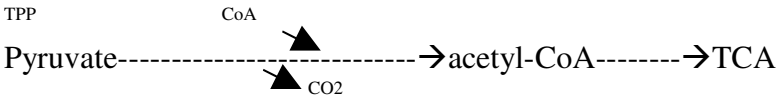
Thiamin

Thiamin consists of pyrimidine and thiazole rings linked by a methylene bridge; alcohol group of the side chain can be esterified with one, two or three phosphates, yielding thiamin monophosphate (TMP), thiamin diphosphate (TDP, also known as thiamin pyrophosphate (TPP), the metabolically active coenzyme) and thiamin triphosphate (TTP). The coenzyme role of TPP in the oxidative decarboxylation of 2-oxo-acids and transketolase has been noted. In addition, TTP has a role (as yet inadequately defined) in nervous transmission.

TPP is the coenzyme for three multi-enzyme complexes in mammalian mitochondria which are involved in the oxidative decarboxylation of 2-oxo-acids: pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase in central yielding metabolic pathways and of other alpha-keto acids such as alpha-ketoglutarate and the branched-chain oxo-acid dehydrogenase in the catabolism of leucine, isoleucine and valine. Pyruvate dehydrogenase is the key enzyme which commits pyruvate (and hence the products of CHO metabolism) to complete oxidation (via the TCA cycle) and lipogenesis. TPP participate in a reaction where a carboxyl group is removed from a compound and released as CO2. An example is the conversion of pyruvate to acetyl-CoA, which is irreversible, during CHO metabolism. This conversion is critical if aerobic metabolism of glucose is to be sustained.



Pyruvate dehydrogenase is subject to regulation by both product inhibition and a phosphorylation/dephosphorylation mechanism. Acetyl-CoA and NADH are both inhibitors, which compete with CoASH and NAD+ respectively. Branched-chain oxo-acid decarboxylase is the enzyme which is affected in maple syrup urine disease (branched-chain oxo-aciduria). A thiamin responsive inborn error of 2-oxoglutarate dehydrogenase has been reported, which results in anemia because of the failure to form sufficient succinyl CoA for haem synthesis.

Transketolase catalyses the transfer of a 2-C unit from a donor ketose onto an acceptor aldose sugar. Transketolase is involved in the pentose phosphate pathway, which is a major pathway of CHO metabolism in some tissues, and a significant alternative to glycolysis in all tissues.

Deficiency

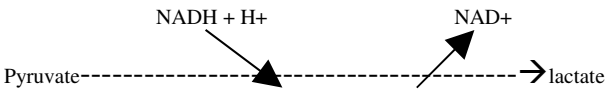
The role of TPP in pyruvate dehydrogenase means that in deficiency there is impaired conversion of pyruvate to Acetyl-CoA, and hence impaired entry of pyruvate into the TCA cycle. Especially in people who consume a high carbohydrate diet, this results in increased plasma concentrations of lactate and pyruvate, which may lead to life-threatening lactic acidosis.

Niacin

Niacin's role is as the precursor of the nicotinamide moiety of the nicotinamide nucleotide coenzymes, NAD and NADP. The nicotinamide nucleotide coenzymes function as electron carriers in a wide variety of redox reactions. The niacin coenzymes

function in at least 200 different reactions in cellular metabolic pathways, especially those that produce ATP. The oxidized coenzymes have a formal positive charge, and are represented as NAD+ and NADP+, while the reduced forms, carrying two electrons and one proton (and associated with an additional proton) are represented as NADH and NADPH. The two-electron reduction of NAD(P)+ proceeds by way of a hydride (H-) ion transfer to C-4 of the nicotinamide ring.

In general, NAD+ participates in catabolic reactions, acting as an electron and hydrogen acceptor in glycolysis (glucose to pyruvate) and in the TCA cycle. Under anaerobic conditions, the resulting reduced form, NADH, is used in converting pyruvate to lactate, thereby regenerating NAD+:



Under aerobic conditions, NADH donates an electron and hydrogen to other acceptor molecules in the ETC. The major coenzyme for reductive synthetic reactions is NADPH. An exception here is the pentose phosphate pathway, which reduces NADP+ to NADPH, and is the principal metabolic source of reductant for lipogenesis. These compounds are also important coenzymes for glycolysis, protein and amino acid metabolism, pyruvate metabolism, pentose biosynthesis, generation of high-energy phosphate bonds, glycerol metabolism, and fatty acid metabolism.

Deficiency

Considering the many reactions niacin is involved in, we can conclude that it is extremely important. NAD allows for catabolic processes to occur that will ultimately lead to ATP production. The oxidation of NADH to NAD+ leads to ATP production in the ETC by creating an electrical gradient. If NAD was not available to accept H+'s, then metabolic processes would not be able to occur. Glucose could not be broken down to pyruvate, pyruvate would not be able to convert to lactate or acetyl-CoA. Isocitrate could not be oxidized to alpha-keto-glutarate. Alpha-ketoglutarate could not be oxidized to Succinyl-CoA. Also, Malate could not be oxidized to OAA. These processes are essential for energy production in the cell. NADH-→NAD+ is involved in Complex 1 of the ETC. Niacin deficiency would prevent glycolysis, protein and amino acid metabolism, pyruvate metabolism, pentose biosynthesis, generation of high-energy phosphate bonds, glycerol metabolism, and fatty acid metabolism from occurring.

Vitamin B6

Vitamin B6 is actually a family of three compounds: pyridoxal, pyridoxine, and pyridoxamine. All three forms can be phosphorylated to the active vitamin B6 coenzymes, the primary one being pyridoxal phosphate (PLP). Vitamin B6 is required for the activity of more than 100 different enzymes involved in CHO, protein and fat metabolism.

The most widespread function of Vitamin B6, as the coenzyme PLP, concerns metabolism of amino acids and other nitrogen containing compounds, including transamination reactions. In transamination reactions, PLP aids in the transfer of an amino acid group from a donor amino acid to a receptor molecule, yielding the carbon

skeleton of the original amino acid and a new amino acid. An example is the transamination between pyruvate (acceptor molecule) and glutamate (donor molecule) to form alanine (an amino acid) and alpa-keto-glutarate. If we didn't have the biochemical action of B6, every amino acid would become essential. The creation of non-essential amino acids, via Vitamin B6 transamination reactions, allows for the "filling-up" of the TCA cycle to occur. This allows for the cycle to continue during times of low energy intake and when the cycle is slowed down.

Vitamin B6 also participates in glycogen breakdown and glucose production from amino acids via gluconeogenesis. PLP also functions as a coenzyme for glycogen phosphorylase, which is an enzyme that catalyzes the sequential phophorolysis of glycogen to release glucose-1-phophate; it is thus the key enzyme in the utilization of tissue glycogen reserves.

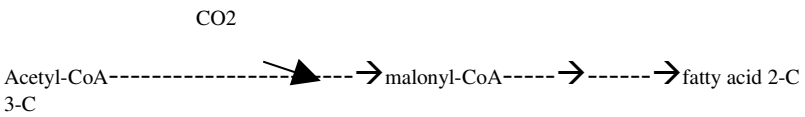
The human requirement for another vitamin, niacin can be met in part by the conversion of the dietary amino acid, tryptophan, to niacin, as well as through dietary intake. PLP is a coenzyme for a critical reaction in the synthesis of niacin from tryptophan. Thus, adequate vitamin B-6 decreases the requirement for niacin in the diet.

Deficiency

Because of its central role in amino acid metabolism, a deficiency of vitamin B6 will cause wide spread disturbance in amino acid metabolism. Considering that Vitamin B6 is dependent of niacin formation via tryptophan, it is indirectly involved in NAD production. NAD is necessary for transamination reactions to occur. Vitamin B6 deficiency could lead to secondary niacin deficiency. Considering its affect on anapleurosis, vitamin B6 deficiency could prevent transamination reactions from occurring, which could prevent the TCA cycle to continue in times of low energy intake, or if at all. Also, the effect of gluconeogenesis, such as the conversion of pyruvate to alanine via transamination, could be detrimental. Alanine is just one of the 8 glucogenic amino acids that can be used to form glucose for energy use. If transamination reactions are not allowed to occur, then a decrease in glucogenic amino acids will result, as well as the 2-ketogenic amino acids. Vitamin B6 is also the coenzyme for glycogen phosphorylase. If a deficiency occurred, we could not expect glycogen to be broken down and therefore no energy could be produced via glucose metabolism.

Pantothenic Acid

Pantothenic Acid is part of Coenzyme A (CoA). This coenzyme is formed when the vitamin combines with a derivative of ADP and the amino acid cysteine. CoA is essential for the metabolism of CHO, protein and fat. CoA may be involved in the assembly of active cytochrome c oxidase and ATP synthetase complexes. The formation of acetyl-CoA from the acetate that arises from their metabolism allows the 2-C acetate to enter the TCA cycle. In another series of reactions acetyl-CoA condenses with CO2 to begin synthesis of fatty acids:



CoA functions as the carrier of fatty acids, as thio-esters, in mitochondrial B-oxidation. The resultant 2-C fragments as acetyl-CoA, then undergo oxidation in the TCA cycle. CoA also functions as a carrier in the transfer of acetyl (and other fatty acyl) moieties in a variety of biosynthetic and catabolic reactions: steroidogenesis, long-chain fatty acid synthesis from palmitate in mitochondria and endoplasmic reticulum, and many others.

Deficiency

Modest deficiency of pantothenic acid in rats leads to elevated serum concentrations of triglycerides and non-esterified fatty acids, reflecting impaired B-oxidation. This is expected considering synthesis of fatty acids would be impaired, leading to increases in serum triglycerides. Also, considering the role the vitamin has with B-oxidation would have an effect on fat use. CoA is also necessary in CHO metabolism, as it is a part of acetyl-CoA.

Biotin

Biotin in its coenzyme form participates in numerous reactions involved in the metabolism of fat and CHO. It also participates in the entry of certain carbon skeletons from amino acids into the energy-yielding pathways, as well as in DNA synthesis. In mammals and birds there are four biotin-dependent carboxylases.

1)Acetyl-CoA carboxylase-catalyzes the carboxylation of acetyl-CoA to malonyl-CoA, the first rate-limiting step of fatty acid synthesis.

2)Pyruvate carboxylase- catalyzes the carboxylation of pyruvate to OAA. It thus represents the first committed step of gluconeogenesis from pyruvate and also an important anapleurotic reaction permitting repletion of TCA cycle intermediates.

3)Propionyl-CoA carboxylase- catalyzes the carboxylation of propionyl-CoA to methylmalonyl-CoA, which in tun undergoes a vitamin B12 dependent isomerization to succinyl-CoA. This reaction thus provides a pathway for the oxidation, through the TCA cycle, of propionyl-CoA arising from the catabolism of the amino acids isoleucine, valine, methionine, and threonine, the rare odd-chain fatty acids and the side-chain of cholesterol.

4)Methylcrotonyl CoA carboxylase-catalyzes the conversion of methylcrotonyl CoA, arising from the catabolism of leucine, to methylglutaconyl CoA. This in turn undergoes hydroxylation catalyzed by crotonase, yielding hydroxymethyl-glutaryl-CoA, which is cleaved to acetyl-CoA and acetoacetate.

Deficiency

Biotin deficiency results in impaired gluconeogenesis, with the accumulation of lactate, pyruvate and alanine, and impaired lipogenesis, with the buildup of acetyl-CoA, resulting in ketosis. The impairment of pyruvate carboxylase in biotin deficiency would be expected to result in impaired gluconeogenesis. Additionally, deficiency results in a lowering of the NADH:NAD+ ratio, and hence further reduction of gluconeogenesis by impairment of glyceraldehyde-3-phosphate dehydrogenase activity. Pyruvate carboxylase deficiency causes depletion of OAA tissue pools which results in impaired citrate synthase activity, and hence a slowing of the TCA cycle leading to accumulation

of lactate, pyruvate and alanine, and also acetyl-CoA-resulting in ketosis. Propionyl-CoA carboxylase deficiency causes sever ketosis and acidosis. Biotin deficiency may sometimes be associate with hyperglycemia. This seems to be due to reduced activity of hepatic glucokinase, to less than half normal activity. Biotin induces glucokinase independently of the effects of insulin, albeit by similar mechanism, and also increases the activity of 2 other key enzymes in glycolysis, PFK and Pyruvate kinase.

Riboflavin

Riboflavin is a component of 2 coenzymes: flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). FMN and FAD participate in many oxidation-reduction reactions in a variety of metabolic pathways. Unlike the nicotinamide nucleotide coenzymes, which act as cosubstrates, leaving the catalytic site of the enzyme at the end of the reaction, the flavin coenzymes remain bound to the enzyme throughout the catalytic cycle. In both the TCA cycle and the pathway for catabolizing fatty acids, FAD accepts electrons (as part of hydrogens), forming the reduced form, FADH2. FADH2 later donates the hydrogens to other acceptor molecules in the mitochondrial ETC. The other riboflavin coenzyme also functions in the ETC, shuttling between its oxidized form, FMN, and reduced form, FMNH2. When cells produce ATP by metabolizing glucose via aerobic pathways or by breaking down fatty acids, the riboflavin coenzymes play an indispensable role. Flavins can undergo a one-electron reduction to the semiquinone radical or a 2-electron reduction to dihydroflavin. They are involved in Complex 2 of the ETC and can yield up to 2 ATP's.

Deficiency

Riboflavin deficiency causes impairment of lipid metabolism. Riboflavin deficient animals have a lower metabolic rate than controls, and require a 15%-20% higher food intake to maintain body weight. There is increased accumulation of triglycerides in the liver, with an increase in liver weight as a proportion of body weight. The activity of succinate dehydrogenase is reduced, but this has only a small effect on the rate of succinate oxidation in isolate mitochondria since succinate dehydrogenase is not normally rate-limiting. The main effect of riboflavin deficiency is on lipid metabolism. There is an increase in 18:2n-6 and decrease in 20:4n-6 fatty acids in phospholipids in deficiency. Within a day of initiating a riboflavin-free diet in weanling rats there is a 35% decrease in the oxidation of palmitoyl CoA. All 3 mitochondrial acyl CoA dehydrogenases are affected, although it is short-chain acyl CoA dehydrogenase which is most severely impaired, and which becomes the rate-limiting step of fatty acid oxidation. B-oxidation in the mitochondria is impaired.

Riboflavin deficiency can also lead to secondary vitamin deficiencies. Riboflavin depletion decreases the oxidation of B6 to pyridoxal. Riboflavin can disturb tryptophan metabolism due to impairment of kynurenine hydroxylase, which can result in reduced synthesis of NAD from tryptophan, and therefore a slight niacin deficiency.