The Roles of Choline in Maintaining Optimal Health

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REVIEW

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ABSTRACT

Choline is an essential nutrient involved in membrane lipid formation, neurotransmission and one carbon metabolism. Most of dietary choline is produced from phosphatidylcholine, a phospholipid abundant in eggs, meat and dairy products. Choline deficiency is implicated in neuronal development, liver disease, insulin resistance, muscle damage and choline is also vital during fetal development. The focus of this review is to shed light on the critical contributions of choline to membrane phosphatidylcholine formation and energy homeostasis. Moreover, this review will also focus on the role of choline in protecting against developmental disorders, particularly during pregnancy and fetal development while also focusing on adult onset metabolic disorders such as non-alcoholic liver disease and diabetes.

Key Words: Choline; Betaine; Neurotransmission; Phosphatidylcholine.

Introduction

Choline is an essential nutrient involved in membrane lipid formation, neurotransmission and one carbon metabolism. In addition to free choline, most dietary choline is produced from the phospholipid phosphatidylcholine (PC) [1]. Choline Adequate Intake (AI) of 550 mg/day for men, 425 mg/day for women, 450 mg/day for pregnant women and 550 mg/day for lactating women and has been considered a required dietary nutrient by the US Institute of Medicine's Food and Nutrition Board since 1998. However, numerous studies have reported that 4 in 5 Americans are not reaching the AI for choline. The Framingham Heart Study reported that Americans consumed on average 203 mg/day of choline whereas the Nurses' Health Study and the Atherosclerosis Risk in Communities study reported 293 and 217 mg/day choline intake respectively, far below the AI value [2-5]. Choline is most abundant in eggs, meat and dairy products [6]. To help improve choline intake, choline rich cereal based functional foods [7], milk [8] and goats [9] have been developed.

Choline deficiency is implicated in fatty liver [10], insulin resistance [11] and muscle damage in humans [12] and rodents [13]. Humans who have mutations in PCYT1A, the gene that encodes the rate limiting enzyme for PC synthesis via the CDP-choline pathway, have been shown to have severe insulin resistance and lipodystrophy [14]. In mice, choline has been shown to be particularly important during fetal development as gestational deficiency leads to memory and learning deficits later in life [15]. The focus of this review is to shed light on the importance of choline in numerous metabolic functions and suboptimal choline intake can hinder the ability for humans to carry out these functions.

Upon entry into the cell, most of choline is incorporated into phospholipid phosphatidylcholine (PC) via CDP-choline (Kennedy) pathway (Figure 1). In the first step of the pathway choline is phosphorylated by choline kinase (CK) to generate phosphocholine (PCho). PCho is then coupled with CTP by the CTP: phosphocholine cytidylyltransferase (CCT/Pcyt1) to generate CDP-choline. In the final step of the pathway, CDP-choline is condensed with diacylglycerol (DAG) by CDP-choline: DAG phosphotransferase in the endoplasmic reticulum to yield PC [16-20]. In the liver, PC is additionally generated from another phospholipid, phosphatidylethanolamine (PE), by a three-step methylation reaction catalyzed by PE methyltransferase (PEMT) [21]. This is an important backup pathway that prevents choline deficiencies when demands for choline are high, such as during embryonal development, pregnancy, and lactation [22]. Moreover, PEMT formed PC is incorporated into very-low density lipoproteins and as such transported from the liver into other tissues [23]. PEMT formed PC is enriched with n-3 PUFA, which is crucial for providing fetuses with n-3 PUFA for proper developmental programming [24] and the optimal function of neurological tissues [25- 27].

Degradation of PC by phospholipases is a critical element of choline homeostasis [28]. Choline is released from PC by phospholipase D (PLD), phospholipase A2 (PLA2) and then PLD, or by the PC base-exchange mechanisms (PSS1) as further described in Figure 1. PC is also converted into glycerophosphocholine (GPC), a prominent acetylcholine precursor and osmolyte via PLA2 [29]. PLD1 and PLD2 cleave PC between the phosphate moiety and choline head group to generate free choline and phosphatidic acid (PA). PA is an important lipid intermediate utilized for DAG formation or directly involved in signaling pathways such as the mTOR pathway [30]. Moreover, in genetic disorders with choline deficiencies such as postural tachycardia syndrome, there is an increase in PLD activity apparently in an attempt to generate more intracellular choline when choline transport in reduced [31]. Free choline is also released at the mitochondria associated ER membranes (MAM) when PC is converted into phosphatidylserine (PS) by PS synthase 1 (PSS1) but the exact utilization of the choline formed at the MAM is not known [32].

Choline oxidative demethylation is linked to energy metabolism

Aside from its role in PC synthesis, choline is oxidized in mitochondria of liver and kidney to betaine. Betaine is a methyl group donor in the one-carbon (methyonine-homocysteine) cycle (Figure 2) [33-35]. Choline and betaine supplementation to positively affect one carbon metabolism to correct perturbations in fatty acid (FA) oxidation and energy balance which are evident in obesity. In mice with excess fat accumulation, 4 weeks of choline supplementation increased plasma glycerol and glycine, which are products of increased lipolysis and choline oxidation respectively [36]. Moreover, plasma creatine and sarcosine were reduced, further indicating an increase in homocysteine/methionine cycling to breakdown choline [36]. In this model, SAM was more devoted to maintaining cellular PC balance, which is often perturbed in obesity, instead of guanidinoacetate methylation for creatine synthesis. In the skeletal muscle of mice, the main beneficial effects of supplemental choline included the reduction of energy stored as free FA, DAG and TAG and increasing energy utilization [37]. Mice with excess fat accumulation supplemented with choline or supplemented for 8 weeks with betaine showed increased oxidative demethylation of these methyl donors [38]. Oxidative demethylation of choline and betaine is beneficial as this requires energy in the form of reducing equivalents produced from succinate and α-ketoglutarate in the TCA cycle to be broken down [38]. In essence, choline and betaine breakdown increased metabolic demand, thereby decreasing the propensity for energy to be stored as fat throughout the body.

Choline and betaine protect against fatty liver and insulin resistance

Non-alcoholic fatty liver disease (NAFLD) has become the most prominent chronic disease in humans and its prevalence has risen concomitant with insulin resistance, type 2 diabetes (T2D) and obesity over the past 30 years [39]. NAFLD comprises a wide spectrum of pathologies, ranging from lipid droplets and simple steatosis to hepatitis to fibrosis and cirrhosis [40]. Dietary factors such as high caloric intake, high fat intake [41], high fructose intake, refined grain and processed meat consumption have been positively correlated with NAFLD development [42]. Though extensively studied, the mechanism responsible for the pathogenesis of NAFLD remains poorly understood.

Dietary choline is an important nutrient for maintaining optimal hepatic function. Choline deficiency has widespread effects on the one carbon metabolic system and lipid synthesis in the liver. In choline deficient mice, SAM concentrations were decreased by 50% after the consumption of a choline deficient diet for 2 weeks [43]. Due to this decrease in SAM concentration, there is a concomitant decrease in PEMT activity, and therefore PE derived PC phospholipid content [44]. The PEMT enzyme is important for the synthesis of PC used in very low-density lipoproteins (VLDL), which is critical for TAG export from the liver [45]. PC is a critical component of VLDL particles and a diminished capacity for the liver to synthesize PC via the PEMT pathway results in decreased lipoprotein secretion and TAG accumulation in hepatocytes [46]. Hepatic steatosis resulting from choline deficiency is a hallmark feature of VLDL deficiency in species such as humans and cats [47]. Choline supplementation improves hepatic function in mice by normalizing the expression of genes involved in lipogenesis [SREBP1, FAS, SCD1] and lipolysis [ATGL, HSL, LPL], as well as FA oxidation [PPARα] and mitochondrial biogenesis [PGC-1α] [36]. These changes result in a decrease in hepatic TAG [36, 48] and plasma acylcarnitines, which is an indication of improvements in mitochondrial fatty acid metabolism [36, 49].

Betaine has been shown to be hepatoprotective in mice with respect to numerous toxic substances such as ethanol, lipopolysaccharide and dimethylnitrosamine [50 - 52]. The liver injury resulting from these toxicants is largely due to altered sulfur amino acid metabolism, and betaine has been shown to be beneficial in this regard [53, 54]. Hepatocyte cell volume in mammalian systems is often altered during oxidative stress and these changes in cell volume activate signal transduction cascades in an attempt to allow the cell to respond to stress more effectively [55, 56]. BHMT, CHDH and PEMT expression is increased in hypotonic conditions, indicating a coordinated response to increase cell volume and regenerate methionine from Hcy for eventual methyl group donation [57]. Additionally, betaine is a lipotropic compound and helps to increase the levels of SAM and GSH in the liver which are critical for maintaining proper methylation and redox states [58].

Betaine has been shown in mice to reduce body weight induced by HFD consumption as well as hepatic and visceral fat mass by increasing AMPK activation [59]. AMPK is a positive regulator of fatty acid oxidation and decreases the expression of genes such as SREBP-1c, ACC and FAS which promote lipogenesis [60]. Furthermore, AMPK can directly phosphorylate PGC-1α to stimulate mitochondrial biogenesis [61]. Betaine has also been shown to reverse increased serum insulin levels and improve glucose tolerance [62] while also reducing serum TAG and cholesterol levels. These findings are supplemented by the activation of insulin signaling in the liver as seen by increasing phosphorylation of IRS1 and activation of Akt [63].

In mice, plasma acyl-carnitine levels are lowered substantially with choline and betaine supplementation, which is beneficial as an abundance of acyl-carnitines in the plasma is indicative of inefficient mitochondrial FA oxidation, a metabolic issue that often affects obese individuals [36, 64]. As a result, acyl-carnitine levels can provide an indication of the ability of the cell to oxidize FA [65] and to maintain optimal mitochondrial function [66]. In mice, long chain acyl-CoA species are critical regulators of metabolism as they inhibit mitochondrial adenine nucleotide translocase [ANT], which regulates ATP/ADP exchange across the inner mitochondrial membrane [66]. Additionally, malonyl-CoA is an allosteric inhibitor of CPT1, the rate limiting enzyme in the oxidation of long chain fatty

acyl-CoA by facilitating its entry into the mitochondrial matrix. Moreover, choline supplementation, decreased expression of genes which are critical for fatty acid synthesis [FAS and ACC] while the expression of genes involved with FA oxidation was increased [PPARα and PGC-1α] [37].

Supplementation of choline and betaine in vivo has been shown to ameliorate perturbations with lipid metabolism that arise in obesity. Choline and betaine supplementation in mice decreased liver and adipose tissue weight while also reducing lipid droplet size which is largely due to decreased FA incorporation into TAG [37]. In addition, betaine supplementation significantly decreased plasma TAG content while choline supplementation reduced collagen deposition, indicating decreased inflammation and fibrosis throughout the liver [38]. Membrane composition was also remodeled with choline supplementation as the ratio of important lipid raft components FC: SM was increased [37]. The optimal balance between FA oxidation and lipogenesis was restored with choline supplementation by activating the main regulator of skeletal muscle FA oxidation AMPK [36, 37]. Subsequently, mTORC1 activation was decreased which in turn facilitate a decrease in SREBP1c nuclear translocation for lipogenic gene transcription [37]. With choline supplementation, glycogen content, which is often depleted in insulin resistant skeletal muscle, was also restored, indicating an enhanced ability to store glucose taken up from the blood.

Therefore, choline and betaine are critical for mitigating the development of NAFLD. Choline and betaine both decrease lipid accumulation in the liver while also decreasing hepatic fibrosis. Metabolism is impacted by stimulating TAG degradation by lipolysis to generate a fasted energy deficient state. Choline is the predominant phospholipid component of VLDL which is important for exporting TAG from the liver. Improving dietary choline and betaine levels has promoted fatty acid oxidation by increasing AMPK activation and improving insulin signaling rodent models [37]. Despite considerable mechanistic research, there is no clear physiological concentration of choline or betaine that is considered adequate for ameliorating fatty liver or insulin. However, as the majority of Americans are deficient in choline [2], reaching the AI for choline should help diminish the incidence of fatty liver [10] and insulin resistance [11].

The role of choline and epigenetics in pregnancy and gestation

During pregnancy, maternal choline affects metabolic and physiological functions of the offspring through numerous inter-related mechanisms. Maternal choline is vital for optimal placental development and maintaining optimal fetal growth [67, 68]. The increased requirement for choline during gestation is largely due to an increased use of betaine as a methyl group donor and a higher demand for choline utilization for PC synthesis [69]. This could lead to substantial depletion of choline derived methyl donors such as betaine and SAM in pregnant women [70, 71]. A reduction in choline and betaine leads to elevated homocysteine and decreased SAM levels, thereby decreasing methyltransferase activity as SAM is a positive regulator of MAT [72].

Genetic variants that increase choline requirements can leave an individual susceptible to choline inadequacy [73], and this effect can be magnified during reproduction [74]. Some of these SNPs are located in genes such as PEMT (rs12325817), choline dehydrogenase (CHDH) (rs12676) and MTHFR (rs1801133) which are critical for proper functioning of the one carbon metabolic system [75-77]. In addition, estimations from the NHANES study estimated that only 1 out of 10 pregnant women in the US are consuming adequate amounts of choline [78], which is a troubling statistic as choline is a vital nutrient for fetal development.

The prenatal period is vital for the establishment and maintenance of the epigenome [79]. The DNA methylation patterns of gametes are mostly abolished after conception; therefore de novo methylation is crucial for gene silencing [80]. DNA methylation is closely linked to histone modification in order to facilitate time-sensitive alterations throughout fetal development [81]. In addition, the fetal epigenome can be affected by numerous maternal environmental factors such as nutrition [82]. During

pregnancy, it has been determined that maternal choline supply has dramatic effects on the fetal epigenome [83]. The fetuses of choline deficient mothers exhibited hypermethylation of the insulin growth factor 2 (IGF2) gene [84], which is critical for embryonic development [85]. Additionally, choline deficient mothers exhibited hypomethylation of DNMT1 and this was correlated with the epigenetic and expression changes of IGF2, suggesting that maternal choline deficiency exerted its effects on IGF2 via DNMT1 hypomethylation [86].

Maternal choline intake during pregnancy is critical for optimal cognitive function [87, 88]. There is substantial evidence that adequate maternal choline levels during pregnancy are required for optimal hippocampal function, and therefore maintaining cognitive abilities [89-91]. Choline deficiency during pregnancy has been shown to decrease hippocampal methylation of the cyclin dependent kinase inhibitor 3 (CDKN3) gene and increase the expression of kinase associated phosphatase [Kap], a known inhibitor of cell proliferation [92]. Maternal PC levels during pregnancy alter hippocampal cholinergic function of the offspring, which is associated with depression and anxiety later in life [93]. This is because PC is important for ensuring adequate neuron density [94], propagation of intracellular signals [95] and optimal membrane configuration [96]. PC can also be used for acetylcholine synthesis, and therefore cholinergic transmission [97]. Choline intake is an important component of neurological development [98] as it has a large influence on structural integrity, function and cell signaling within the brain [99, 100].

Additionally, choline supplementation in pregnant women has been shown to increase placental FATP4 content, which transports DHA to the fetus for neurological development [101]. Moreover, maternal choline supplementation increases the levels of DHA-enriched PC [PC-DHA], which is mainly synthesized by the PEMT pathway [102]. The PEMT pathway is especially important for fortifying phospholipids with DHA as this enzyme prefers PE-DHA as a substrate [103]. This is in contrast to the CDP-choline pathway which predominantly synthesizes PC containing saturated medium length FA [104]. With this in mind, maternal choline supplementation can serve as a dietary approach to supply the developing fetus with DHA. Umbilical cord choline content can be up to 5-fold higher than what is observed in maternal blood, further emphasizing the importance of choline in fetal development [99]. Furthermore, the PEMT gene has an estrogen response element within its promoter region, meaning that its expression can be induced when estrogen is present [101]. Estrogen is typically abundant during pregnancy, and is therefore important for the fortification of the developing fetus with PC-DHA [101]. In fact, women with SNPs in within the estrogen response element are much more susceptible to developing choline deficiency [101]. Prenatal omega-3 fatty acid supplementation in pregnant dams that consuming a diet low in folate and vitamin B12 normalizes global DNA methylation levels in the placenta and the brain [104]. This implies that omega-3 fatty acids are involved in modifying methylation patterns [104].

Taken together, choline and PC have critical roles with respect to pregnancy and fetal development. Choline is a critical molecule which can ultimately serve as a methyl donor within the one carbon metabolic system. As a result, choline deficiency has a negative impact on fetal development due to perturbed epigenetic regulation. In addition, choline deficiency has detrimental effects on hippocampal development, and can lead to cognitive deficiencies. Lastly, PC is an important molecule for fetal DHA enrichment and hormones [i.e. estrogen] and enzymes [PEMT] help facilitate this process.

Neuroprotective roles of choline

Choline levels have been shown to be integral to maintaining optimal neurological function over time. As the number of older individuals in our population increases, the impact of choline deficiency on the health of these populations becomes more important. With aging, cerebral function becomes impaired through myelin degradation, decreased synaptic function and dysregulation of DNA methylation. Due to these pathologies, older adults experience cognitive decline and are increasingly affected by neurological disorders like Alzheimer's disease [AD].

Studies have established a positive correlation between individuals carrying mutations which alter MTHFR activity and AD, linking choline metabolism and neurological function. Choline can act as a reserve methyl donor when MTHFR function is diminished but this will deplete choline pools that are required for various neurological functions. These functions include the integration of choline into the neurotransmitter acetylcholine and lipids like PC, which are associated with hallmark neurological perturbations of AD such as memory impairment and anxiety [105]. Moreover, the quantity of lysoPC species, which are pro- inflammatory lipid mediators, as well as sphingolipid breakdown products have been found to be markedly increased in AD patients [106, 107].

The focus on nutrition has become increasingly important with regards to neurological disorders, largely because synaptic membranes require numerous nutrients to be synthesized. Van Wijk et al. [108] report that cognitively impaired subjects had lower circulating levels of choline and folate, both of which are fundamental to membrane phospholipid synthesis. Mellott et al. [109] have shown that neonatal choline consumption can mitigate AD related cognitive decline later in life by attenuating amyloid plaque formation. As in other models, in utero choline supplementation has been shown to prevent a decline in hippocampal neurogenesis in adulthood while also rescuing cholinergic functions, which are hallmarks of AD [110, 111]. In mice, maternal choline supplementation has therapeutic potential by normalizing the expression of genes involved with synaptic plasticity in offspring. This is key for protecting basal forebrain cholinergic neurons mitigating decline in spatial cognition [112]. Cytidine 5'-Diphosphocholine [citicoline], a PC precursor, has also been shown to improve cognitive performance in AD patients as a safe and effective agent to increase PC levels in the brain [113, 114].

Interplay between fatty acids and phospholipids in modulating membrane function

It is widely conceived that fatty acid esterification in critical for efficiently incorporating n- 3 fatty acids into the brain [115, 116], and that phospholipids are important carriers of n- 3 fatty acids [26]. Esterified fatty acids are more readily absorbed into the body relative to fatty acids in TAG or unesterified fatty acids [117]. Additionally, n-3 fatty acids are more resistant to oxidation when incorporated into phospholipids relative to TAG [118]. Moreover, fatty acids esterified in phospholipids relative to TAG are more bioavailable [119], which is especially important in brain development [120-122].

An important role of n-3 fatty acids is their role in modulating biophysical properties within the cell membrane which play a role in signal transduction cascades [123, 124]. For instance, Li et al. [2007] demonstrated that plasma membrane DHA content is integral for elevating eNOS activity by altering the lipid: protein interactions in caveolar microdomains, thereby facilitating the translocation of eNOS from the plasma membrane [125]. Moreover, glucose transport has been shown to be modulated by the effects of n-3 fatty acids on its configuration within the membrane [126 - 128]. Imbalances in the activity of enzymes that maintain phospholipid homeostasis can facilitate pathological conditions resulting from membrane perturbations [129].

Mutations in the PLA2G6 gene which encodes Ca2+ dependent phospholipase A [iPLA2] have been linked to infantile neuroaxonal dystrophy which is characterized by motor and sensory impairment [130]. iPLA2 works to breakdown PC, generating free fatty acids and lysoPC and serves as an antagonist to Pcyt1, which is a key enzyme in PC production [131]. Imbalances between the activity of iPLA2 and Pcyt1 can lead to lipid imbalances which are detrimental for membrane integrity [132]. One of the lipids that is most often liberated by iPLA2 is arachidonic acid [133, 134], an eicosanoid precursor which can facilitate PLD activation leading to the activation of subsequent signaling cascades [135]. Moreover, excessive iPLA2 mediated arachidonic acid release can lead to 4-hydroxy-2-nonenal [4-HNE] production [136]. 4-HNE is a peroxidized product of arachidonic acid which can have a significant impact on cell functions by forming protein adducts and neuroaxonal dystrophy [137, 138]. Additionally, a subset of individuals

with mutations in the PLA2G6 gene develops brain iron deposits and abnormal EMG readings likely resulting from axonal swelling and deterioration [139]. The mechanism for brain iron accumulation is unclear but it is likely due to many factors from the dysfunction of proteins involved with iron transport and storage [140] and the ability for iron to participate in the Fenton reaction to generate free radicals from products of mitochondrial respiration [141].

Conclusion

Choline is implicated in many biological processes like phospholipid biogenesis, FA oxidation, pregnancy and neurological development. However, a large proportion of the North American population is lacking in dietary choline consumption which is implicated in fatty liver, insulin resistance and obesity. As a result, it is imperative to increase choline consumption to support early life development and to help diminish the prevalence of adult onset metabolic disorders. Recommended intakes of the nutrients required for optimal health typically focus on a small number of nutrients. However, in reality, all nutrients are required in adequate amounts for optimal health, including nutrients such as choline which are often overlooked in the Western diet. The most important point of this review is that dietary choline deficiency is rampant in the Western world, and this can have widespread deleterious metabolic consequences.

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PEER REVIEW

Not commissioned. Externally peer reviewed.

Figures

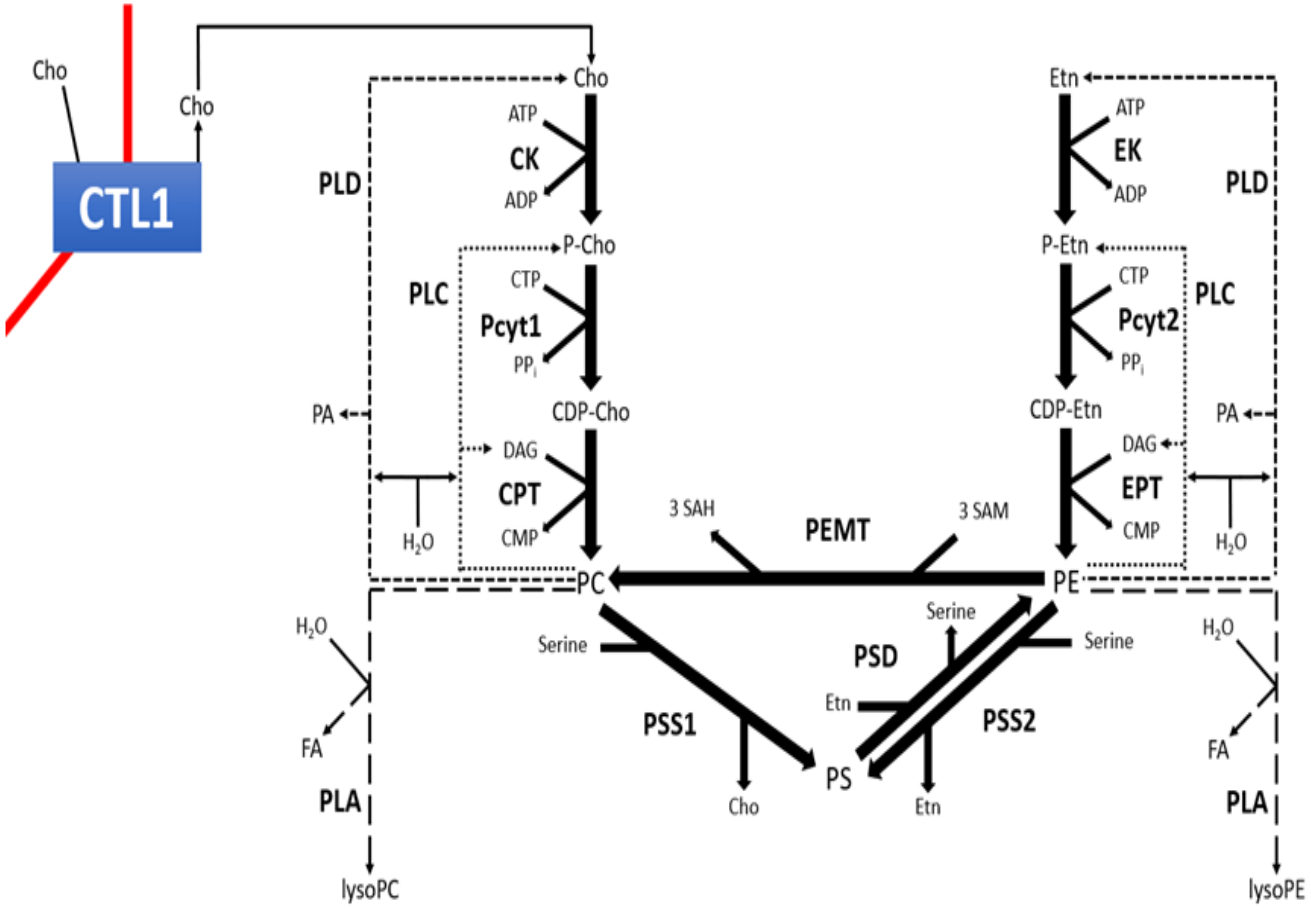

Figure 1: Integration of choline into general membrane phospholipid metabolism.

After entering the cell by the choline like transporter like 1 (CTL1), choline (Cho) is channeled into the CDP-choline (Kennedy) pathway through two sequential activations, to P-Cho by choline kinase (CK) and CDP-Cho by the cytidylyltransferase Pcyt1. CDP-Cho and diacylglycerol (DAG) then produce PC in the final, CTP transferase step of the pathway. Cho could be metabolically released from PC by the action of PLD and PSS1, or from lyso PC produced by phospholipase A2 (PLA). Additional PC and consequently Cho are produced endogenously from phosphatidylethanolamine (PE). PE is made de novo by the CDP-Etn brunch of the Kennedy pathway and additionally from phosphatidylserine (PS) by PS decarboxylation (PSD). To complete the membrane phospholipid cycle, PS is made from both PC and PE by base-exchange mechanisms driven by PS synthase 1 and PS synthase 2, respectively.

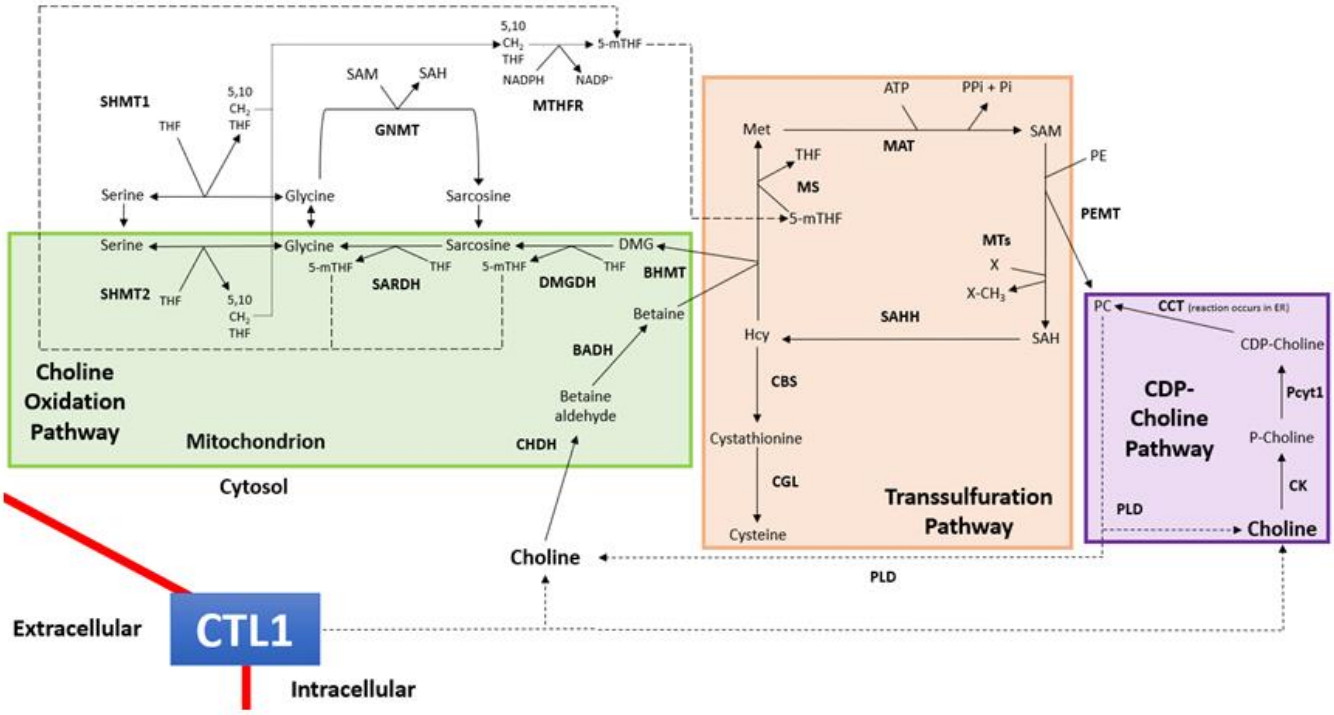

Figure 2: Interplay between choline oxidation, one-carbon metabolism and CDP choline pathway.

A significant portion of choline is metabolically lost by a sequential mitochondrial oxidative demethylation to betaine, dimethylglycine, sarcosine, and the final amino acid product glycine. The process includes three demethylation steps where the choline oxidation product betaine donates first methyl group to homocysteine (Hcy), to regenerate methionine (Met), while the remaining methyl groups are donated to tetrahydrofolate (THF) to regenerate 5-methy-THF. The choline demethylation degradation process includes multiple enzymes in the order of betaine aldehyde dehydrogenase-BADH, betaine methyltransferase-BHMT, DMGDH–dimethylglycine dehydrogenase, GNMT–sarcosine dehydrogenase, glycine N-methyltransferase, SARDH and serine hydroxy- methyltransferase SHMT2. On the other hand, the product of the one-carbon cycle, S-adenosyl methionine (SAM) is utilized for the production of PC by the PE methylation pathway, which regenerates PC and choline for further use. Unmethylated homocysteine (Hcy) is degraded to cysteine by the trans-sulfuration pathway. The Met/Hcy cycle includes MS– methionine synthase, MT–methyltransferase, SAHH–S-adenosylhomocysteine hydrolase, CBS–cystathionine β-synthase, and CGL–cystathionine γ-lyase.

Abbreviations

PC – phosphatidylcholine

AI – adequate intake

CCT/Pcyt1 – choline-phosphate cytidylyltransferase

CDP – cytidine diphosphate

CTL1 – choline transporter-like protein 1

CK – choline kinase

PCho – phosphocholine

CTP – cytidine triphosphate

Pi – inorganic phosphate

DAG – diacylglycerol

ER – endoplasmic reticulum

PE – phosphatidylethanolamine

SAM – S-adenosylmethionine

PEMT – phosphatidylethanolamine N-methyltransferase

VLDL – very low density lipoprotein

PUFA – polyunsaturated fatty acid

GPC – glycerophosphocholine

PLA – phospholipase A

PLD – phospholipase D

mTOR – mammalian target of rapamycin

POTS – postural orthostatic tachycardia syndrome

MAM – mitochondrial associated membrane

PS – phosphatidylserine

PSS1 – phosphatidylserine synthase 1

DNA – deoxyribonucleic acid

FA – fatty acid

TAG – triacylglycerol

TCA – tricarboxylic acid

NAFLD – non-alcoholic fatty liver disease

T2D – type 2 diabetes

SREBP1 – sterol regulatory element-binding protein 1

FAS – fatty acid synthase

SCD1 – stearoyl-CoA desaturase-1

ATGL – adipose triglyceride lipase

HSL – hormone sensitive lipase

LPL – lipoprotein lipase

PPARα – peroxisome proliferator activated receptor alpha

PGC-1α – peroxisome proliferator activated receptor gamma coactivator 1 alpha

BHMT – betaine homocysteine methyltransferase

CHDH – choline dehydrogenase

Hcy – homocysteine

GSH – glutathione

HFD – high fat diet

AMPK – adenosine monophosphate-activated protein kinase

ACC – acetyl-CoA carboxylase

IRS1 – insulin receptor substrate 1

Akt – protein kinase B

ANT – adenine nucleotide translocase

ATP – adenosine triphosphate

ADP – adenosine diphosphate

CPT1 – carnitine palmitoyltransferase 1

FC – free cholesterol

SM – sphingomyelin

MAT – methionine adenosyltransferase

MTHFR – methylenetetrahydrofolate reductase

IGF2 – insulin growth factor 2

DNMT1 – DNA methyltransferase 1

CDKN3 – cyclin dependent kinase inhibitor 3

Kap – kinase associated phosphatase

FATP4 – long chain fatty acid transport protein 4

DHA – docosahexaenoic acid

eNOS – endothelial nitric oxide synthase

4-HNE – 4-hydroxynonenal