UNIT 5

Other Organic Nutrients

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I. CHOLINE

A. Overview

While many nutrition scientists consider that the list of required vitamins is complete, others would argue that there are certain circumstances where a dietary supply of a compound is essential for the support of normal metabolism. Choline is one of these compounds. In rats given a choline-deficient diet, one can observe a fatty liver as well as certain central nervous system deficits. Human cells grown in culture also have an absolute requirement for choline, and humans sustained by choline-free parenteral solutions develop symptoms similar to those of the deficient rat. It is on this basis that the inclusion of choline in a list of "conditionally" essential nutrients is argued.

B. Structure, Chemical and Physical Properties

Choline is the trivial name for 2-hydroxy-N,N,N-trimethyl-ethanaminium. The structure for this compound is shown in Figure 1. Choline is freely soluble in water and ethanol but insoluble in organic solvents such as ether or chloroform. It is extremely hygroscopic. It is a strong base and readily decomposes in alkaline solutions, resulting in the production of trimethylamine. Because of its unique structure, choline serves as a donor of methyl groups. It has a molecular weight of 121.2 Da and belongs to a class of compounds that function either as methyl donors or as membrane constituents. Related compounds are listed in Table 1. Because of its instability, the determination of choline in food and biological tissues is fraught with difficulty. Commonly used is the reineckate method which involve the precipitation of choline as a reineckate salt and the development of a characteristic color. Unfortunately this method lacks the sensitivity and specificity provided by newer chromatographic and isotopic methods that are combined with rapid inactivation, via microwave, of choline degradative enzymes. Work is ongoing for the development of sensitive and specific methods for choline assay.

C. Sources

Choline is widely distributed in foods and is consumed mainly in the form of lecithin (phosphatidylcholine). Lecithin is not only a naturally occurring common food ingredient but is also a

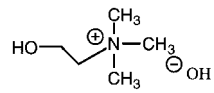

Figure 1 Structure of choline.

Table 1 Choline and Related Metabolites

As methyl donor:
Choline
S-Adenosyl-L-methionine
Methyltetrahydrofolate
Betaine
As choline metabolite:
Choline, acetylcholine
Phosphorylcholine
Betaine
Phosphatidylcholine (lecithin)
Lysophosphatidylcholine (lysolecithin)
Sphingomyelin

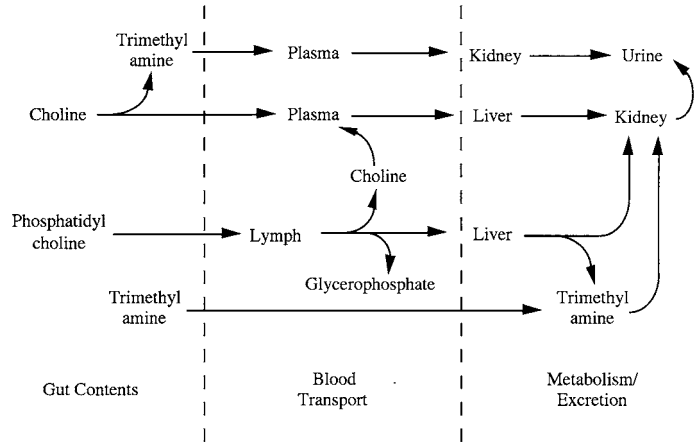

Figure 2 Absorption and metabolism of choline.

common additive to processed foods. It serves as a good food stabilizer and emulsifying agent. Choline chloride and choline bitartrate are added to infant formulas to assure equivalency to breast milk, which contains 7 mg/100 kcal (7 mg/420 kJ): 7 mg is about 0.05 mmol or 50 μmol. Recent assessments of commercial infant formulas, however, showed less choline in the preparation than shown on the label. The choline content of the infant formulas in this report ranged from 100 to 647 μmol. In part, this discrepancy may be due to the lability of choline once in a solution (the infant formula) that is mildly alkaline, and in part due to the relative difficulty in assessing the choline content accurately. If the energy requirement of the infant is 650 kcal (2720 kJ), this infant would need 45.5 mg or 375 μmol of choline a day. Depending on which of the infant formulas is used, the infant could be at risk of insufficient intake.

D. Absorption, Metabolism

There is a good bit of difficulty in assessing choline absorption. Currently it is believed to be absorbed via a sodium-dependent carrier-mediated mechanism. If large amounts of choline are consumed, uptake of the excess is by passive diffusion. One study using labeled choline showed that about 65% of the dose was found in the urine as trimethylamine within 12 hr of ingestion. When labeled choline was incorporated into lecithin and ingested, significantly less of the label was recovered in the urine as trimethylamine. About 50% of the ingested labeled lecithin entered the thoracic duct intact. The use of antibiotics to reduce the population of gut flora reduced the loss of trimethylamine in the urine. This showed that one of the major degradative steps in the loss of choline is through the action of the gut flora. The route of choline and lecithin metabolism and degradation is shown in Figure 2. In addition to the action of the gut flora, phosphatidylcholine is subject to enzymatic degradation. Phospholipase A_1, A_2, and B catalyze the cleavage of the ester bonds that link the fatty acids from the glycerol backbone, resulting in free fatty acids and glycerophosphocholine. Most of the lecithin that is ingested has only one of its fatty acids removed prior to absorption. Sphingomyelin, a related complex lipid containing choline, is not degraded at all in the intestinal lumen. All of the phospholipids are transported into the lymphatic circulation from the gut and appear in the plasma lipoproteins. All classes (high-density lipoproteins, low-density lipoproteins, very-low-density lipoproteins, and chylomicrons) contain phosphatidylcholine. The chylomicrons are the major carriers from the gut, but once into the blood the phosphatidyl-choline is redistributed among the lipoprotein classes. From the blood it is then taken up by all cell types.

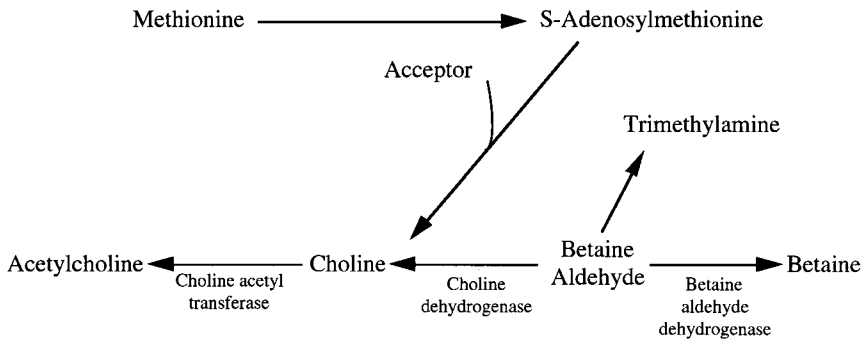

Figure 3 Use of methionine in the synthesis of choline and subsequent use of choline in betaine and acetylcholine synthesis.

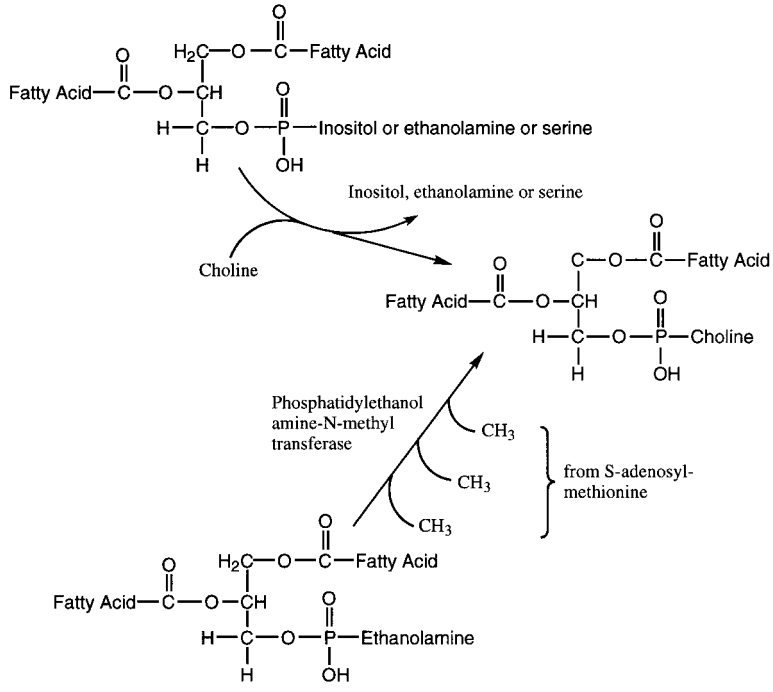

Figure 4 Biosynthesis of phosphatidylcholine.

Most species including humans can synthesize choline using methionine as the methyl donor. This synthesis is shown in Figure 3. Methionine is converted to S-adenosylmethionine (SAM). The methyl groups are then successively transferred to ethanolamine and its monomethyl and dimethyl derivatives to form choline. Aside from its use in the synthesis of acetylcholine, choline's other essential function is as part of the phospholipid, phosphatidylcholine. The synthesis of this lipid occurs via an exchange reaction using phosphatidylethanolamine, another phospholipid, as the starting material. This synthesis is outlined in Figure 4. Also shown in Figure 4 is the interconversion of other phospholipids, through base exchange, to phosphatidylcholine.

E. Function

Choline serves as a precursor for the neurotransmitter, acetylcholine. The intake of choline can affect brain levels of acetylcholine and this may be a benefit to patients showing acetylcholine deficits as in tardive dyskinesia. Some benefit is also claimed to be achieved with people having short-term memory loss as in Alzheimer's disease.

As important as the synthesis of acetylcholine, is the synthesis of the membrane phospholipid, phosphatidylcholine. This phospholipid is an important structural element of the membrane and, depending on the chain length and saturation of the fatty acids attached to carbons 1 and 2, contributes to the degree of fluidity of that membrane. The consideration of fluidity is important to the function of the membrane-embedded proteins. Many of these proteins change shape as part of their action, and the fluidity of the surrounding lipid determines the ease with which they can do this.

Phosphatidylcholine functions in the transport of lipids not only as part of the lipoproteins but also in the transmembrane lipid transport system. In this role, phosphatidylcholine serves as a lipotrope.

Lastly, because choline is a precursor of betaine, it serves as a methyl donor in the one-carbon metabolic pathways. These pathways include the formation of methionine from homocysteine and the formation of creatine from guanidoacetic acid.

F. Deficiency

Because choline can be synthesized in the body and because it is universally present in our food supply, a true deficiency in normal humans is rare indeed. Choline deficiency can occur in poultry fed a low-choline diet or one deficient in methionine and/or methyl donors. Depressed growth, fatty liver, and hemorrhagic renal disease have been reported to occur in deficient animals of a number of species. Of interest is an early report of an effect of choline deficiency on body carnitine pools. A 50% reduction has been reported and, due to the importance of carnitine in fatty acid oxidation, this relationship may explain the fatty liver of deficient animals.

G. Requirement

There are no stated requirements for choline. Zeisel has recently pleaded the case for developing intake guidelines. His arguments have merit and probably will be explored in the coming years.

II. CARNITINE

A. Overview

As is the case with choline and inositol, carnitine can be synthesized in the body in amounts usually sufficient to meet needs. Thus, carnitine is not considered an essential nutrient at all stages of life. However, just as there may be instances where choline or inositol must be provided from external sources, this is also true for carnitine. Interest in the conditional essentiality of carnitine was stimulated by Broquist and colleagues, who showed that carnitine was synthesized from lysine, an amino acid frequently in short supply in Third World malnourished patients. Follow-up work by Borum showed that the premature infant cannot synthesize sufficient carnitine to meet the needs for growth and normal metabolism. These reports thus stimulated the consideration of carnitine as a nutrient that becomes required under some circumstances.

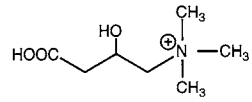

Figure 5 Structure of carnitine.

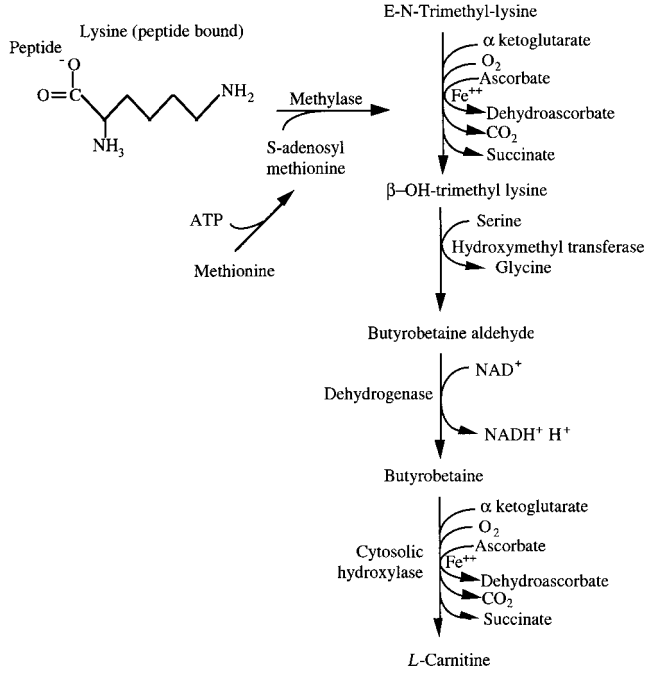

Figure 6 Synthesis of carnitine.

B. Structure, Physical and Chemical Properties

Carnitine is a quaternary amine, β-hydroxy-γ-N-trimethyl aminobutyric acid. Its structure is shown in Figure 5. It is very hygroscopic with a molecular weight of 161.2 Da. As mentioned, it is synthesized in the body (primarily the liver) from lysine. This pathway is shown in Figure 6. There are a number of essential nutrients involved: niacin as part of NAD, iron in the ferrous state, ascorbate to keep iron in its ferrous state and, of course, lysine together with methionine as a methyl donor. As long as the diet provides these nutrients, carnitine will be synthesized to meet the needs of the normal individual. There are instances, however, where despite the provision of these essential nutrients, carnitine synthesis does not take place to the extent that is needed. In this instance, carnitine becomes an essential nutrient. This occurs in the premature infant. Due to its prematurity, its biochemical pathways, especially that for carnitine synthesis, are not well developed. The severely traumatized individual also has a need for carnitine that exceeds endogenous synthesis. The whole-body response to trauma involves a catecholamine-glucocorticoid response that greatly increases lipolysis and fatty acid oxidation. This drives up the need for carnitine, and in this situation endogenous synthesis is inadequate.

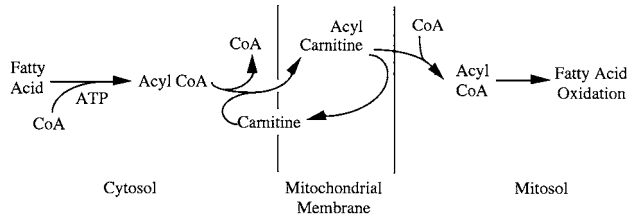

Figure 7 Carnitine acyltransferase system.

C. Sources

The techniques for carnitine analysis of foods are not well developed. However, despite the inadequacies of the methodology, it is safe to indicate that good sources of carnitine include red meats and some organ meats. Milk, whole grains, and some vegetables (i.e., spinach, cauliflower, avocado, and peanuts) contain modest amounts.

D. Absorption, Metabolism

Carnitine is absorbed via an active process involving sodium and a carrier. Carnitine in large amounts is also absorbed by passive diffusion. Concurrent with its absorption is its acetylation. It is transported in both the free and acetylated form to the muscles, where 90% of the total body carnitine may be found. The turnover of carnitine is quite slow. Although needed for fatty acid oxidation, particularly by the working muscle, it is continuously recycled rather than degraded and excreted. The kidney plays an important role in carnitine conservation in that 90% of the carnitine that arrives at the kidney is reabsorbed by the glomerulus and returned to the circulation. In instances of kidney failure this conservation is lost and again we have a situation where exogenous carnitine must be supplied. A small amount of acylcarnitine ester may be found in the urine of normal subjects. This probably represents less than 1% of the total body carnitine pool.

E. Function

Carnitine serves as part of the carnitine acyltransferase system located in the mitochondrial membrane. This system is shown in Figure 7. There are two transferases involved: carnitine acyltransferase I located on the outer side of the inner mitochondrial membrane, and carnitine acyltransferase II located on the matrix side of the membrane. These enzymes catalyze the synthesis and hydrolysis of the fatty acylcarnitine esters as well as work with the transporter protein (acyltranslocase) that catalyzes the movement of the fatty acids into the mitochondrial matrix. There is no other known function for carnitine.

F. Deficiency

Low levels of carnitine in tissues and blood typify the carnitine-deficient individual in addition to hyperlipidemia, cardiomyopathy, and muscle spasm.

G. Requirement

Because carnitine can be synthesized in the body no recommended intake levels have been set for normal children and adults. Work continues on developing intake recommendations for preterm infants and others with special needs.

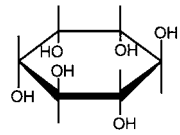

Figure 8 Myoinositol structure.

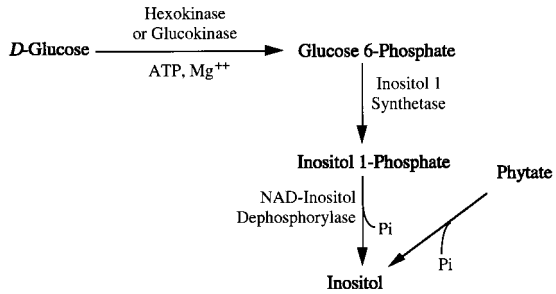

Figure 9 *De novo* synthesis of free inositol from either glucose or phytate. The conversion of glucose to inositol is an insulin-dependent pathway, whereas the dephosphorylation of phytate (phytic acid) is not.

III. INOSITOL

A. Overview

Until fairly recently, little attention has been paid to the role of inositol in the diet. This has occurred despite the recognition that dietary inositol has been shown to prevent the development of a fatty liver in rats and to cure alopecia in rats and mice, and despite a report published over a 100 years ago that diabetic humans excreted large quantities of this substance in the urine. Inositol is an essential part of every cell. It is a key ingredient for one of the membrane lipids, phosphatidylinositol. It is not considered an essential nutrient for humans.

B. Structure, Physical and Chemical Properties

Inositol is a six carbon sugar that is configuratively related to D-glucose. Its structure is shown in Figure 8. It occurs in nature in nine possible isomeric forms. However, only one, myoinositol, is biologically important as a nutrient. Myoinositol is a water-soluble, cyclic, six-carbon compound (*cis*-1,2,3,5 *trans*-4,6-cyclohexane-hexanol). It is widely distributed in foods of both plant and animal origin. In plants and animals it exists as part of the phosphatidylinositol (PI) of the cell membranes or as free inositol. Phytic acid, a component of many grain products, can be converted to myoinositol with the removal of the phosphate groups (see Figure 9). Phytate or phytic acid can bind calcium, magnesium, and other divalent ions within the intestinal compartment, making them unavailable for absorption by mucosal cells. Once the phytate is dephosphorylated through the action of phytase, the inositol residue remains. The divalent ions are released and the free inositol is absorbed. Both free inositol and cell membrane phosphatidylinositol are found in foods of animal origin.

C. Absorption, Metabolism

Dietary phosphatidylinositol is acted on by the luminal enzyme, phospholipase, and converted to lysophosphatidylinositol. This compound can then be further hydrolyzed to produce glycerophosphorylinositol and then free inositol, or acted upon by an acyltransferase in the intestinal cell

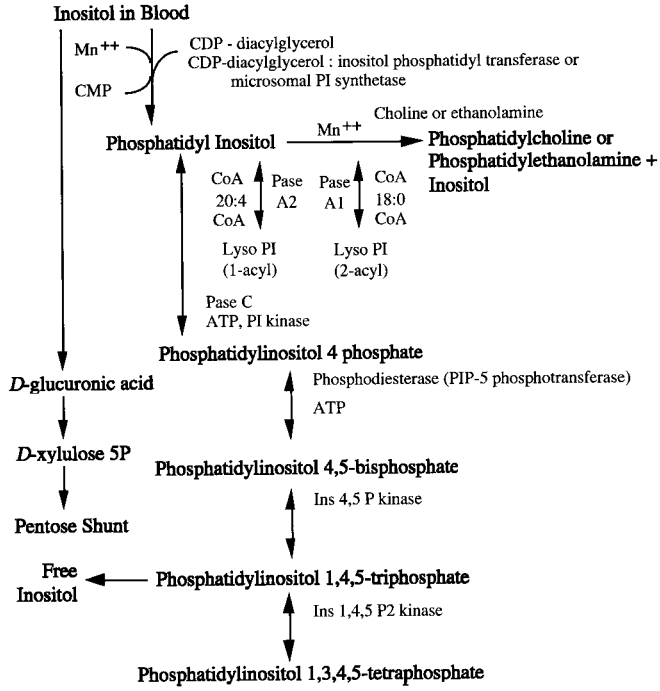

Figure 10 Inositol metabolism and the PI cycle.

which converts it back to phosphatidylinositol. This is then transported out of the gut absorptive cell as a component of the lipoproteins.

Free inositol in the lumen is transported into the luminal cells via an active, energy-dependent, sodium-dependent transport process quite similar to that which transports glucose. Although similar, it is not identical to it. Free inositol is then transported in the blood at a concentration of about 30 μm/l.

As mentioned, inositol can be synthesized from glucose by a variety of mammalian cells. Synthesis in the testes, brain, kidney, and liver has been reported. Humans can synthesize up to 4 g/day in the kidneys alone. Synthesis from glucose proceeds from glucose to glucose-6-phosphate to inositol-1-phosphate to inositol. The enzymes are glucokinase or hexokinase, followed by inositol-1-synthetase and then NAD-inositol-dephosphorylase. Figure 9 illustrates the pathway for the production of inositol from glucose and also from phytate.

D. Function

Inositol functions as a constituent of the membrane phospholipid, phosphatidylinositol. Free inositol is added to diacylglycerol via a CDP reaction producing phosphatidylinositol and CMP. The enzyme catalyzing this reaction is CDP diacylglycerol:inositol phosphatidyltransferase, sometimes called phosphatidylinositol synthetase. This synthesis takes place in the microsomes and the enzyme has a Km of 4.6 m*M* for inositol. This reaction is illustrated in Figure 10. Phosphatidylinositol can also be synthesized via an exchange reaction where free inositol can exchange for either choline or ethanolamine in either phosphatidylcholine or phosphatidylethanolamine. The Km for the Mn^{2+}-dependent reaction is 0.024 m*M*. Once formed, the phosphatidylinositol migrates from the microsomes where it is formed to any one of the membranes within and around the cell. It comprises approximately 10% of the phospholipids in the cellular membranes. Recently, its function

as a part of a unique cellular second messenger system (different from the cyclic AMP system) has been explored. This system, called the PIP system or PIP cycle, has been reported to function in insulin release by the pancreatic insulin-producing β cells, in the regulation of protein kinase C, in the mobilization of intracellular calcium, in the regulation of Na^+K^+ ATPase activity, and may have a role in blood clotting, blood pressure regulation, and renal function.

Once formed, phosphatidylinositol serves as a substrate for one of several enzymes. These reactions are shown in Figure 10. Phospholipase A1 acts on phosphatidylinositol to produce lyso PI (2-acyl PI). Phospholipase A2 acts to produce a 1-acyl PI. Both A1 and A2 act to remove one of the fatty acids from the phospholipids; A1 removes the fatty acid (usually stearic acid, 18:0) from the glycerol carbon 1, while A2 removes the fatty acid (usually arachidonic acid, 20:4) from the glycerol carbon 2. When phospholipase A2 is activated, arachidonic acid is released and this fatty acid serves as the substrate for prostaglandin synthesis. Prostaglandins are another group of hormone-like substances that are important in the regulation of blood pressure and blood clotting.

A third enzyme also has phosphatidylinositol as its substrate. This enzyme is ATP PI kinase (Phospholipase C) and initiates the PIP cycle also illustrated in Figure 10. Phospholipase C action is mediated by the guanine nucleotide-binding protein called the G protein. Phospholipase C cleaves the phosphorylated inositol from the glycerol backbone, producing diacylglycerol (DAG) and phosphatidylinositol-4,5-bisphosphate (PIP_2). DAG serves to activate protein kinase C, an important regulatory enzyme discovered in 1979. Neutral DAG remains within the membrane while the liberated inositol-4,5-bisphosphate migrates into the cytoplasm and, in the process, is again phosphorylated to form inositol-1,4,5-triphosphate (PIP_3). This compound causes a release of calcium ion from nonmitochondrial vesicular intracellular stores. The triphosphate inositol binds to a receptor protein associated with these stores to effect this release. Ca^{2+} release from the endoplasmic reticulum is elicited via an opening of a gated channel. Cyclic AMP dependent-phosphorylation of the receptor protein seems to be involved. The magnesium ion is also involved. Inositol-1,4,5-triphosphate can then either be dephosphorylated to release free inositol or be phosphorylated once again to form inositol-1,3,4,5-tetraphosphate (PIP_4) via the enzyme D-myoinositol-1,4,5-triphosphate-3-kinase. This kinase is stimulated by a Ca^{2+} in the presence of calmodulin and protein kinase C and thus the level of the inositol-1,4,5-triphosphate is carefully regulated. Inositol 1,3,4,5-tetraphosphate also is an active metabolic regulator in that it modulates calcium ion through either the re-uptake of Ca^{2+} into the intracellular stores or through control of the Ca^{2+} transfer process between inositol-1,4,5-phosphate sensitive and insensitive pools. The kinase enzyme might be the target for the enzyme protein tyrosine kinase.

All of the above phosphorylations of inositol are reversible and the amounts of each of the phosphorylated intermediates depend on the hormonal status of the individual as well as on the availability of inositol for phosphatidylinositol synthesis. Insulin, various growth factors, and PGF2α (one of the prostaglandins) have all been shown to stimulate the phosphatidylinositol cycle. Of particular interest are the reports that inositol turnover is increased in acute diabetes. Other observations on the relationship of diabetes to inositol status include the following: anti-insulin antiserum treatment of the diabetic neutralizes the effect of the exogenous insulin on inositol turnover; insulin treatment of acute insulin deficiency reverses the effect of diabetes on inositol turnover; and insulin increases the synthesis of phosphatidylinositol, DAG, and protein kinase C activity in a variety of cells from normal animals. All of these findings suggest that there may be circumstances where the synthesis of inositol by the body might be inadequate to meet the body's need and that this substance must be provided in the diet. Under these circumstances inositol becomes an essential nutrient. One of these circumstances is the disease, diabetes mellitus.

Diabetes, regardless of whether it is insulin dependent or non insulin dependent, is characterized by a failure to appropriately regulate blood glucose levels. With high blood levels of glucose the

sorbitol pathway is stimulated. If this pathway is stimulated, endogenous synthesis of myoinositol is reduced. Further, cellular uptake of glucose is impaired in the diabetic state. If cellular glucose uptake is impaired, less inositol is synthesized from that glucose and thus less is available for phosphatidylinositol synthesis. Hence, the diabetic excretes more inositol in the urine while having an intracellular deficiency because of inadequate endogenous synthesis. In turn, this means that more preformed inositol should be provided to the body via the diet. Thus, the diabetic may have a significantly greater requirement for inositol than the nondiabetic. Indeed, there may be as broad a range in inositol requirements as there is in the range of severity of diabetes.

Recently, there have been reports in the medical literature that have suggested that the secondary complications of diabetes, i.e., renal disease, could be ameliorated by dietary inositol supplementation. Some investigators have shown a reversal of the diabetes-induced increased glomerular filtration rate with a seven- to tenfold increase in dietary levels of myoinositol. At any rate, it would appear that diabetics have a larger than normal need for dietary inositol because (1) they excrete more than do normal people; (2) when hyperglycemic they synthesize less from glucose because less glucose is available inside the cell and because the first two steps in glucose metabolism are insulin dependent; (3) they absorb less from the diet; and (4) when hyperglycemic they have greater sorbitol production which, in turn, inhibits the pathway for inositol synthesis.

E. Deficiency

In normal humans, inositol needs are presumed to be met by endogenous synthesis, so detailed studies have not been performed using healthy volunteers. Indirect evidence of need has been reported sparsely in the medical literature but detailed, controlled feeding studies have not been conducted. Such studies have been performed in laboratory rats and mice. In these animals the most striking feature of the deficient state was the development of a fatty liver. This was reversed with dietary inositol supplementation. Hair loss and poor growth were also reported for deficient animals. At the time these animal studies were conducted (1979–1980) the PIP cycle was not known. Researchers knew about the presence of phosphatidylinositol in the cell membrane but they did not recognize its importance in the lipid signal transduction process. Studies on the PIP cycle in rats made inositol deficient have yet to be conducted.

F. Requirement

Inositol is a conditionally essential nutrient because the body can synthesize it from glucose, but there may be circumstances where this synthesis is inadequate and exogenous inositol might become essential. At this time this information is only suggestive.

IV. OTHER COMPOUNDS WITH BIOLOGIC ACTIVITY

A. Overview

The bulk of the work identifying and describing compounds we now know as vitamins occurred in the first part of the twentieth century. Recent work has suggested other compounds that may also be essential to the maintenance of normal metabolism of some organisms, but for which there is no direct proof for mammals including humans. In this list are pyrroloquinoline quinone, ubiquinone, orotic acid, para-aminobenzoic acid, lipoic acid, and the bioflavinoids. Brief descriptions of these substances follow.

B. Pyrroloquinoline Quinone

Pyrroloquinoline quinone, sometimes called methoxatin, serves as a cofactor for certain methane-forming bacteria. The structure of pyrroloquinoline quinone is shown in Figure 11. It is a tricarboxylic acid with a fused heterocylic (*o*-quinone) ring system. Its C-5 carbonyl group is very reactive towards nucleophiles and it is this action that allows this substance to function in metabolic reactions. At present, information is scarce with respect to its food sources and essentiality. Likely, it can be endogenously synthesized in organisms that can use it, but whether this compound meets the definition of a vitamin has yet to be established for any species.

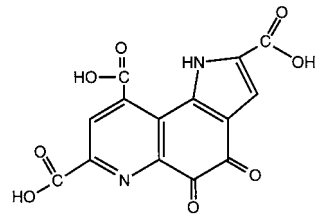

Figure 11 Structure of pyrroloquinoline quinone.

C. Ubiquinone

Ubiquinone is an essential component of the mitochondrial respiratory chain and it has been shown to be synthesized endogenously. Actually, ubiquinone is one of a group of related substances. They are a group of tetra-substituted 1,4-benzoquinone derivatives with isoprenoid side chains of various lengths. The biochemists have termed these substances as coenzyme Q. They function as reversible donors/acceptors of reducing equivalents from NAD, passing electrons from flavoproteins to the cytochromes via cytochrome b_5. Because the ubiquinones can be synthesized endogenously in large amounts even when diets lacking the ubiquinones are offered, these substances fail to meet the definition of the word vitamin.

D. Orotic Acid

Orotic acid is an important metabolic intermediate in the synthesis of pyrimidines. Its structure is shown in Figure 12. It is synthesized endogenously from N-carbamyl phosphate by dehydration and oxidation. It is another of those substances that fails to meet the definition of a vitamin. When used as a dietary supplement (0.1% of diet) orotic acid had deleterious effects. It resulted in a fatty, enlarged liver and increased the levels of hepatic uracil, presumably due to an influence on pyrimidine synthesis. Orotic acid-induced fatty liver is accompanied by falling plasma cholesterol levels and falling activity of HMG CoA reductase. This hepatic enzyme is greatly influenced by its product (cholesterol) and so if the liver does not export it, it feeds back to inhibit synthesis.

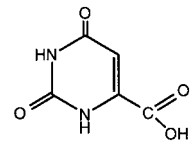

Figure 12 Structure of orotic acid.

E. Para-Aminobenzoic Acid (PABA)

p-Aminobenzoic acid is an essential growth factor for a number of bacteria which use it as a precursor of folacin. Animals, however, cannot synthesize folacin so *p*-aminobenzoic acid does not meet the definition of a vitamin. Its involvement in folacin use is discussed in Unit 4, Section VIII.

F. Lipoic Acid

Lipoic acid is essential to oxidative decarboxylation of α-keto acids. It participates in the pyruvate dehydrogenase complex (see Figures 7 and 8 in Unit 4 on pages 84 and 85). This is a multienzyme complex where lipoic acid is linked to the ε-amino group of a lysine residue from the enzyme dihydrolipoyl transacetylase. As the lipoamide undergoes reversible acylation/deacylation it transfers acyl groups to coenzyme A and results in reversible ring opening/closing in the oxidation of the α-keto acid. Lipoic acid can be synthesized endogenously in amounts sufficient to meet the need. Therefore, it does not meet the definition of the word vitamin.

G. Bioflavinoids

Bioflavinoids are a group of compounds that are presumed by some to augment the action of ascorbic acid in the prevention of scurvy . They are mixtures of phenolic derivatives of 2-phenyl-1,4-benzopyrone. The bioflavinoids are present in a large variety of foods and were first isolated by Szent-Gyorgy from lemon juice and red peppers. More than 800 different flavinoids have been found. They occur naturally as glycosides which are hydrolyzed by the gut flora prior to absorption. No single unique deficiency syndrome has been found or reported in animals fed a bioflavinoid-free diet. Furthermore, there has not been a unique response to the addition of bioflavinoids to the diet. On this basis, despite their activity as potentiators of ascorbic acid, bioflavinoids can not be considered vitamins.

H. Pseudovitamins

The term vitamin was coined many years ago to designate those organic dietary compounds that cannot be made endogenously but are needed in small amounts to sustain normal growth and metabolism throughout life. This term, developed by nutritional biochemists and physiologists, has been used commercially as well as scientifically. Unfortunately, there have been (and continue to be) commercial uses of the term that are inappropriate. Hence we have compounds such as laetrile (an extract from fruit pits), pangamic acid or vitamin B_{15}, and methylsulfonium salts of methionine called vitamin U, and gerovital. Gerovital, also called vitamin H_3 or CH_3, is a buffered solution of procaine hydrochloride (Novocaine™), a local anesthetic. To be effective as an anesthetic it must be injected. Gerovital is advertised as an antiaging substance but claims of its effects have not been substantiated. The advertised use of methylsulfonic salts of methionine to prevent peptic ulcers likewise has not been substantiated. Pangamic acid, another of these pseudovitamins, is not a chemically defined substance. Rather it is a mixture of compounds. Of the materials labeled pangamic acid, one of the compounds is N,N-diisopropylamine dichloroacetate. This is a drug, and when administered to normal rats it caused death preceded by respiratory failure, extreme hypotension, and hypothermia. There is no evidence of essentiality for pangamic acid.

Lastly, laetrile is included in this list of pseudovitamins. This compound has been the focus of a number of litigations due to the claim by its suppliers that it can serve as an anticancer drug. This claim was investigated and found wanting by the U.S. Food and Drug Administration (FDA). The term laetrile has several synonyms: amygdalin and vitamin B_{17}. Amygdalin is a β-cyanogenic glucoside and is a major constituent in preparations named laetrile. Amygdalin is a substance found in peach pits, apricot pits, and the kernels and seeds of many fruits. Neither the U.S. FDA or the Canadian equivalent of this regulatory agency recognize laetrile as a vitamin.

SUPPLEMENTAL READINGS

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