7.3B: Vitamin B₂ (Riboflavin)

Riboflavin, also known as vitamin B₂, is a vitamin found in food and used as a dietary supplement. As a supplement it is used to prevent and treat riboflavin deficiency and prevent migraines. It may be given by mouth or injection. It is nearly always well tolerated. Normal doses are safe during pregnancy. Riboflavin is in the vitamin B group. It is required by the body for cellular respiration. Food sources include eggs, green vegetables, milk, and meat. Riboflavin was discovered in 1920, isolated in 1933, and first made in 1935. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. Riboflavin is available as a generic medication and over the counter. In the United States a month of supplements costs less than 25 USD. Some countries require its addition to grains.

A solution of riboflavin. (CC BY 4.0; PatriciaR)
Riboflavin has been used in several clinical and therapeutic situations. For over 30 years, riboflavin supplements have been used as part of the phototherapy treatment of neonatal jaundice. The light used to irradiate the infants breaks down not only bilirubin, the toxin causing the jaundice, but also the naturally occurring riboflavin within the infant's blood, so extra supplementation is necessary.

Riboflavin functions as a coenzyme, meaning that it is required for enzymes (proteins) to perform normal physiological actions. Specifically, the active forms of riboflavin flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) function as cofactors for a variety of flavoprotein enzyme reactions:

- Flavoproteins of electron transport chain, including FMN in Complex I and FAD in Complex II
- FAD is required for the production of pyridoxic acid from pyridoxal (vitamin B₆) by pyridoxine 5'-phosphate oxidase
- The primary coenzyme form of vitamin B₆ (pyridoxal phosphate) is FMN dependent
- Oxidation of pyruvate, α-ketoglutarate, and branched-chain amino acids requires FAD in the shared E3 portion of their respective dehydrogenase complexes
- Fatty acyl CoA dehydrogenase requires FAD in fatty acid oxidation
- FAD is required to convert retinol (vitamin A) to retinoic acid via cytosolic retinal dehydrogenase
- Synthesis of an active form of folate (5-methyltetrahydrofolate) from 5,10-methylenetetrahydrofolate by Methylene tetrahydrofolate reductase is FADH₂ dependent
- FAD is required to convert tryptophan to niacin (vitamin B₃)
- Reduction of the oxidized form of glutathione (GSSG) to its reduced form (GSH) by Glutathione reductase is FAD dependent

For the molecular mechanism of action see main articles Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD)

Dietary Sources

Food and beverages that provide riboflavin without fortification are milk, cheese, eggs, leaf vegetables, liver, kidneys, legumes, mushrooms, and almonds. The milling of cereals results in considerable loss (up to 60%) of vitamin B₂, so white flour is enriched in some countries such as US by addition of the vitamin. The enrichment of bread and ready-to-eat breakfast cereals contributes significantly to the dietary supply of vitamin B₂. Polished rice is not usually enriched, because the vitamin’s yellow color would make the rice visually unacceptable to the major rice-consumption populations. However, most of the flavin content of whole brown rice is retained if the rice is steamed (parboiled) prior to milling. This process drives the flavins in the germ and aleurone layers into the endosperm. Free riboflavin is naturally present in foods along with protein-bound FMN and FAD. Bovine milk contains mainly free riboflavin, with a minor contribution from FMN and FAD. In whole milk, 14% of the flavins are bound noncovalently to specific proteins. Egg white and egg yolk contain specialized riboflavin-binding proteins, which are required for storage of free riboflavin in the egg for use by the developing embryo.

Dietary Reference Intake

In humans, there is no evidence for riboflavin toxicity produced by excessive intakes, in part because it has lower water
solubility than other B vitamins, because absorption becomes less efficient as doses increase, and because what excess is absorbed is excreted via the kidneys into urine. Even when 400 mg of riboflavin per day was given orally to subjects in one study for three months to investigate the efficacy of riboflavin in the prevention of migraine headache, no short-term side effects were reported. Although toxic doses can be administered by injection, any excess at nutritionally relevant doses is excreted in the urine, imparting a bright yellow color when in large quantities.

The Food and Nutrition Board of the U.S. Institute of Medicine sets Tolerable Upper Intake Levels (known as ULs) for vitamins and minerals when evidence is sufficient. In the case of riboflavin there is no UL, as there is no human data for adverse effects from high doses. The European Food Safety Authority reviewed the same safety question and also reached the conclusion that there was not sufficient evidence to set a UL for riboflavin.

The Food and Nutrition Board of the U.S. Institute of Medicine updated Estimated Average Requirements (EARs) and Recommended Dietary Allowances (RDAs) in 1998. The current EARs for riboflavin for women and men ages 14 and up are 0.9 mg/day and 1.1 mg/day, respectively; the RDAs are 1.1 and 1.3 mg/day. RDAs are higher than EARs so as to identify amounts that will cover people with higher than average requirements. RDA for pregnancy equals 1.4 mg/day. RDA for lactation equals 1.6 mg/day. For infants up to 12 months the Adequate Intake (AI) is 0.3-0.4 mg/day and for children ages 1–13 years the RDA increases with age from 0.5 to 0.9 mg/day. Collectively the EARs, RDAs and ULs (see Toxicity) are referred to as Dietary Reference Intakes.[18][26]

For U.S. food and dietary supplement labeling purposes the amount in a serving is expressed as a percent of Daily Value (%DV). For riboflavin labeling purposes 100% of the Daily Value was 1.7 mg, but as of May 2016 it has been revised to 1.3 mg. A table of the pre-change adult Daily Values is provided at Reference Daily Intake. Food and supplement companies have until July 2018 to comply with the change.

Riboflavin Deficiency

Mild deficiencies can exceed 50% of the population in third world countries and in refugee situations. Deficiency is uncommon in the United States and in other countries that have wheat flour, bread, pasta, corn meal or rice enrichment regulations. In the U.S., starting in the 1940s, flour, corn meal and rice have been fortified with B vitamins as a means of restoring some of what is lost in milling, bleaching and other processing. For adults 20 and older, average intake from food and beverages is 1.8 mg/day for women and 2.5 mg/day for men. An estimated 23% consume a riboflavin-containing dietary supplement that provides on average 10 mg. The U.S. Department of Health and Human Services conducts National Health and Nutrition Examination Survey every two years and reports food results in a series of reports referred to as "What We Eat In America." From NHANES 2011–2012, the latest for which data has been reported, estimates are that 8% of women and 3% of men consume less than the RDA. When compared to the lower Estimated Average Requirements, fewer than 3% do not achieve the EAR level. However, anyone choosing a gluten-free or low gluten diet should as a precaution take a multi-vitamin/mineral dietary supplement which provides 100% DV for riboflavin and other B vitamins.

Riboflavin deficiency (also called ariboflavinosis) results in stomatitis including painful red tongue with sore throat, chapped and fissured lips (cheilosis), and inflammation of the corners of the mouth (angular stomatitis). There can be oily scaly skin rashes on the scrotum, vulva, philtrum of the lip, or the nasolabial folds. The eyes can become itchy, watery, bloodshot and sensitive to light. Due to interference with iron absorption, even mild to moderate riboflavin deficiency results in an anemia with normal cell size and normal hemoglobin content (i.e. normochromic normocytic
anemia). This is distinct from anemia caused by deficiency of folic acid (B9) or cyanocobalamin (B12), which causes anemia with large blood cells (megaloblastic anemia). Deficiency of riboflavin during pregnancy can result in birth defects including congenital heart defects and limb deformities.

The stomatitis symptoms are similar to those seen in pellagra, which is caused by niacin (B3) deficiency. Therefore, riboflavin deficiency is sometimes called "pellagra sine pellagra" (pellagra without pellagra), because it causes stomatitis but not widespread peripheral skin lesions characteristic of niacin deficiency.

Contributors

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