 24
Lung	0.1–4.2	35
Rat		
Liver	5–223	35, 39, 40
Adrenal	80–85	35
Blood	0.02–0.23[b]	35, 39, 40
Prostate	0.020–0.24	34, 35, 39
Lung	0.065–0.70	34, 35
Breast	0.27–0.44	34

[a] Data presented as ranges from cited studies.
[b] Blood lycopene concentration expressed as nmol/mL.

Table VII. Androgen Status and Dietary Lycopene Concentration Affect Hepatic Lycopene Concentrations and Isomer Patterns in Male F344 Rats Fed Lycopene for 8 Weeks[a,b]

Androgen status	Dietary lycopene concentration	Total lycopene (nmol/g)	Percent *cis*
Intact	0.00	0 ± 0[1]	0 ± 0[1]
	0.05	16 ± 4[2]	63 ± 2[2]
	0.50	61 ± 14[3]	69 ± 1[4]
	5.00	49 ± 14[3]	82 ± 2[3]
Castrated	0.00	0 ± 0[1]	0 ± 0[1]
	0.05	32 ± 10[4]	69 ± 3[4]
	0.50	132 ± 31[5]	72 ± 3[4]
	5.00	134 ± 34[5]	84 ± 2[5]

[a] Data are from (35) and represent means ± STDEV, $n = 11$/group
[b] Values in the same column with different superscripts are significantly ($P < 0.05$) different by one-way ANOVA and Fisher's Protected Least-Squares Difference test.

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