Phosphatidylcholine

BEYOND CELLULAR INTEGRITY

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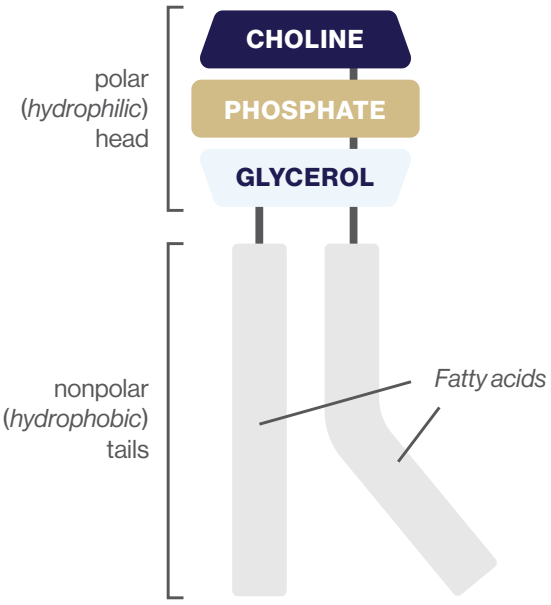
THE CLINICAL USE OF PHOSPHATIDYLCHOLINE

Phosphatidylcholine (PC) is a phospholipid integral to maintaining the structure and fluidity of a cell membrane. Additionally, PC provides structure to circulating lipoproteins and is essential for lipid transport and metabolism.[1] PC is as an essential component of bile, facilitating fat emulsification, absorption and transport and is an important constituent of surfactants in the body, including those of the lungs and gastrointestinal tract, offering protection to epithelial-luminal interfaces.[2]

The abundance of PC within cellular membrane bilayers and organelles, and the intercellular variability in PC concentrations between different cell types, is representative of its physiological importance in the body.[3,4] Comprising 40-50% of total cellular phospholipids, the clinical significance of PC's physiological presence is highlighted by ongoing research into links between endogenous PC levels and its mechanistic functions, with pathologies involving several body organs and systems.[4]

Figure 1. Phospholipid structure.[5]



What is Phosphatidylcholine?

Composed of two hydrophobic fatty acyl chains and a glycerol hydrophobic head, phospholipids are found in cellular membranes, offering structural support to the cell.[3] Phosphatidylcholine is a phospholipid with a phosphate group joined to a molecule of choline at the hydrophobic head, differentiating it from other phospholipids.[4] (See Fig. 1)

Sometimes referred to as lecithin although technically different, PC is in fact a component of lecithin.[5] Acetylcholine, essential for memory, is produced by the body from phosphatidylcholine.[5]

Phosphatidylcholine synthesis

The autogenous synthesis of PC is complex, occurring via the CDP-choline pathway (also known as the Kennedy pathway), phosphatidylethanolamine N-methyltransferase (PEMT) and Lands cycle pathways. (See Fig. 2)[3,4,7,8]

The CDP-choline Pathway

The CDP-choline pathway, expressed by all human nucleated cells, is the main source of de novo PC synthesis.[3,4,7,8] The CDP-choline pathway involves the phosphorylation of choline by ATP to phosphocholine with the assistance of choline kinase found in the cytosol.[3] CTP and phosphocholine are then converted via several enzymatic processes to produce CDP-choline and diacylglycerol (DAG), generating PC.[3]

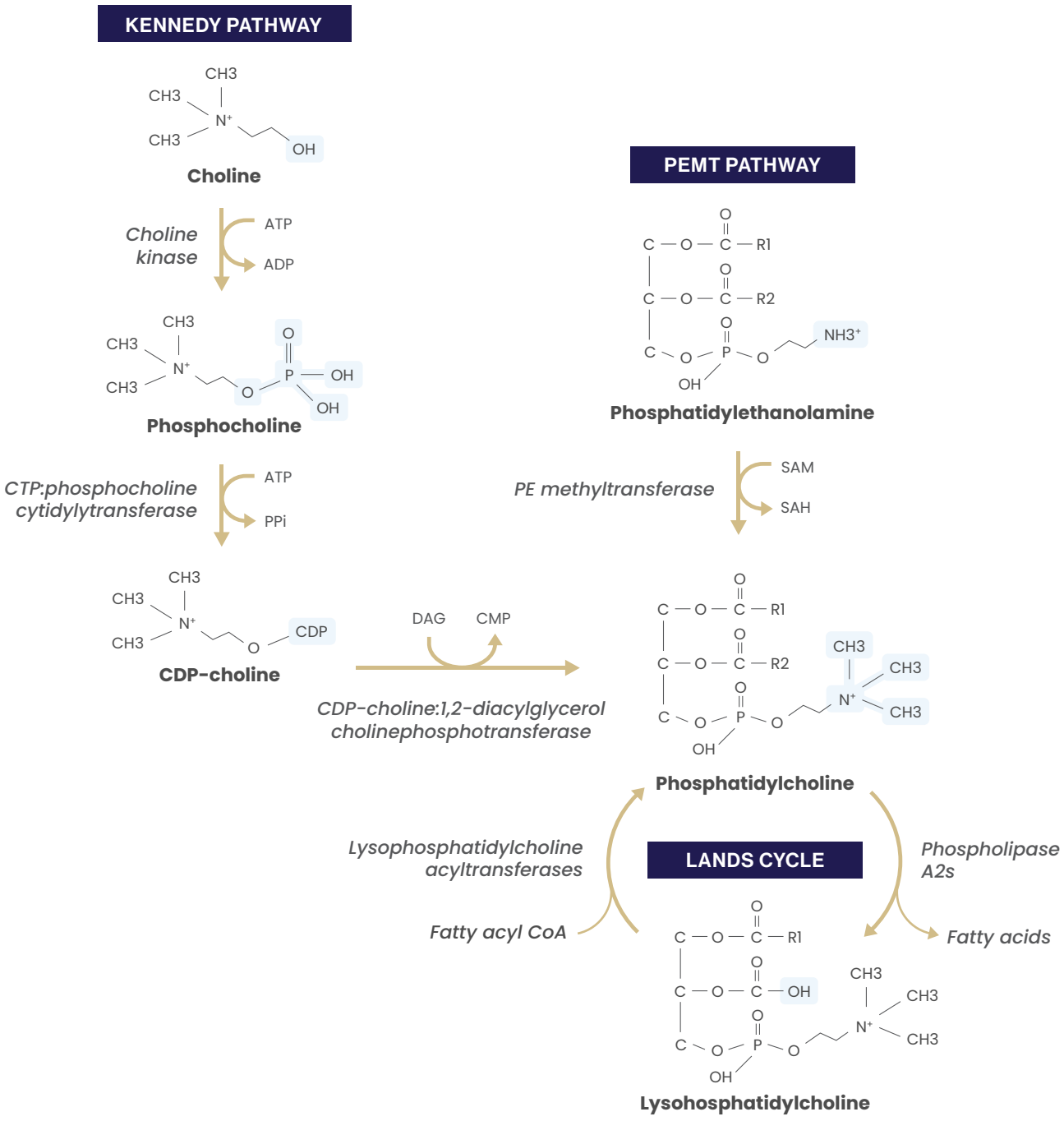
The PEMT Pathway

The PEMT pathway contributes a substantially smaller proportion of endogenous PC, expressed primarily in hepatic tissues, with small amounts expressed in adipose tissue.[3,4,7,8] The PEMT pathway involves phosphatidylethanolamine (PE) undergoing three methylation reactions in a sequence with the methyl group donor being S-adenosylmethionine and the enzyme phosphatidylethanolamine N-methyltransferase (PEMT), producing PC.[3]

The Lands Cycle

The Lands cycle further emphasises the complexity of PC synthesis and its functional/biological effects, involving the remodelling of PC into subspecies (LPCATs 1-4) that are differentially distributed in body tissues including lung alveolar, immune, brain, hepatic, intestinal, adipose,and ovarian cells.[8,9]

Figure 2. Pathways for the production of phosphatidylcholine.



Phosphatidylcholine physiological mechanisms

Current research regarding PC's physiological mechanisms demonstrates its significant involvement in many central nervous system, mitochondrial, hepatic, intestinal, respiratory, and metabolic processes.[3,10] Such mechanisms form the foundational basis for the clinical use and application of PC in a range of pathologies pertaining to these tissues, organs and systems as a consequence of imbalanced endogenous levels. (See Table 1)

Table 1. Phosphatidylcholine mechanisms in the body and clinical applications

SYSTEM / TISSUE / ORGAN	MECHANISMS	CLINICAL APPLICATION
Cellular	• Structural composition of cellular membranes. • Precursor for other membrane phospholipids (sphingomyelin and phosphatidylethanolamine). • Molecular synthesis of second messengers. • Regulates energy synthesis.[3,4,7,31]	• Supports the cellular membrane, organelle structure and functional capacity of the cell. • Promotes mitochondrial energy metabolism.[3,4,7,31]
Central nervous system	• Comprises 32% of total glycerophospholipid content in the human brain. • Maintains structural integrity of neuronal and glial cell membranes. • Involved in cholinergic neuronal and neurotransmitter transmission and signalling in the brain. • Regulates BDNF expression. • Promotes synaptic growth and plasticity. • Down regulates the brain inflammatory response by inhibiting pro-inflammatory cytokines. • Repair of compromised phospholipid membranes in TBI. • Affects enzymes involved in beta-amyloid processing, synaptic function, and neuronal survival.[10-14,34]	• Improved performance in cognitive tests (verbal fluency, memory) (each > 50 mg/d dose = improved performance). • Maintains brain cholinergic function to reduce the risk of cognitive impairment. • Ameliorates functional brain impairment. • **Incident dementia:** increased PC intake is associated with reduced disease risk (each > 50 mg/d dose = further reduced risk). • **Epilepsy:** dysregulation of PC and PE metabolic pathway observed. • **AD:** may modulate associated amyloid deposition, neurodegeneration, and cognitive decline. • **AS:** plasma PC levels positively correlated with verbal and full-scale IQ and verbal performance.[10-14,34]
Hepatic	• Liver cell and tissue structural integrity. • Primary bile phospholipid. • Key modulator of hepatic lipid levels and homeostasis.[3,7,19-21]	• Post-surgery hepatic regeneration. • Alcohol-induced reduction in PC/PE ratio. • **NAFLD:** ameliorates imbalance in hepatic lipid concentrations.[3,7,19-21] • **NB:** a large proportion of NAFLD patients have excessively low or high PC/PE ratios which are both associated with disease progression.
Gastrointestinal	• Promotes TJ integrity. • Modulates beneficial microbiome composition (*Bifidobacterium*, *Lactobacillus*). • Promotes SCFA synthesis. **As a component of intestinal brush border membrane:** • Controls metabolite absorption. • Influences fatty acid uptake and the availability of lipids for chylomicron synthesis. **As a component of the intestinal mucus layer:** • Protects enterocytes from harmful bacteria and particles.[3,15,16-18,33]	• Maintains intestinal barrier function. • Enhances intestinal immune function. • **UC:** associated with clinical remission of disease, histologic activity, and patient QoL. • **IBD:** ameliorates intestinal inflammation and colitis. • **NB:** UC and IBD individuals observed to have intrinsically low/absent concentrations of mucus layer PC which precipitates mucosal inflammation and bacterial invasion.
Respiratory	Component of pulmonary surfactant to decrease lung alveolar surface tension and inhibit expiration- induced alveolar collapse.[3]	Supports healthy respiratory function.[3,15,16-18,33]
Cardiovascular	**Cholesterol biosynthesis:** Key structural component of lipoproteins involved in lipoprotein homeostasis.[3,29,36]	• Supports healthy cholesterol metabolism. • Dyslipidaemia.[3]
Metabolic	• Influences insulin secretion and activity and glucose metabolism. • PC species (C36:3 + C36:4) inversely correlated with HbA1c and FBG.[3,22-28,30]	• Promotes insulin sensitivity. • Dysglycaemia and impaired insulin sensitivity: associated with reduced skeletal muscle concentration of PC and PC/PE ratio. • **T2DM:** high PC levels associated with a lower risk of disease onset.[3,22-28,30]
Musculoskeletal	• Influences muscular function by maintaining muscle cell mitochondrial membrane phospholipid composition. • Main component of cartilage phospholipids.[32]	• Promotes healthy cartilage composition, lubrication, and function. • **Gait speed:** low levels are an independent predictor of gait speed decline in older adults.[32]
Pregnancy	Important source of choline for foetal and offspring development.[35]	Healthy offspring outcomes: less attention deficit and social isolation symptoms.[35]

Abbreviations: AD: Alzheimer's disease; **AS:** Asperger's syndrome; **BDNF:** Brain-Derived Neurotrophic Factor; **FBG:** fasting blood glucose; **HbA1C:** glaciated haemoglobin; **IBD:** inflammatory bowel disease; **IQ:** intelligence quotient; **NAFLD:** Non-alcoholic fatty liver disease; **NB:** Note; **PC:** phosphatidylcholine; **PE:** phosphatidylethanolamine; **QoL:** quality of life; **SCFA:** short-chain fatty acids; **T2DM:** type 2 diabetes mellitus; **TBI:** traumatic brain injury; **TJ:** tight junctions; **UC:** ulcerative colitis; **VLDL:** very low-density lipoprotein).

PC is absorbed more effectively compared with free choline due to reduced catabolism by the gastrointestinal microbiome.[41]

Exogenous sources of Phosphatidylcholine

PC is available in both dietary and supplemental form, with concentrated food sources being primarily eggs, meat, fish, milk, and soy products as well as being present in smaller concentrations in potatoes and leafy greens.[36-38]

Several factors need to be considered when reviewing the suitability of obtaining appropriate quantities of PC from food sources alone versus supplemental sources. These factors include:

- An individuals' normal dietary patterns, with vegetarian, vegan and low-carbohydrate diets associated with lower endogenous levels;
- Life stage (pregnancy, lactating and growth phases may increase need); and
- The presence of physiological imbalances or pathologies associated with suboptimal PC metabolism and levels (Table 1).[38-40]

Another significant consideration observed in a recent animal study demonstrating that compared with dietary PC intake, supplemental PC did not increase plasma levels of trimethylamine-N-oxide (TMAO), elevated levels of which are associated with adverse effects on humans in relation to colorectal cancer, cardiovascular, and kidney health.[41] Further, it has been reported that as a primary source of choline, PC is absorbed more effectively compared with free choline due to reduced catabolism by the gastrointestinal microbiome.[41]

Physiological role of Phosphatidylcholine

Research is ongoing regarding the physiological relevance of PC and its subspecies in human health and disease. The importance of appropriate intake levels of PC to maintain normal physiological function and the impact of impaired or dysregulated metabolism and subsequent PC levels and functional effects may have in many clinical conditions have been established. Insufficient PC levels or changes to the cellular ratio of PC:PE may alter organelle energy metabolism within the cell, disrupting the function of the cell.[3]

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