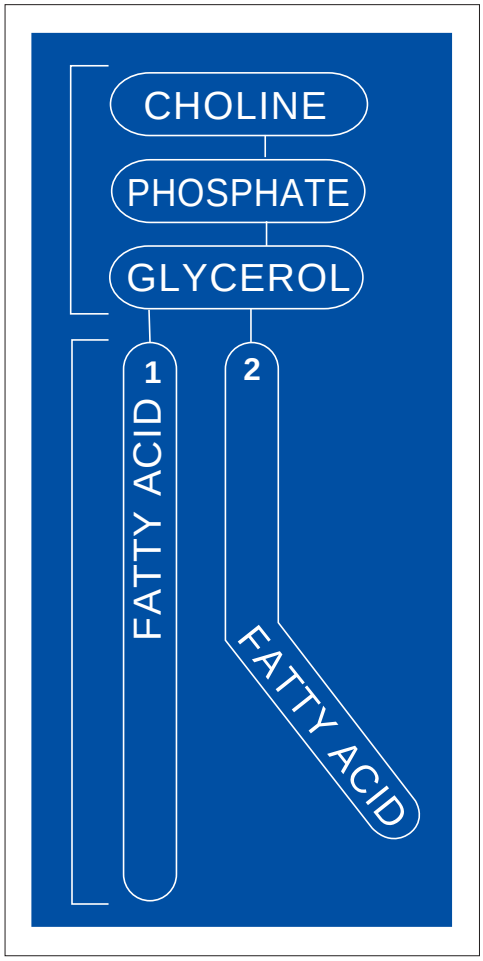

Phosphatidylcholine

Introduction

Phosphatidylcholine (PC) is a phospholipid, one of a primal class of substances ubiquitous among life forms.[1] PC is the predominant phospholipid of all cell membranes and of the circulating blood lipoproteins. It is the main functional constituent of the natural surfactants, and the body's foremost reservoir of choline, an essential nutrient.[2] PC is a normal constituent of the bile that facilitates fat emulsification, absorption, and transport, and is recycled via enterohepatic circulation.

Until recently the nomenclature of PC was confused with lecithin, a complex mixture of phospholipids and other lipids. Lecithin preparations enriched in PC at or above 30 percent by weight are considered PC concentrates

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Pharmacokinetics and Metabolism

Chemically, PC is a glycerophospholipid,[3] built on glycerol (CH_2OH-CHOH-CH_2OH) and substituted at all three carbons. Carbons 1 and 2 are substituted by fatty acids and carbon 3 by phosphorylcholine. Simplistically, the PC molecule consists of a head-group (phosphorylcholine), a middle piece (glycerol), and two tails (the fatty acids, which vary). Variations in the fatty acids in the tails account for the great variety of PC molecular species in human tissues.

In vivo, PC is produced via two major pathways.[4] In the predominant pathway, two fatty acids (acyl "tails") are added to glycerol phosphate (the "middle piece"), to generate phosphatidic acid (PA). Next, PA is converted to diacylglycerol, after which phosphocholine (the "head-group") is added on from CDP-choline. The second, minor pathway is phosphatidylethanolamine (PE) methylation, in which the phospholipid PE has three methyl groups added to its ethanolamine head-group, thereby converting it into PC.

Taken orally, PC is very well absorbed, up to 90 percent per 24 hours when taken with meals. Postprandially, PC enters the blood gradually and its levels peak over 8-12 hours. During the digestive process, the position-2 fatty acid becomes detached (de-acylation) in the majority of the PC molecules.[5] The resulting lyso-PC readily enters intestinal lining cells, and is subsequently re-acylated at position 2. The position-2 fatty acid contributes to membrane fluidity (along with position 1), but is preferentially available for eicosanoid generation and signal transduction. The omega-6/omega-3 balance of the PC fatty acids is subject to adjustment via dietary fatty acid intake.[6,7]

Choline is most likely an essential nutrient for humans,[8] and dietary choline is ingested predominantly as PC. Greater than 98 percent of blood and tissue choline is sequestered in PC,[2] and dietary PC serves as a "slow-release" blood choline source.[9] Malnourished individuals with lowered blood choline frequently display liver steatosis and related dysfunctions; these often respond favorably to PC supplementation.[10]

Methyl group ($-CH_3$) availability is crucial for protein and nucleic acid synthesis and regulation, phase-two hepatic detoxification, and numerous other biochemical processes involving methyl donation.[11]

Methyl deficiency induced by restricted choline intake is linked to liver steatosis in humans, and to increased cancer risk in many mammals. PC is an excellent source of methyl groups, supplying up to three per PC molecule.

Mechanisms of Action

PC is the main structural support of cell membranes, the dynamic molecular sheets on which most life processes occur.[1] Comprising 40 percent of total membrane phospholipids, PC's presence is important for homeostatic regulation of membrane fluidity. The PC molecules of the outermost cell membrane deliver fatty acids on demand for prostaglandin/eicosanoid cellular messenger functions, and support signal transduction from the cell's exterior to its interior.[6]

PC is the main lipid constituent of the lipoprotein particles circulating in the blood. The amphipathic properties of PC render it an obligatory micellizing constituent of bile.[12,13] PC has surfactant (surface-active) properties that substantially protect the epithelial-luminal interfaces of the lungs and GI tract.[14,15]

Biochemically, PC is the preferred precursor for certain phospholipids and other biologically important molecules.[4] PC also provides antioxidant protection *in vivo*.[16] In animal and human studies, PC protected against a variety of chemical toxins and pharmaceutical adverse effects.[1]

Clinical Indications

The best-documented clinical success with PC to date is its significant amelioration of liver damage, probably because liver recovery following damage requires substantial replacement of cell membrane mass. The findings from eight double-blind trials and numerous other clinical reports[1,7] indicate consistently significant clinical benefit, including improvement of enzymatic and other biochemical indicators, faster functional and structural rebuilding of liver tissue, accelerated restoration of subjects' overall well-being, and improved survival following PC treatment.

Alcoholic Hepatic Steatosis and Inflammation

Knuechel conducted a double-blind trial on 40 male subjects with hepatic steatosis (fatty liver) and inflammation linked to alcohol intake.[17] Subjects were taken off pharmaceuticals and randomized into two groups; one group received placebo, the other 1,350 mg PC per day by mouth (fortified with B vitamins). Benefits from PC were evident at two weeks, and by the eighth week a wide variety of biochemical liver function measures were significantly improved over placebo.

Three subsequent double-blind trials corroborated these findings. Schuller Perez and San Martin concluded, "It is our view that the use of highly-unsaturated phosphatidylcholine for therapy of alcohol-dependent steatoses is very productive."[18] Buchman et al administered PC double-blind to 15 subjects with fatty liver as part of a total parenteral nutrition intravenous feeding regimen, and also obtained significant benefit.[19] Other researchers report that subjects with mild to moderate hepatic inflammation benefit the most from PC supplementation.[20]

In an animal study, baboons were placed on a daily alcohol regimen for up to eight years. Following a blinded trial design, PC was added to the diet of some of the animals. After several years, baboons fed alcohol without PC had progressed to advanced fibrosis, while the PC-supplemented baboons developed fatty liver and mild fibrosis, but did not progress further. After three of the animals were taken off PC and kept on alcohol, they rapidly progressed to extensive, life-terminating liver fibrosis.[21]

Drug-Induced Liver Damage

In a double-blind trial, 101 tuberculous subjects who had suffered liver damage from rifampin and two other anti-tuberculosis pharmaceuticals received placebo or 1,350 mg of fortified PC daily. After three months, the PC group had significantly lower SGOT and SGPT enzyme levels.[22]

Hepatitis B

In a double-blind trial on 30 subjects with progressing liver damage from chronic hepatitis B virus infection (negative for HBsAg), standard immunosuppressive therapy was retained and subjects received either PC (2,300 mg per day) or placebo. At one year, the PC group had clinically stabilized, with significant improvement of liver structure, whereas the placebo group had worsened.[23]

Sixty subjects positive for hepatitis B (HBsAg-positive) were placed in a fortified PC group (1,350 mg per day) or a placebo group for 60 days. From 30 days onward the PC group was clinically improved over placebo, with 50 percent becoming HbsAg-negative, compared to 25 percent of the placebo group.[24]

In a double-blind trial of 50 subjects, all HBsAg-positive and manifesting extremely severe liver damage verified by biopsy and immunologic testing, the PC group (1,350 mg fortified PC per day) benefited considerably more ($p<0.001$) than placebo. In the PC group, 80 percent (20 of 25) were judged greatly improved, while 24 percent (6 of 25) moderately improved in the placebo group. Cell-structure, biochemical, immunologic, and hematologic parameters were significantly improved over placebo. Clinical improvement continued well past the end of the one-year trial.[25]

Hepatitis C

In a multicenter, double-blind trial, 176 patients with chronic viral hepatitis (B or C) were begun on interferon alpha for 24 weeks then randomized to PC (1.8 g/day) or placebo for 24 weeks. Significantly more patients responded to PC, particularly in the hepatitis C subgroup. In addition, PC supplementation sustained a longer-term improvement from hepatitis C over another 24 weeks.[26]

A long-term, multicenter, double-blind trial of PC for liver disease is ongoing; its results could signal a breakthrough in nutritional management of this life-threatening disease.[27]

Respiratory Distress Syndrome

The surfactant of premature babies is abnormally low in PC. Treatment with exogenous, mature-profile surfactant (with PC 70-80% of the total phospholipids) is the standard therapy for infants with, or at risk of having, respiratory distress syndrome (RDS). A meta-analysis of clinical trials suggests improved survival and overall better outcome from natural surfactant over synthetic forms.[28] In another randomized trial with 78 RDS babies, natural surfactant proved superior after six hours, and by 24 hours normalized the surfactant PC profile.[14]

Necrotizing Enterocolitis, Gastrointestinal Protection

As the major intrinsic surfactant of the gastrointestinal tract, PC helps maintain the acid barrier properties of the gastric epithelium. Animal research suggests PC helps protect against the adverse GI effects of aspirin and other non-steroidal anti-inflammatory drugs without blocking their efficacy.[15,29,30] Carlson et al reported a lower incidence of necrotizing enterocolitis in pre-term infants fed with formula high in PC and other phospholipids.[31]

Central Nervous System Cholinergic Imbalances

In contrast to persistent anecdotal claims, PC failed to benefit cognition in ten double-blind, placebo-controlled trials.[32] There are indications the "therapeutic window" for PC might be very narrow,[33] which could also explain the disappointing trial results against ataxias, tardive dyskinesia, and other CNS conditions that feature cholinergic imbalances.

Toxicity and Side Effects

PC is freely compatible with other nutrients, and when co-administered may enhance their absorption. Standard toxicological assessments indicate no significant acute or chronic toxicity from PC, as well as no mutagenicity and no teratogenicity. PC is well tolerated at daily intakes of up to 18 grams.[7] Symptoms of intolerance are

almost exclusively restricted to GI discomfort – diarrhea, excessive fullness, and nausea.

Dosage

The therapeutic range of intake is 800-2,400 mg daily, and 4.6 grams or higher for liver salvage. For subjects with severe liver damage, best results may be obtained by initiating therapy with intravenous and oral PC, then maintaining on oral supplementation after improvement has begun. In cases of liver damage from deathcap mushroom poisoning this procedure has proved lifesaving.[34]

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