Absorption and Distribution of Lycopene in Rat Colon

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Summary Colonic absorption and distribution of lycopene, which inhibited rat colon carcinogenesis in our previous studies, were investigated in Sprague-Dawley rats. Three groups of six rats each with or without a single-barreled colostomy at the mid colon were given a single intragastric or intracolonic dose of 0.2 mL of corn oil containing 12 mg of lycopene. Twenty-four hours later, all rats were sacrificed and the blood and some tissues were collected. The contents of lycopene in the samples were assayed by HPLC. Lycopene was detected in an appreciable amount in the liver, but only in trace amount in the serum of all rats treated with an intracolonic dose of lycopene and in rats with an intragastric dose. After an intragastric lycopene treatment, lycopene was detected in the mucosa of the proximal colon and of the distal colon of the colostomized rats, whose distal colon had been excluded from the fecal stream. A large amount of lycopene was recovered in the feces. None was detected in any sample from the control rats treated with an intragastric or intracolonic dose of plain corn oil. The results suggest that lycopene is absorbed from the colon and also from the small intestine. It might be concluded that both ways of absorption contribute to a comparative amount of lycopene accumulation in the colon mucosa after ingestion of this carotenoid.

Key Words lycopene, carotenoid, colonic absorption, rats

Lycopene, a major carotenoid in the blood and tissues as β-carotene (1, 2), has attracted attention because of its biological properties such as potent antioxidant activity (3). Epidemiological studies have suggested a protective role for it against various cancers, including colon cancer (4–10). These studies demonstrated an inverse association between an increased consumption of lycopene, including tomatoes and tomato-based products rich in lycopene, as well as high levels of serum lycopene, and the incidence of cancers. Our previous study showed that the feeding of lycopene suppressed the formation of carcinogen-induced aberrant crypt foci, putative
preneoplastic lesions, in the rat colon in a short-term assay experiment (11). The subsequent long-term experiments demonstrated that the feeding of lycopene or lycopene-rich tomato juice inhibited the colon cancer development in rats (12). In these experiments, a direct-acting carcinogen, \( N \)-methylnitrosourea, was instilled into the colon lumen for colon cancer induction. Thus the accumulation of an effective amount of lycopene in the colon mucosa would be needed to prevent colon carcinogenesis. The absorption of lycopene appears to be by concentration-dependent passive diffusion and to be poor (13). Therefore it is of interest to note whether lycopene, which escapes from uptake at the small intestine and is transported into the colon, is absorbed at the colon and exhibits an increased lycopene level in the colon mucosa. The aim of the present simply designed study was to examine in rats if lycopene is absorbed also from the colon and accumulates in the colon mucosa. A large single dose (12 mg) of lycopene was administered directly into the colon or the stomach, and dynamics in absorption and distribution of lycopene were analyzed.

**Materials and methods**

Female Sprague-Dawley rats (Shizuoka Laboratory Animal Center, Hamamatsu), 10 weeks of age, were used. They had free access to the standard laboratory diet CE-2 (CLEA Japan, Tokyo) and drinking water. All-trans lycopene (Lycored, Beer-Sheva, Israel) was emulsified in corn oil (Nacalai Tesque, Kyoto) at a concentration of 12 mg/0.2 mL.

In experiment 1, six rats in each group received a single intragastric administration of 0.2 mL of plain corn oil (control group) or 0.2 mL corn oil emulsion of lycopene (ig group and stoma/ig group) through a metal feeding tube. The mean body weight was 213 g in the control and ig groups and 202 g in the stoma/ig group. The rats of the stoma/ig group had received a single-barreled colostomy operation 7 d before. Briefly, the abdomen was incised and opened under intraperitoneal pentobarbital anesthesia, and the colon was cut off and separated at mid colon 8 cm proximal to the anus. The proximal stump was sutured and fixed on the abdominal wall to make the fecal stoma, and the distal stump was closed by suture. The abdominal wall was then closed. The operation completely excluded the distal colon from the fecal stream. They had the diet and drinking water well and excreted the soft feces from the stoma after the following day. In experiment 2, six rats each received a single intracolonic administration of 0.2 mL of plain corn oil (control group) or 0.2 mL of corn oil emulsion of lycopene (ic group). Briefly, a metal feeding tube 8 cm long was inserted two-thirds of the way into the colon lumen through the anal orifice, and corn oil was injected. The corn oil filled the distal half of the colon.

Twenty-four hours after the administration of corn oil or corn oil emulsion, all rats were sacrificed by the withdrawal of blood from the abdominal aorta after laparotomy under intraperitoneal pentobarbital anesthesia. The blood was centrifuged and the serum collected. In experiment 1, the mid portion of the jejunum...
and the whole length of the colon were excised, cut open longitudinally, and cleansed with 0.9% NaCl solution. The feces in the proximal and distal colons were collected. No feces was found in the excluded distal colon of the stoma/ig group. The mucosas of the jejunum and the proximal and distal colons were scraped and collected with a blunt steel plate. The liver was removed in both experiments. All the samples collected were stored at $-80^\circ$C until lycopene analysis. The experimental procedures used in this study met the standards set forth in the Guidelines for the Care and Use of Laboratory Animals of the Experimental Animal Facility, Akita University School of Medicine.

Lycopeone in the serum, feces, and tissues was determined by the HPLC technique with a slight modification, described previously (14). The feces and tissues were homogenized and saponified. Lycopene was identified on the basis of its retention time and absorption spectrum recorded from 200 to 600 nm as an all-trans isomer. Results are expressed as mean ± SE. A Student's $t$-test showed that none of the data was different statistically ($p<0.01$).

**Results and discussion**

The results of experiments 1 and 2 are summarized in Table 1. Lycopene was not detected in any sample from the control groups, which had a lycopene-free CE-2 diet and plain corn oil. The mean values of serum lycopene in the ig, stoma/ig, and ic groups were marginal (0.001-0.01 µg/mL), and the mean values in the liver were appreciable and comparable in the three groups: 1.71 µg/g, 1.26 µg/g, and 1.12 µg/g, respectively. The results are consistent with other studies in which lycopene was found in the blood within 4-8 h after a single dose, then eliminated rapidly and deposited in the liver. In humans, the maximum concentration in the serum was reached after 12 h with a half-life of 9 d (2, 14). It is noted that the same amount of lycopene was mostly detected in the liver in all three groups. It is obvious that lycopene instilled into the distal colon in the ic group is absorbed in situ from the colon in an amount great enough to be deposited in the liver. An appreciable amount of lycopene (0.38 µg/g in mean value) was detected in the distal colon mucosa of rats in the stoma/ig group, which was completely excluded from the fecal stream. The result indicates that the lycopene is transported via the blood after absorption at the upper part of the intestine. On the other hand, the lycopene concentration in the mucosas from the distal colon of the ig group and the proximal colon of the stoma/ig group showed to be higher, but not significantly so, compared with the distal colon mucosa of the stoma/ig group: 0.76 µg/g and 2.02 µg/g vs. 0.38 µg/g in mean value. This difference seems responsible for the distinctive ways of lycopene accumulation: the direct uptake from the feces plus distribution via the blood stream vs. distribution via the blood stream alone. The lycopene concentration in the proximal colon mucosa was higher, but not significantly higher, in the stoma/ig group than in the ig group: 2.02 µg/g vs. 0.53 µg/g. This difference seems likely to reflect the fecal concentration of lycopene in the proximal colon: 1.06 mg/g dry weight vs. 0.50 mg/g dry weight, and the direct uptake by concentration-dependent
Table 1. Lycopene levels of serum, liver, jejunum mucosa, proximal and distal colon mucosa, and feces in proximal and distal colons in Sprague-Dawley rats at 24 h after an intragastric (ig) or an intracolonic (ic) dose of 12 mg lycopene.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum (µg/mL)</th>
<th>Liver (µg/g)</th>
<th>Jejunum (µg/g)</th>
<th>Colon (µg/g)</th>
<th>Feces (mg/g dry weight)</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Proximal</td>
<td>Distal</td>
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<td>Experiment 1:</td>
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<tr>
<td>control</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>ig</td>
<td>&lt;0.01</td>
<td>1.71 (0.17)</td>
<td>0.08 (0.03)</td>
<td>0.53 (0.23)</td>
<td>0.76 (0.66)</td>
</tr>
<tr>
<td>stoma/ig&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.01</td>
<td>1.26 (0.22)</td>
<td>0.16 (0.11)</td>
<td>2.02 (0.34)</td>
<td>0.38 (0.14)</td>
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<tr>
<td>Experiment 2:</td>
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<td>control</td>
<td>nd</td>
<td>nd</td>
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<td>nd</td>
<td>nd</td>
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<tr>
<td>ic</td>
<td>&lt;0.01</td>
<td>1.12 (0.11)</td>
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<sup>a</sup> A single-barreled colostomy was performed 7 d before an ig dose of lycopene.

<sup>b</sup> Not detected (<0.001 µg/mL or µg/g).

<sup>c</sup> Mean (SE) of 6 rats each.
fashion. The feces from the ig and stoma/ig groups contained a large amount of lycopene as shown in other study in which a half of the original amount of ingested lycopene was recovered from the feces (15). Taking the present results into consideration, it might be expected that a total amount of lycopene absorption from the small intestine and in the colon (proximal and distal) could participate to make much high concentration of lycopene in the colon mucosa, thereby contributing to colon cancer prevention.

In the present experiments, a large single dose of 12 mg lycopene, which is 2 times the highest dose (6 mg) of daily gavage applied in our previous study (11), and lycopene contents in the blood and tissues were measured at 24 h after lycopene administration, since 80% transit time of unabsorbable substance from the stomach to the anus was 24 h (16). We expect that to be the appropriate time for lycopene given in the stomach to arrive and be absorbed at the distal colon. Further studies, such as analysis with much smaller doses of lycopene and at much shorter times after the dose, are required to clarify the precise dynamics of lycopene on absorption, distribution, and excretion; and on the metabolic change of given lycopene.

REFERENCES

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