Nutritional functions of dietary phosphatidylinositol

Teruyoshi Yanagita

Dietary lipids contain approximately 10% of phospholipids (PL) in which phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are the two major components (Table 1). The intake of dietary PL is estimated to be around 3–4 g/day, which amounts to about 5–8% of total dietary lipids in Japan and other countries. PL is an energy source and also provides polyunsaturated fatty acids such as arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). These fatty acids play important roles in growth and brain development and retinal photoreceptor cells. In addition, PL is a major component of cell membranes and is required for signal transduction, metabolic regulation, and maintenance of living cells.

Canty has suggested that PL might have therapeutic application for certain neurological disorders and liver cirrhosis. The mechanism by which dietary PL exerts its beneficial effects is not clear (inform 11:537–541, 2000). Each PL molecule contains both a hydrophilic (e.g., choline, ethanolamine, serine, or inositol) and a hydrophobic (e.g., fatty acid) component. Either one of them could be responsible for the physiological effects of PL in humans and experimental animals. Earlier reports noted that PE plays a major role in altering serum lipoproteins. The cholesterol-lowering effect of dietary PE was attributed to the constituent base ethanolamine, since feeding ethanolamine, but not choline or inositol, resulted in a similar alteration of serum lipids. Canty and colleagues reported that it is PC in dietary PL that affects profiles of serum lipids and lipoproteins. They stressed the importance of choline in dietary PC based on the fact that choline deficiency enhanced the level of cytokine. An increase in cytokine, such as TGF-β1, suppressed the expression of antioxidation enzymes such as superoxide dismutase and catalase, which led to an increased vulnerability to oxidation. An increased lipid peroxidation has been suggested as being an important factor of apoptosis. Nevertheless, the overall ability of dietary PC in lowering the cardiovascular disease risk factors (such as serum homocystein level, cholesterol level, cholesterol absorption and excretion, and serum lipoprotein profiles) may be attributed to the combined effects of both choline and fatty acids.

Despite the fact that the use of PL for nutritional and therapeutical purposes has significantly increased in recent years, most studies focus on PC and PE. Reports examining the nutritional functions of another minor PL, phosphatidylinositol (PI; Fig. 1) are scarce; further investigations need to be made.

**Effects of dietary PI on lipid metabolism**

We recently studied the effect of dietary PI compared with triacylglycerol (TAG) on weight gain and lipid metabolism in scavenger knockout (ddy) mice. The ddy mice were fed a purified diet supplemented with either PI or TAG of similar fatty acid composition. During the three weeks of feeding, the food intake was found to be comparable between the two groups. However, feeding PI as compared to TAG significantly lowered the body weight gain (Fig. 2). It also reduced the serum concentration of TAG by 50%, cholesterol and PL by 30–35%, and liver TAG concentration by 25% (Fig. 3).

To examine the possible mechanism underlying the TAG-lowering effect of dietary PI, activities of two microsomal membrane-bound enzymes, phosphatidic acid phosphohydrolase (PAP) and diacylglycerol acyltransferase (DGAT), which regulate the synthesis of TAG in liver, were determined. Generally, PAP is located both in cytosol and on the endoplasmic reticulum (ER). The cytosolic form of the enzyme is known to be physiologically inactive until it is translocated to membranes where phosphatidic acid (PA) is synthesized. Results in Figure 4 show that feeding PI increased the cytosolic PAP activity. This finding suggests that feeding PI results in translocation of PAP from the membranes to the cytosolic fraction where it becomes inactive. This effect is opposite to that caused by stress hormones, e.g., glucocorticoids and glucagon, which up-regulate the PAP activity and increase triglyceride synthesis. Results in Figure 4 also show that PI feeding reduced the microsomal DGAT activity whether or not the exogenous substrate diacylglycerol (DAG) was added in the assay medium. This finding suggests that the inhibitory effect of PI on the activity of DGAT is not due to a decrease in DAG concentration. Taking all these find-

---

**Table 1**

<table>
<thead>
<tr>
<th>Food</th>
<th>Total lipids (g/100 g food)</th>
<th>Total PL (mg/100 g food)</th>
<th>PC</th>
<th>PE</th>
<th>PI</th>
<th>PS</th>
<th>SM</th>
<th>LPC</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean</td>
<td>20.8</td>
<td>2,038</td>
<td>917</td>
<td>536</td>
<td>287</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>102</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>31.8</td>
<td>10,306</td>
<td>6,771</td>
<td>1,917</td>
<td>64</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>Milk</td>
<td>3.7</td>
<td>34</td>
<td>12</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Beef</td>
<td>4.1</td>
<td>660</td>
<td>407</td>
<td>207</td>
<td>—</td>
<td>—</td>
<td>46</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Flour</td>
<td>1.0</td>
<td>251</td>
<td>47</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>78</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Apple</td>
<td>0.09</td>
<td>40</td>
<td>21</td>
<td>10</td>
<td>0.4</td>
<td>6</td>
<td>—</td>
<td>0.6</td>
<td>—</td>
</tr>
<tr>
<td>Potato</td>
<td>0.15</td>
<td>76</td>
<td>38</td>
<td>22</td>
<td>1</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>0.4</td>
</tr>
</tbody>
</table>


Abbreviations: PL, total phospholipids; PC, phosphatidylinositol; PE, phosphatidylethanolamine; PI, phosphatidylserine; SM, sphingomyelin; LPC, lyso-phosphatidylcholine; PA, phosphatidic acid.
ings together, the reduced activities of two key enzymes for triglyceride synthesis in the PI-fed animals strongly suggest that PI inhibits triglyceride synthesis in liver.

The second possible mechanism regarding the inhibitory effect of dietary PI on triglyceride synthesis is a decrease in supply of fatty acids. Results from measurement of the activities of two enzymes, malic enzyme and glucose-6-phosphate dehydrogenase, which are markers for de novo fatty acid synthesis, show that the activities of these enzymes were comparable in both groups. In the event that dietary PI reduces the supply of fatty acids in the liver, fatty acid synthesis would be suppressed by feedback regulation. Failure to observe a change in fatty acid synthesis would suggest that PI and its metabolites inhibit de novo synthesis of only triglyceride, but not fatty acids.

PI feeding also alters the composition and metabolism of cellular PL in liver. It increased by 10% the proportion of hepatic PI and PE, while it reduced the proportion of PC and lyso-PC. Biosynthesis of PC is known to regulate very low density lipoprotein (VLDL) assembly and secretion in the liver. PC biosynthesis is modulated by two key enzymes, choline kinase (CK) and CTP:phosphocholine cytidylyltransferase (CT) via the cytidine diphosphate (CDP)–choline pathway. CT is the rate-limiting enzyme. Feeding PI reduced (by 30%) the level of the active membrane-bound CT (Fig. 4), while it increased the inactive cytosolic CT. This finding suggests that PI or its metabolites may regulate PC synthesis through its effect on intracellular distribution of CT between the ER, membranes, and the cytosolic fraction. As a result, feeding PI can mod-

ulate the assembly and secretion of VLDL-containing lipoprotein in the liver.

The other possible mechanism underlying the TAG-lowering effect of dietary PI may be due to the difference in digestive fate of dietary PI and TAG. Generally, dietary PI, similar to other PL fractions, is digested by phospholipase A2 to form lyso-PI and fatty acids, which are then absorbed. However, in the case when phospholipase C or D is active in the intestine, PI can be hydrolyzed into DAG, inositolphosphate, and phosphatidic

Figure 1. Structure of phospholipids.

Figure 2. Effect of dietary phosphatidylinositol (PI) on body weight in mice. Male mice were fed semisynthetic diets containing either PI or triacylglycerol (TAG) for 21 days. The composition and content of fatty acids in both groups were adjusted to the same. Food intake was comparable for both groups. N = 12 per each group. *P < 0.01.

Figure 3. Effects of dietary PI or TAG on triglyceride (TG) and cholesterol (Chol) levels in the serum and the liver. For other abbreviations see Figure 2.
Results from several reports showed that free inositol and CDP-inositol had no effect on lipid metabolism. However, substituting dietary TAG with DAG diminishes the postprandial increase in TAG level and exhibits the anti-obesity activity.

In biological membranes, PI also functions as a cellular mediator responding to external stimuli, nerve transmission, and regulation of enzyme activity through specific interactions with various proteins. It serves as a major source of arachidonic acid for the biosynthesis of prostaglandins and eicosanoids. Myoinositol, the hydrophilic component of PI, is an important metabolite of the signal transduction on the cell membranes. Altered metabolism of inositol was found in patients with diabetes mellitus, chronic renal failure, and multiple sclerosis. This observation prompted the clinical interest in the prevention and treatment of human diseases by modulating dietary inositol. Indeed, reports on clinical trial in patients with panic disorder and depression have shown that myoinositol treatment depressed the occurrence of the neural tube defects (NTD)-disorder in the brain. Inositol deficiency has also been shown to produce fatty liver, intestinal lipodystrophy, and other abnormalities in animals.

In summary, dietary PI can lower TAG levels in serum and liver. The underlying mechanism is likely associated with a decrease in membrane-bound PAP and DGAT activities in the liver. Dietary PI can also reduce the active form of the CT enzyme, suggesting an inhibition of PC synthesis in the liver.

Food processors should take the nutritional significance of PL into consideration when making decisions about functional additions in various applications.

**Background Reading**


Teruyoshi Yanagita is a professor in the Department of Applied Biological Sciences, Saga University, Saga, Japan.